Radiation Oncology for Pediatric CNS Tumors

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Preface

In the United States, brain tumors account for 20% of new cancer cases and 30% of cancer deaths in children. Currently, 70–75% of central nervous system (CNS) patients younger than 19 years will survive. Radiation therapy has been and will continue to be a critical component of the multidisciplinary approach required in the care of children with CNS tumors. Gone are the days when radiation therapy or "radiodiagnosis" was used for germinoma or similarly simple "hockey stick" fields to treat the craniospinal axis. Continued advances in technology and understanding of diagnosis, imaging, and radiotherapy influence management of patients. This book integrates these advances specifically in the radiation therapy management of pediatric neuro-oncology.

The book is organized into four segments: (1) basic principles, (2) disease-specific sections, (3) radiotherapy practice, and (4) radiotherapy toxicity and management. The basic principles cover the epidemiology of brain tumors as well as the various disciplines aside from radiotherapy which are important in the management of CNS tumors. Individual disease-specific sites cover embryonal, glial, germ cell, and other tumor types and are discussed next. Treatment techniques used in radiotherapy practice for children including the use of anesthesia, craniospinal irradiation, proton therapy, and hypofractionated radiotherapy are discussed. Finally, various toxicities that relate to vision, hearing, endocrine, and cognitive function are discussed in radiotherapy toxicity and management.

We have been fortunate to have contributing authors who are experts in the field of pediatric radiation oncology. While many authors are from the United States, there is a representation from countries such as Germany, France, United Kingdom, Ireland, Japan, South Korea, Canada, and Brazil.

We hope this book will provide information and guidance to the pediatric oncology community as a whole and serve as a resource and educational tool to the radiation oncology community. We hope that this book provides a solid foundation as we continue to improve our understanding of pediatric CNS tumors.

Rochester, USA — Anita Mahajan
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Part I

Basic Principles

Epidemiology of Childhood Brain Tumors

1

Philip J. Lupo, Surya P. Rednam, and Murali Chintagumpala

Contents

Abstract

Childhood brain tumors are the most common form of pediatric solid tumors. Significant improvements over the decades in the treatment of brain tumors in children have improved outcomes but mortality and morbidity are still high. Pediatric brain tumors are clinically and biologically distinct from those that occur in adults. Our understanding of risk factors in childhood brain tumors remains limited to several exposures of the head and neck to ionizing radiation and well-described hereditary cancer predisposition syndromes. In this chapter, we review the descriptive and analytic epidemiology of childhood brain tumors, including a discussion of the roles of radiation exposure, established predisposing syndromes, and other suspected risk factors.

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1.1 Introduction

Brain tumors are the leading cause of cancer death in individuals 0–19 years of age in the USA and Canada (Curtin et al. 2016). Furthermore, brain tumors are a significant source of cancer-related morbidity in infants and children. Given the relative frequency of childhood brain tumors and their suboptimal outcome with therapy, it is important to identify their etiologies. Epidemiologic studies help in this endeavor in two ways. Descriptive studies reveal the incidence of brain tumors, and their associated mortality and survival rates with respect to histologic subtype and demographic characteristics. Analytic studies compare the risk of brain tumors in people with and without certain characteristics (cohort studies) or compare the histories of people with and without brain tumors (case-control studies) to identify and assess a wide range of possible risk factors, including exposures to radiation and hereditary cancer predisposition syndromes. In addition to epidemiologic analyses, progress in the molecular classification of these tumors could provide greater insight into the role of tumor genetics in disease progression and sensitivity to radiation treatment and chemotherapy. The hope is that knowledge from epidemiologic and tumor biology studies will lead to improved assessment of pediatric brain tumor risk, development of appropriate approaches to early tumor identification, and eventually individualized prevention and treatment strategies.

1.2 Descriptive Epidemiology

There are more than 100 different histological subtypes of brain tumors, and the incidence of each subtype varies with several factors including age, geography, sex, and race/ethnicity. For instance, childhood brain tumor incidence varies by country from 1.12 to 5.14 cases per 100,000 persons (Table 1.1) (Johnson et al. 2014). Overall, childhood brain tumors are more common in males, although this can vary by histologic subtype. In the USA, non-Hispanic whites and Asian-Pacific Islanders have a higher incidence when compared to Hispanics or non-Hispanic blacks. However, it should be noted that differences in incidence and survival may be related to differences in case ascertainment methodology among cancer registries. Furthermore, cancer registries differ on ascertainment of benign brain tumors. For example, in the USA, registration of nonmalignant tumors was not required by law prior to 2004. However, across registries, the standard approach is to include both benign and malignant brain tumors and other central nervous system (CNS) tumors in all statistics. Therefore information on specific histologic subtypes and all comparison statistics must be interpreted with these potential limitations in mind.

1.2.1 Glioma

Gliomas arise from glial cells and overall are the most common category of childhood brain tumor (Bauchet et al. 2009). Incidence (Table 1.1) and survival (Table 1.2) vary significantly depending on location and histologic subtype. The most common type of glioma in children is pilocytic astrocytoma.

Table 1.1 Incidence of selected childhood brain tumors per 100,000 persons by histology and region

Histologic subtype	Region and reference	Years	Incidence rate (95% CI)
All brain tumors	Europe (Peris-Bonet et al. 2006)	1988–1997	2.99
	United States (Ostrom et al. 2013)	2006–2010	5.26 (5.19–5.33)
	Japan (Makino et al. 2010)	1989–2008	3.61
	Kuwait (Katchy et al. 2013)	1995–2011	1.12
	Denmark, Finland, Norway, and Sweden (Schmidt et al. 2011)	1985–2006	4.20
Pilocytic astrocytoma	United States (Ostrom et al. 2013)	2006–2010	0.90 (0.87–0.93)
	England (Arora et al. 2009)	1995–2003	0.75
Astrocytoma	Europe (Peris-Bonet et al. 2006)	1988–1997	1.18
	Japan (Makino et al. 2010)	1989–2008	1.32
	Denmark, Finland, Norway, and Sweden (Schmidt et al. 2011)	1985–2006	1.79
Ependymoma	Europe (Peris-Bonet et al. 2006)	1988–1997	0.34
	United States (Ostrom et al. 2013)	2006–2010	0.28 (0.26–0.30)
	Japan (Makino et al. 2010)	1989–2008	0.15
	Denmark, Finland, Norway, and Sweden (Schmidt et al. 2011)	1985–2006	0.42
	England (Arora et al. 2009)	1995–2003	0.25
Embryonal tumors	United States (Ostrom et al. 2013)	2006–2010	0.80 (0.77–0.84)
	Denmark, Finland, Norway, and Sweden (Schmidt et al. 2011)	1985–2006	0.73
	England (Arora et al. 2009)	1995–2003	0.28
PNET	Austria (Woehrer et al. 2010)	1996–2006	0.21 (0.15–0.30)
	England (Arora et al. 2009)	1995–2003	0.08
Medulloblastoma	Japan (Makino et al. 2010)	1989–2008	0.37
	Austria (Woehrer et al. 2010)	1996–2006	0.58 (0.16–0.71)
	England (Arora et al. 2009)	1995–2003	0.20
ATRT	Austria (Woehrer et al. 2010)	1996–2006	0.14
	United States (Ostrom et al. 2013)	2006–2010	0.11 (0.10–0.12)

1.2.1.1 Pilocytic Astrocytoma

Pilocytic astrocytoma (World Health Organization [WHO] grade I) is the most common childhood brain tumor, representing approximately 17% of all CNS tumors in children (Ostrom et al. 2013). The incidence of these tumors ranges from 0.7 to 0.9 cases per 100,000 persons (Table 1.1). While these tumors are

Table 1.2 Five-year survival of selected childhood brain tumors by histology and region

Histologic subtype	Region and reference	Years	5-year survival (95% CI)
All brain tumors	Europe (Peris-Bonet et al. 2006)	1988–1997	91.0 (60.0–62.0)
	United States (Ostrom et al. 2013)	2006–2010	72.3 (71.2–73.3)
	Sweden (Lannering et al. 2009)	1984–2005	76.0
Ependymoma	Europe (Peris-Bonet et al. 2006)	1988–1997	53.0 (49.0–57.0)
	United States (Ostrom et al. 2013)	1995–2010	72.2 (67.9–76.1)
	Sweden (Lannering et al. 2009)	1984–2005	72.0
Astrocytoma	Europe (Peris-Bonet et al. 2006)	1988–1997	75.0 (73.0–76.0)
	Sweden (Lannering et al. 2009)	1984–2005	84.0
Pilocytic astrocytoma	United States (Ostrom et al. 2013)	2006–2010	97.2 (96.3–98.0)
Embryonal tumors	United States (Ostrom et al. 2013)	1995–2010	62.1 (59.6–64.5)
PNET	Europe (Peris-Bonet et al. 2006)	1988–1997	49.0 (46.0–51.0)
	United States (Ostrom et al. 2013)	1995–2010	49.5 (45.3–53.6)
	Sweden (Lannering et al. 2009)	1984–2005	47.0
Medulloblastoma	United States (Ostrom et al. 2013)	1995–2010	71.1 (68.5–73.5)
	Sweden (Lannering et al. 2009)	1984–2005	63.0
ATRT	United States (Ostrom et al. 2013)	1995–2010	28.0 (20.7–35.7)

low grade, rarely they may progress to higher-grade malignancies (Fisher et al. 2008; Stokland et al. 2010). Overall 5-year survival is high at 97% (Table 1.2) (Ostrom et al. 2013).

1.2.1.2 High-Grade Glioma

High-grade gliomas represent 7–11% of childhood brain tumors. The most common high-grade gliomas are anaplastic astrocytoma and glioblastoma. Overall, high-grade gliomas (WHO grade III and IV) are less common, with incidence rates of 0.08 for anaplastic astrocytoma and 0.14 for glioblastoma (Ostrom et al. 2013). These tumors have a very poor 5-year survival, which is often <30% (Johnson et al. 2014).

1.2.1.3 Brain Stem Gliomas

Brain stem tumors represent approximately 10% of childhood brain tumors which vary widely by biology, natural history, and outcomes. The most common of these tumors is diffuse intrinsic pontine glioma (DIPG) (Freeman and Farmer 1998). Survival for those diagnosed with DIPG is very poor, with >90% of cases dying within 2 years of presentation (Hargrave et al. 2006). These tumors are rarely biopsied, instead diagnosed by imaging, and as a result, their true incidence from cancer registry datasets is difficult to assess (Hargrave et al. 2006).

1.2.2 Embryonal Tumors

Embryonal tumors are believed to arise from disrupted embryonic cells remaining in the CNS after birth. There are three major embryonal tumor types with distinct differences in age at diagnosis and survival: medulloblastoma, primitive neuroectodermal tumor, and atypical teratoid/rhabdoid tumor (Louis et al. 2007).

1.2.2.1 Medulloblastoma

Medulloblastomas are the most common embryonal brain tumors, with an annual incidence ranging from 0.20 to 0.58 cases per 100,000 persons. Recent data suggest 1-year survival is 52%, 90%, and 92% for children aged 0–1, 1–9, and 10–19 years, respectively (Smoll 2012). Molecular analysis has identified four distinct medulloblastoma subtypes that correlate strongly with survival (Rutkowski et al. 2010). No population-based studies of subtype-specific survival have been reported, but in an international meta-analysis children with WNT tumors had a 95% 10-year overall survival. Children with sonic hedgehog (SHH), group 3, and group 4 tumors had 51%, 50%, and 32% 10-year survival, respectively (Kool et al. 2012).

1.2.2.2 Primitive Neuroectodermal Tumor (PNET)

PNET represents the second most common form of embryonal brain tumor. Average annual incidence rates for PNET range from 0.08 to 0.21 cases per 100,000 persons. PNET survival appears to improve with increasing age of diagnosis. For instance, 1-year survival is 31%, 88%, and 95% for children aged 0–1, 1–9, and 10–19 years, respectively (Smoll 2012). Given that PNETs and medulloblastoma share a similar histology, the 1993 WHO criteria specified a categorization based on location. Specifically, those tumors that are supratentorial are considered PNETs, whereas those that are infratentorial are considered to be medulloblastoma. Classification continues to evolve. PNET is no longer considered to be one disease. In fact, there are several subtypes and the correct classification remains challenging (Pfister et al. 2010).

1.2.2.3 Atypical Teratoid/Rhabdoid Tumor (AT/RT)

AT/RT is a rare embryonal CNS tumor that most commonly occurs in children <3 years of age. The annual incidence ranges from 0.07 to 0.14 per 100,000 persons (Johnson et al. 2014; Woehrer et al. 2010). Prognosis is generally poor, though survival increases with age (Hilden et al. 2004; Lafay-Cousin et al. 2012; von Hoff et al. 2011;

Woehrer et al. 2010). Overall, median survival is usually between 6 and 18 months (Athale et al. 2009; Lafay-Cousin et al. 2012; Lee et al. 2012; von Hoff et al. 2011). This tumor is typically more common among males (Heck et al. 2013; Lafay-Cousin et al. 2012) and among non-Hispanic whites (Bishop et al. 2012). A systematic diagnostic approach for AT/RT was not common until 2005; prior to that these tumors were frequently misclassified, mostly as medulloblastoma or PNET (Woehrer et al. 2010).

1.2.3 Other Brain Tumors

1.2.3.1 Choroid Plexus Carcinoma

Choroid plexus carcinomas constitute a very small percentage of childhood brain tumors (1–4%). Most of these tumors (70%) occur during the first year of life, and 5-year survival can be <30% (Johnson et al. 2014).

1.2.3.2 Ependymoma

Ependymomas constitute approximately 10% of all brain tumors in children. Over 90% of these tumors are intracranial. The highest incidence occurs within the first 7 years of life and the overall 5-year relative survival rate is 82% (Johnson et al. 2014). Additionally, males appear to be more likely to develop ependymoma compared to females (Johnson et al. 2014).

1.2.3.3 Craniopharyngioma

While craniopharyngiomas account for between 6 and 9% of all brain tumors in children, these tumors rarely occur in infants. In fact, the peak incidence during childhood is between 8 and 10 years of age. A recent assessment using data from the Surveillance, Epidemiology and End Results (SEER) Program indicated that 1-year survival rates were >90%. However, up to 75% of these children have significant complications including hypothalamic obesity (Hoffmann et al. 2015).

1.2.3.4 Germ Cell Tumors

Germ cell tumors are a mixed grouping of brain tumors classified on the basis of histological and immunohistochemical features. The WHO recognizes multiple different types of germ cell tumors, ranging from pure germinomas, mature teratomas to variety of highly aggressive nongerminomatous germ cell tumors. The incidence of these tumors is relatively low at 0.051 per 100,000 but varies by geography (e.g., the incidence is higher in some Asian countries compared to the USA) (de Robles et al. 2014c).

1.3 Analytic Epidemiology

1.3.1 Environmental Risk Factors

1.3.1.1 Radiation Exposure

High-dose radiation to the head and neck for treatment of cancer or other conditions is an established risk factor for childhood brain tumors (Kleinerman 2006). Cranial radiation therapy for acute lymphoblastic leukemia is associated with a particularly

high risk for developing (Ohgaki and Kleihues 2005) brain tumors (gliomas, PNETs) in children who received prophylactic CNS irradiation (usually a cumulative dose of 25 Gy, which is no longer part of contemporary therapy). Additionally, childhood exposure to low-dose ionizing radiation for tinea capitis has been associated with benign meningiomas and malignant brain tumors (Sadetzki et al. 2005). The latency between radiation therapy and subsequent brain tumor development has been estimated at 7–9 years with a higher risk for children diagnosed earlier in life (Ohgaki and Kleihues 2005). It has also been broadly accepted for several decades that in utero diagnostic radiation exposure is associated with a small to moderate dose-dependent increase in childhood cancer risk, including brain tumors (Streffer et al. 2003).

Ionizing Radiation

A study using data from the Childhood Cancer Survivor Study reported that children who received radiation therapy for their first primary CNS tumor were 7 times more likely to develop a subsequent CNS tumor (Neglia et al. 2006). The evidence regarding diagnostic X-ray exposure and childhood brain tumor risk is not well established. For example, in one study, while those who were exposed to diagnostic X-ray as neonates were 2 times more likely to develop a childhood brain tumor, this association was not statistically significant (Mellemkjaer et al. 2006). A Swedish study of individuals born between 1975 and 1984 examined the association between prenatal abdominal radiation exposures and childhood brain tumors. While there was not an increased risk overall, exposed individuals were twice as likely to develop a PNET (Stalberg et al. 2007). In a recently conducted study in the USA, maternally reported postnatal exposures to diagnostic X-rays were not associated with childhood medulloblastoma or PNET (Khan et al. 2010).

Nonionizing Radiation

Sources of nonionizing radiation that have been studied for their role in childhood brain tumor risk include radio frequency/microwave (e.g., cell phones, AM and FM radio, televisions, microwaves) and extremely low-frequency magnetic fields (e.g., power lines and electrical wiring). These exposures have been classified as possibly carcinogenic by the International Agency for Cancer Research (International Agency for Cancer Research 2014). However, epidemiologic studies have shown few significant positive associations between nonionizing radiation exposure and childhood brain tumors (Johnson et al. 2014).

1.3.1.2 Other Environmental Risk Factors

While there have been several epidemiologic studies of childhood brain tumors, few risk factors have been confirmed and established. Additionally, very few of these have led to prevention strategies. A recent review concluded that the strongest evidence for childhood brain tumor risk factors was for hereditary cancer predisposition syndromes and therapeutic ionizing radiation (Johnson et al. 2014). While some risk factors including parental age, birth defects, and pesticides have suggestive evidence, other factors including maternal medications and parental

occupational exposure during pregnancy have only weak or insufficient evidence (Johnson et al. 2014).

1.3.2 Genetic Factors

1.3.2.1 Hereditary Cancer Predisposition Syndromes

Up to 10% of pediatric cancers occur in the context of a set of well-described hereditary cancer predisposition syndromes (HCPSs) (Strahm and Malkin 2006). Individuals affected by these rare conditions are at greatly increased risk of developing malignancies at levels 10–100 fold above those seen in the general population. Several clues may raise suspicion for the presence of one of these conditions. An individual may have a specific tumor (or subtype) which is commonly associated with genetic susceptibility (e.g., optic pathway glioma with Neurofibromatosis Type 1) (Listernick et al. 2007). A tumor may occur at a significantly younger age than seen in the general population (e.g., childhood meningioma and Neurofibromatosis Type 2) (Evans et al. 1999, 2005; Thuijs et al. 2012). Family history, clinical features, certain laboratory values, or imaging abnormalities may indicate the presence of HCPS. Multiple primary tumors may occur in the same individual. A comprehensive family history may also trigger a genetic evaluation either due to a relative who has been diagnosed with a hereditary cancer predisposition syndrome or suggestive clinical history evident in the pedigree.

HCPSs are associated with increased risk of pediatric brain tumors (Table 1.3) may be categorized by their pattern of inheritance: autosomal dominant or autosomal recessive. The autosomal dominant syndromes can be further subdivided into neurocutaneous disorders, familial colon cancer syndromes involving elevated risks of brain tumors (i.e., Turcot Syndrome), and conditions exclusively having oncologic features. The autosomal recessive syndromes associated with increased childhood brain tumor susceptibility share impaired DNA repair as their underlying defect. Select examples for each of these syndrome groupings will be presented (extended listing in Table 1.3).

Neurocutaneous Disorders

Neurofibromatosis Type 1 (NF1 gene) occurs in approximately 1 in 2500–3000 people and is associated with both neoplastic and nonneoplastic features including multiple café-au-lait spots, axillary and inguinal freckling, cutaneous neurofibromas, and iris Lisch nodules (Hirbe and Gutmann 2014). Approximately 15–20% of affected individuals develop optic pathway gliomas (OPGs) (Fisher et al. 2012). When OPGs progress, usually in children less than 6 years of age, significant visual impairment may occur (approximately 1 in 3 with OPGs). There is also a significant risk of developing gliomas at other sites, predominantly low-grade. Radiation is considered the definitive therapy for non-NF1 OPGs, especially in the older child when the risk for significant neurocognitive effects is less. However, it is typically avoided in NF1 due to the risk for secondary malignancies and radiation-induced vasculopathy (Listernick et al. 2007).

Table 1.3 Hereditary cancer predisposition syndromes associated pediatric brain tumors

Syndrome	Select clinical features	Brain tumors
Autosomal dominant		
Neurocutaneous disorders		
Neurofibromatosis Type 1 (Fisher et al. 2012; Hirbe and Gutmann 2014; Listernick et al. 2007)	Dermatologic: Café-au-lait macules, axillary and inguinal freckling, neurofibromas Other: Lisch nodules and vasculopathy	Optic pathway glioma Other low-grade glioma
Neurofibromatosis Type 2 (Baser et al. 2000; Lloyd and Evans 2013)	Dermatologic: Café-au-lait macules (few) Ophthalmologic: Posterior subcapsular lens opacity, epiretinal membrane	Bilateral vestibular schwannomas Other schwannomas Meningioma Ependymoma
Tuberous Sclerosis Complex (Northrup and Krueger 2013)	Neurologic: Seizures, cortical tubers, subependymal nodules Dermatologic: Facial angiofibromas, hypomelanotic macules, shagreen patches Other: Renal angiomyolipoma, cardiac rhabdomyoma, retinal hamartoma	Subependymal giant cell astrocytoma (SEGA)
Von Hippel–Lindau Disease (Lonser et al. 2014; Maher et al. 2011)	Oncologic: Pheochromocytoma, renal cell carcinoma, tumors and cysts of abdominal visceral organs Other: Retinal angiomas	Cerebellar hemangioblastoma Spinal hemangioblastoma
Nevoid Basal Cell Carcinoma Syndrome (Gorlin Syndrome) (Amlashi et al. 2003; Cowan et al. 1997; Evans et al. 2010; Lam et al. 2013; Sartip et al. 2013)	Dermatologic: Basal cell nevi/carcinoma, palmar/plantar pits Skeletal: Macrocephaly, frontoparietal bossing, bifid ribs, vertebral anomalies, odontogenic jaw cyst	Medulloblastoma
Familial colon cancer (Turcot)		
Mismatch repair gene-related (Barrow et al. 2009; Jasperson et al. 2010; Therkildsen et al. 2015)	Oncologic: Gastrointestinal, hepatobiliary, uterine, ovarian, ureteral cancers	Glioblastoma multiforme Other glioma
APC-associated (Attard et al. 2007; Jasperson et al. 2010)	Oncologic: Gastrointestinal and thyroid cancers, desmoid tumor, osteoma Other: Congenital hypertrophy of retinal pigment epithelium	Medulloblastoma
Exclusively cancer predisposing		
Li–Fraumeni Syndrome (Chompret et al. 2000; Gonzalez et al. 2009; Heymann et al. 2010; Hisada et al. 1998; Limacher et al. 2001; Olivier et al. 2003; Ruijs et al. 2010; Tabori et al. 2010)	Oncologic: Sarcoma, breast cancer, leukemia, lymphoma, adrenocortical carcinoma	High-grade glioma Choroid plexus carcinoma Medulloblastoma

(continued)

Table 1.3 (continued)

Syndrome	Select clinical features	Brain tumors
Rhabdoid Predisposition Syndrome (Bourdeaut et al. 2011; Eaton et al. 2011)	Oncologic: Renal and extrarenal rhabdoid tumors	Atypical Teratoid/ Rhabdoid Tumor (AT/ RT)
Multiple Endocrine Neoplasia Type 1 (Cuny et al. 2013; Stratakis et al. 2010)	Oncologic: Parathyroid tumor, well-differentiated endocrine tumors of the gastro-entero-pancreatic tract, carcinoid, adrenocortical tumor	Pituitary tumor (Most commonly prolactinoma)
DICER1 Syndrome (de Kock et al. 2014a, b; Schultz et al. 2014)	Oncologic: Pleuropulmonary blastoma, multinodular goiter, differentiated thyroid carcinoma, Seroli–Leydig cell tumor, cystic nephroma, cervical rhabdomyosarcoma	Pituitary blastoma Pinealoblastoma
Other conditions		
Rubinstein–Tabyi Syndrome (Bourdeaut et al. 2014; Milani et al. 2015)	Skeletal: Microcephaly, distinctive facies, broad/ angulated thumbs, and great toes Other: Congenital heart defect and intellectual disability	Medulloblastoma
Autosomal recessive		
Constitutional Mismatch Repair Deficiency Syndrome (Bakry et al. 2014)	Dermatologic: Café-au-lait macules Oncologic: Leukemia, lymphoma, gastrointestinal cancers	High-grade glioma
Fanconi Anemia (Dewire et al. 2009; Eiler et al. 2008; Pollard and Gatti 2009; Rizk et al. 2013)	Hematologic: Bone marrow failure Musculoskeletal: Microcephaly, thumb/radial abnormalities Oncologic: Leukemia, myelodysplastic syndrome, squamous cell carcinomas, and cervical cancer Other: Abnormal skin pigmentation and renal anomalies	Medulloblastoma

Nevoid Basal Cell Carcinoma (or Gorlin) Syndrome (PTCH1 and SUFU genes) is an uncommon condition affecting approximately 1 in 30,000 individuals (Evans et al. 2010). Characteristic clinical features typically emerge in adolescents or young adults including jaw keratocysts and basal cell carcinomas (Lam et al. 2013). The diagnosis may be suspected in childhood based on their distinctive cranial features including macrocephaly, frontoparietal bossing, and coarse facies and skin findings (e.g., multiple basal cell nevi and palmar/plantar pits). Approximately 5% of children develop medulloblastoma, generally of desmoplastic subtype, in the first few years of life (Amlashi et al. 2003; Cowan et al. 1997).

The utility of using radiotherapy in affected individuals should be carefully weighed against the high risk of shortly developing numerous basal cell carcinomas in the radiation field and the possibility of other secondary malignancies (e.g., meningiomas) (Sartip et al. 2013).

Turcot Syndrome

Turcot syndrome is characterized by the occurrence of brain tumors in the setting of a familial colon cancer syndrome. In these rare scenarios, pediatric brain tumors may be associated with germline mutations of the *APC* gene which cause Familial Adenomatous Polyposis (FAP) or mutations in the mismatch repair (MMR) genes (*MSH2, MLH1, MSH6, PMS2*) which cause Hereditary Nonpolyposis Colon Cancer (HNPCC, heterozygous MMR gene mutation) or Constitutional Mismatch Repair Deficiency Syndrome (CMMRD, biallelic MMR gene mutations, autosomal recessive) (Bakry et al. 2014; Hamilton et al. 1995). Constitutional *APC* mutations (FAP) confer a risk of medulloblastoma significantly higher than the general population, but still below 1% (Attard et al. 2007). Heterozygous MMR gene mutations (HNPCC) are associated with glioblastoma (GBM) with an estimated lifetime risk of about 1–3% (Barrow et al. 2009; Therkildsen et al. 2015). These GBMs typically occur in adults (peak around 40–50s); however, pediatric cases have been reported. In the absence of family history, these brain tumors may be the first indication of the underlying condition, with other features developing later. Patients with CMMRD, based on their café-au-lait macules, may initially be suspected to have NF1 (Bakry et al. 2014). They are at high risk of developing malignancies from early childhood: particularly leukemia, lymphoma, gastrointestinal cancers, and brain tumors. Brain tumors occur in about one-third to one-half of individuals and are predominantly high-grade gliomas. For all of the variations of Turcot Syndrome, there is a lack of information regarding radiation toxicities.

1.3.2.2 Conditions Exclusively Having Oncologic Features

Li–Fraumeni Syndrome (TP53 gene) is a rare condition associated with a high lifetime risk for developing a variety of different cancers. Approximately 73% of men and almost 100% of women with *TP53* mutations develop cancer (Chompret et al. 2000). This includes soft tissue sarcoma, osteosarcoma, brain tumors, premenopausal breast cancer, leukemia, and adrenocortical carcinoma which together comprise almost three-quarters of all LFS-associated malignancies (Gonzalez et al. 2009; Olivier et al. 2003; Ruijs et al. 2010). The median age of brain tumor diagnosis is 16 years of age. The primary brain tumor risks for children with LFS are high-grade glioma, choroid plexus carcinoma (CPC), and medulloblastoma (Olivier et al. 2003; Tabori et al. 2010). Due to the strong association that has been established between CPC and germline *TP53* mutations, a genetic evaluation should be considered in all of these patients (Tabori et al. 2010). At baseline, patients with LFS have a significant risk of multiple primary cancers. It is broadly accepted that radiation exposure raises this risk, although this has not been well quantified (Heymann et al. 2010; Hisada et al. 1998; Limacher et al. 2001). The standard practice is to treat with radiation when deemed necessary, with attempts to limit the field and/or dose, when possible.

1.3.2.3 Hereditary Cancer Predisposition Syndromes Summary

Multiple HCPSs associated with significant childhood brain tumor risks have been identified. Ongoing challenges in this area are further refining our understanding of risks associated with these conditions by better establishing genotype–phenotype correlations, identifying genetic modifiers, and environmental influences. Additionally, there is an urgent need to develop and/or implement appropriate screening and prevention strategies for these high-risk children.

Conclusion

It is likely that the greatest gains in understanding the etiology of childhood brain tumors in the near future will come from "omics" studies seeking to understand innate and exogenous factors that contribute to susceptibility. It will also be important to identify interactions between genetic and environmental factors and to conduct studies that integrate germline and somatic tumor data to determine how germline variation influences tumor mutation profiles and prognosis. For progress in these areas to occur, a coordinated investment in systematic collection of clinically annotated biological specimens (both tumor and normal) from a large number of childhood brain tumor cases should be an international priority since cancer is a leading cause of death in children and childhood brain tumors have the highest cancer mortality rate among childhood cancers (Ward et al. 2014).

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Histopathology of Primary Tumors of the Central Nervous System

2

Adekunle M. Adesina

Contents

Abstract

Primary central nervous system (CNS) tumors are the second most common cancers among children ages 0–19 years, of which 70% of childhood tumors are infratentorial. Metastatic solid tumors in the brain are frequent in the adult population but are rare in childhood.

The classification of tumors in the CNS is based on the pattern of cell differentiation and assumes that the pattern of differentiation is a reflection of the histogenesis

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of such tumors and is the basis of the World Health Organization (WHO) classification. In spite of its limitation, there is a strong correlation between the degree of cell differentiation and clinical prognosis. However, the clinical outcome is influenced not only by histology (i.e., degree of differentiation) but also by tumor location and extent of surgical resectability, as well as radio- and chemosensitivity. This chapter provides an overview of the pathologic characteristics and salient diagnostic features of brain tumors with special emphasis on the pediatric population.

2.1 Meningeal Tumors

Primary tumors arising in the leptomeninges include meningioma and mesenchymal non-meningothelial tumors such as solitary fibrous tumor (hemangiopericytoma) and melanocytic tumors.

2.1.1 Meningioma

Meningioma is a tumor composed of neoplastic meningothelial cells and accounts for 13–26% of intracranial tumors. Meningiomas are most common in the middle age group and the elderly. The peak incidence is in the sixth and seventh decades and frequently meningioma can occur as an incidental finding at autopsy. When seen in children, meningiomas are often aggressive. Although most tumors are sporadic, multiple meningiomas can be seen as part of the presentation of neurofibromatosis type 2 (NF2), as well as in genetically predisposed non-NF2 individuals.

Histological features allow for the division of meningiomas into three grades which include: (1) benign meningiomas (WHO Grade I) accounting for the bulk of meningiomas, (2) atypical meningiomas (WHO Grade II) which represent 4.7–7.2% of all meningiomas, and (3) anaplastic (malignant) meningiomas (WHO Grade III) representing 1.0–2.8% of all meningiomas.

In general, meningiomas occur more commonly in females, with a female:male ratio of 3:2 for intracranial tumors and a much higher 10:1 ratio for spinal meningiomas. This female predominance, as well as the positivity of about two-thirds of meningiomas for progesterone receptors, is consistent with a putative role for sex hormones in their development. However, for currently unclear reasons, atypical and anaplastic meningiomas predominate in males and in children.

A number of etiologic factors have been proposed for the neoplastic transformation of meningothelial cells. Notable among these is exposure to ionizing radiation. The lag time between exposure to ionizing radiation and clinical diagnosis of meningioma varies from 35 years [as was observed following low dose (800 rads) scalp radiation for tinea capitis] to 19–24 years following higher dose (>2000 rads) radiotherapy for brain tumors. These observations suggest a positive correlation between lag time and the dose of ionizing radiation.

Meningiomas have been referred to by specific names depending on their location, such as the falx, sphenoid ridge, olfactory groove, over the hemispheric

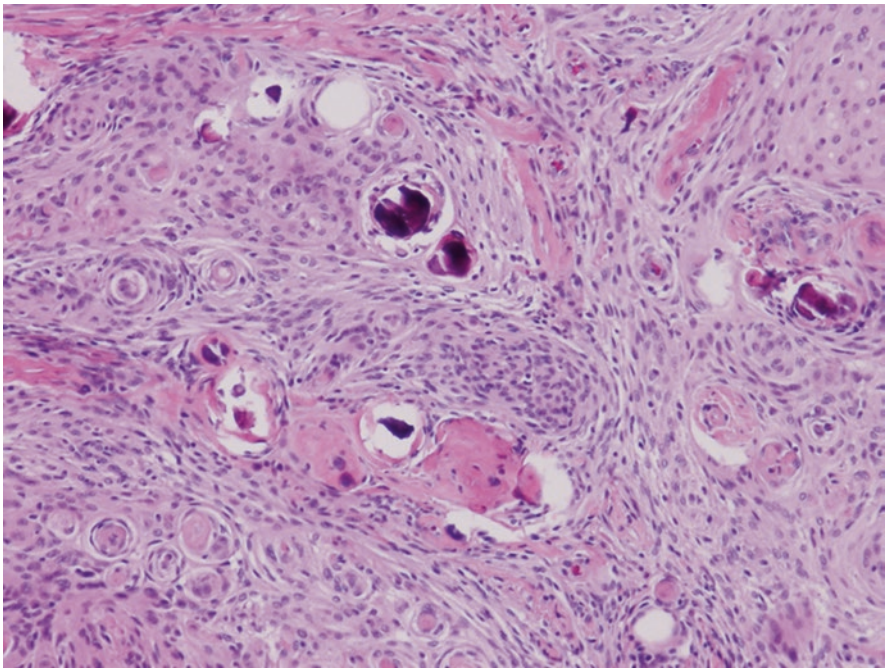

Fig. 2.1 Transitional meningioma showing characteristic concentric whorls and basophilic psammoma bodies. Magnification ×200

convexities, and the foramen magnum with differing clinical presentations related to the functional deficits induced at these specific sites of origin. Meningiomas are usually firm or rubbery, well demarcated, round, and occasionally lobulated masses. They may also grow as flat masses termed "en plaque" meningioma.

The classic meningothelial or syncytial meningioma is composed of epithelioid cells with indistinct cytoplasmic borders, uniform nuclei with frequent intranuclear cytoplasmic pseudoinclusion but no discernible nucleoli. Other subtypes range from the fibroblastic with a predominant benign spindle and fibrous component to the transitional form with a mixture of spindle fibroblastic cells of the fibroblastic meningioma and the epithelioid cells of the meningothelial meningioma arranged in characteristic whorls (Fig. 2.1). Any of the subtypes can have psammoma bodies. A benign vasculature component may be prominent in the angiomatous meningiomas. Prominent microcystic degeneration or pale lipid-containing xanthomatous cells characterize other subsets of meningioma. Gland-like structures with lumina containing eosinophilic periodic acid Schiff (PAS) and epithelial membrane antigen (EMA) positive secretion are seen in the secretory (pseudoglandular) meningioma. Myxomatous or myxoid meningiomas are characterized by the presence of a diffuse myxoid stroma with stellate cells. Identification of such tumors as meningiomas requires the presence of more classic meningothelial components. Such areas can be a minor component requiring generous tissue sampling before identification. In the absence of such a component, the differential diagnosis would include a metastatic

mucin secreting adenocarcinoma. Similarly, the presence of abundant clear cells can raise the differential diagnosis of a metastatic renal cell carcinoma. A diffuse infiltrate of mature, benign lymphocytes and plasma cells is a major component of the lymphoplasmacyte-rich meningioma. There is a need to distinguish these tumors from non-Hodgkin's lymphoma. Metaplastic meningiomas exhibit focal or sometimes florid differentiation into other mature cell types such as osteoid, chondroid, and adipose tissue. Invasion of dura or dural sinuses is common. Skull invasion is usually associated with hyperostosis.

Meningiomas located in the cerebellopontine angle or in relation to cranial/spinal nerve roots raise a differential diagnosis of Schwannoma (neurilemmoma). Histologic differentiation can often be done readily based on light microscopic and immunostaining features. Schwannomas typically show positivity for S-100 protein and negative staining for epithelial membrane antigen. In contrast, meningothelial cells are positive for epithelial membrane antigen and claudin-1 among others and are rarely positive for S-100 protein. Furthermore, electron microscopy demonstrates desmosome junctions, cytoplasmic interdigitations, and a lack of basal lamina in the tumor cells as is characteristic of meningioma, while the presence of a basal lamina and a lack of true desmosome junctions are consistent with Schwann cell differentiation.

A demonstrable invasion of underlying brain is indicative of an aggressive meningioma and is often accompanied by histological features of an atypical or malignant meningioma.

2.1.1.1 Atypical Meningioma (WHO Grade II)

Atypical meningioma represents subset of meningioma with slightly higher risk of recurrence when compared with benign meningiomas (29–39% vs. 7–20%). Such tumors are characterized by increased mitotic rate (>4/10 hpf in the area of highest mitotic activity) *or* at least three of the following histologic findings: hypercellularity, small cell change, prominent nucleoli, sheet-like growth, or foci of spontaneous or geographic necrosis (i.e., not induced by therapeutic embolization). Proliferation index (MIB-1 index) is usually greater than 5% (mean 2.1% vs. mean for benign meningiomas of 0.7%).

Meningiomas with tongue-like invasion of underlying brain and chordoid or clear cell features are clinically aggressive and classified as atypical meningiomas (WHO grade II).

2.1.1.2 Anaplastic (Malignant) Meningioma

1. *Papillary meningioma*
   Papillary meningiomas are by definition malignant meningiomas and the presence of a distinct papillary pattern is the hallmark of this subset of meningiomas (Fig. 2.2). They represent a WHO grade III. Papillary meningiomas tend to occur more commonly in children. Papillary features in a dural-based lesion should raise the differential diagnosis of a metastatic papillary adenocarcinoma.
2. *Malignant (non-papillary) meningioma*
   The diagnosis of anaplastic or malignant meningioma in a non-papillary tumor requires the presence of overt or frank anaplasia and/or metastases. The more classic lesions are usually characterized by increased cellularity, frequent mitotic

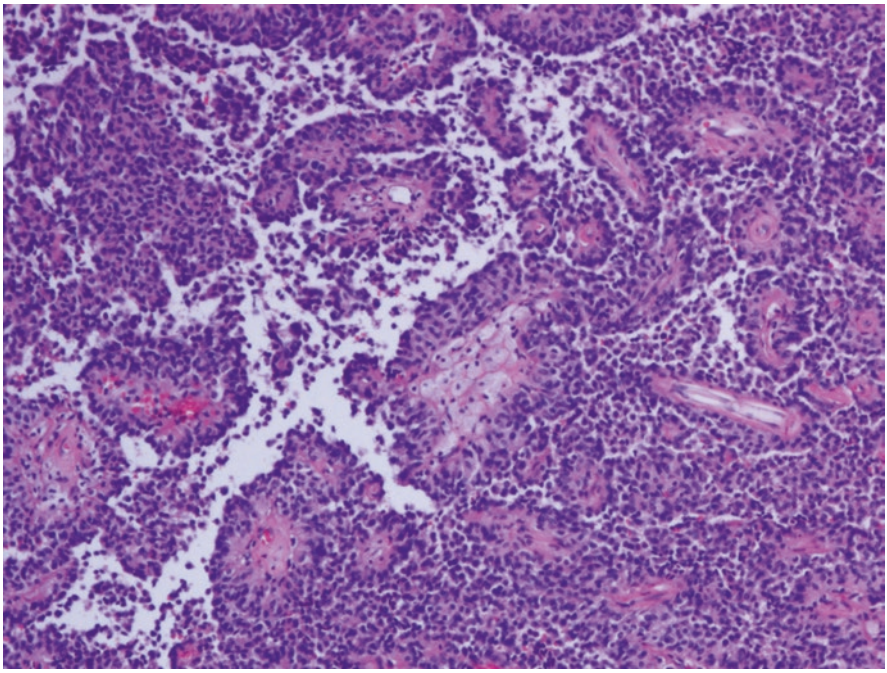

Fig. 2.2 Papillary growth pattern is a characteristic feature of papillary meningioma. Magnification ×100

figures (>20 mitoses/10 hpf), and conspicuous necrosis. The proliferation index (MIB-1 index) is usually greater than 10% (mean = 11%). Rhabdoid meningioma is an aggressive variant of meningioma and is classified also as a WHO Grade III.

Postsurgical recurrence is a common feature of meningiomas and is seen in up to 20% of benign meningiomas after 20 years of follow-up. Indicators of possible recurrence (apart from incomplete resection) are histological subtype and tumor grade. Anaplastic meningiomas have the highest recurrence rate of about 50–78%.

2.1.2 Mesenchymal, Non-meningothelial Tumors

This group of tumors share similar histological features with their counterparts in peripheral soft tissues. They include:

1. Adipose tissue tumors, such as lipomas [fibrolipomatous hamartomas, angiolipomas, and epidural lipomatosis (related to chronic corticosteroid administration)] and intracranial liposarcoma. Lipomas occur most often in the midline, typically located in the corpus callosum, cerebellar vermis, or mammillary bodies. They may also occur as part of a complex malformation. Mature lipocytes

have been described as part of a low-grade cerebellar tumor called liponeurocytoma that is composed of intermixed mature lipocytes and neurocytic cells.
2. Fibrohistiocytic tumors, including benign and malignant fibrous histiocytoma.
3. Fibrous tumors including solitary fibrous tumor, hypertrophic intracranial pachymeningitis, and fibrosarcoma.
4. Muscle forming tumors, such as leiomyoma, intracranial leiomyosarcomas, rhabdomyoma, embryonal rhabdomyosarcoma, and malignant ectomesenchymoma.
5. Osteocartilaginous tumors, including chondroma, osteoma and osteochondroma, mesenchymal chondrosarcoma, and osteosarcoma.
6. Vascular tumors, such as hemangiomas, epithelioid hemangioendotheliomas, angiosarcoma, and Kaposi's sarcoma.
7. Tumors of undefined histogenesis, such as hemangiopericytoma, capillary hemangioblastoma, and meningeal sarcoma/sarcomatosis.
8. Melanocytic tumors.

Since many of these tumors are curiosities in the CNS, only the relatively more frequent tumors will be discussed further. The histological features of the other tumors are similar to those of their soft tissue counterparts and are well discussed in the soft tissue sections of other standard textbooks.

2.1.2.1 Solitary Fibrous Tumor/Hemangiopericytoma

Historically, this tumor has been referred to by various obsolete names such as "angioblastic meningioma" and hemangiopericytic variant of meningioma reflecting a lack of understanding of its true histogenesis. Hemangiopericytoma accounts for only 0.4% of all brain tumors and is a rare tumor in children. It is usually dural based and is rarely intraparenchymal. Clinical presentation is similar to that of meningioma. The cellular variant of solitary fibrous tumor (SFT) shows histologic and immunohistochemical overlap with that of hemangiopericytoma with nuclear immunopositivity for STAT6 and both are regarded as same entities.

Grossly, the tumor is firm, well demarcated, globoid, slightly lobulated, and can bleed profusely during surgical removal. Histologically, it is characterized by monotonous sheets of oval to elongated nuclei, variable degrees of nuclear atypia, and prominent mitotic activity (Fig. 2.3). "Staghorn" vessels of variable prominence are also apparent. Invasion of underlying brain can occur. Since many soft tissue tumors can have hemangiopericytomatous-like areas, immunostaining and electron microscopy, if available, are important aids in ensuring accurate diagnosis. Hemangiopericytomas show an identical immunohistochemical profile as its soft tissue counterpart (now regarded as solitary fibrous tumor) with diffuse positivity for vimentin, CD99, and bcl-2, and more variable positivity for Leu-7, CD34, and factor XIIIa in individual tumor cells. CD34 positivity is generally patchy as opposed to the diffuse positivity typical of solitary fibrous tumor. Unlike the strong diffuse positivity for EMA and claudin-1 displayed by meningiomas, staining is typically patchy and weak for these antibodies in hemangiopericytoma. They are negative for S-100, CD31, and progesterone receptor. Actin, desmin, and cytokeratin (CAM5.2) staining is rare. p53 immunoreactivity may be seen in about one-half of HPC, whereas this is not generally a feature of meningioma or SFT.

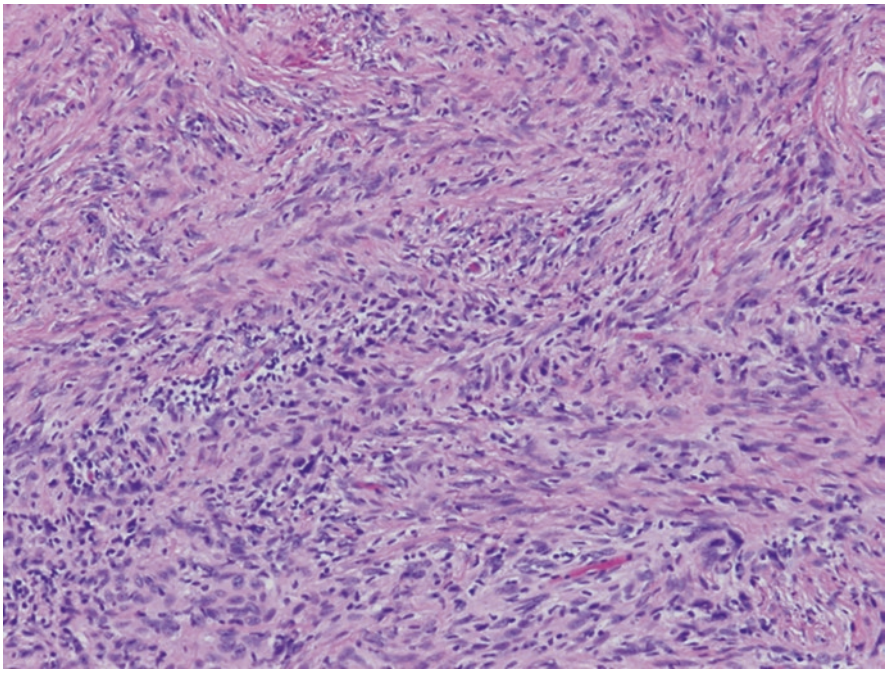

Fig. 2.3 Cellular and fibrosing spindle cell proliferation of a cellular solitary fibrous tumor/hemangiopericytoma. Magnification ×200

The proliferation index (MIB-1 index) varies widely with median values ranging between 5 and 10%. Hemangiopericytomas exhibit a high 15-year local recurrence rate of 85–91% and metastases are also seen in about 65% of cases when followed for over 15 years.

2.1.2.2 Capillary Hemangioblastoma

Capillary hemangioblastoma is a WHO grade I vasoformative tumor of uncertain histogenesis which commonly occurs in the cerebellum. Spinal and brain stem lesions also occur, but less frequently, and supratentorial lesions are very rare. About 25% of cases occur in the setting of Von Hippel–Lindau disease. Von Hippel–Lindau disease-associated tumors occur in younger patients while the non-Von Hippel–Lindau disease-associated tumors occur in adults. Von Hippel–Lindau disease is a neurocutaneous syndrome associated with retinal hemangioblastoma, pheochromocytoma, renal cell carcinoma, and visceral (liver and pancreas) cysts. Hemangioblastomas are slow growing tumors often presenting with features of raised intracranial pressure secondary to the blockage of CSF flow. There is often an accompanying secondary polycythemia due to erythropoietin production by the neoplastic stromal cells.

Grossly, capillary hemangioblastoma consists of well-circumscribed red nodules often in the wall of large cysts. Histologically, the tumors are composed of large vacuolated stromal cells and a rich capillary network. The stromal cells show immunopositivity for vimentin, but the tumors do not show evidence of immunoreactivity for glial fibrillary acidic protein or for endothelial markers such as CD34 or

Von-Willebrand factor. The "clear cell" appearance of the stromal cells can be confused with metastatic renal cell carcinoma. Rosenthal fibers can be seen in the wall of the cysts. The slow growth of capillary hemangioblastoma is consistent with a low proliferation index (MIB-1 index <1%). The stromal cells are consistently positive for vimentin, alpha inhibin, D2-40, and aquaporin, while variably positive for S-100, NCAM, NSE, erythropoietin, EGFR, VEGF, alpha-1-antitrypsin, and antichymotrypsin. Progesterone receptor and Factor XIIIa positivity have also been reported in a high percentage of cases. They may be focally positive for GFAP, keratin, EMA, or desmin, while specific neuronal (neurofilament, synaptophysin, and chromogranin) and endothelial cell (CD31, CD34, and VWF) markers are typically negative.

2.1.2.3 Meningeal Sarcomatosis

Meningeal sarcomatosis is a diffuse leptomeningeal sarcomatous tumor lacking the distinct circumscribed nature that is characteristic of most meningeal tumors. It is composed of poorly differentiated spindle cells characteristic of undifferentiated sarcomas. Apart from immunostaining for vimentin, the tumor cells are negative for all neuroglial markers.

2.1.2.4 Mesenchymal Chondrosarcoma

The most common extraosseous site for mesenchymal chondrosarcoma is the CNS. Mesenchymal chondrosarcoma has a distinct small cell tumor component interrupted by islands of atypical hyaline cartilage (Fig. 2.4). The small cell

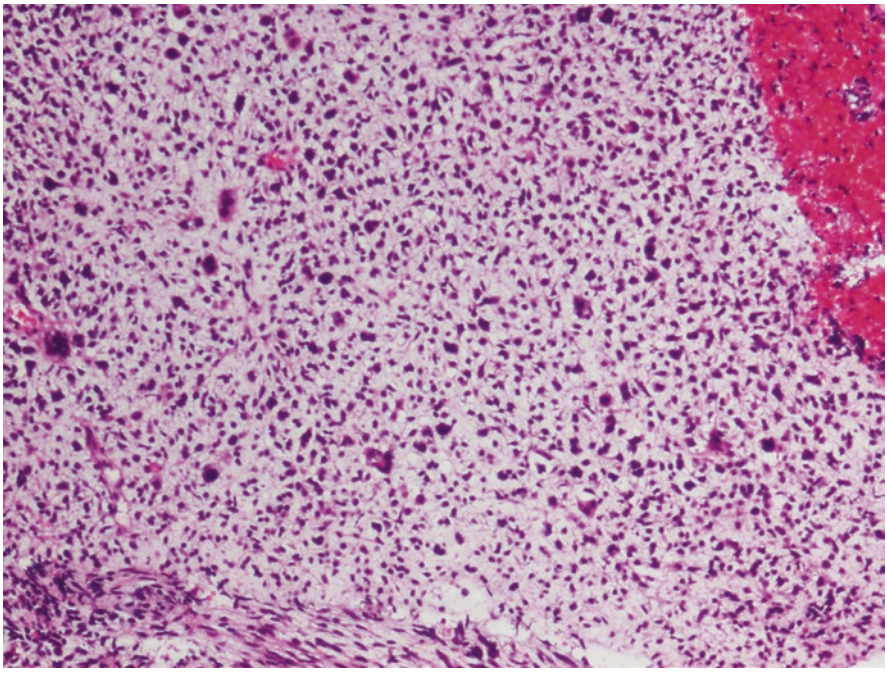

Fig. 2.4 Malignant chondromyxoid proliferation of mesenchymal chondrosarcoma. Note the nuclear pleomorphism. Magnification ×200

component shares histological features with hemangiopericytoma and can be confused with it in small biopsies that lack the characteristic chondroid component.

2.1.2.5 Melanocytic Lesions

Primary melanocytic lesions of the CNS are relatively uncommon, accounting for only 0.06–0.1% of brain tumors. Melanocytic lesions are more common in Caucasians and arise from melanocytes of the leptomeninges. There are three possible forms of CNS melanocytic lesions: (1) diffuse melanocytosis, (2) melanocytoma, and (3) primary leptomeningeal malignant melanoma.

1. *Diffuse melanocytosis* usually presents in childhood with seizures, behavioral disturbances, and hydrocephalus. Histologically, the lesion shows a diffuse proliferation of uniform nevoid polygonal cells within the leptomeninges.
2. *Melanocytomas* present as mass lesions composed of a monomorphic population of spindle, fusiform, epithelioid, or polyhedral cells arranged in whorls, sheets, nests, or interlacing bundles of storiform configuration with infrequent mitotic figures. Melanin can be present. The tumors are S-100 protein positive and in our experience are usually negative for the melanoma antigen markers, HMB-45, and Melan A.
3. *Primary meningeal malignant melanomas* also present as mass lesions. They occur classically in the setting of neurocutaneous melanosis, such as in the autosomal dominant Touraine syndrome and in patients with the congenital nevus of Ota. The tumors have similar aggressive behavior as seen in cutaneous melanoma and are characterized histologically by marked pleomorphism, high mitotic activity, necrosis, hemorrhage, and invasion of underlying brain. The diagnosis of a primary CNS melanoma can only be made after a metastatic melanoma has been excluded. As in cutaneous melanoma, the tumor cells are S-100 protein, HMB-45 and Melan A positive while being negative for glial fibrillary acidic protein (GFAP), neurofilament protein (NFP), epithelial membrane antigen (EMA), and cytokeratin. Electron microscopy shows the presence of melanosomes.

2.2 Astrocytic Tumors

Pilocytic astrocytoma (PA) represents a slow growing, often circumscribed fibrillary astrocytoma with a distinctly good prognosis warranting its designation as a WHO grade I. It accounts for 20–25% of all childhood brain tumors occurring frequently as a cystic cerebellar tumor with a mural nodule. Similar tumors may involve the optic nerve, presenting as optic nerve glioma in children and frequently in individuals with neurofibromatosis type 1 (NF1). Supratentorial intra-axial tumors are common in the temporal lobe and may also involve the hypothalamus or thalamus. The characteristic cells are the glial fibrillary acidic protein-positive piloid (elongated or "hair-like") astrocytes which are arranged in a biphasic pattern of cellular fibrillary astrocytes with intervening loose microcystic areas (Fig. 2.5). Rosenthal fibers and eosinophilic granular bodies (EGBs) are frequently present and the abundance of Rosenthal fibers is a helpful diagnostic feature in frozen

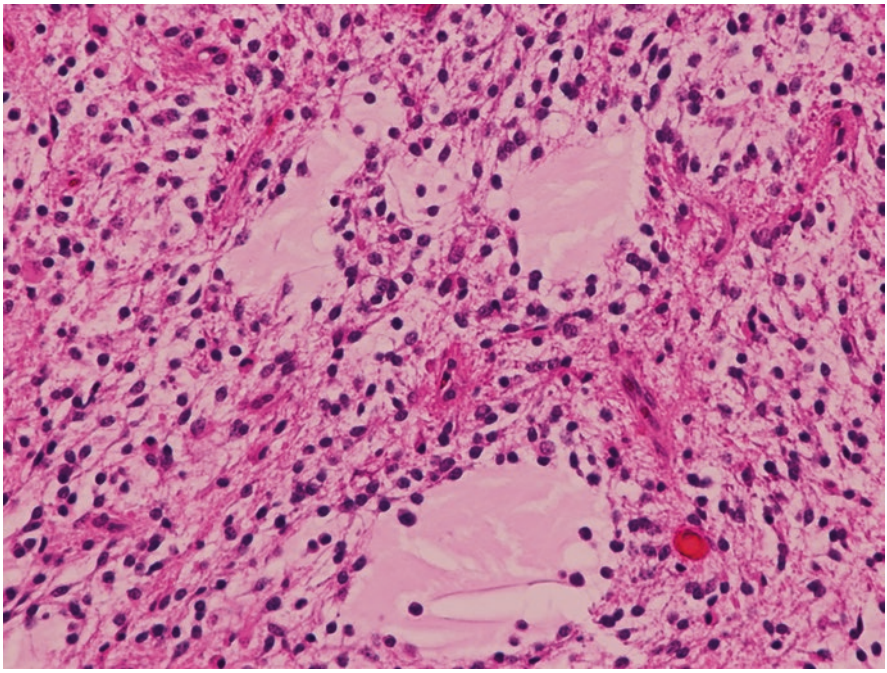

Fig. 2.5 Pilocytic astrocytoma with biphenotypic microcystic and compact cellular components. Eosinophilic Rosenthal fiber is present. Magnification ×200

sections or crush preps made during intraoperative consultation. Unlike the classic diffuse infiltrating astrocytoma, the presence of vascular proliferation and slight pleomorphism does not imply an aggressive high histologic grade. However, in the rare case, the presence of frequent mitotic figures, a significantly increased cellularity, and necrosis justifies the diagnosis of a pilocytic astrocytoma with anaplastic features. Tandem duplication at 7q34 with BRAF-KIAA1549 duplication/fusion rearrangement is seen in 70% of PA. BRAFV600E mutation is seen in 10% of extracerebellar PA, particularly diencephalic tumors. Rare co-occurrence of both events has been seen.

The *pilomyxoid astrocytoma* (PMA), WHO grade II, shares histologic features with the PA. It shows additional features including a monomorphous population of bipolar cells with delicate elongated "piloid" processes in an abundant myxoid matrix. The cell processes frequently radiate from vessels with a pseudorosette pattern. In its pure form, Rosenthal fibers and EGBs are absent. Mitoses may be seen. Maturing PMAs show intermediate histologic features of both PA and PMA.

BRAF-KIAA1549 duplication/fusion rearrangement is seen in 60% of PMA.

Pleomorphic xanthoastrocytoma (PXA), WHO Grade II, is a tumor with distinct radiopathologic features including a superficial meningocerebral location, common location in the temporal lobe, and frequent association with a long-standing history of seizures. Pleomorphic xanthoastrocytoma accounts for <1% of all astrocytic

neoplasms but 2/3 of cases occur in individuals below the age of 18 years. Histologically, it exhibits significant pleomorphism with many atypical giant cells and astrocytic cells with slightly prominent nucleoli. Mitotic activity and necrosis are conspicuously absent in the typical pleomorphic xanthoastrocytoma. There is a variably discernible population of foamy (xanthomatous) cells and focal lymphocytic and plasma cell infiltrate in a background of reticulin-positive desmoplasia. The astrocytic origin of this tumor has come into question because of the demonstration of neuronal markers in subpopulations of tumor cells. In addition, the morphologic pattern seen in pleomorphic xanthoastrocytoma may form the glioma component of a ganglioglioma. BRAFV600E mutation is a frequent event seen in 75% of PXA.

Pleomorphic xanthoastrocytoma with anaplastic features is a variant which may represent WHO Grade III. These are often seen as part of tumor progression in recurrent lesions. They show features indicative of aggressive behavior such as increased mitotic activity [> 5 mitosis per 10 high power fields], necrosis, and endothelial proliferation.

Diffuse astrocytomas are infiltrating fibrillary neoplasms with varying degrees of differentiation and tumor grade. They account for 50% of primary brain tumors. Astrocytic tumors characteristically have infiltrative margins and range from the low grade diffuse astrocytoma which is WHO grade II (peak age of 30–39 years) to the anaplastic (malignant) astrocytoma which is WHO grade III (peak age of 40–49 years), and the most aggressive glioblastoma which is WHO grade IV (peak age of 50–69 years). Approximately 10% of all glioblastomas occur within the first two decades of life. Infiltrative astrocytomas are second to pilocytic astrocytoma in frequency in the pediatric age group.

Diffuse infiltrating astrocytoma, WHO grade II, or well-differentiated (low grade) astrocytoma is most common in the cerebral white matter and accounts for 20% of primary brain tumors. Low grade astrocytomas are composed of a relatively uniform population of proliferating astrocytes in a fibrillary matrix (Fig. 2.6). Mitotic figures are rare. In contrast to reactive gliosis, diffuse astrocytomas have infiltrative poorly defined margins and can have microcystic degeneration. The tumor cells show slight atypia, an important criterion for distinguishing them from reactive gliosis. The tumor cells can have plump eosinophilic cytoplasm (gemistocytes) and are often a minor component of most diffuse astrocytomas. Tumors composed of greater than 20% of gemistocytic tumor cells are called gemistocytic astrocytoma. The astrocytic tumor cells show cytoplasmic positivity for glial fibrillary acidic protein.

2.2.1 Anaplastic (Malignant) Astrocytoma

Anaplastic astrocytoma represents a high grade diffuse fibrillary astrocytoma classified as WHO grade III. It has a similar distribution to low grade astrocytoma but is characterized by a greater degree of cellularity and pleomorphism. Mitotic figures are readily discernible (Fig. 2.15).

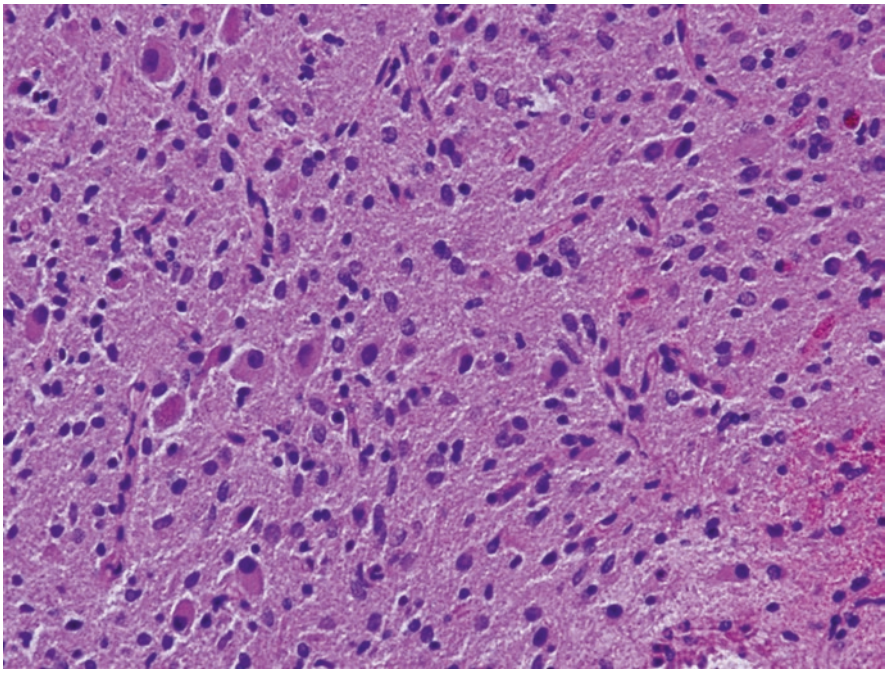

Fig. 2.6 Low grade diffuse infiltrating astrocytoma with mild increase in cellularity, astrocytic differentiation, and rare mitotic figures. Magnification ×200

2.2.2 Glioblastoma

Glioblastoma is the most common glioma, accounting for 50% of all gliomas. It is clinically the most aggressive glioma and represents an extreme expression of astrocytic anaplasia. Glioblastoma occurs frequently as a white matter lesion, is diffusely infiltrative, and can cross the midline by involving the corpus callosum to produce the radiologic "butterfly pattern." Glioblastoma is characteristically grossly hemorrhagic and necrotic. Histologically, it shows marked cellular pleomorphism, frequent mitotic figures, tumor giant cells, endothelial proliferation, and necrosis with or without pseudo-palisading (Fig. 2.7). A high proliferation index and immunopositivity for p53 protein is a common feature of glioblastoma.

A predominant population of highly proliferative small cells can be seen in the variant form called small cell glioblastoma. The predominance of such cells often raises a differential diagnosis of "small blue cell tumors." Although cellular pleomorphism is an inherent histologic feature of glioblastoma, an extremely pleomorphic variant with florid multinucleated giant cells constitutes the giant cell glioblastoma. A spindle mesenchymal sarcomatous transformation can also be seen in a variant referred to as the gliosarcoma which must be differentiated from the secondary diffuse spindle (fibroblastic) cell proliferation that can accompany the invasion of the leptomeninges by glioblastoma cells. The giant cell glioblastoma has

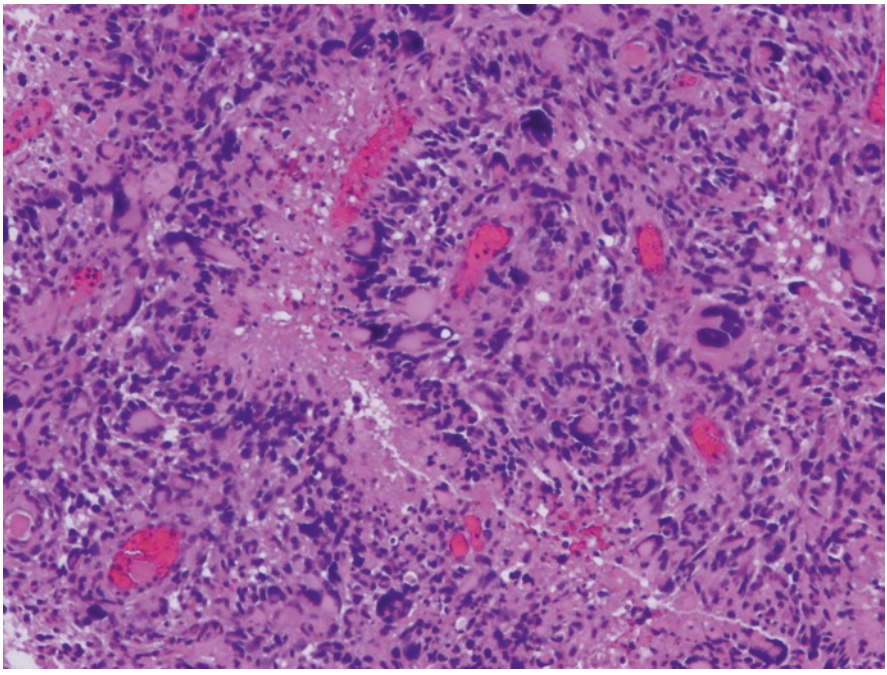

Fig. 2.7 Glioblastoma with increased cellularity, marked pleomorphism and pseudo-palisaded necrosis. Vascular endothelial proliferation is also present (not shown). Magnification ×200

a slightly better prognosis than the classic glioblastoma while the gliosarcoma has no significantly different outcome from the classic glioblastoma.

Mutation of the p53 gene has been shown to be especially common in the evolution of low grade astrocytoma and in the progression from low grade astrocytoma to high grade astrocytoma. Amplification of mdm2 gene which provides an alternative pathway for p53 inactivation only occurs in a minor subset of glioblastomas. The subset of glioblastomas arising secondary to p53 mutation or inactivation has been designated as secondary glioblastoma. In contrast, de novo or primary glioblastomas are less likely to have mutations of the p53 gene and are more likely to have amplification of the epidermal growth factor receptor gene. Therefore, there seem to be at least two largely separate operant pathways in the biologic evolution of the classic types of glioblastoma.

Additional genetic events in the development of high grade gliomas include epidermal growth factor (EGF) and transforming growth factor-α (TGF-α) expression providing a loop for autocrine stimulation. Fibroblast growth factor and vascular endothelial growth factor overexpression probably plays a major role in the development of angiogenesis, a critical element in the transformation of low grade astrocytoma to glioblastoma multiforme. Other reported genetic events in astrocytoma progression include loss of the deleted in colon carcinoma (DCC) gene, loss of heterozygosity (LOH) for chromosome 10q23.3 (PTEN gene locus) which is

mutated in 30–49% of high grade gliomas, total loss of chromosome 10, loss at chromosome 19q13.3, and loss of chromosome 22q. The giant cell glioblastoma does not appear to share these molecular pathways thus suggesting that it is a distinctly different biologic entity, a feature consistent with its differing clinical aggressiveness.

Based on a combination of studies including determination of epigenetic/methylation status as well as gene copy number and expression profiles, glioblastomas can be divided into distinct molecular and prognostic subgroups:

1. H3F3a K27M and G34R mutated subgroups which represent a predominant group among pediatric glioblastomas. These are usually negative for IDH1 mutations, frequently show TP53 mutations, and generally display widespread genomic hypomethylation.

   The K27M subgroup is more frequent in children and is associated with midline tumors (DIPG and GBM of thalamus and spinal cord). The G34R subgroup is most frequent in adolescents with tumors of cerebral hemispheric location.
2. IDH1 mutated tumors represent a minor proportion of pediatric glioblastomas, display global genomic hypermethylation, and frequently harbor TP53 mutations. This group includes older children/young adults with tumors of cerebral hemispheric location.
3. PDGFRA amplified tumors are associated with a proneural gene expression profile. This group has a wide age distribution, with a proportion occurring in pediatric tumors with cerebral hemispheric location.
4. Mesenchymal subgroup tumors exhibiting a mesenchymal gene expression signature and no defining gene copy number alterations or point mutations. This group also has a wide age distribution, with a proportion occurring in pediatric tumors of cerebral hemispheric location.
5. “Classic” subgroup is limited to GBM arising in older adults, and this group shows high frequency of chromosome 10 loss, homozygous deletion of CDKN2A, and EGFR amplification.

Diffuse infiltrating pontine glioma (DIPG) represents a diffusely infiltrative glioma involving the basis pontis which may histologically be low grade or high grade. It accounts for 10% of childhood brain tumors and is composed of fibrillary astrocytes. The diagnosis is often based on its classic neuroradiologic presentation with no attempts at resection or biopsy. Treatment usually involves radiotherapy, but there is an attendant high propensity of surviving tumor cells to dedifferentiate to a more anaplastic histology including glioblastoma.

A number of genetic events have been reported in DIPGs including: (1) K27M mutations in H3F3A (H3.3) or HIST1H3B (H3.1) which are extremely common and present in nearly 80% of DIPG. (2) Gain of function ACVR1 mutations found exclusively in DIPG (up to 30% of cases), whereas FGFR1 mutations or fusions are seen in thalamic HGAs. (3) Global DNA hypomethylation is an epigenetic alteration frequently encountered in DIPG, and may be detectable as decreased tumor staining by H3K27me3-specific immunohistochemistry. (4) TP53 (75%) and ATRX

(10%) mutations may be encountered in subpopulations of DIPG, with ATRX mutations being more frequent in tumors arising in older children. PIL3CA mutations and PDGF-a gains/amplifications have been reported. Subgroups with frequent loss of 17p and 14q and others with lack of IDH1/2 mutations or CDKN2a/CDKN2B deletions have also been reported.

2.3 Ependymal Tumors

Ependymomas are the most common tumor of the spinal cord (particularly in adult patients), and the third most common pediatric central nervous system (CNS) tumor, representing up to 30% of intracranial tumors in those under 3 years old. Infratentorial tumors have their peak age of occurrence in the first decade, while spinal tumors tend to peak at age 30–40. Ependymal tumors are subdivided into the low grade ependymoma (WHO grade II) and the higher grade anaplastic ependymoma (WHO grade III). Variants include the very low grade, WHO grade I myxopapillary ependymoma which occurs exclusively in the conus medullaris-cauda equina-filum terminale region, as well as the subependymoma usually found in the floor of the fourth ventricle which is also low grade and is often an incidental finding at autopsy in the elderly. Subependymomas can rarely undergo spontaneous intratumoral hemorrhage with associated intraventricular hemorrhage. Recent evidence supports radial glia as the candidate cell of origin for ependymomas while subependymomas appear to derive from subependymal glial precursors.

Ependymoma, WHO grade II, is classically a ventricular tumor. It may also arise in extraventricular sites, as well as the spinal cord, and the filum terminale. It is most frequent in the fourth ventricle, often presenting with obstructive hydrocephalus. Ependymoma is most common in childhood, accounting for 20% of childhood brain tumors but only 5% of adult brain tumors.

The characteristic feature of ependymoma is the gland-like ependymal rosette with blepharoplasts. However, the perivascular pseudorosette with the central blood vessel and the radiating a cellular glial fibrillary acidic protein-positive processes is more commonly seen (Fig. 2.8). The tumor cells are round, relatively uniform with only slight hyperchromasia. Prominent gemistocyte-like cells with fibrillary processes can occasionally be evident especially in frozen sections, creating a diagnostic dilemma during intraoperative consultation. Infrequently, CSF dissemination can occur. A prominent papillary pattern, a predominance of clear cells evidence of tanycytic (bipolar spindle) cells, lipomatous differentiation, signet ring cell features, or the presence of melanin define some of the histologic subsets of ependymoma. Increased cellularity without significant increase in mitotic activity constitutes the cellular ependymoma, an entity without any additional adverse prognostic implication. Although most ependymomas have well-demarcated borders, infiltrative tumors can occur in the cerebral hemispheres and spinal cord. Electron microscopic features of ependymal differentiation include formation of cilia, blepharoplasts, luminal microvilli, junctional complexes, and cell processes with intermediate filaments.

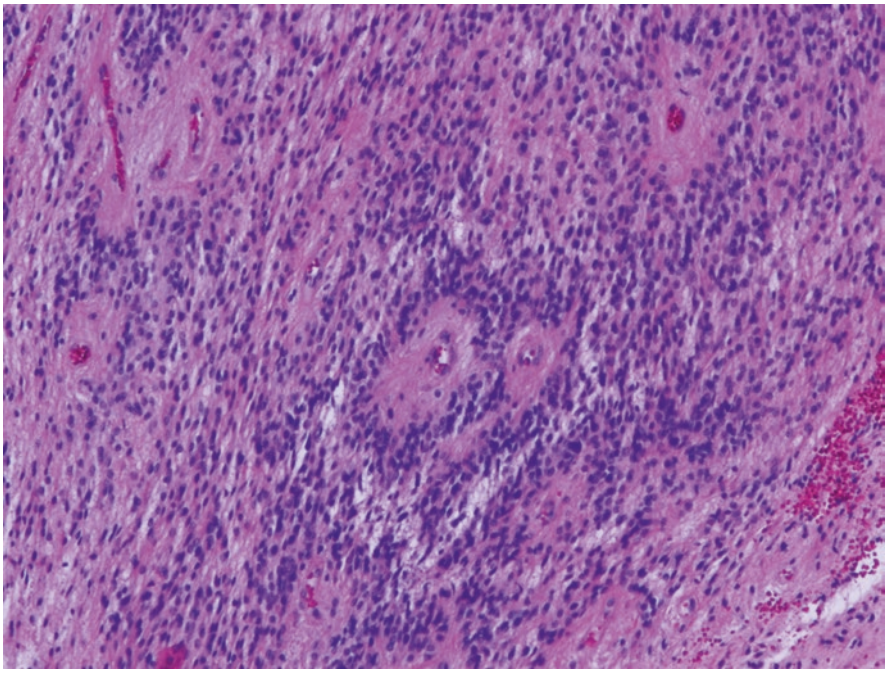

Fig. 2.8 Ependymoma with variable cellularity and characteristic perivascular pseudorosettes. Magnification ×100

The anaplastic ependymoma shows a significantly increased cellularity with anaplasia, frequent mitotic figures, endothelial proliferation, and necrosis. This tumor has a propensity for CSF dissemination. The presence of necrosis alone without the other cytologic changes and mitotic activity does not imply aggressive behavior since necrosis can be seen even in the low grade ependymoma. Predictors of poor prognosis in ependymomas include age below 3 years, anaplastic features (high cell density and frequent mitotic figures), incomplete tumor resection, and CSF dissemination. Molecular genetic studies of ependymomas have not identified any of the genetic events associated with astrocytomas. Mutations involving the NF2 have only been found in spinal cord ependymomas, raising the possibility that ependymal tumors of the spinal cord represent a distinct molecular subset.

Ependymomas are positive for S100, GFAP, and vimentin. Epithelial membrane antigen (EMA) often shows a characteristic punctuate, dot-like positivity and membranous staining. Stains for neuronal markers are generally negative except for NeuN which may show nuclear positivity in some anaplastic ependymomas.

Transcriptional profiling studies suggest that ependymomas can be divided into two clinically and molecularly distinct subgroups of posterior fossa ependymomas.

Group A (Group 1) tumors are seen in younger patients, occur in lateral location, have balanced genome with increased frequency of chromosome 1q gain, and with more biologically aggressive behavior having shortened PFS and OS. Immunostaining for Laminin alpha-2 (LAMA2) detection may serve as a marker for this group of tumors.

Group B (Group 2) tumors are seen in older patients, occur in midline, have numerous cytogenetic abnormalities involving whole chromosomes or chromosomal arms, with frequent chromosome 6q and 22q loss and 9p, 15q, and 18q gain. Neural Epidermal Growth Factor Like-2 (NELL2) detection by immunohistochemistry may serve as a marker for these tumors.

On the other hand, supratentorial ependymomas show significant overexpression of neuronal markers in comparison to their infratentorial counterparts; in particular, neurofilament light polypeptide 70 (NEFL) is overexpressed in supratentorial tumors. Nestin and VEGF are both expressed more frequently in supratentorial ependymomas, and are associated with a poor PFS.

Greater than 2/3 of supratentorial ependymomas contain oncogenic fusions between RELA (involved in canonical NF-κB signaling) and C11orf95.

2.4 Oligodendroglioma

Oligodendroglioma is a low grade, slow growing glial tumor with oligodendroglial differentiation and has a predominant proportion involving the frontal and parietal lobes. Oligodendrogliomas are uncommon in pediatric age group. Frequently, there is a long history of poorly controlled seizures. The tumors are composed of uniform round cells with the characteristic delicate capillary vasculature (so-called "chicken wire" vasculature) (Fig. 2.9). Formalin fixation of the tumor produces an artifactual

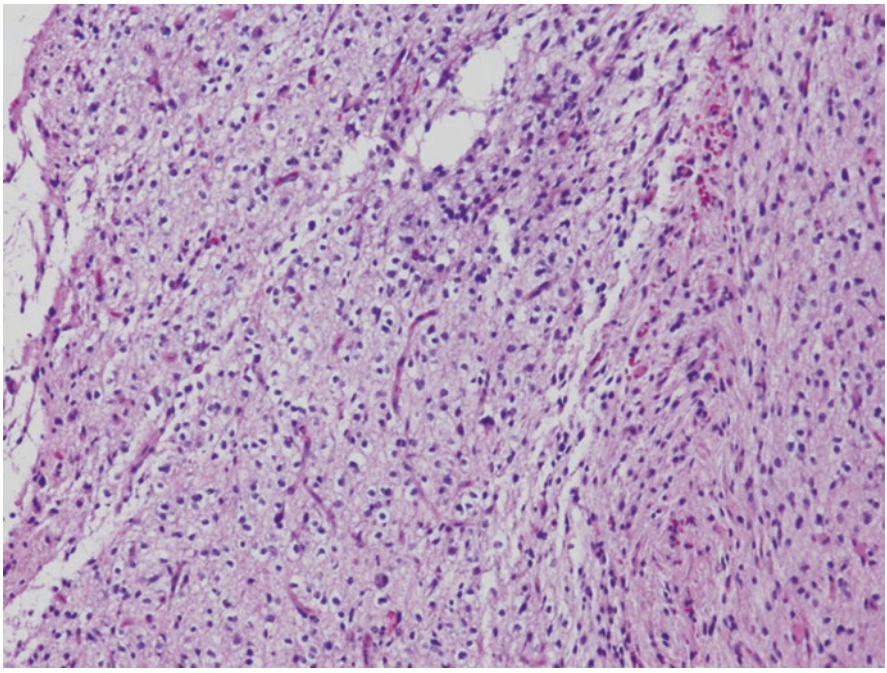

Fig. 2.9 Oligodendroglioma with infiltrating uniform round cells showing perinuclear halo (fried egg pattern) and delicate "chicken wire" capillary network. Magnification ×200

perinuclear halo giving the so-called "fried egg" appearance to the cells of an oligodendroglioma. Calcification is also frequent. A striking pattern of nuclear palisades is sometimes seen. An uncommon variant of oligodendroglioma can have a significant component of minigemistocytes. The gliofibrillary oligodendrocyte and minigemistocytes represent transitional forms that express glial fibrillary acidic protein. Differential diagnosis of the classic oligodendroglioma includes: (1) central neurocytoma which can be distinguished by the presence of acellular neuropil islands and positive immunostaining for neuronal antigens such as synaptophysin and (2) clear cell ependymoma which can be readily recognized by the presence of focal areas with the more classic ependymal rosettes and positive immunostaining for epithelial membrane antigen (EMA) and/or cytokeratin.

Anaplastic oligodendroglioma is characterized by a significantly increased cellularity with nuclear overlap, necrosis, increased mitotic activity, and endothelial proliferation. Increased cellularity and mitotic activity are helpful indicators of anaplastic progression in otherwise classic oligodendrogliomas.

Occasional familial clustering of oligodendroglioma cases has been reported. However, hereditary cancer syndromes involving oligodendrogliomas are rare. Loss of heterozygosity at chromosome 1p36 and 19q13 represents the most common genetic alterations in low grade oligodendrogliomas (Kros et al. 1999 and Reifenberger et al. 1996). Mutations of IDH1 (R132H) are also frequent in these tumors occurring concomitant with codeletion of 1p/19q. In pediatric oligodendroglial tumors, these genetic events are uncommon and are seen in tumors in children >10 years old. Anaplastic oligodendroglioma while showing chromosome 19q and 1p alterations also shows epidermal growth factor receptor overexpression often without gene amplification. Cdk4 amplification has been reported in a small subset of anaplastic oligodendroglioma. Chromosome 1p and/or 19q deletions in anaplastic oligodendrogliomas are positive predictors of prolonged survival and response to combination chemotherapy with procarbazine, cyclophosphamide, and vincristine (PCV).

Disseminated oligodendroglial-like leptomeningeal neoplasm (*DOLN*) is a recently described entity showing typical cytomorphologic features of low grade (WHO grade II) oligodendroglioma diffusely involving the leptomeninges. No associated intra-axial mass is seen in these patients. Significant desmoplasia is prominent in the involved leptomeninges. Rare cases show ganglion/ganglioid cells or anaplastic features. DOLN has been reported to show isolated 1p deletions with concurrent BRAF-KIAA1549 gene fusion. Occasional 1p/19q codeletion has been reported as well. Unlike oligodendroglioma, IDH1R132H mutations are infrequent in DOLN.

2.4.1 Mixed Glioma

Mixed gliomas are being increasingly recognized. Histologically, they are composed of two or more distinct populations of glial elements which can be diffusely mixed or have predominant cell types in varying proportions in different areas of the tumors. The more common mixed glioma is the oligoastrocytoma which can present

as a WHO grade II tumor or as an anaplastic oligoastrocytoma which is WHO grade III. The recognition of mixed gliomas and, in particular, the presence of an oligodendroglial component can have therapeutic implications.

2.4.2 Choroid Plexus Tumors

Choroid plexus tumors are intraventricular papillary tumors ranging from the benign choroid plexus papilloma (WHO grade I) to the malignant choroid plexus carcinoma (WHO grade III). Choroid plexus papillomas (CPPs) occur more commonly in children with about 10–20% presenting within the first year of life.

The majority of these tumors are sporadic with a minority arising in the context of hereditary cancer predisposition syndromes, including the Li–Fraumeni syndrome (germline TP53 mutation), Rhabdoid Predisposition Syndromes (germline mutation of SNF5/INI1/SMARCB1), Aicardi syndrome and rarely in von Hippel–Lindau disease. Congenital tumors can also occur. Most lateral ventricle tumors are seen in individuals below the age of 20 years. Grossly, choroid plexus papillomas present as well-circumscribed cauliflower-like masses. Histological features include a distinct papillary pattern with fibrovascular core and a single layer of cuboidal to columnar epithelium reminiscent of the normal choroid plexus (Fig. 2.10).

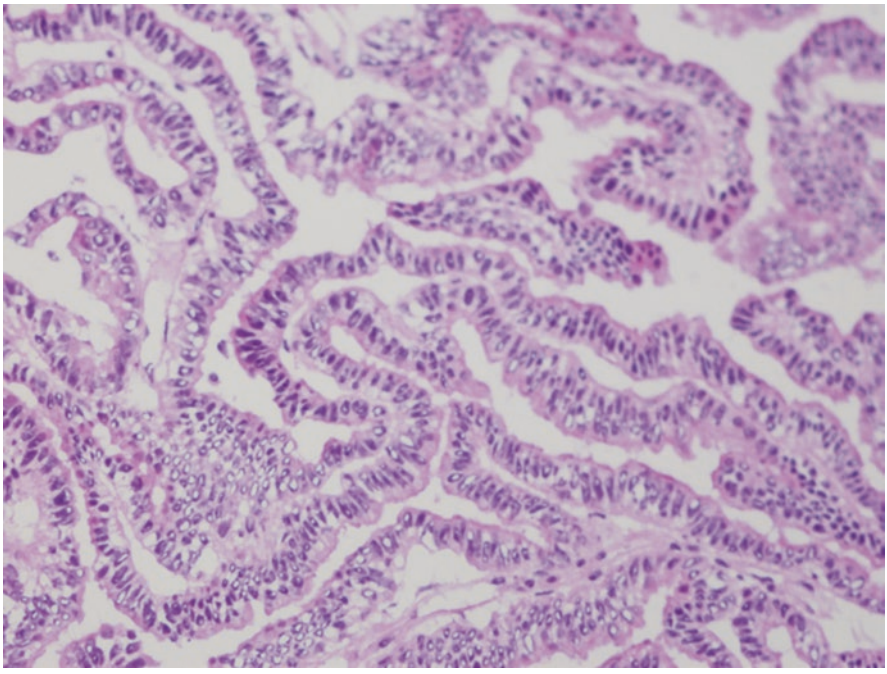

Fig. 2.10 Well-differentiated papillary configuration of choroid plexus papilloma. Magnification ×200

Atypical choroid plexus papillomas (WHO grade II) are CPPs with elevated mitotic activity (>2 mitoses per 10 high power fields). Notable histologic features in atypical CPPs include hypercellularity, nuclear pleomorphism, focal loss of papillary architecture/solid growth pattern, and necrosis. Complex growth with formation of cribriform and anastomosing papillary architecture may be seen.

In contrast, the choroid plexus carcinoma is an invasive tumor which can appear solid, hemorrhagic, and necrotic. Histologic features are those of a poorly differentiated anaplastic epithelial-like invasive tumor with significant increase in cellularity, brisk mitotic activity, and necrosis. Expression of cytokeratin, vimentin, S-100 protein, and synaptophysin are helpful in distinguishing choroid plexus carcinoma from a metastatic adenocarcinoma, since the latter should be negative for S-100 protein and synaptophysin. Nuclear immunopositivity for INI1 allows a distinction between a CPC with a rhabdoid phenotype and a true AT/RT lacking nuclear INI1 positivity.

2.5 Embryonal Tumors

Embryonal neuroepithelial tumors represent a significant group of brain tumors that occur predominantly in the pediatric population and less frequently in the adult population. They are characterized by "small blue cells" and exhibit a distinct pattern of divergent differentiation and have been referred to as primitive neuroectodermal tumors (PNETs). Other distinctive histologic features, though uncommon, can be seen in subsets of PNETs. These include characteristic ependymoblastic rosettes (multilayered rosettes which merge with surrounding tumor cells) in ependymoblastoma, fleurettes or Flexner–Wintersteiner rosettes in pineoblastomas, and florid desmoplasia (mesenchymal component) in supratentorial PNETs. A subset including medulloepithelioma, ependymoblastoma, some PNETs without rosettes, and embryonal tumor with abundant neuropil and true rosettes (ETANTR)] share a common genetic signature of C19MC (at chr19q13.41-42) amplification and together represent a subset of supratentorial PNETs now referred to as embryonal tumors with multilayered rosettes. Medulloblastoma represents a subset of "small blue cell" tumors that occur specifically in the cerebellum, accounts for 25% of childhood intracranial tumors, and is the second most common malignant tumors in childhood. This leaves a vanishing small subset of supratentorial PNETs designated as embryonal neuroepithelial tumors, not otherwise specified (NOS).

The most primitive of the embryonal tumors is the medulloepithelioma which corresponds to WHO grade IV. It occurs characteristically in young children below the age of 5 years. Medulloepithelioma can arise in any part of the neuraxis but the most frequent site is a periventricular location within the cerebral hemispheres. Intraorbital medulloepitheliomas can also occur. The medulloepithelioma is a primitive neoplastic neuroepithelium mimicking the primitive neural tube and can be papillary, tubular, or trabecular, and represents a distinctive and diagnostic histologic pattern. Aggressive histologic features such as mitotic figures, necrosis, and a population of undifferentiated cells can be present. The tumor cells are positive for

nestin and vimentin. Divergent differentiation along neuronal, glial, or mesenchymal elements can also occur.

Bailey and Cushing proposed the name medulloblastoma for a specific group of highly aggressive childhood tumors that they presumed arose from the putative stem cell "medulloblast" in the cerebellum. Although this name has been widely used for these tumors over the years, the "medulloblast" has remained undefined and has no counterpart in neurogenesis.

The morphologic spectrum of medulloblastoma and related PNETs is varied. It often includes a predominant population of sheets of round to oval (carrot-shaped) undifferentiated highly proliferative [proliferation index (MIB-I Index) is usually >30%] small blue cells (Fig. 2.11). These cells constitute the characteristic histology of the classic medulloblastoma. Anaplasia may vary from slight to moderate to severe. Regions with monomorphic discohesive large round cells with prominent nucleoli are suggestive of the presence of a large cell component. Predominance of large cells or severe anaplasia represents the *large cell/anaplastic* (Fig. 2.12) subtype and accounts for about 4% of medulloblastoma. Severe anaplasia is often associated with increased apoptosis, increased frequency of mitotic activity, and "cell wrapping" or cannibalism. Other histologic variants include the *nodular (desmoplastic) medulloblastoma* (Fig. 2.13) which is characterized by the presence of multiple reticulin-free pale nodules of neurocytic cells within a neuropil-like background, rarely mitotic with increased apoptosis; the

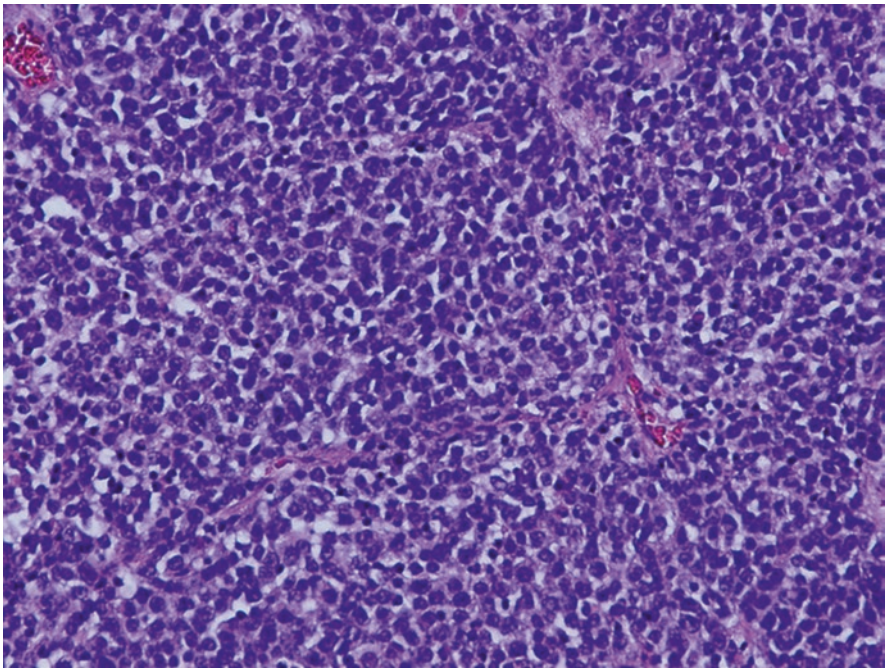

Fig. 2.11 Classic medulloblastoma with diffuse sheets of undifferentiated "small blue cells." Magnification ×200

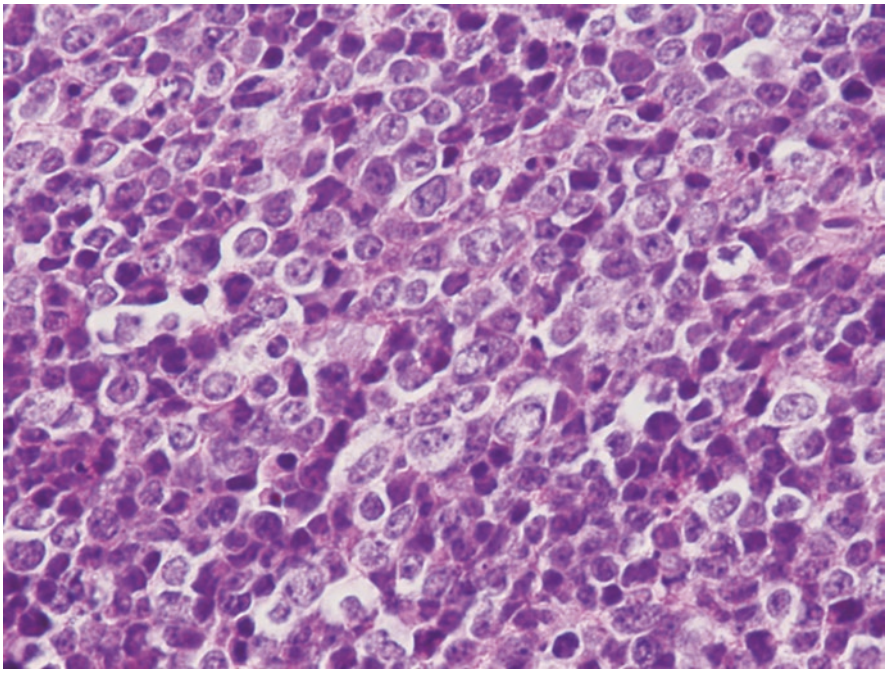

Fig. 2.12 Anaplastic/large cell medulloblastoma. Note enlarged cells with vesicular nuclei and prominent nucleoli as well as cellular pleomorphism. Magnification ×200

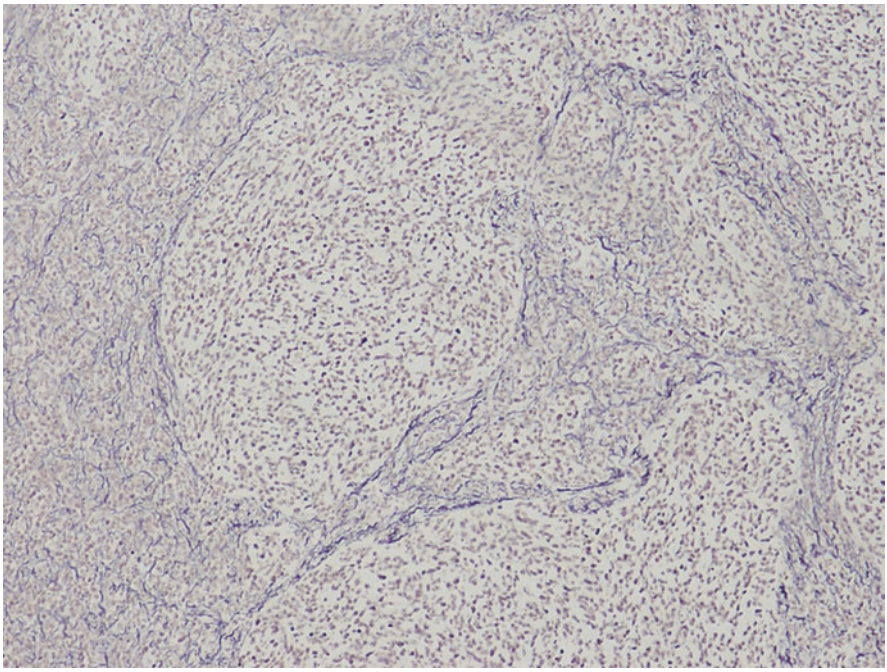

Fig. 2.13 Reticulin stain showing reticulin-free nodules of desmoplastic medulloblastoma. Magnification ×200

extensively nodular medulloblastoma (previously termed cerebellar neuroblastoma) showing florid nodularity and neurocytic differentiation with absent or minimal undifferentiated internodular component; and *biphasic medulloblastoma* which represents a tumor with mixed classic and nodular components in which the nodular component is not surrounded by desmoplasia, i.e., the internodular areas are reticulin free. This represents an important distinction from the nodular/desmoplastic medulloblastoma. In a minority of these tumors, neuroblastic differentiation is demonstrated by formation of Homer-Wright rosettes. Focal areas of astrocytic differentiation can be seen. Divergent differentiation with rhabdomyosarcomatous (medullomyoblastoma) and melanocytic differentiation can also be seen. Neuroblastic and astrocytic differentiation when present are accompanied by immunopositivity for synaptophysin or other neuronal antigens and glial fibrillary acidic protein, respectively.

Further molecular profiling studies of medulloblastomas have emphasized tumor heterogeneity and association of developmental signaling pathways with the establishment of four molecular subgroups. Groups A and B are associated with activation of the Wnt and Sonic hedgehog pathways, respectively. Subgroups C and D are non-wnt, non-SHH and are biologically more aggressive and may overexpress *MYCN* (group C) and/or *OTX2* and *FOXG1*. They are more likely to show i17q as well. Deregulation of p53 expression confers a poor prognosis. Molecular subgrouping can be done immunohistochemically by using a combination of antibodies to beta catenin for *wnt* pathway activation detection and *GAB1, YAP1, filamin 1,* and *Gli2* for *SHH* pathway activation detection.

Clinical determinants of poor outcome in medulloblastomas include age <3 years, dissemination at time of presentation, and partial surgical resection. The desmoplastic subtype appears to be associated with favorable outcome while the anaplastic/large cell variant is associated with shortened survival.

The *atypical teratoid/rhabdoid tumor* is a CNS embryonal tumor with histological features similar to those of the malignant rhabdoid tumor of the kidney. Even within the same tumor, histologic features can be extremely variable, including rhabdoid, primitive neuroepithelial, epithelial, and mesenchymal components. Irrespective of the spectrum of histologic features, the typical rhabdoid cells with eccentric nuclei and prominent nucleoli represent a constant feature. The cytoplasm is notably dense pink containing whorled bundles of intermediate filaments on electron microscopy (Fig. 2.14). Mitotic activity is very brisk with areas of necrosis often noted. A germ cell component is notably lacking. The cells show variable immunostaining for vimentin, epithelial membrane antigen, glial fibrillary acidic protein, smooth muscle actin, and sometimes neurofilaments; keratin and desmin can be focally positive. Germ cell tumor markers are usually negative. Molecular studies confirm that this tumor is biologically distinct from the PNETs, with 90% of tumors demonstrating monosomy and/or loss of heterozygosity for chromosome 22. Mutations/deletions in the hSNF/INI1/SMARCB1 is the hallmark of this subset of CNS tumors and related renal rhabdoid tumors with lack of detectable nuclear INI1 protein expression (Fig. 2.15).

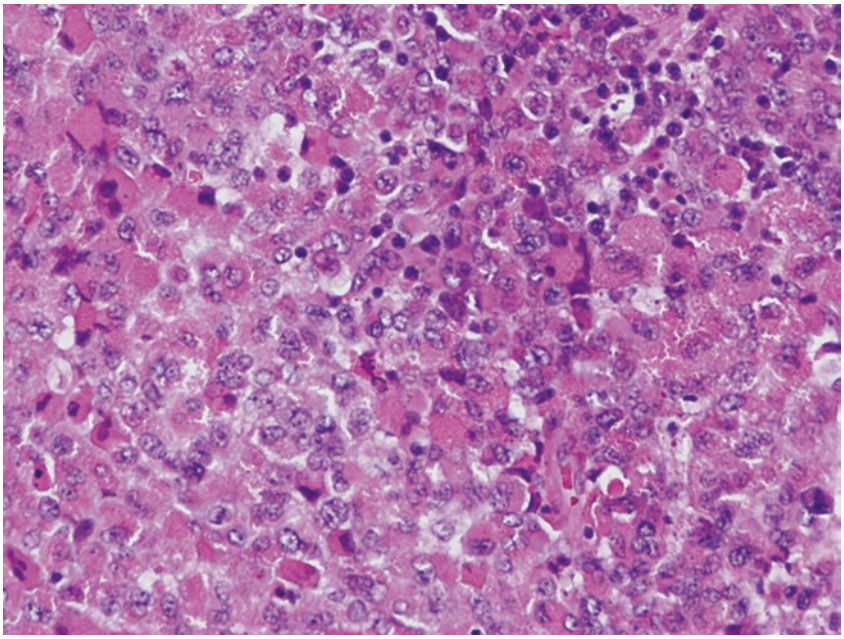

Fig. 2.14 Rhabdoid cells with eosinophilic cytoplasmic globules and eccentric nuclei are characteristic of the atypical teratoid rhabdoid tumor. Magnification ×200

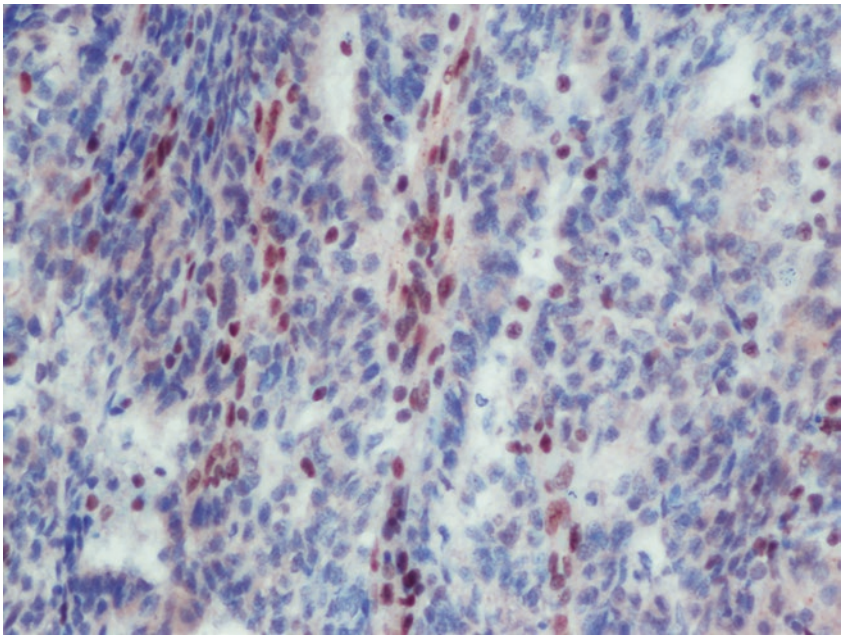

Fig. 2.15 Immunostain showing loss of nuclear expression of INI1 in tumor cells. Endothelial cells with immunopositivity (*brown*) serve as positive internal control. Magnification ×200

2.6 Neuronal and Mixed Neuronal-Glial Tumors

Gangliocytoma (WHO grade I) and ganglioglioma (WHO grade II) are uncommon tumors accounting for only 0.4–1.3% of all brain tumors with a median age of 8.5–25 years. Although these tumors can occur anywhere in the neuraxis, the majority are supratentorial. They are commonly associated with seizures and most tumors arise in the temporal lobe as a cystic lesion with a mural nodule.

The hallmark of these tumors is the presence of large, multipolar dysplastic neurons (Fig. 2.16). In the gangliocytoma, a stroma of nonneoplastic glia cells and reticulin fibers is present, while in the ganglioglioma, there is a neoplastic gliomatous (often pilocytic) component. Perivascular lymphocytic infiltration is a frequent feature of this tumor. Eosinophilic granular bodies (similar to those in pilocytic astrocytomas), microcysts, and calcification can be seen. The gliomatous component can sometimes show anaplastic features warranting a diagnosis of anaplastic ganglioglioma (WHO Grade III). BRAF V600E mutations are seen in approximately 45% of pediatric gangliogliomas while KIAA1549-BRAF fusion gene is rare and has only been reported in infratentorial gangliogliomas with prominent pilocytic glial components.

Recently described variants of glioneuronal tumors include the papillary glioneuronal tumor characterized by a pseudopapillary histology, and rosette forming glioneuronal tumor of the fourth ventricle.

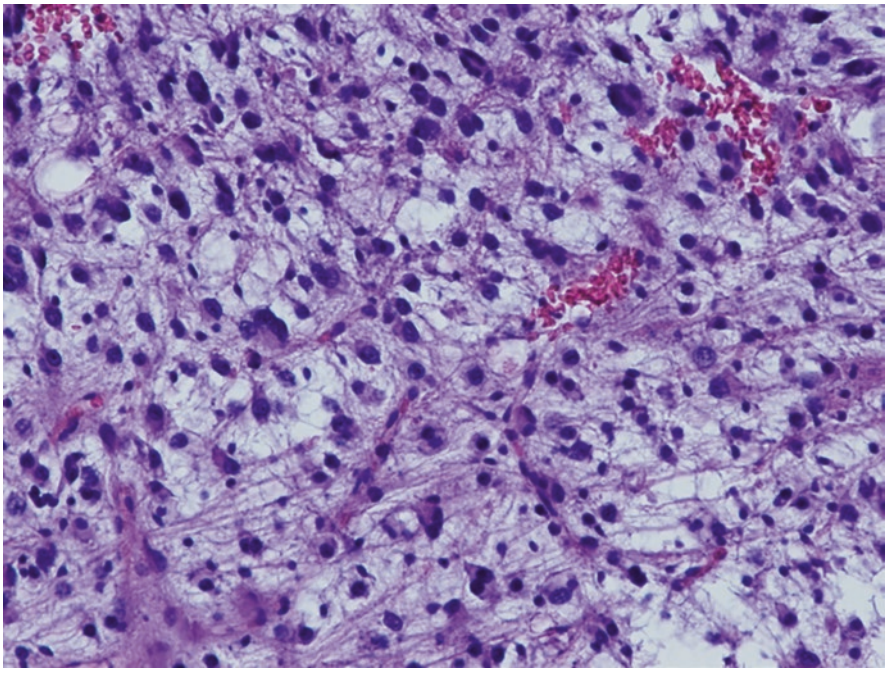

Fig. 2.16 Ganglioglioma showing pleomorphic ganglion/ganglioid cell differentiation. Magnification ×200

Desmoplastic infantile astrocytoma (DIA) represents a distinct low grade (WHO grade I) meningocerebral astrocytoma with a prominent desmoplasia characteristically occurring in children below the age of 2 years, although cases occurring in older children have now been reported. When a neuronal component is demonstrable, the lesion is referred to as desmoplastic infantile ganglioglioma (DIG). An immature population of neuroepithelial cells can be present. Notable is the frequent attachment of this tumor to dura. Tumors can have a uniloculated or a multiloculated cystic component and a solid (often superficial) component. The desmoplastic component can have a prominent storiform pattern and florid reticulin fibers, mimicking a mesenchymal tumor. Immunostaining shows only glial fibrillary acidic protein and vimentin positivity in the desmoplastic infantile astrocytoma, or a neuronal component with positivity for synaptophysin and other neuronal antigen markers in the desmoplastic infantile ganglioglioma.

2.6.1 Central Neurocytoma

The central neurocytoma is a neuronal tumor that is typically supratentorial, arising in relation to the lateral and third ventricles, but origin from intraparenchymal sites and the spinal cord has also been described. Peak incidence of the tumor is from 20 to 29 years and central neurocytoma corresponds to WHO grade II. It is composed of oligodendroglioma-like cells with intervening nucleus free neuropil. Central neurocytomas show immunopositivity for synaptophysin and other neuronal antigens. Ganglionic/ganglioid differentiation may be seen. Astrocytic differentiation, though rare, has been observed.

Anaplastic variants characterized by increased cellularity and increased mitotic activity can occur. The anaplastic central neurocytomas often have a proliferation index (Ki-67 index) greater than 2% and demonstrable parenchymal invasion.

Dysembryoplastic neuroepithelial tumor is a benign WHO grade I tumor arising predominantly in the superficial cortex. This tumor bridges the border land between hamartoma and neoplasia. Dysembryoplastic neuroepithelial tumor occurs predominantly in children and young adults who often have a long history of poorly controlled partial seizures. The classic complex dysembryoplastic neuroepithelial tumors are multinodular and are characterized by "specific glioneuronal elements" arranged in columns perpendicular to the cortical surface. The columns are formed by bundles of axons with intimately associated oligodendroglia-like (occasionally synaptophysin-positive) cells. Microcystic basophilic areas with floating neurons are also present (Daumas-Duport et al. 1988 and Daumas-Duport 1993). Cortical dysplasias are often present in adjoining cerebral tissue. In the simple form, the histology is less dramatic, can be patchy, and consists of the unique glioneuronal elements only. Deep-seated basal ganglia origin/localization though reported is extremely rare. It cannot be overemphasized that combined clinical, radiologic, and pathologic correlation is critical in the accurate diagnosis of dysembryoplastic neuroepithelial tumor (Fig. 2.17).

Subependymal giant cell astrocytoma (WHO grade I) is an intraventricular mass seen in the setting of tuberous sclerosis complex. It appears to evolve from the enlargement of subependymal hamartomatous nodules. It is composed of large eosinophilic astrocyte-like cells with prominent neuron-like nucleoli (Fig. 2.18). The cells typically immunostain for glial fibrillary acidic protein have also been reported to be positive for neuronal antigen markers such as synaptophysin.

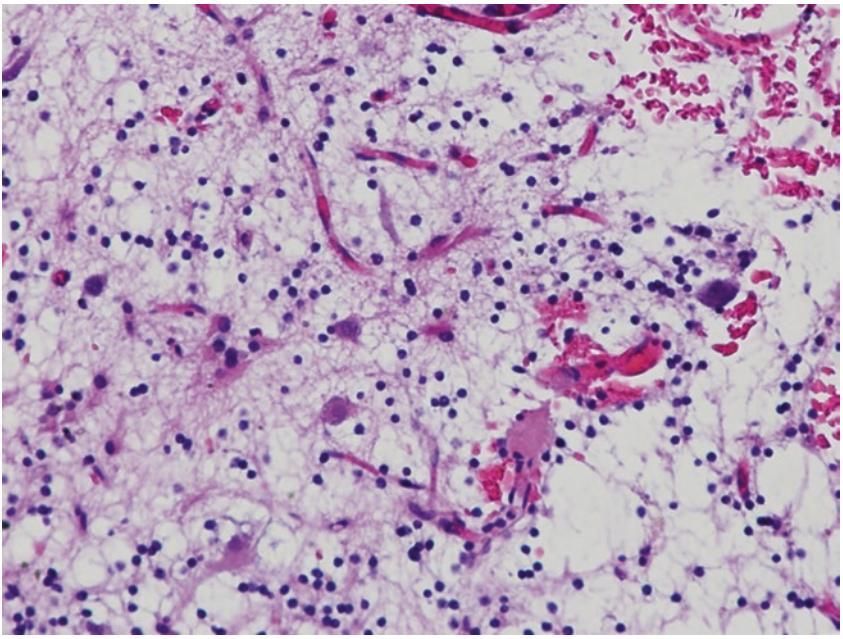

Fig. 2.17 The specific glioneuronal element of DNET with myxoid microcystic pattern and "floating neurons." Magnification ×200

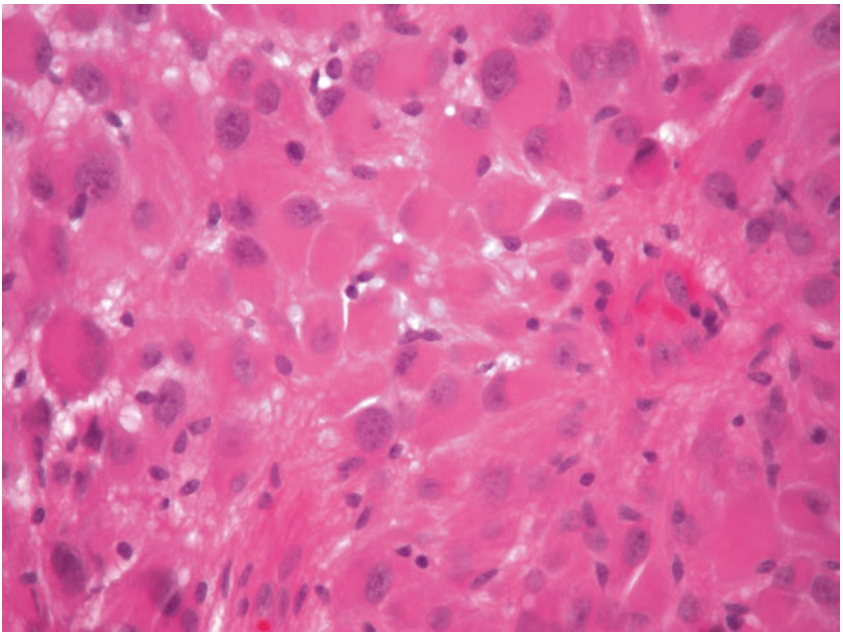

Fig. 2.18 Subependymal giant cell astrocytoma with uniform cells having plump eosinophilic cytoplasm. Magnification ×200

2.7 Miscellaneous Tumors

2.7.1 Schwannoma (Neurilemmoma)

Schwannoma is a benign tumor of the peripheral nerve sheath with predilection for sensory nerves. It most commonly affects the vestibular portion of the eighth cranial nerve producing the cerebellopontine angle mass lesion commonly referred to as the acoustic schwannoma. Bilateral acoustic schwannoma is a feature of neurofibromatosis type 2 (NF2). Although seen less frequently, schwannoma can also involve the fifth cranial nerve, but other cranial nerves are only rarely involved. The classic histologic features include the cellular Antoni A areas, Verocay bodies, and loose myxoid Antoni B area (Fig. 2.19). The presence of thick walled hyalinized vessels is a histologic hallmark of schwannomas. Immunostains show positive staining for S-100 protein and vimentin and negative staining for epithelial membrane antigen. Malignant transformation is rare in these tumors.

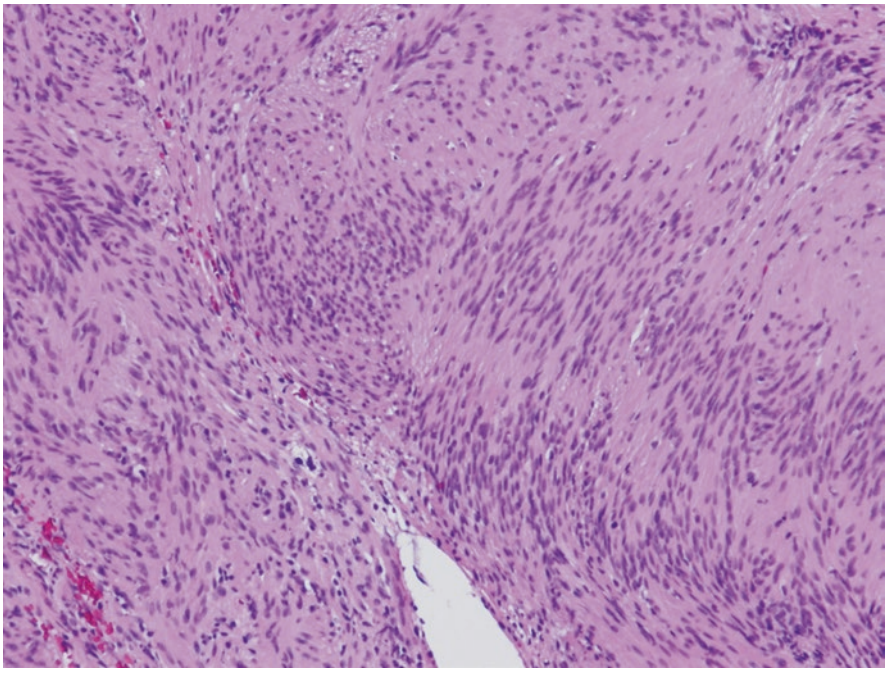

Fig. 2.19 Benign spindle cell proliferation with nuclear palisades having intervening acellular stroma to form Verocay bodies characteristic of Schwannoma. Magnification ×100

2.7.2 Germ Cell Tumors

Germ cell tumors are uncommon in the CNS accounting for 0.3–0.5% of all primary intracranial tumors. They present as midline tumors often in the region of the pineal gland and the suprasellar region in children and adolescents below the age of 20 years. Other sites of tumor occurrence include the basal ganglia, thalamus, intraventricular, bulbar, and intramedullary spinal cord locations. Histologically, the dysgerminoma is similar to gonadal seminoma with a uniform population of cells having large vesicular nuclei, prominent nucleoli, and a clear glycogen-rich cytoplasm (Fig. 2.20). Lymphocytic infiltrate and syncytiotrophoblastic giant cells can be seen. Immunostaining for placental alkaline phosphatase (PLAP) and c-kit (CD107) is usually positive. OCT3/4 and SALL4 immunostains are often positive as well. The identification of a cytotrophoblastic component is aided by immunostaining for beta-human chorionic gonadotropin (β-HCG) and human placental lactogen (HPL). Other germ cell tumors can also occur showing either a pure histologic subtype or a mixed germ cell tumor composed of any combination of embryonal carcinoma, yolk sac carcinoma, choriocarcinoma, and immature or mature teratomatous components.

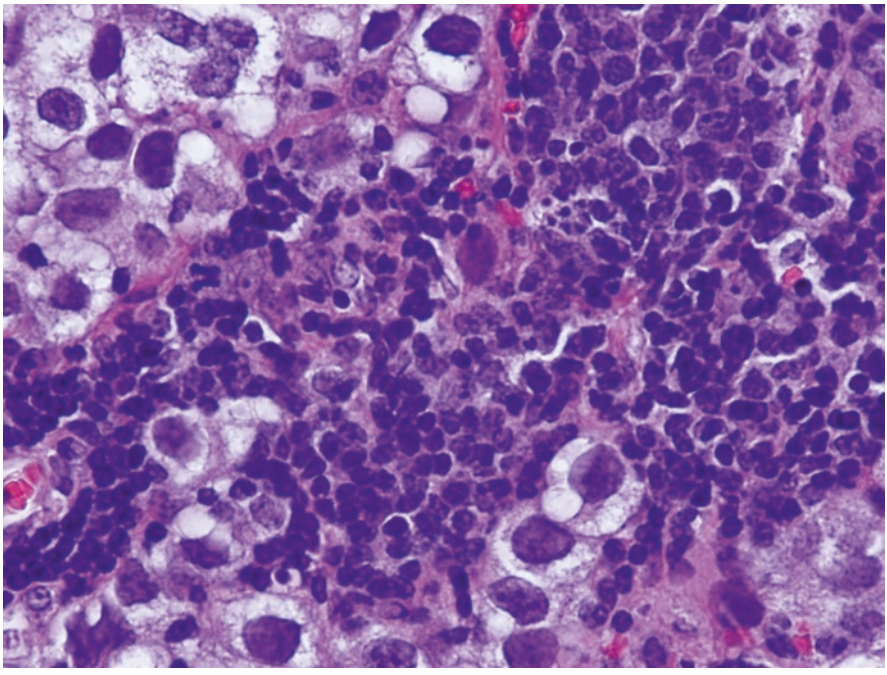

Fig. 2.20 Germinoma with mixed mature lymphocytes and neoplastic vacuolated epithelioid germ cells. Magnification ×400

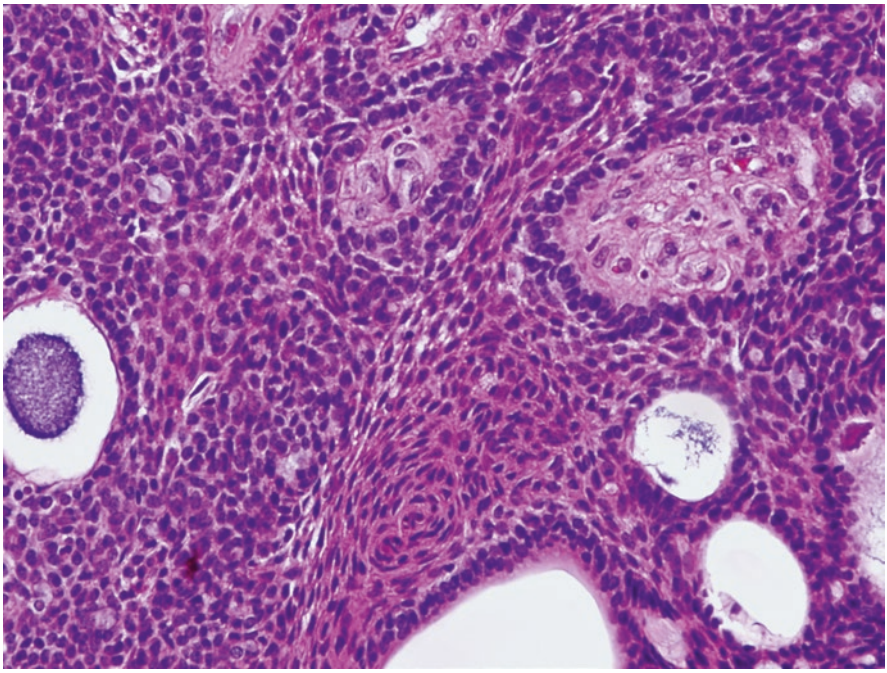

Fig. 2.21 Adamantinomatous craniopharyngioma with mixed microcystic epithelial elements and cellular reticular stroma. Magnification ×200

Craniopharyngiomas are derived from Rathke's pouch cell rests and present as intrasellar or suprasellar mass lesions with compressive effect on the optic chiasm, third ventricle, hypothalamus, and pituitary. They are usually partly cystic with prominent calcification. The epithelial component is characterized by keratinizing squamous epithelium with peripheral palisading, sometimes having a close histologic resemblance to adamantinoma (Fig. 2.21). A pseudopapillary pattern is another histologic subtype. A xanthogranulomatous component can also be seen. The cysts often contain oily material, (so-called "machinery oil"), and spillage of this material into CSF causes chemical meningitis. Tumor recurrence is frequent when incompletely resected. Beta catenin mutation is a frequent event in craniopharyngiomas.

Chordomas are formed from remnants of the notochord in the clivus or in the vertebral column, most frequently the sacrum. Chordomas are slow growing, lobulated with variable cellularity arranged in rows or cords in a myxoid matrix. The typical cell is the vacuolated physaliphorous ("bubble bearing") cell. Chordomas show positive immunostaining for vimentin, cytokeratin, epithelial membrane antigen (EMA), brachyury, and S-100 protein. A histologic subtype with a distinct chondroid component has been referred to as the chondroid chordoma.

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Imaging of Pediatric Central Nervous System Tumors

3

Edgar G. Ordóñez-Rubiano, Rachel S. Hicklen, Laura Rivera-Osorio, and Jason M. Johnson

Contents

Abstract

Central nervous system (CNS) tumors are the most common type of solid tumors in the pediatric population. Neuroimaging is the *sine quo non* for state-of-the-art care of pediatric patients with central nervous system neoplasms. A variety of noninvasive imaging techniques are described which have shown utility in patient

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care from the time of initial diagnosis to surgical and radiation planning and then also during posttreatment surveillance for treatment effects, complications and to exclude recurrent disease. This overview of imaging techniques will hopefully give the reader a better understanding in choosing appropriate imaging strategies for optimal individualized patient care.

Central nervous system (CNS) tumors are the most common type of solid tumors in the pediatric population and are a major cause of death from cancer in children (Ostrom et al. 2015). Unlike brain tumors in the adult population, pediatric brain tumors are typically primary, as opposed to metastatic. CNS tumors in children are often difficult to detect because the symptoms can be unremarkable and unclear. For example, meningiomas in pediatric population are often detected late, with advanced compression of adjacent healthy tissue (Fig. 3.1) (Liu et al. 2008).

Patient age, tumor location, and imaging characteristics are key pieces of information for establishing the diagnosis. Supratentorial tumors are more common in neonates and infants up to 2 years old, whereas infratentorial tumors are typically seen in children over 2 years old (Yu et al. 2015) Although some tumors may be found both supra- and infratentorially, tumors that are considered mostly supratentorial and intra-axial include, but are not limited to, astrocytomas, such as diffuse astrocytoma, anaplastic astrocytoma, pleomorphic xanthoastrocytoma (PXA), subependymal giant cell astrocytoma (SEGA), and glioblastoma multiforme (GBM);

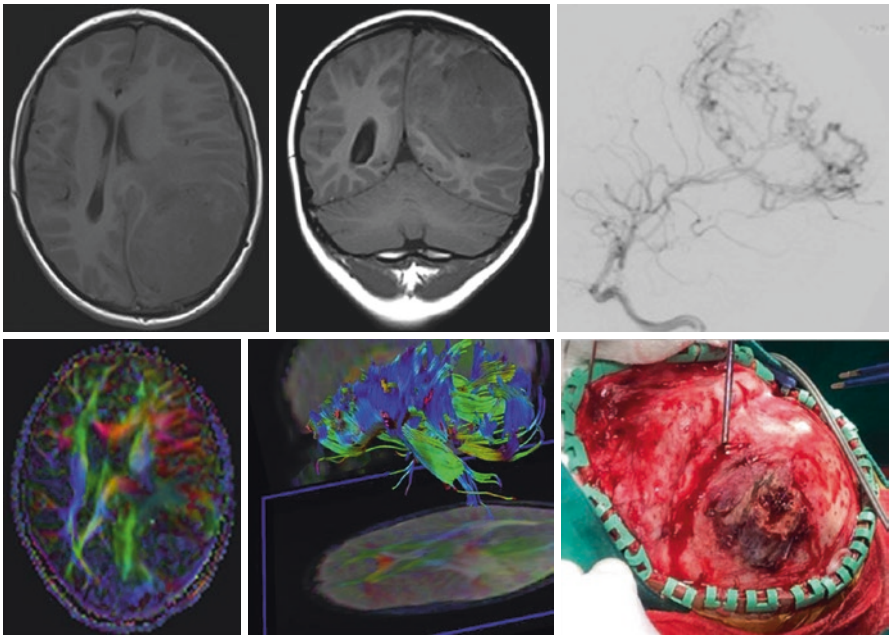

Fig. 3.1 10-year-old boy. 6 months with headaches. 15 days with visual disturbances. Atypical meningioma (WHO II) preoperative imaging and intraoperative extracranial tumor invasion illustration

oligodendrocytoma; primitive neuroectodermal tumor (PNET); dysembryoplastic neuroepithelial tumor (DNET); ganglioglioma; and desmoplastic infantile ganglioglioma. Some supratentorial extra-axial masses include arachnoid cysts, pineal region masses, and choroid plexus tumors.

Conventional Computerized Tomography (CT) and Magnetic Resonance Imaging (MRI) provide tumor characteristics and location information that are paramount in the diagnostic workup. MRI, with and without gadolinium-based contrast, remains the gold standard for neuroimaging in children with suspected CNS lesions. Advanced neuroimaging consists of noninvasive tools for assessing the metabolic and physiologic characteristics of these lesions. Other goals for imaging in the evaluation and treatment of pediatric central nervous system neoplasms include surgical and radiation therapy planning and posttreatment assessment for response.

3.1 Imaging Tools

3.1.1 Computerized Tomography

Advances in CT scanning have greatly improved the ability to detect intracranial neoplasms in a quick and highly replicable manner. Iodinated contrast agents are often utilized to improve characterization of tumors related to their ability to identify alterations in vascular patterns and breakdowns of the blood–brain barrier—both of which are features associated with higher grades of malignancy. However, CT can suffer from beam-hardening artifacts in middle and posterior fossa, and its inability to delineate subtle alteration of tissue affects both its sensitivity and specificity. The physics of CT imaging relies preferentially on changes in electron density for differentiation of normal and abnormal tissue. This is not as robust as the physics involved in the greater tissue differentiation experienced with magnetic resonance imaging and relating to its greater sensitivity and specificity (Hodler et al. 2016).

3.1.2 Magnetic Resonance Imaging

MRI remains the primary tool for characterizing brain tumors, the basic parameters of T1 and T2 relaxation, blood–brain barrier and tissue vascularity assessment with postcontrast imaging, and the diffusion of water molecules in the microarchitecture aid in tumor characterization. Additional MR imaging parameters include various methods of tissue perfusion evaluation, spectroscopic imaging, and blood oxygen level dependent (BOLD) imaging (Hodler et al. 2016).

3.1.2.1 Advanced MRI Applications

Diffusion-Weighted Imaging (DWI), Diffusion-Tensor Imaging (DTI) and Tractography

The addition of a diffusion gradient to an MRI pulse sequence renders acquired images sensitive to the random motion of water along directions parallel to the

orientation of the diffusion gradient (Le Bihan and Iima 2015). Early experiments revealed that images in the brain vary significantly with changes in the direction of the applied diffusion gradient: *diffusion is highly anisotropic in white matter*. In addition to this orientational variability, varying the strength of the gradient (the diffusion weighting, or *b*-value) sensitizes the image to water diffusing over different distances; stronger gradients encode motion over smaller distances (microns), and weaker gradients are only sensitive to bulk shifts in water over larger distances (millimeters). By systematically varying the strength and direction of the applied diffusion gradients, it is thus possible to collect diffusion data that characterizes the probability of water movement over various spatial scales along each direction in space. Diffusion imaging provides white matter landmarks. Armed with knowledge of the location and trajectory of the principal association, commissural, and projection tracts, the radiologist should use color FA images and fiber tractography to provide clinic-anatomic correlation to the patient's presenting symptomatology. It is also critical that physicians basing clinical decisions on DTI be familiar with the limitations and potential pitfalls inherent to the technique. DTI can demonstrate different compromise of subcortical fibers. The analysis of the FA values can also grade the compromise of the fibers: displacement, edema, infiltration, or disruption. Comparisons are performed between fibers of both hemispheres and also with normalized tables (Borja et al. 2013; Plaza et al. 2013). Quantitative analyses of the number of fibers, the FA values, and the direction of the fibers can be performed. Additionally, the fMRI provides information about the eloquent cortical brain matter and the DTI, aiding in the determination of the best surgical approach and the extent of subcortical resection to avoid unnecessary fiber injury.

Diffusion-tensor imaging (DTI) has the potential to show the direction of water diffusion (isotropic or anisotropic) to identify white matter tracts and thus to establish a spatial relationship between a white matter tract and the tumor. Quantitative DTI analysis based on a region of interest is conducted in manually selected cross-sectional areas of the main tracts of both hemispheres. For each region of interest, the mean fractional anisotropy (FA), the SD of the mean FA, the mean diffusivity, and the SD of the mean diffusivity are obtained. Major and minor eigenvalues are also estimated. The regions of interest are placed on the internal capsules, superior longitudinal fasciculi, inferior longitudinal fasciculi, inferior occipitofrontal fasciculi, and corpus callosum. Comparisons are performed between hemispheres and with normalized tables.

Diffusion tractography is a development of diffusion-weighted imaging (DWI) that enables identification of the connectivity of specific tracts such as the corticospinal, corpus callosum, arcuate, inferior orbitofrontal, and uncinate tracts (Fig. 3.1) and allows 3D reconstruction of these fibers. A deterministic algorithm based on the connection of voxels surviving arbitrary FA and bending thresholds may be used. Quantitative analyses of the tracts—the number of fibers per tract and the maximum length of each tract—are computed. Lateralization indexes may also be derived from these measures.

The identification of white matter tracts is essential for planning surgery to determine the best surgical approach and the extent of resection to avoid unnecessary fiber injury. DTI and tractography may also help determine the progression or regression of white matter tracts as a result of either tumor growth or resection.

3.1.2.2 MR Perfusion Imaging

Perfusion imaging to determine the hemodynamic parameters of the brain and brain lesions can be performed through either CT or MRI. In children, however, perfusion imaging is limited in most cases to MRI because of the exposure of ionizing radiation from CT examinations. Perfusion MRI evaluates several hemodynamic parameters including cerebral blood volume (CBV), cerebral blood flow (CBF), and mean transit time (MTT); however, CBV has been shown to be the most useful parameter for the evaluation of intracranial masses. More commonly, dynamic susceptibility contrast (DSC) enhanced echo-planar imaging is used for tumor evaluation in the pediatric population. With the use of gadolinium-based contrast agents, differences in local magnetic susceptibility changes (T2*) in the vessels and surrounding tissues are revealed as contrast material passes through these vessels. The amount of signal dropout with the administration of contrast material is detected and the relative CBV (rCBV), CBF, and MTT are calculated and displayed as color maps. Perfusion MRI has improved target selection and increased diagnostic yield with stereotactic biopsy.

Perfusion MRI is a helpful adjunct in differentiating low-grade tumors from high-grade tumors. Typically, high-grade tumors tend to have increased angiogenesis with leaky capillaries and therefore elevated rCBV compared with low-grade tumors. And while processing for rCBV has received the greatest attention among perfusion processing algorithms in differentiating tumor grades in adult tumors (Law et al. 2003), tissue signal-intensity time curves have also demonstrated useful additional diagnostic information including in differentiating primary CNS lymphoma from glioblastoma multiforme and metastases (Mangla et al. 2011). These curves have been shown to have good interobserver agreement for pediatric brain tumors and have also been shown to be useful in identifying low-grade tumor and also sensitive and specific for pilocytic astrocytomas (Ho et al. 2016). Improved target selection and decreased sampling error with stereotactic biopsy have also been described with the use of perfusion MRI to identify and localize the higher-grade component of the tumor. In patients who have undergone treatment, perfusion MRI has been found to be useful for differentiating recurrent tumor from radiation necrosis because recurrent tumor tends to have increased CBV.

Additionally, quantification of vascular permeability (contrast transfer coefficient [Ktrans]) within a tumor can now be obtained through DSC imaging. These Ktrans measurements have been proven useful for grading glioma and may correlate with patient prognosis and survival.

Other relatively newer techniques such as arterial spin labeling (ASL) are also used for perfusion imaging of brain tumors. Although ASL is used primarily in adults, the frequency of this application is increasing in children because ASL is a completely noninvasive technique and requires no contrast administration. In ASL techniques, arterial blood water is magnetically "labeled" using radiofrequency pulses. Two images—one labeled (tag image) and the other non-labeled (control image)—are created and subtracted from each other, resulting in a perfusion contrast image (Paiva et al. 2007).

DSC and ASL may have complementary roles in perfusion imaging of brain tumors. ASL methods use arterial blood water as a freely diffusible tracer perfusion measurement, which makes it more sensitive to absolute quantification of tumor blood flow. DSC, on the other hand, is more sensitive to changes in permeability and capillary blood volume and can be used to image permeability changes in brain.

3.1.2.3 Magnetic Resonance Spectroscopy (MRS)

MRS provides in vivo biochemical and cellular metabolite analyses of tissue. There are five predominant metabolite peaks in proton MRS: choline containing compounds, which reflect membrane turnover; creatine, which represents energy synthesis and serves as an internal control for determining metabolite ratios given its relative stability; *N*-acetyl aspartate (NAA), which is found mostly in neurons but may also be found in glial cells and serves mostly as a marker of neuronal cells; lactate (Fig. 3.2), which results from anaerobic metabolism and is seen in necrotic tumors and hypoxic or infarcted tissue; and lipid, which peaks when there are increased cellular and myelin breakdown products or nonviable necrotic tissue. Other metabolites such as myoinositol (a glial cell marker) can also be detected. The spectroscopic hallmark of brain tumors relative to normal brain is elevated choline and decreased NAA levels.

MRS is useful in the evaluation of brain tumors in pediatric patients by helping determine the diagnosis, grade, and extent of the tumor. MRS can also differentiate radiation necrosis from tumor recurrence because normal metabolite levels after treatment favor edema and postsurgical changes. Quantitative, rather than qualitative, MRS has been recently suggested for the assessment of the metabolic profiles of pediatric brain tumors. Work has also shown that incorporating functional MRI and spectroscopic imaging into the radiation treatment planning process was feasible and resulted in significant changes in target location and volumes compared with anatomic imaging alone. A major benefit of this strategy was that higher-grade elements within the low-grade gliomas could be more appropriately targeted (Narayana et al. 2007). MRS provides in vivo biochemical and cellular metabolite analyses of brain tissue. It is useful in determining the diagnosis, grade, and extent of the tumor (Panigrahy and Bluml 2009). Additionally, MRS can differentiate radiation necrosis from tumor recurrence.

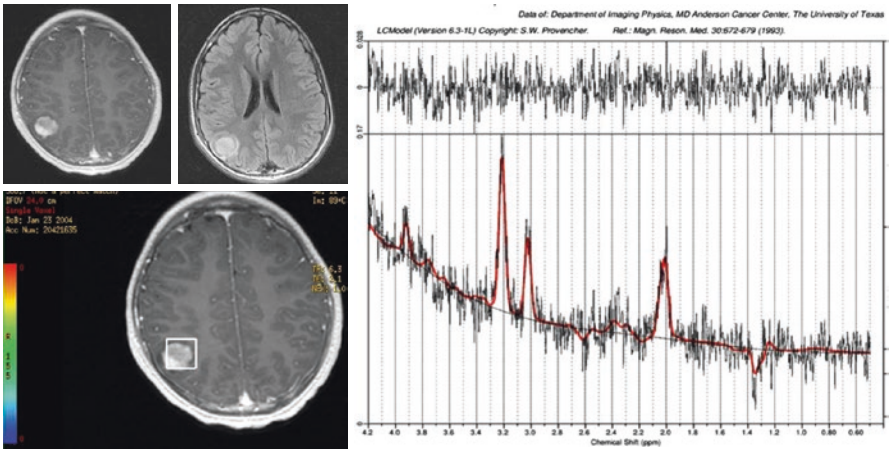

Fig. 3.2 Magnetic resonance spectroscopy of a ganglioglioma. Axial enhanced T1 and axial T2 images are demonstrating a right parietal intra-axial hyper intense lesion. MRS is demonstrating elevation of choline and lactate, compatible with a ganglioglioma

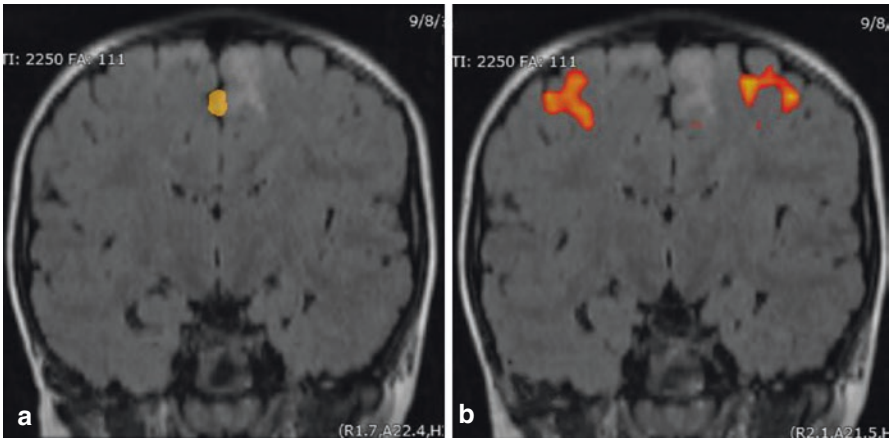

Fig. 3.3 fMRI motor tasking. Coronal FLAIR imaging of the head showing BOLD acquisitions of motor tasking, including (**a**) the toes and (**b**) hand in relation to an intra-axial mesial frontal lesion

3.1.2.4 Functional MRI (fMRI)

Mapping the language function before brain tumor resection is crucial for preventing postsurgical deficits and maximizing restoration of language function following surgery (Duffau 2007). Preoperative language mapping via task-fMRI provides noninvasive functional localization of eloquent cortex by contrasting the blood oxygenation level-dependent (BOLD) signal changes between the task and baseline state (Fox et al. 1984; Ogawa et al. 1992). However, its effectiveness is often limited by patient's cognitive ability and task performance (Pujol et al. 1998). fMRI is able to localize eloquent cortical gray matter that controls language, motor, and memory functions by imaging the local changes in CBF when activated or stimulated. This process is necessary for achieving a maximal safe resection of tumors located in cortical eloquent areas. It can determine the extent of resection according to the location of functional areas. Given the increasing attention to both early and late radiation effects to normal tissue, particularly in children (Marx et al. 1999), techniques such as fMRI to improve planning strategies are gaining increasing attention (Fig. 3.3). There is continued investigation in using fMRI in radiotherapy planning to define functional areas at risk when high doses are considered along tracts in the region of a lesion (Garcia-Alvarez et al. 2006).

3.1.3 Vascular Imaging

Angiographic evaluations such as CT angiography (CTA) and MR angiography (MRA) remain relevant for pretreatment planning in highly vascularized neoplasms (Vogl et al. 1992). Digital subtraction catheter based angiography also remains relevant despite advances in CTA and MRA, but it is typically reserved for cases with possible preoperative embolization (Wang et al. 2013). CTA is widely

available, minimally invasive, and allows for high-resolution rapid assessment of the cerebral arteries. The short scan time also enables evaluation of patients who may be unable to tolerate the longer scan times involved with other modalities, such as critically ill children or those with altered mental status. Furthermore, CTA is less prone to motion-related artifacts in patients compared to flow-related imaging such as MRA (Johnson et al. 2012). Modern multi-detector CT provides rapid scan time, increased resolution, and decreased radiation dose (Mahesh 2002). Unlike MRA, metallic foreign bodies, implanted metallic hardware, such as pacemakers, aneurysm clips, and various orthopedic devices are not a contraindication to CTA. Therefore, a greater percentage of patients are able to undergo imaging with CT compared to MRI.

MRA is a safe, convenient, and noninvasive screening tool for cerebrovascular evaluation. Unenhanced MRA is frequently used to evaluate the cerebral vasculature and is usually performed using time-of-flight (TOF) or phase contrast (PC) flow sensitive imaging techniques, which can be either a two-dimensional (2D) or 3D volumetric acquisition. Although these methods have the benefit of no contrast material administration, there are issues with the diagnostic quality of this technique, particularly in the setting of either pulsation artifacts (e.g., from large vessels), diminutive vessels, or in the case of slow flow. These sequences are also vulnerable to signal-intensity dropout artifacts in stenotic vascular segments that can cause issues with distinguishing near from total occlusion (Mustert et al. 1998; Nederkoorn et al. 2002).

The addition of intravenous gadolinium for contrast-enhanced MRA (CE-MRA) helps to overcome the limitations seen with unenhanced MRA; however, it also adds to the cost and complexity of imaging (Carr et al. 2001; Leclerc et al. 1999; Yang et al. 2005). CE-MRA is increasingly used for evaluation of the carotid and vertebral arteries due to high sensitivity and specificity compared with DSA, but it does not offer enough significant advantages to be routinely used for intracranial vascular evaluation. Surgical blood loss that would be of little concern for an adult can represent a much more significant risk in pediatric patients, as their total blood volume is much lower. Intraoperative MRI (structural sequences, DTI, fMRI) has improved surgical precision for making accurate approaches without injury to eloquent or deep cortical structures (Fan et al. 2016; Jolesz 2005).

3.1.4 Positron Emission Tomography (PET)

Although it provides a direct and multiplanar visualization, MR imaging may present some limitations in surgical planning such as in accurately delineating tumor margins. Pediatric brain tumors may appear to be particularly infiltrative on MR imaging, especially on T1-weighted sequences with or without Gd. Enhancement may be discrete or heterogeneous (as with oligodendrogliomas and fibrillary astrocytomas) and does not always provide precise delineation for complete image-guided resection. MR imaging modalities have been shown to be inaccurate in

identifying tumor boundaries in many low- and high-grade gliomas in both children and adults. The sensitivity and specificity for detecting tumor tissue have been reported to be 96 and 53%, respectively; those for detecting anaplastic tissue have been reported to be 72 and 65%, respectively (Plathow and Weber 2008). The accuracy of MR imaging is also limited in detecting residual tumor immediately after surgery (even when T1-weighted, T2-weighted, and FLAIR imaging sequences are obtained within 3 days), in delineating abnormal residual signals, and in differentiating residual tumor signals from inflammatory reactions. As the early confirmation of a complete resection represents a key prognostic factor and allows for early second-look surgery, the value of early postoperative imaging is crucial. A final limitation of MR imaging is the inaccuracy of T1-weighted images with or without Gd-DTPA sequences in identifying anaplastic tissue in histologically heterogeneous brain tumors, especially gliomas. Therefore, MR imaging guidance may either lead stereotactic biopsies to inaccurate targeting and sampling, suboptimal diagnostic yield, and underestimated tumor grading, or lead navigation-based volumetric resections to inaccurately target tumor parts presenting with the highest evolving potential.

Multiples studies have shown that integrating PET imaging in the diagnostic workup of pediatric brain tumors revealed metabolic data influenced the surgical management at different steps in selected situations, accounting for about 30% of all pediatric brain tumors treated at one institution (Pirotte et al. 2010). The use of PET guidance in children also represents an opportunity for the evaluation of the role of functional neuroimaging in pediatric neuro-oncology and inaugurates a new approach in the management of pediatric brain tumors, in which functional data may influence the therapeutic decision-making process.

3.1.5 Protocol Optimization

3.1.5.1 Supratentorial Tumors

The approach to the supratentorial tumors should be guided depending on the nature of the lesion. Independently of the type of tumor, in every case a complete basic non-enhanced MRI should be performed, including the following sequences: axial structural T1 high-resolution 1-mm slice thickness volume acquisition images, axial T2, axial FLAIR, axial SWI, axial DWI, axial perfusion, and axial DTI. In cases where neuronavigation should be applied, an initial axial structural post-gadolinium T1 high-resolution 1-mm slice thickness volume acquisition should be performed. Sagittal, coronal, and axial post-gadolinium T1 images should be acquired as well. Extra-axial lesions such as meningiomas could be initially analyzed with non-enhanced MRI T1 and T2 sequences, as well as with CE-MRI and also, if possible, with a CE-MRA. For specific intra-axial lesions, especially for those located deeply or in eloquent areas (motor, speech, visual, etc.), it is highly recommended to perform always fMRI, MRS, and DTI protocols. Fusion of images allows physicians to combine information regarding cortical and

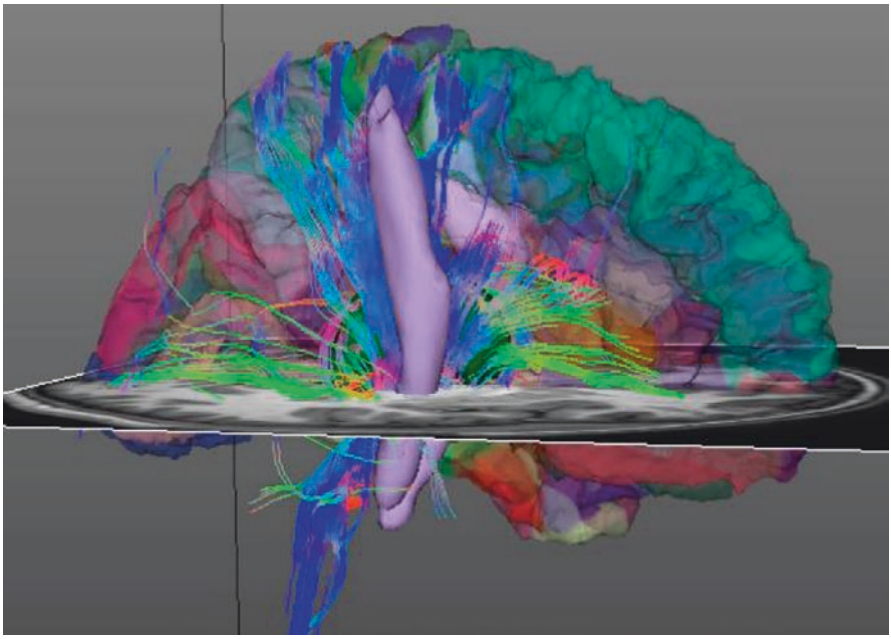

Fig. 3.4 Post-processing of MRI for preoperative planning for supratentorial lesions. Combined information of fMRI cortical superficial distribution, volumetric DTI of both corticospinal tracts as well as subcortical thalamic projections are depicted in a healthy 1-year-old female

subcortical remarkable structures. If available, the use of a post-processing software would be of great help for determining structural relationships of the tumor (Fig. 3.4).

3.1.5.2 Infratentorial Tumors

Protocols for posterior fossa tumors are focused on compromise due to compression of the cranial nerves, the CSF spaces, and the cerebellum. A volumetric axial T1, sagittal T1, axial FIESTA (or 3D T2-weighted sequence), axial FLAIR, axial DWI/ADC, and coronal, sagittal and axial post-GAD T1 sequences must be acquired. Additional DTI or MRS can be complimentary if necessary. Additional scans of the rest of the neuraxis are suggested, as many of the posterior fossa tumors can have meningeal spinal seeding (Fig. 3.5). Analysis of the nodular and cystic components of posterior fossa tumors in children is remarkable, as well as their relationships with neurovascular structures.

Most pediatric brain stem tumors are glial in origin (Ostrom et al. 2014). The diagnosis of diffuse intrinsic pontine glioma (DIPG) deserves special note due to the typical reliance on conventional MR imaging for diagnosis given the risk of biopsy in the brain stem. MR has remarkably high accuracy for this diagnosis (approximately 95–97%). The typical DIPG appears as a poorly marginated, intra-axial mass lesion that is centered on the ventral pons, involves 70% of the

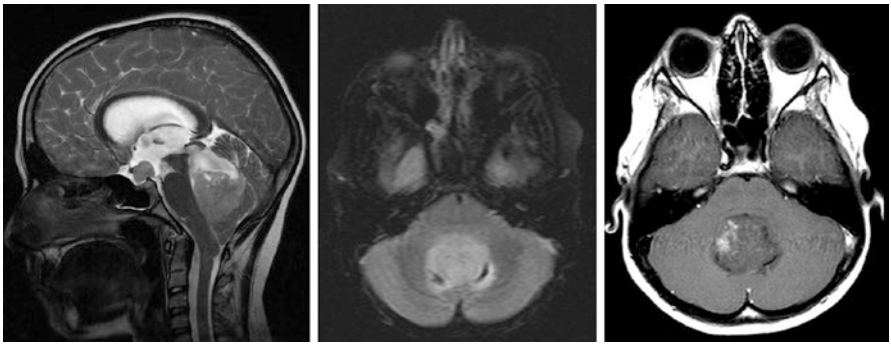

Fig. 3.5 Medulloblastoma. Sagittal T2, axial FLAIR and axial T1 post-GAD images of the brain are demonstrating an intraventricular heterogeneous mass, with irregular enhancing with gadolinium

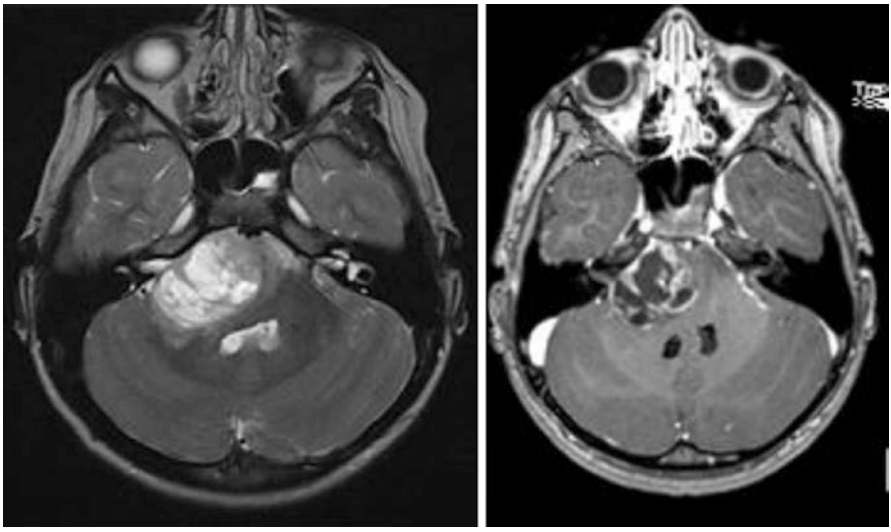

Fig. 3.6 Diffuse intrinsic pontine glioma (DIPG). Axial T2 and T1 post-GAD MR images are depicted

cross-sectional area of the brain stem, and extends into the prepontine cistern with variable encasement of the basilar artery (Warren 2012) (Fig. 3.6).

3.1.5.3 Orbital Tumors

Intraocular and optic nerve tumors are rare in children; however, their radiologic appearances reflect their pathologic features. The most common intraocular in children remains the retinoblastoma (Chung et al. 2007). The emphasis in this entity is determinant. Orbital ultrasonography (US) is well tolerated in young children and is very sensitive to calcification, a typical feature of retinoblastoma. 3D US techniques

can increase sensitivity and specificity for orbit tumor evaluation. Even though, CT scans are more sensitive for extraocular spread of the lesions, especially for tumors invading the surrounding bony tissue. Unfortunately, CT has the disadvantage of radiation, as well as its lower sensitivity for intracranial invasion compared to MRI. For pediatric population, it is almost always necessary to perform MRI under sedation, and is less sensitive for calcifications, but more sensitive for optic nerve and subarachnoid invasion. A T1 fat-suppressed post-GAD sequence should always be included, due to the orbital fat artifact.

3.1.5.4 Sellar and Suprasellar Tumors

MRI examination of the sella turcica should include high-resolution non-contrast and contrast-enhanced sequences (Chen et al. 2016). Non-contrast sagittal and coronal fast spin echo (SE) T1-weighted sequences, a coronal T2-weighted sequence, postcontrast coronal, and sagittal T1-weighted sequences should be included. CT is almost limited for situations when MRI is contraindicated. CT also provides information regarding surrounding osseous structures, such as the sellar floor (usually non-pneumatized in children).

3.1.6 Imaging Applications for Patient Management

3.1.6.1 Surgery

Principal characteristics for adequate resection imply structural delineation (T1-GAD volumetric, perfusion, spectroscopy), identification of cortical eloquent areas (fMRI), and subcortical eloquent pathways (DTI, tractography).

Advanced imaging for preoperative planning has become available in most major pediatric centers. The use of newer MRI techniques, such as perfusion MRI, functional MRI (fMRI), MR Spectroscopy (MRS), and intraoperative MRI (iMRI), has widely increased during the past two decades, becoming a sophisticated complement to routine enhanced and non-enhanced CT and MRI scans (Craig et al. 2012).

3.1.6.2 Radiotherapy Planning and Management

CNS imaging is necessary for modern radiation techniques including three-dimensional conformal radiotherapy and stereotactic radiosurgery. The initial evaluation should determine the extent of the lesion and also establish baselines in anticipation of toxicities. Radiation energy causes ionization of water molecules, generating reactive free radicals, causing damage in multiple macromolecules at the cellular level. An irradiated cell may experience one of several phenomena: mutations, DNA repair, reproductive cell death, necrosis, or apoptosis. Normal CNS tissue radiation-induced changes include demyelination, glial degeneration, vascular lesions, and perivascular lymphocytic infiltration. Delayed intracranial radiation changes also include extensive demyelination, neuroendocrine dysfunction, associated areas of coagulation necrosis, calcification, fibrinoid exudates, and gliosis. Extracranial effects include facial growth retardation, dental abnormalities, hearing loss, and hypothyroidism (Muller 2002; Paulino et al. 2000). These postradiation complications are correlated with the dose delivered to different organs at risk surrounding the tumor (Loeffler et al. 1990).

MRI is increasingly being used in radiotherapy (RT) planning owing to its superior soft-tissue contrast compared with CT. MRI plays a dominant role in delineating the GTV and potential organs at risk (OAR) in radiation therapy treatment planning software packages. MRI sequences including both routine diagnostic sequences (Axial T2 FLAIR and Axial SE T1 Postcontrast) and geometrically optimized 3D sequences with T1 and T2 weighting are routinely incorporated into treatment plans. The soft-tissue data from MRI is typically relied upon for guidance on lesion margination whereas CT guidance is preferred for its relationship to electron density mapping which is superior for accurate dose calculation (Metcalfe et al. 2013).

Stereotactic Radiosurgery (SRS) requires very precise tumor delineation and spatial accuracy to allow a single high dose of radiation to be delivered appropriately. A stereotactic enhanced MRI scan is typically performed with high-resolution ~1-mm slice thickness volume acquisition. A 512 × 252 matrix provides adequate exclusive anatomical detail in the majority of cases.

There is growing interest in MRI scanner placement in radiotherapy clinics as an adjunct to CT simulators. In principle, it would be desirable to be able to replace the CT planning scan entirely with a corresponding MRI planning scan, particularly for children given greater radiation concerns. The problem of ensuring geometric accuracy and estimating electron density for tissue dose calculations with MRI have largely been addressed, but in most clinical practices, MRI is currently mainly used in combination with a standard CT planning scan (Schmidt and Payne 2015).

3.1.6.3 Treatment Complications

The most common serious complications related to the treatment for central nervous system neoplasms are hemorrhage, infarction, and recurrent malignancy. Other than the challenges described above relating to differentiating pseudoprogression from true progressive disease, conventional MR imaging should readily be able to identify the serious complications of hemorrhage and infraction.

Chemobrain: Neurotoxicity is a common complication of cancer chemotherapy and often the main dose-limiting factor. It is clinically manifest in various ways and has attracted increasing attention during the past decade related to concerns voiced by patients, family members, and caregivers of impaired cognitive function, often labeled as “chemobrain.” Objective neuropsychological testing has confirmed the validity of these concerns, and a substantial growing literature examining different aspects of cognitive impairment has developed (Weiss 2008; Verstappen et al. 2003). While cognitive dysfunction is the major neurological complication receiving clinical attention, sensory and motor dysfunction are also reported.

3.2 Summary

Neuroimaging is the *sine quo non* for modern state-of-the-art care of pediatric patients with central nervous system neoplasms. A variety of noninvasive imaging techniques as described above have shown utility in patient care from the time of initial diagnosis to surgical and radiation planning and then also during

posttreatment surveillance for treatment effects, complications and to exclude recurrent disease. This overview of imaging techniques will hopefully give the reader a better understanding in choosing appropriate imaging strategies for optimal individualized patient care.

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Surgical Principles in the Treatment of Pediatric Brain Tumors

4

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Abstract

Contemporary surgical neuro-oncology traces its roots to Harvey Cushing in the study and treatment of brain tumors. Neurosurgical intervention plays a significant role in the management of brain tumors for tissue diagnosis through biopsy, and treatment through resection in most cases of isolated well-circumscribed brain tumors, often in combination with radiation therapy and chemotherapy. Neurosurgical consultation is almost always indicated for intracranial mass lesions in pediatric patients, and a general familiarity with principles of surgical management can be useful to the oncologist and radiation oncologist in providing appropriate counseling and creating a comprehensive multidisciplinary treatment plan. This chapter provides an overview of five important topics of surgical management and provides relevant clinical pearls: surgical approaches to brain tumors, hydrocephalus management, posterior fossa syndrome, steroid administration, and seizure management.

4.1 Introduction

Modern neurosurgery derives much of its origin from the pioneering work of Harvey Cushing in the study and treatment of brain tumors (Canale 1989). Today, surgical resection continues to be the first-line management in most cases of isolated well-circumscribed brain tumors, often in combination with radiation therapy and chemotherapy. Neurosurgical consultation is almost always indicated for cerebral mass lesions in pediatric patients, and a general familiarity with principles of surgical management can be useful to the oncologist and radiation oncologist in providing appropriate counseling and creating a treatment plan. This chapter provides an overview of five critical topics of surgical management: surgical approaches to brain tumors, hydrocephalus management, posterior fossa syndrome, steroid administration, and seizure management.

4.2 Surgical Approaches to Brain Tumors

Surgical resection remains the mainstay for definitive diagnosis and treatment for most brain tumors. A list of indications for surgery is beyond the scope of this chapter; however, tumors that are amenable to surgical resection usually fall under one of the following categories: (1) a primary brain tumor with well-defined margins; (2) a single intracerebral metastasis; (3) in the case of multiple metastases in a symptomatic patient, resection of the single metastasis that is causing symptoms; (4) a very large tumor causing mass effect amenable to debulking or complete resection; and (5) a tumor causing obstructive hydrocephalus. For tumors where surgery is not first-line treatment, an open or stereotactic biopsy may be performed to obtain tissue diagnosis. In rare circumstances, such as diffuse pontine glioma, with pathognomonic radiological findings, no surgical intervention (resection or biopsy) is necessary before proceeding with chemotherapy or radiation therapy.

Sampling cerebrospinal fluid for tumor markers, including beta-human chorionic gonadotropin and alfa-fetoprotein; tumor staging; and pathologic diagnosis from the lumbar cistern through a lumbar puncture is safe in the absence of tumor causing mass effect and obstructive hydrocephalus. Removal of cerebrospinal fluid in the setting of mass effect or hydrocephalus may precipitate a fatal herniation syndrome. Consultation with neurosurgical colleagues prior to lumbar puncture should be secured in uncertain cases of mass effect or hydrocephalus.

Most tumors in pediatric patients can be accessed and resected via one of five main types of craniotomies: pterional, suboccipital, retrosigmoid, interhemispheric, and regional craniotomies. Endonasal endoscopic or open transsphenoidal surgery may be considered in children with intrasellar and suprasellar tumors such as craniopharyngioma. The lack of aeration of the sphenoid sinus in young children remains the most important anatomic limitation to this approach. In the pediatric population, lesions affecting the skull base are rare and not necessarily treated by aggressive surgery. Because of this, skull base surgery, such as transcondylar far lateral approach, in children has not received much attention in the pediatric neurosurgical literature except by a few authors (Patel et al. 2012). A pterional craniotomy provides direct access to the middle cranial fossa, much of the anterior cranial fossa, and the lateral skull base. A skin incision is made just behind the hairline to preserve cosmesis. Common complications include transient swelling of the ipsilateral eye, atrophy of the temporalis muscle, temporalis muscle pain, and ptosis due to injury to the frontalis branch of the facial nerve. The suboccipital craniotomy provides direct access to the midline posterior fossa up to the midbrain. A dorsal midline skin incision is made near the occipital cervical junction and is mostly covered by the hairline with good cosmesis. Cerebrospinal fluid (CSF) is prone to leak from these incisions, and a known complication is the posterior fossa syndrome (discussed later in this chapter). Vertebral artery injury causing posterior circulation stroke is an uncommon but potentially devastating complication. The retrosigmoid craniotomy is used to gain access to the lateral posterior fossa and anterior pons. Portions of cranial nerves V through XII can be exposed via this approach. The retrosigmoid craniotomy is often used to resect cerebellopontine angle tumors. A common complication of this approach includes CSF leak (the air cells are usually exposed during this approach). The interhemispheric, or transcallosal craniotomy, provides access to the body to the lateral ventricles and the anterior portions of the third ventricle, including the foramen of Monroe. Common complications of this approach include injury to interhemispheric veins and “disconnection” syndromes from sectioning of the corpus callosum. Finally, various regional craniotomies (frontal, parietal, orbital, etc.) are often used to access superficial tumors. These involve small linear or S-shaped incisions, or horseshoe-shaped flaps directly over the tumor, and a craniotomy underneath. Convexity meningiomas are usually amenable to such craniotomies.

A variety of adjunctive options are available to assist the surgeon in performing an adequate resection with minimal or no postoperative neurological deficit. These include intraoperative neuro-navigation, intraoperative imaging (ultrasound and MRI), and neurophysiological monitoring.

4.2.1 Neuro-Navigation

Intraoperative navigation is now ubiquitous in most surgical centers. Navigation allows the surgeon to identify an anatomic point of interest during surgery (using a special pointed tip instrument) and to view the corresponding location on the patient's preoperative MRI scan (Ng et al. 2010). This technique is useful to identify structures that must be avoided (such as a venous sinus or a large vein) or to have a sense of how much of a tumor remains to be resected (Orringer et al. 2012). Resection of a tumor often causes the brain to shift, so navigation is not completely reliable by itself for ensuring complete resection of a tumor. Another use is to assure accurate proximal placement of a shunt or Ommaya reservoir. Neuro-navigation requires a high-resolution MRI sequence called a *STEALH MRI* or, in the case of shunt or Ommaya placements, a *STEALTH CT* scan will suffice. If an MRI of the brain is ordered to work up a possible brain tumor (such as a patient with a mass lesion identified on a CT scan), it is useful to add a contrasted STEALTH sequence to the study. Doing so avoids a future trip back to the scanner for the sole purpose of obtaining the STEALTH sequence when surgery is being planned.

4.2.2 Intraoperative Imaging

Intraoperative ultrasound can be used once the dura is exposed, and this modality is useful for localizing the tumor when planning a durotomy and to assess for completeness of tumor resection (El Beltagy et al. 2010). In most centers, ultrasound is the only real-time intraoperative imaging available to assess for extent of tumor resection, in combination with direct visualization (Cheon 2015). Intraoperative MRI is becoming increasingly more common. There is level 2 evidence that intraoperative MRI-guided surgery is more effective than conventional neuro-navigation in increasing extent of tumor resection in glioblastoma patients (Kubben et al. 2011). Intraoperative MRI is especially helpful when dealing with an infiltrating tumor, when the margin between the tumor and normal brain is difficult to discern by direct visualization.

4.2.3 Intraoperative Monitoring

Finally, intraoperative neurophysiological monitoring utilizes various electrophysiological techniques to monitor the integrity of neural structures during surgery (Ng et al. 2010). Somatosensory evoked potentials can be used to localize the central sulcus (and hence to know the location of the motor strip just anterior) because a characteristic phase reversal (inversion of the N20/P20 component) occurs across the central sulcus (Cedzich et al. 1996). Motor evoked potentials can be used to monitor the integrity of the corticospinal tract during resection of motor strip tumors (Taniguchi et al. 1993). Brainstem auditory evoked potentials are often used to monitor cochlear function during surgery for a cerebellopontine angle tumor, when hearing preservation is the goal, and also to monitor patients during brainstem surgery

(Yamakami et al. 2009). EMG and stimulated EMG are useful during surgery in the posterior fossa or in the cerebellopontine angle to monitor the function of various cranial nerves, especially the facial nerve (Isaacson et al. 2003).

4.3 Hydrocephalus Management

Hydrocephalus is defined as the excessive accumulation of CSF within the ventricles of the brain. It is among the most common complications of cerebral mass lesions. Hydrocephalus in the pediatric population always warrants neurosurgical consultation and often requires immediate treatment. Therefore, knowledge of this condition and prompt recognition are critical.

Various anatomical locations are especially susceptible to obstruction of CSF flow, including the cerebral aqueduct (only a few millimeters in diameter), the foramen of Monroe, and the arachnoid granulations. In addition, certain mass lesions can obstruct the temporal horn of the lateral ventricle, causing a "trapped temporal horn" (Chen et al. 2013) These are examples of *obstructive hydrocephalus,* which occurs when CSF circulation is blocked proximal to the arachnoid granulations (Oreskovic and Klarica 2011). By contrast, *communicating hydrocephalus* occurs when CSF absorption is blocked at the level of the arachnoid granulations. If physiologic CSF circulation is restored, hydrocephalus often resolves or at least stabilizes without the need for CSF diversion. For example, it was long known that the incidence of hydrocephalus after removal of a fourth ventricular tumor was somewhat common—about 18–40%. This frequency caused some early authors to recommend prophylactic CSF diversion in all patients who underwent surgery to resect a posterior fossa tumor (Sainte-Rose et al. 2001). A recent study, however, identified the risk factors for postoperative hydrocephalus in this population, allowing surgeons to risk-stratify preoperatively the need for CSF diversion (Table 4.1). The risk factors for developing hydrocephalus after surgery for a posterior fossa tumor include age less than 2 years, presence of transependymal edema, moderate or severe hydrocephalus, cerebral metastases, and preoperative suspicion for medulloblastoma, ependymoma, or dorsal exophytic brainstem glioma (Riva-Cambrin et al. 2009; Foreman et al. 2013). The implication of these results is that many patients who undergo resection of a posterior fossa tumor do not need prophylactic CSF diversion (such as a shunt or endoscopic third

Table 4.1 The Modified Canadian Preoperative Prediction Rule for Hydrocephalus. Total scores of 5 or above are considered high risk for developing hydrocephalus after resection of a posterior fossa brain tumor

Predictor	Score
Age < 2 years	3
Presence of transependymal edema	1
Moderate/severe hydrocephalus	2
Cerebral metastases	3
Preoperative estimated tumor diagnosis	
Medulloblastoma	1
Ependymoma	1
Dorsally exophytic brainstem glioma	1
Total possible	10

ventriculostomy [ETV]) since removal of the tumor restores physiologic CSF circulation and cures the hydrocephalus.

Prompt recognition of hydrocephalus is critical. In a nonverbal patient, the first indication is often that the parents notice lethargy, irritability, nausea, vomiting, or a seizure (Shiminski-Maher and Disabato 1994). In a patient who is able to communicate, headaches are the cardinal symptom. The headaches are worse in a recumbent position at night or on first rising in the morning and improved with sitting or standing throughout the day. Bradycardia probably results from pressure on the dorsal motor nucleus of the vagus nerve in the medulla and on the nucleus ambiguous, which contains preganglionic parasympathetic neurons whose axons travel with the vagus nerve (Siegel et al. 2015). Papilledema is a key physical finding and almost always indicates that intracranial pressure (ICP) is elevated. However, its absence does not exclude elevated ICP as papilledema can take several days to develop (Hayreh and Hayreh 1977; Steffen et al. 1996). In cases where the physical finding of papilledema is in doubt and the rest of the workup is equivocal, evaluation by an ophthalmologist may be necessary. Other physical findings of subacute/chronic hydrocephalus include distended scalp veins, upward gaze palsy from pressure on the midbrain, a bulging fontanelle, and a head circumference that crosses percentiles. In infants with an open fontanelle, the initial symptoms may be more subtle since the open fontanelle initially provides compliance against changes in ICP.

Cerebral imaging often provides the first indication of hydrocephalus in a cancer patient. On CT scans, ventriculomegaly is the obvious sign and, in acute cases, there is a distinct hypodense-blurred margin to the ventricles. The third ventricle is the most compliant; often, the first radiographic sign of increased ventricular pressure is a distended or "rounded" third ventricle. Cortical sulcal effacement may occur with large ICP elevations. T2 MRI sometimes shows hyperintense transependymal CSF flow, which is especially prominent around the ventricular horns. The corpus callosum may be thinned and stretched upward. Quantitative measures include an Evan's ratio (ratio of the bifrontal horn diameter to the intracranial diameter) greater than 1/3 and a temporal horn width greater than 3 mm (Osborn 2013). In practice, the Evan's ratio is more useful for trending ventricle size rather than diagnosing hydrocephalus since the diagnosis is usually apparent from other radiographic features.

Procedures for treating hydrocephalus are among the most established in the field of neurosurgery. They include the external ventricular drain (EVD or "ventriculostomy"), ETV, and shunts. The most rapid method for treating obstructive hydrocephalus is an EVD. This procedure can be done in the operating room or (in emergency circumstances) at the bedside with local anesthesia. It utilizes a frontal approach to target drain placement near the foramen of Monroe. The distal tip of the ventricular drain is tunneled under and out through the skin and connected to a reservoir to collect CSF through the siphon effect of gravity. CSF is drained either by pressure (0–20 cm above the ear of the patient) or by volume (a fixed volume of 10–15 cc per hour). Under or over drainage of CSF should be avoided. The EVD is an ideal choice in several scenarios: acute hydrocephalus to temporize the patient pending operating room availability or pending operative planning for complex tumors, when hydrocephalus is known to be due to a cause that will soon be reversed (such as a fourth ventricle obstructive tumor), or when diagnostic ICP readings are

necessary if the diagnosis of hydrocephalus is unclear but strongly suspected (lumbar puncture opening pressure is not a reliable indicator of ICP in noncommunicating hydrocephalus and may precipitate life-threatening herniation).

Long-term treatments for hydrocephalus are the ETV and ventricular shunts. ETV involves endoscopic navigation via a cranial burr hole to the floor of the third ventricle and fenestration of the third ventricle through the tuber cinerium. This provides an alternate route of egress, as CSF can flow directly from the third ventricle to the pre-pontine cistern after this procedure is performed. The complications of an ETV are primarily periprocedural. Visual obscuration of the endoscopic camera can be caused by even a slight amount of intraventricular blood. Coagulating the bleeding vessel is difficult through a single channel endoscope. Damage to the fornices may occur with devastating clinical outcomes, including the loss of short- and long-term memory. Hypothalamic damage can manifest as diabetes insipidus, amenorrhea, change in appetite, growth hormone disturbance, hypothyroidism, loss of thirst, electrolyte abnormalities, or other components of hypothalamic-pituitary axis disruption (Bouras and Sgouros 2011). Damage to the basilar artery, which has a variable location in relation to the floor of the third ventricle and is sometimes difficult to visualize at the time of puncture, can be fatal. Postoperative complications include CSF leak (3.1%), meningitis (2.3%), hemorrhage (1.7%), subdural CSF collection (1.7%), and seizure (1%) (Sacko et al. 2010). Furthermore, an ETV may obstruct at any time, but the majority of failures occur within the first 6 months after surgery; in patients with aqueductal stenosis or tumors, there may be a second "peak" of failures 3 years after surgery (Lam et al. 2014).

Ventricular shunts are among the most well-established procedures in the field of neurosurgery. They usually utilize either a frontal or occipital entry point to target the lateral ventricle. A peritoneal termination is usually favored (ventriculoperitoneal shunt) with enough catheter length coiled in the abdominal cavity to account for the child's growth, but other sites can be used, including the heart (ventriculoatrial shunt), lung (ventriculopleural shunt), or gallbladder (least commonly used). Non-peritoneal sites are usually used after several prior peritoneal insertions have been performed, after which peritoneal adhesions will develop. CSF diversion from the lumbar spine to the peritoneum (lumboperitoneal shunt) is also an option in patients with communicating hydrocephalus. Shunts carry a high risk of failure. In a study of new shunts placed in pediatric patients, there was a 40% risk of failure in 1 year and a 50% risk of failure in 2 years. Overall, there is a 5% risk of failure per year. Obstruction (31%) and infection (8%) are the most common causes of failure, but after 6 months, the infection risk is miniscule (Drake et al. 1998). Compared to endoscopic techniques, shunts have a low upfront cost, but the cost increases over time. Retrospective data showed that 42% of shunt procedures are shunt revisions. Of the $100 million spent on caring for shunt patients each year, about half is spent on revisions (Bondurant and Jimenez 1995). Shunts also carry a significant risk of seeding tumor at the distal site; a recent meta-analysis showed that 27% of cases of primary brain tumors in children that metastasized were related to shunt placement, with germ cell tumors being the most common shunt-related metastasis (Rickert 2003). Due to the major complications associated with shunt placement in patients with brain tumors, the decision to commit a patient to a shunt requires

Table 4.2 The Endoscopic Third Ventriculostomy (ETV) Success Score. Age score + etiology score + previous shunt score = estimated percentage probability of ETV success at 6 months after surgery

Score	Age	Etiology	Previous Shunt
0	<1 month	Postinfectious	Yes
10	1 month to <6 months		No
20		Myelomeningocele, intraventricular hemorrhage, non-tectal brain tumor	
30	6 months to <1 year	Aqueductal stenosis, tectal tumor, other etiology	
40	1 year to <10 years		
50	≥10 years		

careful consideration. If a shunt is placed, programmable valves susceptible to the effects of the strong magnetic field in an MRI scanner should be avoided, as patients with brain tumors usually require serial MRIs into the foreseeable future. If a programmable shunt valve is used, patients need a skull X-ray (orthogonal to the shunt valve such that its setting can be determined) before and after each MRI to ensure that the valve settings was not inadvertently changed by the strong magnetic waves.

When endoscopic capabilities are available to a neurosurgeon, the decision of whether to perform an ETV or shunt can be aided by the ETV success score (Table 4.2) (Kulkarni et al. 2009). The ETV success score assigns a higher likelihood of ETV success by 6 months for older children, children with brain tumors (especially tumors causing aqueductal stenosis), and patients with no previous shunt. Since an ETV is often technically difficult in newborns and infants, a practical derivation of the ETV success score is that for a child 6 months or older with tumor-related hydrocephalus, an ETV would be expected to have at least 50% success rate by 6 months. Because placing a shunt commits a patient to a high near-term risk of infection and an unremitting risk of obstruction, some practitioners tend to give patients a trial of an ETV before resorting to a shunt. The role of ETV in the management of hydrocephalus is actively being studied. As technological advancements arrive (including flexible endoscopes capable of entering the temporal horns, which will allow near full coagulation of the CSF-producing choroid plexus), ETV will gain a greater role in treating hydrocephalus. A recent study showed that when ETV is combined with partial choroid plexus cauterization, the 6-month success rate is improved from 45% expected from the ETV success score to 59% (Stone and Warf 2014).

Rapid recognition of ETV failure or shunt failure is critical, and if there is any concern for failure, a neurosurgeon must be consulted. The radiographic finding of newly enlarged ventricles in a patient with a shunt or ETV indicates failure; no other workup is necessary. However, many times comparison CT scans are not available or the CT scan is equivocal for ventricular dilatation. Also, patients with shunt failure do not always have dilated ventricles (Sellin et al. 2014). In such cases, one must rely on the clinical history and physical exam to diagnose the failure, or a shunt tap of the reservoir. If an ETV was performed, a CINE MRI scan of the brain can be performed to evaluate for flow through the fenestration in the floor of the third ventricle.

In the uncommon case that a patient presents with acute hydrocephalus due to distal shunt failure (usually symptoms of distal failure are more indolent), a shunt

tap to remove CSF may be lifesaving. When distal failure of a ventriculoperitoneal shunt is suspected, an abdominal CT is often performed to check for a pseudocyst, infection, or very uncommonly tumor seeding at distal end of the shunt. In cases of symptomatic shunt obstruction, the only definitive treatment is emergent shunt revision or temporization with an EVD.

4.4 Posterior Fossa Syndrome

In 1985, Rekate reported several cases of mutism in children after posterior fossa surgery (Rekate et al. 1985). Since then, there have been many reports of mutism following surgery for cerebellar tumors. The posterior fossa syndrome (PFS) includes various specific linguistic, cognitive, and behavioral symptoms that occur after surgery for lesions of the cerebellum. Symptoms typically develop a few days after an otherwise normal postoperative course after resection of a posterior fossa tumor in a child (Wells et al. 2008). (PFS has been reported in adults, but it is uncommon (Marien et al. 2013)) The hallmark symptom of PFS is mutism ("cerebellar mutism"), which is often accompanied by frontal-like behavioral symptoms such as abulia, apathy, or lack of concern (Levisohn et al. 2000). After remission of the mutism, patients continue to be dysarthric; speech is present but impaired by motor difficulty, and this rarely normalizes (Wells et al. 2008). Hence, PFS is sometimes called "mutism and subsequent dysarthria syndrome." Importantly, there are no long tract signs and no supranuclear or cranial nerve palsies (Wells et al. 2008). The presenting symptoms are usually transient and resolve with time, but long-term adverse sequela may include decline of general intelligence and scholarly underachievement (Steinlin et al. 2003; De Smet et al. 2009). PFS was initially reported as "rare," but a recent prospective series of patients undergoing medulloblastoma resection reported an incidence of 24% (Robertson et al. 2006).

The pathophysiology behind PFS has not yet been determined. Two main hypotheses, which are not mutually exclusive, have been advanced to explain the symptoms of PFS: interruption of the dentatothalamocortical pathway due to bilateral damage to the dentate nuclei and cerebellar swelling.

4.4.1 Interruption of the Dentatothalamocortical Pathway as a Possible Cause of PFS

The dentatothalamocortical pathway is the primary outflow tract from the cerebellum. It originates at the dentate nucleus, sends projections through the ipsilateral superior cerebellar peduncle, decussates in the midbrain tegmentum, and synapses in the contralateral ventrolateral thalamus. There, synapses occur with second order neurons that project to the supplementary motor area (Kandel 2013). Myelination is incomplete in children, and this may lead to greater susceptibility to disturbances of this pathway in younger patients (Ildan et al. 2002). Crutchfield observed that lesions along this pathway lead to mutism (Crutchfield et al. 1994): Mutism has been reported after stereotactic lesioning of both dentate nuclei for

treatment of a dyskinetic syndrome (Fraioli and Guidetti 1975). Mutism has been reported after bilateral thalamotomy for Parkinson's disease (Siegfried et al. 1970). Finally, lesions of the supplemental motor area can also cause mutism (Crutchfield et al. 1994). MRI studies of patients with PFS often show evidence of proximal injury along this pathway (Morris et al. 2009). In fact, a recent anatomical study demonstrated in cadavers the high susceptibility of the dentate nuclei to damage during various posterior fossa surgical approaches (Akakin et al. 2014). Sagging of the cerebellum into a postsurgical resection cavity may cause distortions of these tracts as well, exacerbating injury. Crutchfield observed that when lesions occur in this pathway, symptomatic recovery (when it occurs) is usually quite sudden—from mutism to the immediate return of words and sentences (Crutchfield et al. 1994). From this clinical observation, the authors hypothesized that lesions along this pathway cause an inhibition of cortical language centers, and recovery reverses the inhibition. It is possible that the dentatothalamocortical pathway contributes a permissive input to cortical language circuitry that, when restored, allows rapid recuperation of linguistic ability.

4.4.2 Cerebellar Swelling as a Possible Cause of PFS

Ferrante proposed that postoperative vasospasm of cerebellar arteries could cause ischemia and subsequent cerebellar swelling and edema (Ferrante et al. 1990). To date, there have been no clinical studies of cerebral angiography after posterior fossa surgery to evaluate for vasospasm. SPECT studies have shown hypoperfusion of the left cerebellar hemisphere in a patient with PFS, and the abnormality resolved together with the mutism (Clerico et al. 2002; Ersahin et al. 1996). A recent series also showed that 92% of patients with PFS had postoperative cerebellar edema, and the edema often affected the middle and superior cerebellar peduncle (Wells et al. 2010). The same study showed that patients who developed PFS often had tumors that invaded into the brainstem. It is conceivable that the cerebellar swelling may result from retraction and other manipulations during surgery and not necessarily from vasospasm.

Splitting of the vermis, especially the inferior part, has been suggested to cause PFS (Dailey et al. 1995). In fact, the telovelar approach for resecting posterior fossa tumors was developed specifically to avoid splitting the vermis (Mussi and Rhoton 2000). However, this association between splitting the vermis and PFS is questioned by some modern authors (Pitsika and Tsitouras 2013). Robertson showed no correlation between vermis tumor location and the development of PFS (Robertson et al. 2006). They noted that the majority of patients with posterior fossa tumors underwent radical resection through the vermis and did not develop mutism afterward. Hydrocephalus had, at one time, been proposed as the cause of PFS (Ferrante et al. 1990). However, later studies showed no association between hydrocephalus and PFS (Crutchfield et al. 1994; Catsman-Berrevoets and Aarsen 2010).

4.5 Mass Effect/Intracranial Pressure Management

Several temporizing measures can be employed to treat tumor-related mass effect and the associated increase in ICP, pending definitive treatment. The head of the bed should be elevated to 30–45°. This reduces ICP by enhancing venous outflow but, at the same time, slightly diminishes MAP and cerebral perfusion pressure. The head should face straightforward (not turned to one side)—this also enhances venous drainage. The first-line pharmacological agent for the non-emergent treatment of tumor-associated mass effect is steroids, usually dexamethasone (discussed later in this chapter). Hyperventilation lowers ICP by reducing the partial pressure of CO_2, which, by various physiologic mechanisms, reduces cerebral blood volume. Hyperventilation can be used for brief periods of time with a pCO_2 goal of 30–35 but should not be used for long-term treatment of elevated ICP, as it places patients at risk for cerebral ischemia. The mechanism by which mannitol lowers ICP is controversial, but it may involve improved rheology (plasma expansion reduces the hematocrit, which increases cerebral blood outflow) (Burke et al. 1981). Diuresis and osmotic effects are more delayed and take 15–30 min for onset. In urgent situations, 1 g/kg of mannitol can be given intravenously over 30 min. Hypertonic saline also has an osmotic effect, and 3% saline is often given therapeutically through a central line with serum sodium checks performed every 6 h to maintain sodium levels of 145–155.

4.6 Steroids

Glucocorticoids are a well-established treatment for tumor-associated edema. They are frequently used in the following scenarios: (1) to temporize a patient who has a surgically resectable brain tumor while the definitive resection is being planned; (2) to reduce swelling in the perioperative period (after the operation, the dose is tapered down); (3) in combination with certain chemotherapy regimens to reduce edema during administration of the therapeutic agent; (4) to minimize swelling during radiation therapy; and (5) to palliate swelling in the setting of an inoperable brain tumor. Clinically, a response is usually seen within a few hours (because the pharmacologic action of steroids modifies DNA transcription (Ratman et al. 2013)). Thus, steroids are not the first-line agent for a tumor-associated ICP crisis (Alberti et al. 1978). Dexamethasone is the most commonly used glucocorticoid for treating tumor-associated cerebral edema, as its low level of mineralocorticoid activity reduces the potential for fluid retention (Galicich et al. 1961). Dexamethasone may also have a lower risk of infection and cognitive impairment compared to other steroids (Batchelor and DeAngelis 1996). Steroids are effective in treating vasogenic edema, which occurs due to disruption of the blood–brain barrier (Bebawy 2012). In contradistinction, they are not effective in treating cytotoxic edema, which occurs due to cellular swelling (such as the edema that occurs after a stroke).

Steroids are associated with a number of common complications, which usually occur after chronic use. These are three of the most important complications that

are of particular concern: peptic ulcers, steroid myopathy, and adrenal insufficiency (Addison's disease). Peptic ulceration is a well-known complication of steroids, and this is magnified by the intrinsic risk of ulceration posed by a brain tumor ("Cushing's ulcer"). Gastrointestinal prophylaxis, usually by way of a proton pump inhibitor, is the standard of care whenever steroids are administered. Patients affected by steroid myopathy typically develop proximal muscle weakness between the ninth and twelfth weeks of glucocorticoid treatment, with no muscle pain and normal reflexes (Pereira and Freire de Carvalho 2011). Withdrawal or lowering the steroid dose is the treatment, although it is not always possible, and doing so is not always effective in symptom amelioration. Glucocorticoids suppress the HPA axis, and this can lead to secondary adrenal insufficiency, which can manifest as life-threatening hypotension (Krasner 1999). Among brain tumor patients treated with glucocorticoids, 1% will develop secondary adrenal insufficiency (Da Silva and Schiff 2007). Symptoms of adrenal insufficiency (e.g., somnolence, nausea and vomiting, confusion, delirium, abulia, and coma) are prone to manifest during tapering (Gordijn et al. 2012) and are often incorrectly attributed to mass effect. Therefore, a high index of suspicion is necessary, and an ACTH stimulation test should be considered when such symptoms are encountered during glucocorticoid tapering.

4.7 Seizure Management

Anywhere from 30 to 50% of patients with a brain tumor will present initially with a seizure (Perucca 2013). Commonly used antiepileptic medications in children include levetiracetam (Keppra), phenytoin (Dilantin), valproate (Depakote), phenobarbital, carbamazepine (Tegretol), lamotrigine (Lamictal), felbamate (Felbatol), pregabalin (Lyrica), and topiramate (Topomax). The choice of which to use as a long-term first-line agent usually depends on the side effect profile. Evaluation by a pediatric neurologist is advised for all patients who have had a seizure to determine an appropriate antiepileptic regimen.

In the setting of an active seizure, the immediate goal is to stabilize the patient and then seek evaluation by a pediatric neurologist for long-term antiepileptic management. A representative protocol for seizure management is shown in Table 4.3 (Greenberg 2010). When a patient has sustained seizure activity that does not resolve spontaneously, the first-line agent to administer is a benzodiazepine. Several doses of lorazepam (Ativan) can be used in an attempt to break the seizure. Intravenous loading doses of Keppra and/or Dilantin can be then given. If these measures fail, then the next course of action would be an intravenous sedative drip (versed or propofol for example), which will require intubation (Treatment of convulsive status epilepticus. Recommendations of the Epilepsy Foundation of America's Working Group on Status Epilepticus 1993; Sirven and Waterhouse 2003). Even if a sedative drip is not used, the airway should always be monitored closely; sometimes, intubation becomes necessary due to the combined effects of benzodiazepines and mental alteration impairing protection of the airway.

Table 4.3 Representative algorithm for the management of status epilepticus, adapted for pediatric patients, from Greenberg (Greenberg 2010)

1. ABCs, Start O_2, check vitals. Neurological exam. Turn patient to side.
2. Fingerstick glucose, electrolytes, CBC, ABG, LFTs, Mg, Ca, AED levels, EKG
3. Head CT
4. First-line AED: lorazepam (Ativan) 0.1 mg/kg IV @ <2 mg/min
5. Second-line AED (can be given simultaneously with first-line AED or after): phenytoin (Dilantin) 20 mg/kg IV @ 25 mg/min; or fosphenytoin 20 mg PE (phenytoin equivalent)/kg IV @ 75 mg/min.
6. Third-line AED (only 7% chance of stopping a seizure with third-line AEDs can skip to next step): levetiracetam (Keppra) 20 mg/kg IV over 15 min; or sodium valproate 15–30 mg/kg IV (max rate 6 mg/kg/min)
7. If seizures persist for >30 min, intubate in ICU and start versed drip (load 0.2 mg/kg slow IV bolus, maintenance 0.1–0.4 mg/kg/h, maximum 2.0 mg/kg/h) or propofol drip (load 1–2 mg/kg IV @ 10 mg/min, maintenance 2–10 mg/kg/h, maximum 15 mg/kg/h).
8. Evaluation by pediatric neurologist

The perioperative prophylactic use of antiepileptic agents in a patient with a brain tumor who has never had a seizure is controversial. The use of prophylactic antiepileptic agents is well established in the setting of head trauma (Temkin et al. 1990), but the "trauma" that occurs in the surgical resection of brain tumors is different in that it occurs in a controlled environment and locally around the tumor. Conclusions from the trauma literature, therefore, do not generalize to patients with brain tumors. A prospective single-institution randomized trial of 123 adult postsurgical primary brain tumor patients compared seizure-free survival in patients who received either prophylactic phenytoin or no prophylaxis (Wu et al. 2013). However, the trial was terminated because the incidence of clinically significant early seizures was so similar between the arms (3% in the observation group versus 2% in the prophylaxis group) that it was deemed unlikely that a significant difference would ever be found. Nonetheless, the prophylaxis group did experience significantly higher adverse events (18% versus 0%, $p < 0.01$). Another randomized trial of prophylactic antiepileptic agents in 100 adult brain tumor patients (39 of whom had surgery) was also terminated early due to no statistically significant differences in seizure incidence (28% in the observation group versus 24% in the prophylaxis group) (Forsyth et al. 2003). These were trials in adults, and no trials exist in pediatric patients. It remains to be seen whether patients with tumors in certain high-risk locations, such as the temporal lobe, would benefit from perioperative seizure prophylaxis. In practice, there tends to be a very low threshold for starting antiepileptic agents in pediatric patients who have tumors in high-risk locations in whom there is a suspicion for a seizure. Among adult patients with astrocytomas who presented with preoperative seizures, 77% were seizure-free, and 95% had meaningful improvement in seizure control, a year after surgery (Chaichana et al. 2009). The implication is that the actual removal of the tumor itself may be the most important factor in providing long-term seizure control.

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Chemotherapeutic Strategies in Brain Tumors

5

Soumen Khatua

Contents

Abstract

Brain tumors are the commonest solid tumor in children and chemotherapy remains an important treatment as a part of a multidisciplinary approach to treat these malignancies. Over the last two decades, cooperative groups have evaluated clinical trials geared to enhancing therapeutic efficacy and better understanding of the toxicity profile of conventional drugs. Recent molecular characterization of the genomic and epigenomic landscape of these tumors have resulted in an explosion of biological data, providing insights into the signaling pathway and paving the way to target druggable oncogenic drivers. This has ushered in an era of targeted therapy. Even with refinement of these strategies, challenges remain in the inability to comprehensively understand the mechanistic of drug resistance, and suboptimal drug delivery through the blood brain barrier (BBB). The ultimate therapeutic optimism will be achieved, if we are able to combine all these scientific discernments, and be able to depict the most effective chemotherapy and efficient delivery techniques for childhood brain tumors.

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5.1 Introduction

Chemotherapy remains a major therapeutic approach for central nervous system (CNS) tumors in children. It is used in a neoadjuvant or adjuvant setting with local control measures, i.e., surgery and/or radiation. Over the last three decades, cooperative trials including the Pediatric Oncology Group (POG), Children's Cancer Group (CCG), Children's Oncology Group (COG), and Pediatric Brain Tumor Consortium (PBTC) have explored various approaches enabling therapy advances. Examples of cooperative group accomplishments include: evaluating the role of concurrent and adjuvant chemotherapy and radiation for medulloblastoma, neoadjuvant therapy for patients with CNS germ cell tumors, and adjuvant chemotherapy in the management of pediatric high-grade gliomas (HGG), all while defining clinical efficacy and or reducing toxicity (Taylor et al. 2003; Murray et al. 2013; Sposto et al. 1989). Defining optimal chemotherapy regimens, however, remains a challenge due to the diverse biological origins of pediatric brain tumors, the development of drug resistance, and suboptimal drug delivery through the blood brain barrier (BBB). As we gain understanding of oncogenic signaling pathways and molecular drivers, a paradigm shift focused on targeted therapy is evolving. This chapter will discuss the use of conventional chemotherapeutic drugs and their toxicities, mechanistic of drug resistance, endeavors to enhance drug delivery to tumors, and evolving newer targeted therapeutics in childhood brain tumors.

5.2 Chemotherapeutic Drugs

In general, chemotherapeutic drugs are administered systemically through oral or intravenous routes. Locoregional delivery techniques continue to be evaluated in an effort to bypass the BBB to allow increased drug concentration at tumor sites. Chemotherapy may be used as a single agent or in combination therapy with or without radiation. Commonly used drug categories are discussed below.

5.2.1 Nitrosoureas

Nitrosoureas are lipid soluble alkylating agents that acquire good levels in the brain. These drugs alkylate DNA in the guanine, adenine, and cytosine locations, resulting in DNA cross-links that induce single or double stranded breaks resulting in inhibition of DNA repair, RNA synthesis, and division of tumor cells. Lomustine (CCNU) and carmustine (BCNU) are commonly used nitrosoureas. CCNU and BCNU have been evaluated with radiation or in an adjuvant setting and have shown a moderate response for the treatment of HGG or medulloblastoma (Middleton and Margison 2003; Bouffet et al. 1997). BCNU has also been used at higher doses in transplant preparative regimens. The combination therapy of lomustine with procarbazine, 6-thioguanine, and vincristine has been shown

to result in a greater than 50% 5-year event-free survival rate (EFS) in pediatric low-grade gliomas (PLGG) (Ater et al. 2012). Myelosuppression and nephrotoxicity are major side effects of nitrosoureas. Pulmonary fibrosis is also seen with prolonged high-dose exposure to these agents.

5.2.2 Ifosfamide/Cyclophosphamide

Ifosfamide and cyclophosphamide are prodrugs that facilitate the covalent bonding of nucleophilic groups leading to DNA cross-linking that results in inhibition of DNA replication. These drugs have been used for treatment of intracranial germ cell tumors, HGG, medulloblastoma, and recurrent brain tumors. Efficacy of these drugs ranges from stable disease to responses. A regimen using ifosfamide with carboplatin and etoposide showed tumor response in choroid plexus tumors that facilitated a second look surgery (Lafay-Cousin et al. 2010). Common toxicities include nausea, vomiting, myelosuppression, cystitis, nephrotoxicity, and encephalopathy. Infertility with prolonged use of cyclophosphamide is also seen (Adamson et al. 2006; Duffner et al. 1998).

5.2.3 Temozolomide

Temozolomide is a prodrug that induces single-strand breaks and cytotoxicity by methylating DNA mainly at the O6 position of guanine. It does not require enzymatic activation in the liver, but at physiologic pH it spontaneously decomposes to the active metabolite methyltriazenyl carboximide (MTIC). Temozolomide is used in pediatric HGG along with radiation and adjuvant therapy, based on the success of the Stupp trial in adult HGG (Stupp et al. 2002). Variable responses have been noted with the use of temozolomide in recurrent medulloblastoma and PLGG (Cefalo et al. 2014; Khaw et al. 2007). Myelosuppression is the common dose-limiting toxicity (DLT). Additional side effects include nausea, constipation, and serum transaminase elevations.

5.2.4 Platinums

Carboplatin and cisplatin are commonly used drugs in this category. They form intra-strand DNA cross-links by alkylating the N7 position of guanine. These agents are used in various regimens in combination with other drugs. Platinums have also been used as "radiosensitizers," due to their potential role of preventing the development of radiation-resistant clones that allow lethal or sublethal DNA damage repair following radiation (Wilkins et al. 1993). Pre-irradiation cisplatin based chemotherapy in intracranial ependymoma therapy showed benefit in patients who had greater than 90% tumor resection (Garvin et al. 2012). The use of carboplatin with radiation in pineoblastoma showed 5-year OS rate of greater than 80% in patients with near total resection of the tumors (Jakacki et al. 2015). A 5-year EFS rate of

39% ± 4% was noted in patients with progressive LGG when carboplatin was used with vincristine (Ater et al. 2012). Though these drugs have similar CNS penetration, their toxicity profile is different. Cisplatin has increased toxicity including hearing loss, nephrotoxicity, nausea, vomiting, and peripheral neuropathy. It is also known to be associated with delayed and severe emetogenesis. Carboplatin has similar efficacy in brain tumors and the toxicities are different than cisplatin. It is less ototoxic and nephrotoxic but is more myelosuppressive. It is also less emetogenic and induces milder peripheral neuropathy (Reed et al. 1996).

5.2.5 Vinca Alkaloids

Vincristine and vinblastine are the most common drugs used in this category. They exert cytotoxic effects by inhibiting intracellular microtubule assembly by depolymerization of tubulin, which results in mitotic arrest and cell death. Vincristine is used in a combination therapy with radiation in medulloblastoma and PNET tumors (Tarbell et al. 2013; Gnekow et al. 2012). Vinblastine has shown efficacy in progressive PLGG (Bouffet et al. 2012). Constipation and peripheral neuropathy are seen more commonly with vincristine and myelosuppression is usually the dose-limiting toxicity of vinblastine.

5.2.6 Etoposide

Etoposide, an epipodophyllotoxin, results in single and double stranded DNA breaks by stabilization of covalent intermediates formed between the DNA substrate and topoisomerase II. It is used in regimens to treat newly diagnosed medulloblastoma, ependymoma, and germ cell tumors and in a combination therapy for recurrent brain tumors (Gerber et al. 2014; Venkatramani et al. 2013; da Silva et al. 2010). It is usually delivered parenterally, but can be given orally alone or in combination with other drugs (Robison et al. 2014). Its major toxicities include myelosuppression, mucositis, and allergic infusion reactions. Prolonged uses are known to cause secondary leukemia (Duffner et al. 1998).

5.2.6.1 Chemotherapy in Infantile Brain Tumors

Twenty-five percent of childhood brain tumors are diagnosed before 36 months of age. Common tumors at this age include medulloblastoma, atypical teratoid rhabdoid tumor (AT/RT), ependymoma, and choroid plexus tumors. Intensive chemotherapy has been evaluated in these young children, due to the aggressive nature of these tumors and in an effort to avoid or delay radiation. Cooperative group studies completed in the early 1990s that used multiple-drug regimens to avoid irradiation resulted in good initial responses. The “Baby-POG” (POG 8663) trial treated 198 patients younger than 36 months of age, with pre-irradiation cisplatin, etoposide, vincristine, and cyclophosphamide resulted in an overall survival rate of 32% (Duffner et al. 1999). The CCG 921 experience using a “8 drugs in 1” regimen versus a combination of prednisone, vincristine, lomustine in infants with PNET and

ependymoma reported a 3-year PFS rate of 23% (Geyer et al. 1994). Currently an ongoing trial through COG (ACNS 0334) is evaluating the clinical efficacy of adding methotrexate during induction phase to cisplatin, vincristine, etoposide, and cyclophosphamide, followed by high-dose chemotherapy and autologous stem cell rescue in young children with medulloblastoma. This approach is based on the encouraging data from the "Head Start" study that showed a 5-year PFS rate of 52% (Dhall et al. 2008). Though encouraging results are seen in young children with these irradiation avoiding dose-intensive chemotherapeutic strategies, toxicity profile can be deleterious and needs to be closely monitored.

Because of the poor results with chemotherapy alone for infant ependymoma and with refinement of radiation technologies, conformal radiation therapy (CRT) is now delivered to children as young as 12 months for localized ependymoma. For this patient population, chemotherapy is used in an effort to allow complete resection of subtotally resected tumors prior to radiation (Merchant et al. 2009). An ongoing trial through COG (ACNS0831) is evaluating the role of adjuvant chemotherapy following radiation in infratentorial ependymoma, based on responses of these tumors to certain chemotherapy drugs like cisplatin, cyclophosphamide, and etoposide.

5.2.6.2 Resistance to Chemotherapeutic Drugs

Intrinsic or acquired drug resistance induced by environmental, genetic, epigenetic, and kinetic mechanisms undermines clinical efficacy and causes therapeutic failure. Genetic aberrations, induced by various mechanisms such as mutation, deletion, and translocation, are a leading cause of drug resistance (Goldie 2001). Many anticancer drugs can incite these phenomena. A well-known phenomenon seen in CNS pharmacology is the development of multi-drug resistance (MDR) induced by MDR gene-1, which induces transcription of its protein product P-glycoprotein (P-gp). The best studied MDR phenotypes are associated with decreased intracellular drug accumulation and an increase in the plasma membrane ATP-dependent drug efflux pumps, which belong to the family of transporter genes, the ATP-binding cassette (ABC) transporter (Schneider et al. 1999; Leonard et al. 2003). The P-gp and the MDR1 gene are responsible for efflux of toxic compounds from the cells and decreased intracellular accumulation of drugs leading to treatment failure. Expressions of these genes are seen in medulloblastoma, ependymoma, and glioblastoma. This finding suggests the role of de novo or acquired drug resistance in these tumors after exposure to chemotherapeutic agents (Tishler et al. 1992; Chou et al. 1996; Valera et al. 2009). Such phenomenon is seen with anthracyclines, vinblastine, temozolomide, and epipodophyllotoxins. Active efflux of dasatinib an oral BCR/ABL and Src family of tyrosine kinase inhibitor, limits drug delivery to glioblastoma tumor cells and consequently impedes treatment efficacy (Agarwal et al. 2012). In vitro cytotoxicity of melphalan, doxorubicin, mitoxantrone, BCNU, vandetanib, and bortezomib against pediatric HGG and diffuse intrinsic pontine glioma (DIPG) cells were demonstrated (Veringa et al. 2013). Also noted were the presence of P-gp in the tumor vasculature and expression of MRP1, a MRD protein in the glioma cells. These results suggest that pediatric glioma and DIPG tumors per se may not be resistant to chemotherapy, but early treatment failure could be caused by the presence of drug efflux transporters that constitute a first line of drug resistance

located at the BBB, in addition to other resistance mechanisms. Currently clinical trials using inhibitors to P-gp in combination with other drugs are in use to enhance therapeutic efficacy, but translation into clinical success remains suboptimal.

Another important mechanism of CNS drug resistance is the multifaceted role of alkyltransferase and related proteins involved in the DNA repair. O6-methylguanine-DNA-methyltransferase (MGMT) is a unique widely distributed DNA repair protein, that acts by removing alkyl groups located on the O(6)-position of guanine from DNA and restoring its function, thereby impairing clinical efficacy of the alkylating drug (Pegg 2011). It is a major factor in undermining the cytotoxic effects of alkylators such as BCNU, CCNU, and temozolomide. Epigenetic silencing of the MGMT DNA-repair gene by promoter methylation is seen to prolong survival in adult glioblastoma and derive increased benefit from temozolomide (Hegi et al. 2005). Use of AGT inhibitors such as O6-benzylguanine (06-BG) that might overcome this resistance has been used in clinical trials against brain tumors. Though tumor regression was not noted with the use of 06-BG and nitrosoureas, stable disease was noted in adult patients with recurrent malignant gliomas (Quinn et al. 2002). A recently completed phase II study using 06-BG with temozolomide did not achieve the target response rate for activity in pediatric patients with recurrent or progressive HGG and brain stem glioma, which highlights the need to target other drug resistance mechanisms (Warren et al. 2012).

5.2.6.3 Blood Brain Barrier and Mechanisms to Overcome Its Resistance

The BBB, functioning as a physical barrier, comprises a single layer of specialized endothelial cells lining the brain microvesicles and neighboring cells including pericytes, astrocytes, and microglia. These cells form tight junctions, lack fenestrations, and express transport mediators. These highly functional anatomic layers allow specific nutrients to cross into the brain and waste products produced in the brain to move out. This selective process significantly impedes the transfer of small molecule drugs such as carboplatin, vincristine, and cisplatin across the BBB (Pardridge 2007). Attempts to manipulate the BBB do not result in uniform disruption in pediatric brain tumors and do not usually facilitate penetration of biologic agents easily as was believed earlier, thus reinforcing the need to profile strategies to circumvent this anatomical barrier. This effort could achieve higher concentration of drugs locally and potentially ameliorate systemic toxicity. Various methods are used to overcome the impedance of drug delivery through the BBB (Table 5.1).

Intrathecal administration of drugs like Ara-C and mafosfamide has been used in medulloblastoma, pineoblastoma, and recurrent brain tumors to bypass the

Table 5.1 Mechanisms to overcome blood brain barrier resistance

• Intrathecal administration
• Convection enhanced delivery
• Blood Brain Barrier disruption
• Intra-arterial administration
• Intratumoral delivery

BBB. The persistent therapeutic challenge due to nonhomogeneous dispersion is associated with ineffective volume of drug dispersion due to varying molecular weights and diffusivities. In addition, one must consider that follow-up neuropsychological evaluations suggest that these therapeutic regimens are not without consequences to the developing nervous system (Partap et al. 2011; Blaney et al. 2005).

Convection enhanced delivery (CED) is another regional administration method of biologic agents using intracranial catheters connected to target sites with a continuous positive pressure gradient. This provides improved delivery of molecules to the tumor and overcomes limitations of intrathecal chemotherapy. Using this technique, delivery of transferrin-CRM107, a conjugate of human transferrin (Tf) and a genetic mutant of diphtheria toxin (CRM107) to tumoral areas, showed peritumoral toxicity, tumor response, and safety in adults. Studies are in development to translate this application to deliver immunotoxins to tumoral cavities after surgical resection of pediatric brain tumors (Laske et al. 1997). Recently, CED delivery of topotecan has shown responses in glioblastoma and currently is in clinical trial for patients with DIPG (Bruce et al. 2011); however, challenges continue in optimal defining of convective distribution based on volume of agents infused, and concerns of retrograde reflux of drugs which can cause CNS toxicity.

BBB disruption is a method used to enhance drug delivery to tumor sites by using vasoactive substances. This allows therapeutics to enter the brain through this barrier. Bradykinin, a potent vasodilator, and its analogue lobradimil (RMP-7) have been used in clinical trials to enhance and facilitate the entry of carboplatin in treating PNET, HGG, and ependymoma. Though initial response was seen in phase I trials, the use of lobradimil and carboplatin in phase II trials was found to be inactive in childhood HGG and other tumors (Felix et al. 2013; Warren et al. 2006; Ford et al. 1998).

Intra-arterial (IA) delivery of chemotherapeutic agents through cannulated carotid or vertebral artery has been used for over three decades in different malignancies with evidence of higher concentration of infused agents at tumor sites (Hori et al. 1987). This approach has been performed alone or with the use of agents like mannitol, which induce BBB disruption, and enhances delivery of drugs. Phase III studies in adults with glioblastoma using this modality showed increased toxicities and no survival benefit over conventional delivery techniques (Imbesi et al. 2006; Hiesiger et al. 1995). Few studies using IA chemotherapy in children with brain tumors have been performed. Methotrexate or carboplatin delivered through this route in CNS tumors showed objective responses in some patients (Dahlborg et al. 1998). IA use of cisplatin or carboplatin in adults and children with brain stem glioma along with etoposide and intravenous interferon has been studied and indicates good responses in patients with reasonable tolerability (Fujiwara et al. 1994). Another study using IA chemotherapy with disruption of BBB was performed in 27 patients as a salvage therapy for recurrent CNS tumors, which showed some promising survival results and acceptable toxicity data (Jahnke et al. 2008). The use of IA melphalan in DIPG patients is in clinical trial. Though this route of administration sounds promising, to date, no data has

shown benefit over intravenous route. Further studies need to be profiled to conclusively define safety and efficacy of this route of administration of biologic agents in children with brain tumors.

Intratumoral use of chemotherapeutic agents into CNS tumors directly using chemotherapy impregnated wafers, gels, spheres, or injection of agents into the site has been evaluated. In addition to overcoming the BBB, it also helps in reducing dispersion of the drug beyond the desired site. Adult studies using wafers containing BCNU within a biodegradable polymer (Gliadel®) were inserted at the surgical sites in recurrent or newly diagnosed malignant gliomas. This approach showed some efficacy; however, toxicities included cerebrospinal fluid leak, edema, and treatment-related necrosis (Nagpal 2012; Valtonen et al. 1997). To enhance clinical efficacy, use of carmustine wafers followed by chemoradiotherapy with temozolomide in adults with newly diagnosed malignant gliomas showed a modest overall survival of 18 months (Kleinberg et al. 2004). A limitation of the use of these wafers is the restricted diffusion of chemotherapeutic agents across tissues beyond implanted surgical cavity site, undermining its access and clinical efficacy in infiltrative brain tumors. Although the role of these agents has been demonstrated in adults, no study has shown convincing safety and efficacy of its use in childhood brain tumors.

5.2.6.4 Targeted Chemotherapy

Over the last two decades, great strides have been made in the discernment of the molecular biology of childhood brain tumors, enabling us to better understand the oncogenic drivers that induce angiogenesis, tumor invasion, and migration. This knowledge has led to the development of targeted therapeutic trials (Fig. 5.1, Table 5.2). Key receptor tyrosine kinases include epidermal growth factor receptor (EGFR), platelet derived growth factor receptor (PDGFR), and vascular endothelial growth factor receptor (VEGFR). Major signaling pathways involved in tumorigenesis of childhood CNS tumors are phosphatidylinositol 3-kinase/Akt/mTOR, Ras-mitogen-activated protein kinase, and the Sonic Hedgehog (SHH) (de Bont et al. 2008; Brantley and Benveniste 2008; Lo 2010; Nageswara Rao et al. 2012).

Nimotuzumb, an IgG1 antibody that targets the EGFR, has been used in pediatric HGG, which was tolerated well and yielded a 2-year survival rate of 54.2% (Cabanas et al. 2013). Erlotinib a potent and selective oral inhibitor of EGFR and HER2, used along with local radiotherapy in newly diagnosed pediatric HGG showed acceptable toxicity but did not change the poor outcome of these tumors (Qaddoumi et al. 2014). Gefitinib another oral inhibitor of EGFR when used along with radiotherapy in newly diagnosed DIPG showed tolerability and an overall survival rate of 12 months, no better than historical controls (Pollack et al. 2011). PDGFR alpha has been shown to be expressed in HGG and medulloblastoma and remains an attractive target. Imatinib is a small molecule inhibitor of the kit oncogene and PDGFR. Though it has been used in clinical trials, its poor outcome due to its limited CNS penetration has undermined therapeutic efficacy and also showed risk of intratumoral hemorrhage (Baruchel et al. 2009). Dasatinib, a potent PDGFR inhibitor with better CNS penetration, is now being developed in clinical trials (Broniscer et al. 2013).

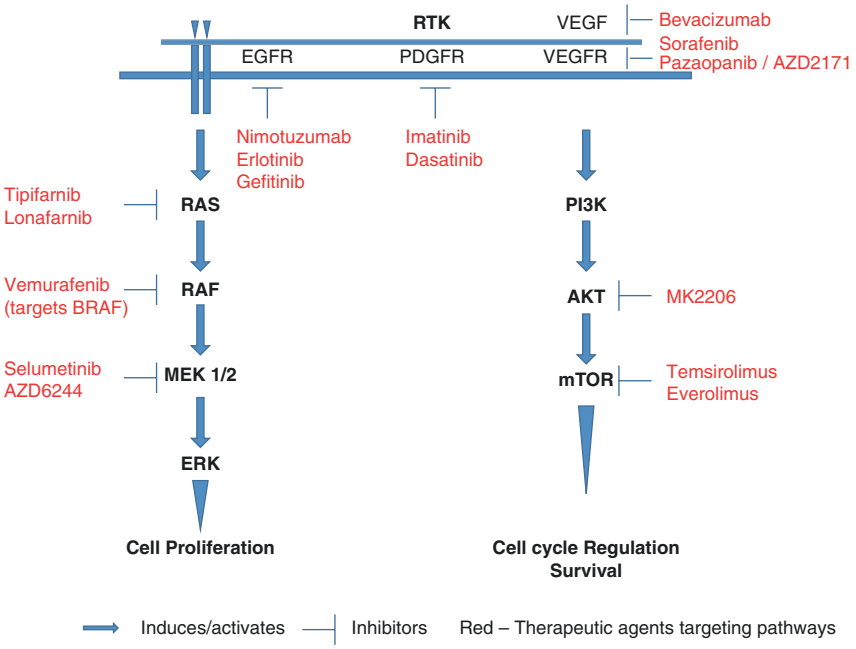

Fig. 5.1 Cell signaling pathways and therapeutic targets. *AKT* protein kinase B, *EGFR* epidermal growth factor receptor, *ERK* extracellular signal-regulated kinase, *MEK* mitogen-activated protein kinase, *mTOR* mammalian target of rapamycin, *PDGFR* platelet derived growth factor receptor, *PI3K* phosphatidylinositol 3-kinase, *RAS* Ras proteins, *RTK* receptor tyrosine kinase

Table 5.2 Targeted therapy in pediatric CNS tumors

Target	Drug
EGFR	Nimotuzumab, erlotinib, gefitinib
PDGFR	Imatinib, dasatinib
PI3K/AKT/mTOR pathway	MK2206, everolimus, temsirolimus
Ras/Raf/MEK/ERK pathway	Tipifarnib, lonafarnib, AZD6244
Angiogenesis/VEGF pathway	Bevacizumab, pazopanib
Histone deacetylase	Suberoylanilide hydroxamic acid, valproic acid
Sonic Hedgehog pathway	GDC0449, LDE225
BRAF mutation	Vemurafenib

The PI3K/Akt/mTOR pathway is well known to drive downstream signaling in various childhood brain tumors. MK2206, an allosteric inhibitor of Akt, is currently in clinical trials in recurrent/refractory gliomas, based on its efficacy in malignant gliomas, when used with other synergistic therapies (Cheng et al. 2012). mTOR is a downstream major gatekeeper receiving signals from Ras/Raf/MAPK/ERK and the PI3K/Akt/mTOR pathway, inducing oncogenic events. Drugs like everolimus

and temsirolimus which inhibit this key mTOR molecule are being evaluated in clinical trials based on preliminary studies demonstrating efficacy in brain tumors (Cappellano et al. 2013; Piha-Paul et al. 2014).

Ras is an effector molecule in the Ras-mitogen-activated protein kinase pathway. Activation of growth factor receptors leads to farnesylation of the Ras molecule by farnesyl transferase (FT), which induces its activation. Blocking this phenomenon using FT inhibitors tipifarnib and lonafarnib has been studied. Though these drugs were well tolerated, no clinical benefit was seen as monotherapy in recurrent CNS tumors thus far (Haas-Kogan et al. 2011; Kieran et al. 2007). Selumetinib (AZD6244), a mitogen-activated protein kinase inhibitor against MEK1/2, showed activity against juvenile pilocytic astrocytoma xenografts in preclinical testing (Kolb et al. 2010). Based on this data, the PBTC is performing a clinical trial using AZD6244 in recurrent refractory LGG (ClinicalTrials.gov Identifiers NCT01386450 and NCT01089101). The BRAF V600E mutation seen in pediatric gliomas results in constitutive activation of the BRAF kinase with subsequent activation of the MAPK/ERK pathway (Schindler et al. 2011). To date, few reports of response to pediatric LGG and HGG to vemurafenib, a BRAF inhibitor, have been published (Skrypek et al. 2014; Robinson et al. 2014).

Angiogenic inhibitors targeting the VEGF are now well established. Bevacizumab, a humanized monoclonal antibody that is highly specific for all VEGF isoforms, is now being used in recurrent pediatric brain and optic pathway tumors with disease response and variable toxicities (Gururangan et al. 2014; Avery et al. 2014). Small molecule inhibitors of the VEGF pathway, pazopanib and AZD2171, along with multikinase inhibitor (MTKI), sorafenib, that has angiogenic properties are in various phase I/II pediatric clinical trials.

Activation of the Sonic Hedgehog (SHH) pathway is identified in nearly 25% of medulloblastoma. SHH ligand binding to transmembrane protein PTCH leads to disinhibitory effects of the *PTCH* gene. This results in constitutive activation of the transmembrane protein SMO, which in turn activates downstream glioma associated oncogene homolog 1 proteins, resulting in tumorigenesis. Preclinical data and clinical responses in patients led to the translation of specific SMO inhibitors vismodegib (GDC-0449) and LDE225 into clinical trials. Preliminary data showed that these drugs were well tolerated with some antitumor activity (Gajjar et al. 2010; Geoerger et al. 2012).

With the emerging era of epigenetics in brain tumors, the role of histone acetylation and deacetylation (HDAC) in chromatin remodeling and oncogenesis is gaining importance. HDAC inhibitors, vorinostat and valproic acid, are associated with variable responses in recurrent CNS tumors (Hummel et al. 2013; Felix et al. 2013). Valproic acid was well tolerated in heavily pretreated pediatric patients with HGG (Wolff et al. 2008).

Though explosion in the data from the molecular and genomic research on childhood brain tumors continues to temper enthusiasm, challenges remain in keeping pace with designing optimal trials with meaningful therapeutic benefit against these formidable malignancies.

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Part II

Embryonal Brain Tumors

Medulloblastoma

6

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Contents

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Abstract

The current survival outcome for children with medulloblastoma is a remarkable testimony for the multidisciplinary approach in the management of pediatric brain tumors. Children older than 3 years of age who have a less than 1.5 cm^2 residual tumor after resection with no evidence of dissemination (M0) are classified as having standard-risk disease, while those with a larger tumor bed residual or with tumor dissemination are classified as having high-risk disease. Treatment for these patients includes craniospinal irradiation followed by a boost to the posterior fossa or posterior fossa tumor bed as well as cisplatin-based chemotherapy. For children younger than 3 years, surgery followed by chemotherapy is the most common treatment approach with or without primary site radiotherapy (RT). Currently, four molecular subtypes of medulloblastoma with prognostic implications have been identified. Current protocols are examining de-escalation of treatment for some children with Wnt-pathway tumors with more aggressive therapy for Group 3 and 4 subtypes.

6.1 Epidemiology

Medulloblastoma is an embryonal tumor of the cerebellum and accounts for about 20% of brain and 40% of all posterior fossa tumors in children. In the United States, there are approximately 400 cases per year, with a peak age of incidence between 5 and 6 years (Gurney et al. 1996). More than 70% are seen in children younger than 10 years while about 20% of cases are seen in those younger than 2 years of age. Medulloblastoma is more common in males and accounts for two-thirds of all cases.

6.2 Predisposing Factors

A previous report showed that 6.4% of patients with medulloblastoma have an associated genetic syndrome or congenital anomaly (Evans et al. 1993). Gorlin syndrome or basal cell nevus syndrome, a rare autosomal dominant condition characterized by multiple basal cell carcinomas, odontogenic keratocysts, and ocular abnormalities, has been associated with desmoplastic medulloblastoma. Type 2 Turcot syndrome has been associated with medulloblastoma and familial adenomatous polyposis (Paraf et al. 1997).

6.3 Presenting Symptoms

Children can present with a constellation of signs and symptoms related to cerebellar involvement, hydrocephalus (from obstruction of the fourth ventricle), invasion of the brainstem (direct extension), and tumor dissemination. Gait abnormalities, truncal unsteadiness, and difficulty with fine motor coordination are often seen.

Patients with hydrocephalus may present with morning emesis and headaches, while those with brainstem involvement can present with double vision. Patients with spinal dissemination can present with back pain, and rarely cord compression can be a presenting sign.

6.4 Radiographic and Pathologic Findings

6.4.1 Radiology

The classic location of a medulloblastoma is midline and involves the vermis. However, in older children and adolescents, medulloblastoma may present as a well-lateralized lesion or as a tumor in the cerebellopontine angle. Some have suggested that the different molecular subtypes of medulloblastoma may have tumors whose origins are in certain locations in the posterior fossa. In one report, the wingless (Wnt) tumors were likely to be midline and infiltrative of the brainstem while the sonic hedgehog (SHH) pathway tumors were more likely to be in the cerebellar hemisphere (Gibson et al. 2010). Others have not seen any correlation with molecular subtype and tumor location (Teo et al. 2013).

6.4.2 Pathology

The different subtypes of medulloblastoma have traditionally included the classic, nodular desmoplastic, and large cell anaplastic histologies. The nodular desmoplastic histology has been reported to be the most common subtype in infants and has a more favorable outcome. The large cell, anaplastic subtype has the worst prognosis, while the classic subtype, which is the most common, has an intermediate prognosis. More recently, medulloblastoma has been subdivided into four molecular subtypes: Wnt, SHH, Group 3, and Group 4 (Northcott et al. 2011). Medulloblastoma activated through the Wnt signaling pathway has the best outcome with more than 90% survival; it comprises only 10% of all medulloblastoma. It is typically seen in older children and young adults and tends to be the classic histology. Most of these tumors have mutations in the *CTNNB1* gene. Wnt medulloblastoma is associated with complete or partial loss of chromosome 6, while the other subtypes are most frequently associated with alterations in chromosome 17. The SHH subtype has a bimodal peak in infancy and in late childhood and early adulthood. It comprises 30% of all medulloblastoma and has an intermediate prognosis. The *PTCH1* tumor suppressor gene is most commonly mutated but other genes such as *SMO and SUFU* may also be mutated. The desmoplastic histology tends to be of SHH subtype. Group 3 tumors have the worst outcome and comprise 25% of all medulloblastoma. They have the highest incidence of tumor dissemination at initial diagnosis and typically occur in infants and young children. Boys are affected more than girls. Recurrent amplification of *MYC* has been identified. Group 4 tumors comprise the remaining medulloblastomas and also have an intermediate prognosis. They tend to

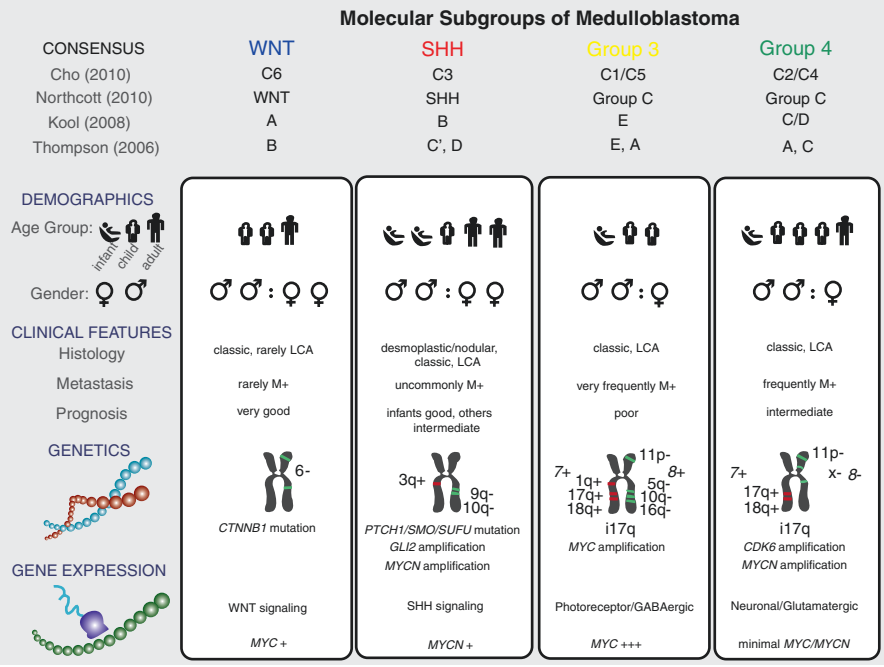

Fig. 6.1 Molecular subgroups of medulloblastoma. Four molecular subgroups have been identified in children. The patient demographic and tumor characteristics are presented (Taylor et al. 2012)

occur in boys and seen in children of all ages. Isochromosome 17q has been described more often in Group 4 tumors. Figure 6.1 shows the different molecular subtypes and associated demographic, clinical, and genetic features (Taylor et al. 2012). Significant differences in patterns of failure within the molecular subtypes are evident with local relapse within the posterior fossa most frequent for patients with SHH while metastatic relapse seems to be more frequent in the Group 3 and 4 tumors (Ramaswamy et al. 2013).

6.5 Workup

Children with medulloblastoma typically will have a magnetic resonance imaging (MRI) scan of the brain prior to resection and diagnosis. Postoperatively, patients undergo a MRI of the brain within 24–48 h after surgery to determine the amount of residual tumor. About 2 weeks after surgery, children with medulloblastoma should have a lumbar tap to rule out malignant cells in the cerebrospinal fluid and a MRI of the entire spine to evaluate for leptomeningeal dissemination. In one study looking at detection of malignant cells, the lumbar tap was more sensitive than ventricular shunt taps (Gajjar et al. 1999). Both lumbar tap and MRI of spine are complementary; if either exam is not done, leptomeningeal dissemination can be missed in about 15% of cases (Fouladi et al. 1999). Bone scan and bone marrow biopsy are

Table 6.1 Modified Chang staging system for medulloblastoma

Stage	
M0	No leptomeningeal spread
M1	Malignant cells on cerebrospinal fluid from a lumbar tap
M2	Gross leptomeningeal spread in the brain
M3	Gross leptomeningeal spread in the spinal axis
M4	Extraneural metastasis

only performed nowadays in the rare case of bone pain or abnormal blood count in the setting of leptomeningeal dissemination. Extraneural metastasis is uncommon at initial diagnosis and seen in ≤2% of cases (Mazloom et al. 2010).

The modified Chang staging system is used to note the absence or presence and degree of leptomeningeal spread (Table 6.1) (Chang et al. 1969). In general, about two-thirds of patients will have M0 disease. M1 disease is designated in the presence of malignant cytology from a lumbar tap without MRI evidence of gross tumor spread. Patients with M2 and M3 disease traditionally have worse outcome compared to M1 disease (Harisiadis and Chang 1977).

Prior to the age of molecular subtyping of medulloblastoma, the two most important prognostic factors have been the amount of residual in the tumor bed and the M status (Zeltzer et al. 1999). Patients with disease limited to the primary site with less than 1.5 cm^2 residual and no dissemination (M0) are classified as having standard- or average-risk disease. Patients with either more than 1.5 cm^2 residual or leptomeningeal or extraneural spread (M1–M4) are classified as having high-risk disease.

6.6 Acute Management

Hydrocephalus leading to increased intracranial pressure can be managed by an extraventricular drain, ventriculostomy, or a shunt. In general, most patients with posterior fossa tumors will have an intraoperative extraventricular drain (EVD) if there is significant pre-resection hydrocephalus. The EVD is weaned postoperatively and removed if tolerated. If persistent hydrocephalus remains with inability to wean EVD, a CSF shunt or endoscopic third ventriculostomy is performed (Lin and Riva-Cambrin 2015). The most common type of shunt used is the ventriculoperitoneal shunt. Possible complications of a shunt include malfunction and obstruction, infection, and the rare case of extraneural metastasis.

6.7 Treatment

6.7.1 Surgery

In addition to diversion of CSF to manage hydrocephalus, resection of the primary tumor is an important component of treatment. Maximal safe resection is performed with little or no residual as possible. As stated above, a tumor residual of more than

1.5 cm^2 has been associated with a worse survival outcome (Zeltzer et al. 1999). Possible complications of surgery include aseptic meningitis, cervical spine instability, and posterior fossa syndrome. The posterior fossa or cerebellar mutism syndrome is classically seen at 1 or 2 days after surgery and can be accompanied by personality changes, emotional lability, decreased initiation of voluntary movements, and disturbance of ingestion (Pollack 1997). Although it can be associated with surgery for nonneoplastic and neoplastic conditions, children with medulloblastoma are the most commonly affected, and mutism usually lasts for 2–4 months with residual dysarthria. Approximately 8–25% of children with medulloblastoma develop posterior fossa syndrome (Doxey et al. 1999). The underlying cause is still not known, but involvement of the dentate nucleus, bilateral interruption of the dentothalamocortical pathway, and injury to median structures of the cerebellum have been postulated as a possible explanation for this condition. There is some evidence that the incidence of posterior fossa syndrome is increasing, proportional to the increase in more aggressive surgery (Korah et al. 2010).

6.7.2 Radiotherapy

Medulloblastoma is a radiosensitive tumor. The mean inactivation dose and surviving fraction after 2 Gy have been reported to be 1.43 Gy and 27% (Deschavanne and Fertil 1996). RT is a very important component of treatment in the curative management of these patients. Radiotherapy dose, volume, and sequencing of RT and chemotherapy have all been implicated as factors which can influence outcome and are discussed below (Castro-Vita et al. 1980; Garton et al. 1990; Tarbell et al. 1991; Jenkin 1969; Paulino 1997). RT technique is likewise important (Carrie et al. 1992, 1999). It has been previously shown that inadequate coverage of the cribriform plate can lead to a higher risk of subfrontal recurrences (Jereb et al. 1984). Protraction of RT treatment duration for more than 45–50 days has been associated with worse posterior fossa control and survival (Paulino et al. 2003; del Charco et al. 1998; Taylor et al. 2004).

6.7.2.1 Radiotherapy Volume

Historically, the greatest advance in the curative management of medulloblastoma has been the use of craniospinal irradiation (CSI). The landmark Paterson and Farr study established that CSI is the appropriate RT treatment for medulloblastoma (Paterson and Farr 1953). The use of less extensive RT fields (posterior fossa only, posterior fossa and spinal RT) has been associated with worse outcome (Castro-Vita et al. 1980; Jenkin 1969). In the era of chemotherapy, the French M4 protocol utilized chemotherapy to decrease the RT volume to just the posterior fossa and spine (Bouffet et al. 1992). Of 16 children treated, only 3 (18%) were alive and disease-free at a mean follow-up of 6 years. The most common site of relapse was in the supratentorial brain, the site which was not irradiated, accounting for 69% of relapses. Currently, the only children not treated with CSI are the very young patients (<3 years old) where CSI may result in severe neurocognitive and musculoskeletal sequelae (Ashley et al. 2012; Duffner et al. 1993).

After CSI, additional radiation is given to the posterior fossa where the original tumor is located. Historically, the entire posterior fossa (PF) received the boost RT dose. Treatment fields were largely based on using bony landmarks in the skull. Because of advances in imaging and RT treatment delivery and concerns regarding toxicity of RT, some investigators have boosted only the tumor bed and any residual tumor with a safety margin. Current available data indicate that isolated non-tumor bed PF failures occur in <5% of patients when only the tumor bed receives the boost RT dose (Merchant et al. 2008; Paulino et al. 2011; Douglas et al. 2004; Wolden et al. 2003). A study from Toronto suggests that this approach improves neurocognitive outcome compared to treatment of the entire posterior fossa (Moxon-Emre et al. 2014). The recently closed Children's Oncology Group (COG) ACNS0031 protocol randomized standard-risk patients to PF boost vs. tumor bed boost (tumor bed with a 1.5 cm safety margin for clinical target volume or CTV); the preliminary results of this phase III study showed that the entire posterior fossa does not need to receive the boost dose (Michalski et al. 2016).

6.7.2.2 Radiotherapy Dose

Prior to the era of routine use of chemotherapy, the standard CSI dose was approximately 36 Gy in 20 fractions. In a Children's Cancer Group study, Packer and colleagues reported a 79% 5-year progression-free survival in standard-risk medulloblastoma with a 23.4 Gy CSI dose followed by a boost with vincristine, lomustine, and cisplatin (Packer et al. 1999). A subsequent COG study randomizing standard-risk patients to two different chemotherapy regimens confirmed the efficacy of 23.4 Gy CSI dose (Packer et al. 2006). Currently, the standard CSI dose for standard-risk patients is 23.4 Gy in 13 fractions followed by a RT boost in conjunction with chemotherapy. When delivering 23.4 Gy CSI for standard-risk patients, RT is started within 30 days of the surgery. The SIOP II study showed an inferior survival outcome for 23.4 Gy CSI patients when RT was delayed, by giving initial chemotherapy; however, one of the criticisms of the study is the possible use of a less efficient chemotherapy regimen (Bailey et al. 1995). The SFOP M7 protocol delivered pre-RT chemotherapy with a reduced supratentorial dose of 27 Gy; RT was delivered at 7 weeks after surgery (Gentet et al. 1995). The 5-year EFS was 74% for patients with macroscopically complete or subtotal excision and M0 disease. The MSFOP 93 nonrandomized protocol delivered pre-RT chemotherapy with RT delivered at the latest 15 weeks after surgery (Oyharcabal-Bourden et al. 2005). RT dose was 25 Gy CSI and 55 Gy PF RT and showed a 5-year recurrence-free survival rate of 64.8%. Although the latter 2 studies suggest that RT can be delayed, the best outcomes that have been reported using a reduced CSI dose with chemotherapy have delivered upfront RT (Packer et al. 1999, 2006).

Some groups have recommended a 36 Gy CSI dose for standard-risk anaplastic medulloblastoma because of their inferior prognosis compared to other histologic subtypes. Currently, the COG ACNS0332 guidelines recommend the use of 36 Gy CSI even for M0 anaplastic medulloblastoma, and this subgroup is currently excluded from the ongoing European PNET5 protocol for standard-risk patients (Chintagumpala et al. 2016).

Studies using a 23.4 Gy CSI dose have shown neurocognitive deficits especially in children younger than 7 years of age (Ris et al. 2001, 2013). Pilot studies from Children's Hospital of Philadelphia and Indiana University have conflicting results on efficacy and neurocognitive outcome in young children treated with 18 Gy CSI (Goldwein et al. 1996; Jakacki et al. 2004). The COG ACS0031 protocol randomized standard-risk children 3–7 years old to either 18 Gy or 23.4 Gy CSI dose followed by a boost with chemotherapy; the preliminary results inidicate an inferior event-free survival outcome for those treated with 18 Gy CSI (Michalski et al. 2016).

For patients with high-risk disease, CSI doses have typically ranged from 36 to 39.6 Gy in 20 to 22 fractions followed by a posterior fossa/tumor bed boost. Results from the POG 9031 study indicate that the use of this dose regimen with chemotherapy was associated with a favorable 5-year event-free survival (Tarbell et al. 2013). POG 9031 looked at the sequencing of chemotherapy and RT with patients either receiving 3 cycles of cisplatin and etoposide before RT or after RT. Both arms of the study received consolidative vincristine and cyclophosphamide. The 5-year event-free survival (EFS) rates were 66% for chemotherapy first arm and 70% for RT first arm ($p = 0.54$). The HIT '91 study showed no difference in EFS or OS among M2 and M3 patients receiving maintenance chemotherapy (RT first) and sandwich chemotherapy (chemotherapy first) (Kortmann 2014; Kortmann et al. 2000). The CSI dose given in this study was 35.2 Gy in 22 fractions with a boost to the posterior fossa for a total dose of 55.2 Gy. In patients with M0 or M1 disease, patients who had RT first had a better EFS and OS. The SIOP/UKCCSG PNET3 tested pre-RT chemotherapy including vincristine, etoposide, carboplatin, and cyclophosphamide followed by 35 Gy CSI and 55 Gy total PF dose for M2–M3 patients with a 5-year PFS of 35% (Taylor et al. 2005).

Some studies have looked at using altered fractionation RT to increase dose for better tumor control. The HIT-SIOP PNET 4 Trial randomized patients with standard-risk medulloblastoma to 23.4 Gy CSI and 54 Gy posterior fossa (1.8 Gy/fraction) over 30 fractions in 6 weeks to 36 Gy CSI, 60 Gy to posterior fossa and 68 Gy to tumor bed (1.0 Gy/fraction given twice daily) over 68 fractions in 6.8 weeks. Both arms included vincristine during RT followed by post-RT 8 cycles of vincristine, lomustine, and cisplatin (Lannering et al. 2012). The 5-year EFS and OS rates were the same in both arms. The PNET 4 showed that hyperfractionation was associated with a better executive function with a trend for better verbal outcomes in the children less than 8 years at the time of RT (Kennedy et al. 2014; Camara-Costa et al. 2015). A study from Mumbai utilizing hyperfractionated RT showed no significant decline in all tested domains of cognitive function in 20 children with a 2-year follow-up (Gupta et al. 2012). Regarding the high-risk group, the Milan strategy for disseminated medulloblastoma included pre-RT chemotherapy, a hyperfractionated accelerated radiotherapy (HART) regimen of 39 Gy CSI (1.3 Gy/fraction twice daily) followed a posterior fossa boost to a total dose of 60 Gy (1.5 Gy/fraction twice daily) and 2 myeloablative courses for persistent disseminated disease before HART (Gandola et al. 2009). The 5-year event-free and overall survival rates were 70 and 73%, comparable to results of the POG 9031 protocol discussed above. To date, the results of altered fractionation RT to increase dose have not shown any significant survival benefit over conventional fractionation.

Table 6.2 outlines some of the major trials performed in standard- and high-risk childhood medulloblastoma (Packer et al. 2006; Bailey et al. 1995; Tarbell et al. 2013; Lannering et al. 2012; von Hoff et al. 2009; Taylor et al. 2003; Gajjar et al. 2006).

Table 6.2 Selected studies in standard- and high-risk medulloblastoma

Study (first author, reference)	Number of patients	Treatment	Outcome
SIOP II (Bailey et al. 1995)	364 SR	Pre-RT chemotherapy vs. upfront RT followed by chemotherapy. Standard-risk randomized to 25 vs. 35 Gy CSI, both followed by boost to total dose of 55Gy	Worse outcome in standard-risk patients receiving pre-RT chemotherapy and 25 Gy CSI compared to patients receiving upfront RT or pre-RT chemotherapy and 35 Gy CSI
HIT '91 (von Hoff et al. 2009)	137 SR HR	Pre-RT chemotherapy vs. upfront RT followed by chemotherapy. CSI dose 35.2 Gy with total dose of 55.2 Gy to PF	Upfront RT better than pre-RT chemotherapy with 10-year OS (91% vs. 62%, $p = 0.001$) for M0 and (70% vs. 31%) for M1 patients. No difference in OS for M2 and M3 patients
SJMB-96 (Gajjar et al. 2006)	134 SR HR	23.4 Gy CSI for standard and 36–39.6 Gy CSI for high risk followed by boost and four cycles of cyclophosphamide-based dose-intensive chemotherapy	5-year OS/EFS were 85%/83% and 70%/70% for standard- and high-risk groups
PNET-3/SIOP III (Taylor et al. 2003)	179 SR HR (M1 only)	RT alone (35 Gy CSI and 55 Gy total to PF) with or without chemotherapy	Improvement in 5-year EFS (74.2% vs. 59.8%, $p = 0.036$) but not 5-year OS (76.7% vs. 64.9%, p = n.s.) with chemotherapy
COG AA9961 (Packer et al. 2006)	379 SR	23.4 Gy CSI and 55.8 Gy total dose to PF followed by randomization to 2 chemotherapy regimens (VCR, CDDP, CCNU vs. VCR, CDDP, CPM)	No difference in 5-year PFS (82% vs. 80%) or OS (87% vs. 85%)
POG 9031 (Tarbell et al. 2013)	224 HR	Pre-RT chemotherapy vs. Upfront RT. 35.2–40 Gy CSI and 53.2–54 Gy total dose to PF	No difference in 5-year EFS (66% vs. 70%) or OS (73.1% vs. 76.1%)
MSFOP 98 (Carrie et al. 2009)	48 SR	Hyperfractionated RT (36 Gy CSI, 60 Gy PF, 68 Gy tumor bed at 1 Gy BID). No chemotherapy	3-year OS and PFS were 89% and 81%
HIT-SIOP PNET 4 (Lannering et al. 2012)	340 SR	Hyperfractionated (36 Gy CSI, 60 Gy PF, 68 Gy tumor bed at 1 Gy BID) vs. conventional RT (23.4 Gy CSI, 54 Gy PF at 1.8 Gy daily) followed by chemotherapy	No difference in 5-year EFS (78% vs. 77%) and OS (85% vs. 87%)

SR standard-risk, *HR* high-risk, *CSI* craniospinal irradiation, *RT* radiotherapy, *OS* overall survival, *EFS* event-free survival, *PFS* progression-free survival, *PF* posterior fossa

6.7.3 Chemotherapy

Most patients with medulloblastoma will receive chemotherapy. In infants, chemotherapy is used to delay the institution of RT; in older children, chemotherapy is used to lower the CSI dose in standard-risk patients and improve survival outcome in high-risk patients. Earlier randomized trials have not demonstrated an improvement in survival outcome in patients treated with chemotherapy; however on subset analysis, there is a suggestion that patient with high-risk tumors may have a benefit for the addition of chemotherapy (Krischer et al. 1991; Evans et al. 1990; Tait et al. 1990).

A latter study, SIOP/UKCCSG PNET-3, randomized patients to 35 Gy CSI with 20 Gy posterior fossa boost or chemotherapy followed by the same RT (Taylor et al. 2003). Chemotherapy consisted of vincristine, etoposide, carboplatin, and cyclophosphamide. The 3- and 5-year EFS were 78.5% and 74.2% vs. 64.8% and 59.8% for chemo + RT and RT alone, respectively. There was no statistically significant difference in 3- or 5-year OS.

Although currently, the use of chemotherapy in standard-risk medulloblastoma is considered "standard of care" practice, there is some evidence that RT alone given in a hyperfractionated regimen may give the same survival outcome with acceptable neurotoxicity. The French M-SFOP 98 protocol delivered hyperfractionated RT to 36 Gy in 36 fractions followed by a conformal tumor bed boost to a total dose of 68 Gy in 68 fractions (1 Gy BID) (Carrie et al. 2009). The 3-year progression-free and OS rates were 81% and 89%, respectively. Of the 48 patients <19 years of age, 22 were evaluable and there was no decrease in IQ scores during the first 2 years of follow-up.

6.8 Infant Medulloblastoma

Unfortunately about 20% of medulloblastoma occur in the very young. The survival outcomes of these children have traditionally been poor because of the omission or delay in delivering CSI. Radiotherapy to the craniospinal axis in the very young has been associated with severe cognitive dysfunction and musculoskeletal abnormalities (Johnston et al. 2009; Walter et al. 1999). For many years, the standard approach was to perform resection followed by chemotherapy; CSI was delayed until the child had turned 3 years. The Baby POG study showed a 1- and 2-year progression-free survival (PFS) of 42% and 34% with this approach (Duffner et al. 1993). One of the major advances in infant medulloblastoma has been the discovery that the completely resected desmoplastic subtype without evidence of leptomeningeal spread (M0) has a favorable outcome (Rutkowski et al. 2005; von Bueren et al. 2011). The HIT-SKK '92 trial delivered chemotherapy after resection to 43 children younger than 3 years of age; the regimen included intravenous cyclophosphamide, vincristine, methotrexate, carboplatin and etoposide and intraventricular methotrexate (Rutkowski et al. 2005). RT was not part of the treatment regimen. The 5-year PFS for patients with completely resected, M0 tumors and desmoplastic tumors

were 82% and 85%, respectively. The HIT-SKK '2000 trial showed the excellent outcome of this approach for tumors with desmoplastic histology and medulloblastoma with extensive nodularity (von Bueren et al. 2011). This study also showed that local recurrence was the predominant pattern of failure for infants with M0 disease. Building on this knowledge, the COG P9934 study routinely delivered local RT to the primary site in M0 patients (Ashley et al. 2012). The results showed that the local control and EFS were better with conformal RT compared to a previous infant medulloblastoma study, POG9233, which delivered only adjuvant chemotherapy (Geyer et al. 2005). However, an analysis of children with non-desmoplastic histology did not reveal any improvement in EFS with conformal RT (23% vs. 14%, $p = 0.92$). The BB SFOP French protocol enrolled 79 patients (15 with metastases) who were treated with postoperative chemotherapy, with RT reserved at progression. The 5-year OS was 73% for no local residual, 41% for patients with local residual disease, and 13% for metastatic patients; the 5-year PFS was 41% for no local residual compared to 0% for those with subtotal resection (Grill et al. 2005). At present, the use of local RT remains controversial and is done at the discretion of the treating physicians.

6.9 Target Delineation and Technique

Target delineation and technique for craniospinal axis irradiation will be discussed in another chapter. In general, there is a theoretical advantage of using protons for children because of the lack of the exit dose when treating the spinal field. There should be lower dose to the thyroid gland, heart, lungs, abdominal organs, and gonads with the use of protons when compared to photons (Johnstone et al. 2013). Acute toxicity such as nausea and vomiting, decrease in blood counts, intervention for management of esophagitis and weight loss are less with proton compared to photon-treated adult medulloblastoma patients (Brown et al. 2013). There are also several modeling studies which indicate that proton beam therapy may reduce the risk of radiation-induced secondary tumors (Miralbell et al. 2002). Many of these patients are currently being treated in the supine position as this is more comfortable for the patient, provides better airway access during anesthesia, and is more reproducible (Verma et al. 2015).

For target delineation of the posterior fossa, the entire posterior fossa is contoured and considered as the clinical target volume (CTV). A 0.3–0.5 mm margin is added depending on institutional practice for the planning target volume (PTV). For tumor bed delineation, the preoperative and postoperative MRI of the patient needs to be reviewed. The tumor cavity is outlined in addition to any residual tumor. The preoperative MRI can help guide which areas need to be included based on where tumor had contact with normal brain tissue. An additional margin of 1–1.5 cm to the contoured cavity and residual tumor is added, respecting boundaries of normal anatomic structures such as bone. Examples of contours for posterior fossa boost and tumor bed boost are presented in Fig. 6.2. As shown above, the bilateral cochlea is also contoured. For standard- and high-risk patients, we try and limit the mean dose to the cochlea to <37 Gy and <43 Gy, respectively (Paulino et al. 2010).

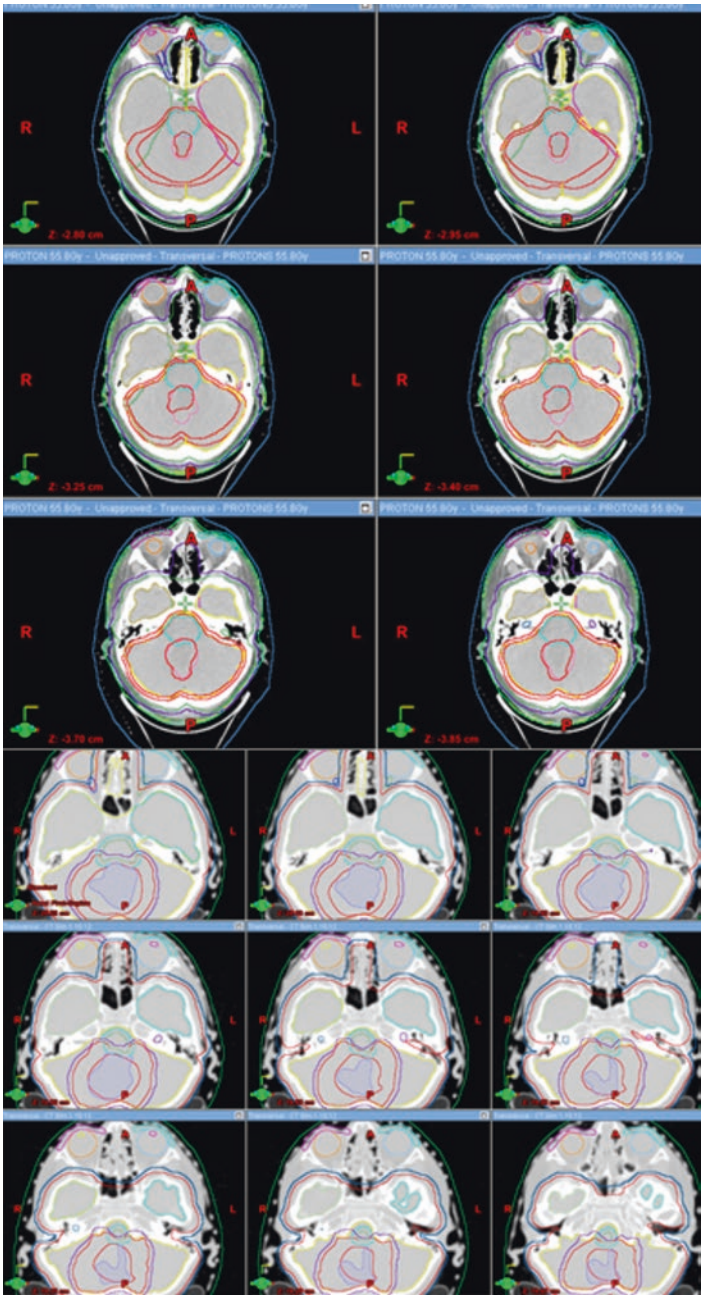

Fig. 6.2 A patient with standard-risk medulloblastoma. Note the coverage of the cribriform plate as part of the planning target volume or PTV (dark blue) for craniospinal irradiation. The upper 6 slices show a posterior fossa boost while the lower 9 slices show a tumor bed boost. For the posterior fossa boost, the clinical target volume (CTV) is the entire posterior fossa delineated in red and PTV is the orange line. For the tumor bed boost the gross tumor volume (GTV) is the purple shaded area, CTV is orange line and PTV is purple line. (Buchsbaum and Paulino 2015)

For the boost portion of treatment, both protons and intensity modulated radiotherapy (IMRT) have been used. One advantage of the tumor bed over the posterior fossa boost is a lower cochlear dose. Long-term studies using an intensity modulated radiation therapy (IMRT) boost to the tumor bed indicate that only 25% of patients have Grade 3–4 ototoxicity, compared to about 65% Grade 3–4 ototoxicity in the era of parallel-opposed lateral fields, treating the entire posterior fossa (Paulino et al. 2010; Huang et al. 2002). Protons also have a theoretical advantage of reducing dose to the hippocampus, hypothalamus, and pituitary which may translate to better cognitive and endocrine function compared to photon treatments. For standard-risk medulloblastoma, there does not seem to be a difference in progression-free or OS in patients treated with protons vs. photons (Eaton et al. 2016a). There is also some evidence that proton patients have a reduced risk of hypothyroidism, sex hormone deficiency, requirement for any endocrine replacement therapy, and height impairment (Eaton et al. 2016b).

6.10 Follow-Up and Outcomes

6.10.1 Follow-Up Guidelines

In general, follow-up is scheduled every 3 months for the first year after completion of therapy, every 6 months for the next 2 years, and annually after 3 years. A history and physical examination is performed in addition to MRI of the brain and spine during these visits. It is uncommon to get recurrences after 7 years of therapy so patients usually are followed up for possible complications of treatment (Belza et al. 1991). The patient will also require endocrine evaluation every 6 months for the first 3 years and annually thereafter. Audiograms are often performed yearly after therapy and may depend on the patient's symptomatology and auditory findings. The topic of surveillance for treated medulloblastoma patients has been questioned as salvage is poor for these patients (Torres et al. 1994; Shaw et al. 1997). Some have argued that patients who recur will be symptomatic.

6.11 Future Directions

Current studies are underway to determine whether treatment of children with medulloblastoma can be tailored according to molecular subtypes. For example, children with M0 classic medulloblastoma with a Wnt molecular signature may need less treatment such as RT omission or lowering of RT dose, whereas for Group 3 tumors, treatments may be more intensive with use of systemic or targeted agents. For Group 3 and 4 tumors, further delineation of biological targets is needed for better outcomes. Long-term follow-up of patients treated with protons is necessary to determine efficacy and long-term complications when compared to children treated with photons (Wolden 2013).

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Supratentorial Primitive Neuroectodermal Tumor

7

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Contents

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Abstract

Supratentorial primitive neuroectodermal tumors (SPNET) are rare small round blue cell malignancies with distinct genetic alterations and worse outcomes than the more common infratentorial PNET, medulloblastoma, that most often affects young children less than 5 years of age. Clinical presentation varies with tumor location, and these tumors are often identified by distinct radiographic features including abnormal diffusion restriction on diffusion-weighted magnetic resonance imaging and absence of peritumoral edema, despite the large size of many of these tumors at presentation. Standard therapy for patients with SPNET has been extrapolated from medulloblastoma regimens and combines maximal safe resection and adjuvant radiotherapy and chemotherapy. Outcomes of patients with SPNET have been shown to vary with tumor location (pineal vs. non-pineal), stage, extent of resection, and patient age. This chapter summarizes the data supporting current management strategies, with particular focus on role and delivery of radiation treatment, for pediatric patients with this rare, aggressive brain tumor.

7.1 Epidemiology

Pediatric supratentorial primitive neuroectodermal tumors (SPNET) comprise approximately 2% of malignant small round blue cell brain tumors, most commonly affecting children 5 years of age or younger, and represent a distinct neuropathological entity with worse outcomes and unique molecular signature than medulloblastoma ("cerebellar PNET") (Rickert and Paulus 2001; Chintagumpala et al. 2009). There is a subset of patients with SPNET originating in the pineal region ("pineoblastoma") with distinct molecular profile and improved prognosis compared with other patients with SPNET (Jakacki et al. 1995; Pizer et al. 2006).

7.2 Predisposing Factors

7.2.1 Etiology

Given the infrequent occurrence of SPNET, no well-defined predisposing factors have been identified. Association of SPNET with congenital, metabolic, or genetic conditions is rare (Varan et al. 2012).

7.2.2 Genetic Issues

Although histologically similar to medulloblastoma, SPNET demonstrate unique genetic alterations from the more common cerebellar tumors (Pomeroy et al. 2002; MacDonald et al. 2003). An investigation of gene expression using mRNA

microarray analysis demonstrated that medulloblastomas and SPNET have distinct transcriptional profiles, potentially related to their site of intracranial origin and response to therapy (Pomeroy et al. 2002). In a study by Russo et al., comparative genomic hybridization revealed 10 of 10 tested SPNET tumors to have copy number aberrations compared to only 14% of 43 infratentorial PNET samples (Russo et al. 1999). In this analysis, loss of long arm (q) of chromosomes 14 and 19 was found to be statistically more common in SPNET, whereas gain of chromosome 17q was identified in 37% of cerebellar PNET and absent in all SPNET tumors (Russo et al. 1999). Subsequent work by other investigators, however, has identified different genetic changes in SPNET compared with those reported by Russo and colleagues, including inactivation of *TP53* and *PTEN*, known tumor suppressor genes commonly identified in glioblastoma (Dubuc et al. 2010). Miller and colleagues examined the genetic profiles of SPNET and pineoblastomas, and confirmed high incidence of copy number alterations in the former not identified in the latter, suggesting possible distinct origins of these two tumor types (Miller et al. 2011). This work also identified genetic abnormalities common to both SPNET and pineoblastoma, not identified in medulloblastoma, underscoring the molecular diversity of these histologically similar entities as well as potential limitations of comparative genetic analyses of uncommon SPNET and pineoblastoma tumors as opposed to the more prevalent cerebellar PNET (Miller et al. 2011).

7.3 Presenting Symptoms

Depending upon specific tumor location, patients with SPNET may present with variable symptoms including headache, nausea/vomiting, lethargy, seizure, focal weakness, visual changes including Parinaud syndrome (pineal tumors), and endocrinopathies (MacDonald et al. 2003). Symptoms related to increased intracranial pressure from SPNET may be delayed in infants due to non-fused cranial sutures, and these tumors have been identified in children up to 3 years of age by detection of increased head circumference (Dai et al. 2003).

7.4 Radiographic Findings

The radiographic modality of choice for identifying brain tumors in the pediatric patient population is magnetic resonance imaging (MRI). Due to the high cellularity of PNET, regardless of intracranial location, both SPNET and medulloblastomas are able to be distinguished from other pediatric brain tumors by abnormal diffusion restriction on diffusion-weighted imaging and by isointense signal compared to normal gray matter on non-contrast T1-weighted, T2-weighted, and fluid-attenuated inversion recovery (FLAIR) sequences (Erdem et al. 2001). Another imaging characteristic of SPNET is the absence of peritumoral edema, despite the large size of many of these tumors at presentation (Dai et al. 2003) (Fig. 7.1).

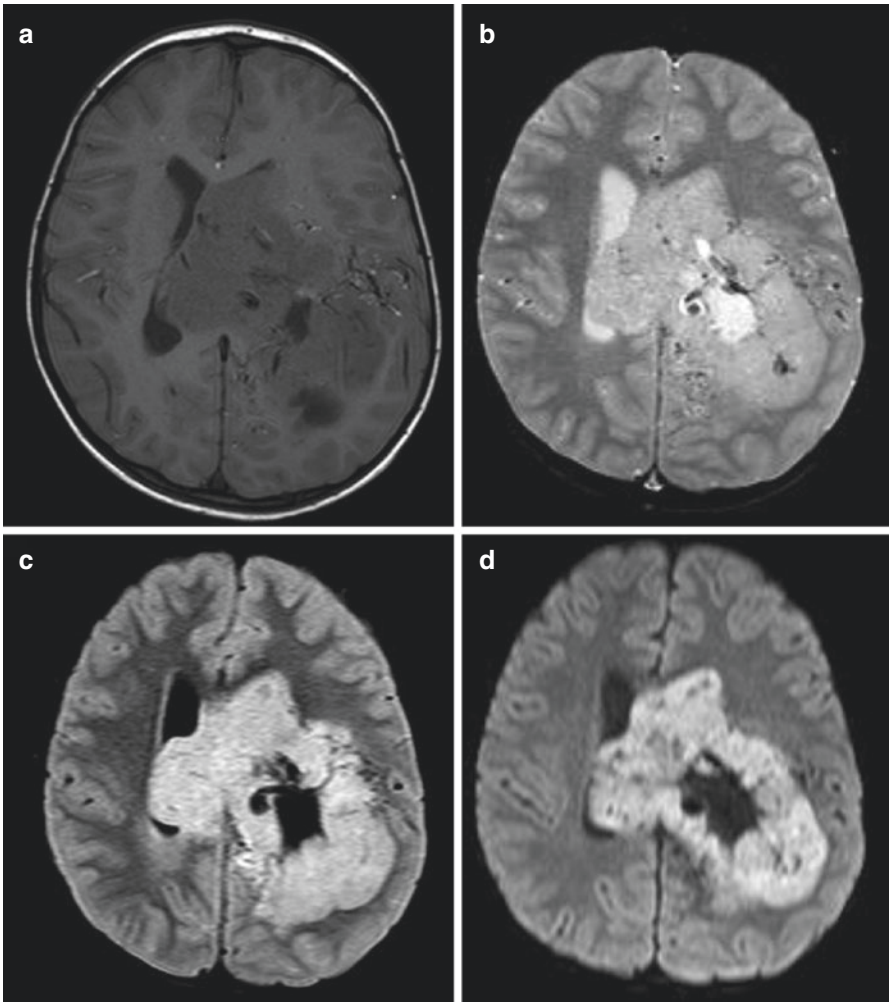

Fig. 7.1 Representative axial images from MRI of a 4-year-old patient with SPNET. On non-contrast T1-weighted (**a**), T2-weighted (**b**), and fluid-attenuated inversion recovery (FLAIR, **c**) images, tumor has isointense signal equivalent to normal gray matter, whereas the tumor demonstrates abnormal diffusion restriction on diffusion-weighted imaging (DWI, **d**) due to high cellularity of the tumor. Note characteristic absence of associated vasogenic edema on T2-weighted and FLAIR images

7.5 Workup

Due to a high predilection for central nervous system PNET to disseminate in the cerebrospinal fluid (CSF), with incidence of CNS metastasis identified in up to one-fourth to one-third of patients at diagnosis (Jakacki 2005), workup of patients suspected of having SPNET includes complete imaging of the neuraxis, preferably with

gadolinium-enhanced MRI, and assessment of CSF cytology (Terterov et al. 2010). While there is some debate as to the optimal timing and method of CSF sampling, due to risk of both false positive and false negative results (Terterov et al. 2010), pathologic analysis of CSF should be evaluated prior to surgery or at least 10 days following resection of the primary tumor for staging. Postoperative MRI of the brain within 48 hours of surgery is also necessary to assess extent of tumor resection, and thereby determine the risk grouping of the patient (Chintagumpala et al. 2009). The risk of extracranial spread of PNET is rare, but complete metastatic evaluation includes bone scintigraphy, bone marrow biopsy, and imaging of lungs, liver and nodal regions to confirm the absence of distant spread of disease to these sites.

7.6 Acute Management

Given the preponderance of SPNET to present as large tumors with associated symptoms of increased intracranial pressure, acute management of patients often includes external ventricular drain placement for hydrocephalus and medical management of seizure. The benefit of steroids in SPNET is less clear, since these tumors tend not to have associated vasogenic edema despite significant mass effect (see Fig. 7.1).

7.7 Treatment

Because of the relative rarity of SPNET, the current standard therapy for patients with this diagnosis has been extrapolated from that for the more common medulloblastoma and combines maximal safe resection and adjuvant radiotherapy and chemotherapy (either concurrent or sequential), ideally to be initiated within 30 days of surgery.

7.7.1 Evolution to Current Practice

7.7.1.1 Role of Surgery

The principle role of surgery in the management of SPNET is for pathologic diagnosis and cytoreduction, but because of the high propensity for SPNET to disseminate throughout the neuraxis, this disease is considered not surgically curable (Jakacki 2005). Results of both prospective and retrospective cohorts of SPNET subjects have revealed both positive and negative correlation between extent of tumor resection and outcome.

In a report of the subgroup of 44 pathologically confirmed SPNET (including pineoblastoma) subjects enrolled on the prospective Children's Cancer Group (CCG) study of high-risk PNET, CCG-921, only a minority had gross total resection (GTR) of tumor (37% non-pineal and 18% pineal SPNET) (Cohen et al. 1995). Excluding patients with known metastatic disease or pineal primary tumor, extent of

resection was not found to be associated with progression-free survival (PFS) in the SPNET cohort, although impact of surgery on neurologic function and quality of life (QOL) was not assessed (Cohen et al. 1995). In the combined HIT 88/89 and HIT 91 trials in Germany and Austria, the survival outcomes of 63 SPNET (52 of which were non-pineal) patients treated with multimodality therapy were comparable for the 1/3 who had GTR compared with the remaining 67% who had subtotal resection (STR) (Timmermann et al. 2002). Analysis of 68 eligible patients with SPNET (54 of which were non-pineal) enrolled on the PNET 3 study conducted by the Société Internationale d'Oncologie Pédiatrique (SIOP)/United Kingdom Children's Cancer Study Group (UKSCCG) also failed to demonstrate statistically significant improvement in event-free survival (EFS) or overall survival (OS) following GTR (Pizer et al. 2006). Similarly, in a retrospective series of 48 SPNET pediatric patients from Canada, at least 90% resection (with residual <1.5 cm^2) was not found to have improved survival compared with lesser extent of resection (Johnston et al. 2008).

An early retrospective analysis evaluated 36 patients with SPNET (26 of which were non-pineal), who were treated at Hospital for Sick Children in Toronto (Dirks et al. 1996). In this series, there was a trend for improved outcomes in patients undergoing GTR, and half of those still alive at last evaluation had complete resection. The median survival was very poor at only 23 months for this entire group, which may be attributed, at least in part, to 50% of patients being less than 3 years of age and only a minority receiving chemotherapy. In a series of 22 consecutive patients with SPNET (nine of which were non-pineal), 5-year PFS rate was doubled from 25% in patients undergoing biopsy/STR to >50% in those undergoing near or gross total resection. The benefit of more aggressive surgery did not reach statistical significance in this analysis due to small patient numbers (Reddy et al. 2000).

Except where noted, the analyses above primarily included subjects at least age 3 years or greater. In the combined Pediatric Oncology Group (POG) 9233/34 randomized controlled study of dose-intensive (DI) versus standard chemotherapy for patients younger than 3 years of age, GTR was associated with significantly improved EFS of 40% in the subset of 29 patients with non-metastatic SPNET (Strother et al. 2014).

While the studies above included mixed populations of pineal and non-pineal SPNET, a comprehensive literature review of over 100 studies of 299 patients with pineoblastoma demonstrated that 5-year survival rates improved from 29% following debulking to 53% with STR, and to 84% with GTR (log-rank $P < 0.001$, (Tate et al. 2012)). The importance of GTR was confirmed on multivariate analysis, where effects of patient age, M stage, and other adjuvant therapies were taken into account. Of note, this analysis did include young adult patients (mean age 28 years) who comprised the cohort treated with surgery followed by radiation therapy (RT). In a retrospective series of 11 patients with pineoblastoma from Children's Hospital of Boston/Dana-Farber Cancer Institute, three of these patients who had GTR were disease free at 1-year post diagnosis, whereas half of the remaining eight patients were alive >6 months from diagnosis. This finding suggested a trend for improved outcomes relative to greater extent of resection (Gilheeney et al. 2008).

The preponderance of data supports aggressive surgery to improve outcomes for both non-pineal and pineal SPNET.

7.7.1.2 Role of Chemotherapy

Standard Chemotherapy

Given a high predilection for dissemination, chemotherapy has been utilized as part of aggressive multimodality therapy for SPNET. While these tumors have been found to be sensitive to chemotherapy, particularly in infants and very young patients in whom deferral of RT is considered preferential in order to avert or delay potential adverse late sequelae of radiation, the response of SPNET to chemotherapy has been found to be of short duration (Jakacki 2005).

Although early studies examined single agent efficacy in medulloblastoma, combination drug regimens and timing of chemotherapy have been evaluated in subjects with the clinically more aggressive SPNET in multiple prospective clinical trials. The CCG-921 study randomized half of the 44 confirmed SPNET subjects to standard eight cycles of chemotherapy with CCNU, vincristine (VCR), and prednisone after surgery and craniospinal irradiation (CSI) versus two postoperative cycles of 8-in-1 chemotherapy with methylprednisolone, CCNU or carmustine, VCR, procarbazine, hydroxyurea, cisplatin (CDDP), cytarabine, and cyclophosphamide (CYCLO), followed by CSI and an additional eight cycles of 8-in-1 therapy (Cohen et al. 1995). Three-year PFS and OS were 45% and 57%, respectively, and were not statistically different between subjects treated with the two chemotherapy regimens, although the 8-in-1 had greater toxicity (predominantly hematologic). The subset of patients with pineal tumors had significantly improved 3-year PFS and OS (61% and 73%, respectively) compared with non-pineal SPNET.

Timing of chemotherapy was also assessed by a single-arm pilot trial and phase 2 trial of intense, multi-agent chemotherapy prior to RT (CSI plus boost) conducted by the German HIT group (HIT 88/89) that included ten subjects with SPNET (Kuhl et al. 1998). The chemotherapy regimen included up to two cycles of procarbazine, ifosfamide (IFOS) with mesna, etoposide (ETOP), high-dose methotrexate (MTX), CDDP, and cytarabine (Ara-C). Five-year overall response rate (complete response [CR] plus partial response [PR]) in the SPNET cohort was 57%, although the 5-year PFS of 20% was lowest in this subset of patients and was worse than observed in the CCG-921 study. The follow-up expansion study HIT 91 randomized a total of 515 pediatric patients aged 3–18 years with PNET to the pre-radiation chemotherapy regimen of HIT 88/89 or to standard therapy with concurrent VCR and CSI plus boost followed by eight cycles of CCNU, CDDP, and VCR. Of the 515 patients, 53 were found to have SPNET, and 30 of these received the experimental HIT 88/89 therapy (Timmermann et al. 2002). In the combined analysis of all 63 SPNET subjects on the HIT 88/89 and HIT 91, almost 2/3 had disease progression, and nine of the 10 patients who progressed during adjuvant therapy were treated with pre-radiation chemotherapy. The 3-year PFS for the combined groups was 39%, and median time to progression was 10 months (Timmermann et al. 2002). Thus, while the early HIT 88/89 studies demonstrated sensitivity of SPNET to aggressive

multidrug chemotherapy, outcomes in these patients were not improved using this approach. Of note, only half of the children with SPNET in HIT 91 were randomized due to parental refusal.

The SIOP/UKCCSG PNET 3 study was designed to evaluate the efficacy of four alternating cycles of VCR/ETOP/carboplatin (CBDCA) with VCR/ETOP/CYCLO combination chemotherapy prior to RT versus adjuvant RT alone in pediatric subjects ≥3 years of age with SPNET (Pizer et al. 2006). Addition of chemotherapy prior to RT was associated with increased toxicity, especially grade 3–4 drop in blood counts, but had no impact on EFS or OS compared to adjuvant RT alone. It is worth noting, however, that, of the 68 eligible SPNET patients on this study, only 13 were randomized according to the protocol specifications.

Chemotherapy for Very Young Patients

Although addition of chemotherapy prior to RT did not show clear benefit in patients 3 years or older, several prospective studies investigated aggressive multi-agent chemotherapy regimens in the very young as a means to delay or omit RT in this vulnerable population. In the highly cited Pediatric Oncology Group (POG) study of adjuvant chemotherapy for children with malignant brain tumors under 3 years of age ("Baby POG"), Duffner et al. reported on the outcomes of 198 children treated with two cycles of CYCLO and VCR followed by one cycle of CDDP and ETOP for 1–2 years, at which time RT was permitted (Duffner et al. 1993). Thirty-six (18%) of these children had SPNET, and of these, 22 were <2 years old at diagnosis. Only eight of 30 of these children who underwent surgery had GTR of tumor, the only factor identified on multivariate analysis to be associated with improved PFS. Among all the histologies included in this analysis, the children with SPNET had the worst outcomes, with 2-year PFS and OS rates of 19% and 21%, respectively. Most tumor recurrence in these children occurred within the first 12 months of treatment. Given this finding, use of this chemotherapy regimen was not recommended for young children with SPNET (Duffner et al. 1993).

The Société Française d'Oncologie Pédiatrique (SFOP) also conducted a study of postoperative multi-agent chemotherapy alone for children <5 years of age with malignant brain tumors. In their report of the subgroup of 25 patients with SPNET (five of which were pineal), 17 had stage M0 disease and nine underwent GTR (Marec-Berard et al. 2002). Patients were treated adjuvantly with a planned total seven cycles of CBDCA and procarbazine followed by ETOP, CDDP and then VCR and CYCLO with mesna. Only two children completed the full seven cycles. Despite >1/3 of patients demonstrating positive response (CR + PR), the 2-year PFS was 4% and 2-year OS rate was 29% for all patients in this analysis. There was a trend for improved outcomes with extent of surgical resection, although patients with relapse all failed locally. The outcomes of the SPNET patients treated with adjuvant chemotherapy were equally dismal in the SFOP study as in the POG study.

Intensified Chemotherapy

The CCG investigated non-randomized use of a more intensive "eight drugs in 1 day" for children younger than 18 months of age following resection of

malignant brain tumors in an attempt to reduce or delay RT (Geyer et al. 1994). The agents used included VCR, BCNU, procarbazine, hydroxyurea, CDDP, Ara-C, CYCLO, and prednisone, and were delivered in 1 day, repeated for a total of eight cycles at 2 weeks for cycle 2 and then monthly thereafter. Of the 82 children enrolled, 19 (23%) had SPNET (11 of these being non-pineal). Six of these 19 had GTR, and 14 had stage M0 disease. In contrast to the other studies, extent of resection was not associated with improved outcomes, suggesting a benefit of this aggressive chemotherapy to treat residual disease. Also contrary to other analyses, the 3-year PFS was significantly improved for patients with non-pineal SPNET versus those with pineal SPNET or cerebellar PNET (55% compared with 0% or 26%, respectively). Similar to the POG and SFOP studies, the recurrences in this group of young patients occurred early (within 6 months), and most frequently were local. Thus deferral of RT after completion of chemotherapy was not considered likely to benefit PFS in these patients. Of note, only a minority of the patients without progressive disease received RT as part of their therapy (Geyer et al. 1994).

As mentioned in the section on 7.7.1.1 above, the POG 9233/34 randomized controlled trials were designed to evaluate standard versus DI chemotherapy for improved EFS in patients less than 3 years old with malignant brain tumors, of which 38 (12%) had SPNET (Strother et al. 2014). These studies employed two different chemotherapy regimens, both including the same agents (CYCLO, VCR, ETOP, and CDDP) administered at slightly different dosages and timing, for a total of 72 weeks. In the combined study, there was no benefit of DI over standard chemotherapy in young patients with SPNET with respect to EFS and OS, and only 20% of these children had disease control without RT.

In an effort to improve outcomes of conventional chemotherapy alone following resection of SPNET, intensification of chemotherapy with autologous stem cell rescue (ASCR) has been investigated. One such multi-institutional trial included 62 children with brain tumors all <6 years of age, 14 of which had SPNET (11 of these being non-pineal), and of these, 50% were <3 years of age at diagnosis (Mason et al. 1998). The children on study received five cycles of CDDP, VCR, ETOP, CYCLO, and mesna over 12–16 weeks, after which they received consolidation with CBDCA, ETOP, and thiotepa followed by ASCR if they were found to have no residual tumor, GTR at time of second-look surgery, or stable residual disease that could be treated with adjuvant RT. Seven of all 14 SPNET patients had GTR, five with STR, and two with "partial" resection. Of the seven who did not have GTR, one died from treatment toxicity, while 2/3 of the remaining children had positive response to the induction therapy. Reported 2-year EFS and OS from diagnosis for all 14 SPNET patients was 43% and 64%, respectively, which was comparable to the 13 children with medulloblastoma included in this study (Mason et al. 1998). Extent of resection tended to correlate with improved outcome. Although the results of this intensive chemotherapy regimen were encouraging, toxicity was not insignificant, with high reported incidence of mucositis (100%), dermatitis (100%), and hearing loss (34%), in addition to the anticipated hematologic toxicity, and there was an 8% incidence of toxic deaths among all the study subjects. Neuropsychological testing

also revealed impairment of language and fine-motor functioning in the children who did not receive RT on this trial. The number of children with SPNET requiring RT was not reported, although nearly 50% of all subjects who received the ASCR were able to avoid RT in this study.

The German HIT 2000 study investigated the impact of various adjuvant chemotherapy regimens on outcomes of 17 young children <4 years old with "CNS-PNET" (eight not otherwise specified, eight pineoblastoma, one ependymoblastoma) (Friedrich et al. 2013). For the 11 stage M0 patients, up to five cycles of combination CYCLO, VCR, MTX, CBDCA, and ETOP were given within 8 months, followed by CSI. A shorter 2- to 3-month course of induction CBDCA and ETOP followed by HDCT, both with intrathecal MTX, were administered to three of six positive responders in the M+ group. These three also received CSI after completing systemic therapy. The EFS rate was 24% and OS was 40% at 5 years for all patients, with trend for increased survival noted for those patients receiving the intensified therapy. No difference was detected between patients with pineal and non-pineal tumors. Thirteen patients relapsed, all of which failed during the induction chemotherapy and 11 of which had local recurrence, suggesting limited effectiveness of chemotherapy in treating SPNET.

The Gustave Roussy conducted a more recent study of HDCT with ASCR in 24 high-risk PNET patients over 5 years of age, of which three had SPNET (Dufour et al. 2014). In this trial, following resection, the children received two cycles of induction chemotherapy with CBDCA and ETOP followed by two cycles of high-dose thiotepa with ASCR, after which they were treated with craniospinal irradiation (CSI, to be discussed in more detail in the section 7.7.1.3 below). Nineteen of 21 evaluable patients demonstrated positive response (CR + PR) to HDCT, with expected hematologic and gastrointestinal toxicity. No patients died from the HDCT, and all were able to receive RT. Eight patients relapsed, of which two had SPNET. The 3-year event-free survival (EFS) and OS rates for all evaluable patients were 79% and 82%, respectively. The positive outcomes of this study likely reflect the large percentage of these high-risk patients having cerebellar PNET.

Head Start (HS) I and II are two important multi-institutional, prospective studies investigating benefit of HDCT with ASCR to delay or defer RT for young children with malignant brain tumors. Eligible children <6 years of age were treated on HS I with maximal safe resection followed by HDCT with CDDP, VCR, ETOP and CYCLO plus mesna for five cycles of induction therapy followed by consolidative chemotherapy with CBDCA, ETOP, and thiotepa followed by ASCR. The age was increased to <10 years for subjects on HS II, and patients on this study with M+ disease received high-dose MTX in addition to the HS I regimen above. Children with residual disease after induction underwent second-look surgery as feasible prior to consolidation therapy. Children with unresectable bulky, symptomatic, or progressive disease did not receive consolidation therapy. A total of 43 children with SPNET were treated on the HS trials (Fangusaro et al. 2008). GTR was achieved in 21 of these children. Of the remaining 22 patients with less than GTR, 82% demonstrated positive response to the induction chemotherapy. A total of 32 were able to proceed to consolidation chemotherapy with ASCR. The 5-year EFS

and OS for all SPNET patients were 39% and 49%, respectively. Recurrent and/or progressive disease was identified in 25 patients, of which 23 had a local disease component. While the authors report that 15 of 20 survivors were able to avoid CSI and 12 received no RT, it is noteworthy that over 90% of the 25 patients with recurrent disease had local failure. Common adverse effects of this therapy included high-grade hematologic toxicity and hearing impairment, and 5% of the children in this cohort died from this therapy.

Post-RT Chemotherapy

Chemotherapy following RT has also been examined in subjects with SPNET. A multi-institutional study of 53 patients with newly diagnosed PNET, including both supratentorial and cerebellar tumors, demonstrated feasibility of receiving four cycles of HDCT with CDDP, CYCLO, and VCR followed by ASCR after maximal safe resection and CSI (Strother et al. 2001). Forty-nine patients between 3 and 17 years of age were able to complete all four cycles of HDCT, with 2-year PFS of 94% for average-risk and 74% for high-risk patients, based on stage and extent of resection. The proportion of patients with cerebellar PNET was not specified in this work, which may account in part for the very encouraging results compared with those generally observed for SPNET.

The role of maintenance chemotherapy following concurrent VCR and CBDCA with RT in children with newly diagnosed PNET was examined in the phase I/II CCG-99701 study, which was completed in 2012. The results of this study are eagerly awaited.

Chemotherapy for Pineal SPNET

The role of chemotherapy in the treatment of pineal PNET was assessed in the comprehensive analysis of 299 patients with pineoblastoma identified in a literature review by Tate et al. (Tate et al. 2012). In this work, 2-year OS was lowest following treatment with standard postoperative chemotherapy compared with adjuvant RT or chemoradiotherapy (31%, vs. 35% or 60%, respectively). This finding was still observed even after correcting for age, extent of surgical resection, and stage, supporting the limited utility of chemotherapy even in this more favorable subgroup of SPNET patients.

7.7.1.3 Role of RT

Given the overall poor outcomes of patients with SPNET treated with surgery and postoperative chemotherapy alone, RT is considered an essential component of therapy for this aggressive disease.

Standard Fractionated RT

Standard RT regimens for SPNET include CSI followed by a boost to the primary tumor bed, largely extrapolated from studies for cerebellar PNET and retrospective series (Jakacki 2005). One such retrospective study from the University of California San Francisco (UCSF) examined outcomes of 10 children <18 years of age with SPNET treated with RT (McBride et al. 2008). While the RT regimens were quite

varied in this review, all five children who received RT early in their treatment course had no evidence of disease, whereas two of five treated with salvage RT recurred, and another three of five who did not receive any RT were deceased at the time of follow-up, with median 6.5 months time to progression in the latter two cohorts. Only half of the patients treated with RT received CSI, ranging from 23.4 to 36 Gy in 1.8 Gy per fraction, five fractions weekly, which was reserved for children >3 years of age at the time of diagnosis. The total dose to the tumor bed ranged from 50.4 to 72 Gy. Given the small patient numbers and range of treatment given in this series, no conclusion could be drawn regarding radiation dose or volume in this disease setting. In contrast, the prospective HIT 88/89 and 91 studies identified radiation dose and target volumes as the only significant prognostic factor for PFS in the subgroup analysis of 63 SPNET patients treated, since those children receiving less than the study-mandated 35 Gy to the neuraxis or 54 Gy to the primary site had 3-year PFS of 7% compared with 49% for those treated with the study regimen (Timmermann et al. 2002).

Due to concerns of adverse sequelae following high-dose CSI, particularly in young patients, Chintagumpala et al. attempted to address the issue of radiation dose in a multi-institutional, prospective pilot study of risk-adapted therapy for SPNET patients between 3–21 years of age (Chintagumpala et al. 2009). A total of 16 subjects with SPNET (seven of these being pineal) were enrolled on this study. Half of the patients were considered average risk (M0 and $\leq$1.5 cm^2 residual tumor) and received 23.4 Gy CSI followed by a boost to a total 55.8 Gy to the tumor bed plus 2-cm margin in once-daily 1.8-Gy fractions. The other eight patients were considered high-risk and received 36–39.6 Gy CSI with same total dose to the boost volume. All patients completed RT, and 14 went on to receive HDCT with CYCLO, CDDP, and VCR followed by ASCR. The 5-year EFS and OS for the average-risk patients were 75% and 88%, respectively, and for the high-risk patients, these outcomes were 60% and 59%, respectively. Outcomes were worse in the patients with pineal tumors compared with non-pineal ones (54% vs. 78% 5-year EFS, and 67% vs. 78% 5-year OS). Four patients relapsed after completing RT: two had some local component and two only had disease outside the primary site. Despite utilizing a reduced CSI dose in the favorable patients, the results of this small study superseded those of other studies using the same or higher dose of RT, suggesting potential benefit of the combined lower CSI dose and more aggressive chemotherapy in these patients (Fig. 7.2).

Altered Fractionation RT

In another effort to reduce the late effects associated with standard fractionated RT in this young patient group, Massimino et al. conducted a single-institution study of hyperfractionated accelerated RT (HART) in 15 patients >3 years of age diagnosed with SPNET (three of which were pineal). All patients were treated with surgery followed by moderate dose-intense chemotherapy with MTX, VCR, ETOP, CYCLO, and CBDCA prior to 1.3 Gy per fraction, twice daily, 5 days weekly CSI to 31.2 Gy (for <10 years old) or 39 Gy (for $\geq$10 years old) and 1.5 Gy per fraction, twice daily, 5 days weekly boost to tumor bed for total dose of 59.6–60 Gy, for a

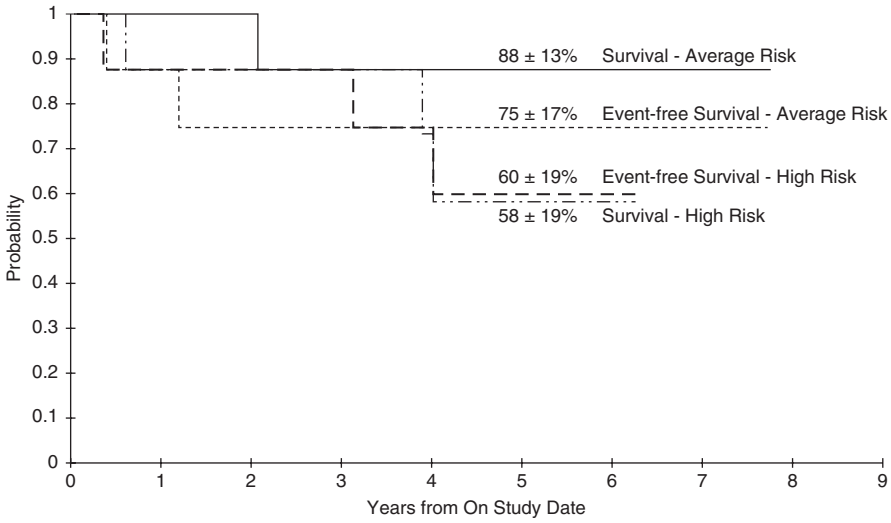

Fig. 7.2 Outcomes of subjects 3–21 years of age with SPNET treated with risk-adapted therapy (from Chintagumpala et al. [2009]). Event-free and overall survival of average-risk and high-risk pediatric patients age 3–21 years treated with risk-adapted chemotherapy and radiation therapy. Note overall improved outcomes compared with historic outcomes

total number of treatment days ranging from 17.5 to 22 (Massimino et al. 2006). The patients then received additional maintenance chemotherapy, initially standard chemotherapy with VCR and CBDCA, changed to HDCT with thiotepa and ASCR due to early relapses in three of five patients in the former cohort. For all patients, 3-year PFS and OS were 54% and 61%. Five of six patients who relapsed had a local component, occurring by a median of 6 months from start of induction chemotherapy. All patients were able to complete HART without significant toxicity, and five of seven patients with residual disease at time of HART had positive response (1 CR + 4 PR) to the radiation. While the authors suggest benefit of HART by delivering higher biologic effective dose with minimal increase in late effect, the observed outcomes were no better than observed in comparable aggressive multimodality therapies, and late effects from treatment were not reported in this study. The logistical issues of delivering twice daily RT to pediatric population (e.g., need for anesthesia) were also not addressed. Consequently, use of HART is not recommended for SPNET.

RT for Very Young Patients

Due to concerns of markedly increased toxicity following RT when administered to children <3 years of age, many studies have been conducted to defer or omit RT in this particularly vulnerable patient group. However, as highlighted in the sections on "Chemotherapy for Very Young Patients" and "Intensified Chemotherapy" above, a high incidence of early recurrence and local failure has been observed in these very young children with SPNET treated with delayed or no RT.

In the prospective POG 9233/34 trials investigating standard versus DI chemotherapy in young children with malignant brain tumors discussed above, RT was delivered to patients with M+ disease at diagnosis, with residual, nonprogressive disease post-chemotherapy (POG 9233), or to those with progressive disease within 6 months of completed chemotherapy (POG 9234) (Strother et al. 2014). The RT dose was based on patient age at the time of treatment and ranged from 48 to 52.2 Gy. The radiation target was focal-only for patients with M0 disease, and included dose-reduced CSI from 27 to 34.5 Gy for those with M1 disease with an additional 3–4 Gy CSI for gross neuraxis disease. A total of 291 of all 328 patients enrolled on the combined study were eligible for RT, and only 49 evaluable patients received RT on POG 9234, including some with ependymoma and medulloblastoma. Of these 49 irradiated children, 43 later developed progressive disease. The proportion of subjects with SPNET receiving RT was not reported, although the benefit of delayed and reduced-dose RT in the entire irradiated cohort is unclear.

The multi-institution, prospective HIT 2000 study also allowed treatment with a lower-dose CSI (24 Gy in 15 once-daily fractions) for the 17 children younger than 4 years of age with SPNET (Friedrich et al. 2013). Only 11 of these children were treated with CSI, and eight of these were irradiated as salvage therapy. Only two of these eight remained in remission following CSI, whereas all three of the children irradiated up-front after CR following HDCT remained without evidence of disease at last follow-up. While the authors conclude that the benefit of CSI is unclear in the setting of CR following intensive chemotherapy, reserving RT for salvage therapy, potentially due to reduced RT doses used, did not improve tumor control. Further, despite use of lower-dose RT, the combination of intensive chemotherapy and neuraxis RT resulted in worse neurocognitive function in two evaluable subjects compared with two others receiving CSI without HDCT.

Another means of reducing RT-related toxicity that has been studied in very young patients with SPNET is use of proton beam RT (PBT). In a single-institution report of 15 patients younger than age 5 diagnosed with CNS-PNET (of which three had SPNET), PBT at a median 21.6 relative biologic equivalent Gy (RBE-Gy) to the neuraxis and median 54 RBE-Gy boost after surgery and HDCT with ASCR, 13 of these children were alive without evidence of disease after a median follow-up of 39 months (Jimenez et al. 2013). Of the three subjects with SPNET, one was treated with focal RT only, and this child plus one treated with CSI were among those alive at the end of this study. The toxicities following this therapy included hearing loss and perturbed endocrine function, with no change in neurocognitive function detected in the 13 survivors. The focally irradiated child with SPNET had normal hearing and endocrine function, supporting potential benefit of PBT with respect to late effects of RT.

Despite the real and perceived risks associated with RT in pediatric patients, the preponderance of evidence supports the need for RT in the management of SPNET for optimal patient outcome.

7.8 Target Delineation

7.8.1 RT Volumes

The current accepted target volumes for children with SPNET, as defined in the ongoing phase III COG ACNS0334 protocol, include:

Gross tumor volume (GTV) = contrast-enhancing tumor on postoperative MRI
Clinical target volume (CTV) = GTV and tumor bed + 1-cm expansion, excluding anatomical barriers (bone, dura)
Planning target volume (PTV) = CTV + 3–5-mm isotropic expansion to account for immobilization and setup variability

Because SPNET can occur anywhere within the supratentorial region, the adjacent organs at-risk (OARs) for RT injury depend upon tumor location and may include brainstem, optic nerves, optic chiasm, eyes, lenses, pituitary, hypothalamus, hippocampi, temporal lobes, cochleae, and normal brain. The RT dose constraints for these structures are discussed in Part VII of this book.

7.8.2 Dose

Given the rarity of SPNET and limited numbers of patients included in prospective studies evaluating RT as part of management of children with this disease, the RT dose information provided here should be deemed relative and not absolute guidelines, and enrollment on clinical trial should be the first consideration for these patients.

7.8.2.1 For Patients 3 Years of Age or Older

Stage M0

+ Standard chemotherapy: ≥35 Gy CSI followed by 18–20 Gy tumor bed boost
+ HDCT with ASCR: 23.4 Gy CSI followed by 30.6 Gy tumor bed boost

Stage M1–2

≥ 35 Gy CSI followed by 18–20 Gy tumor bed boost

Stage M3

≥ 35 Gy CSI followed by 18–20 Gy tumor bed boost; consider additional 3–4 Gy boost to gross residual disease along spine

7.8.2.2 For Patients <3 Years of Age

Stage M0

50–54 Gy tumor bed only

Stage M+

≥18 Gy CSI followed by 27–36 Gy tumor bed and gross residual disease boost

7.8.3 Techniques

CSI may be delivered using once-daily, standard-fractionated mega-voltage photon- or proton-based therapy at 1.8 Gy per fraction, with opposed lateral beams for the cranial fields and PA beams for the spine fields, with field junctioning after every five fractions. Either prone or supine positioning may be used, with consideration of patient comfort, reproducibility of setup, and need for anesthesia (South et al. 2008).

Focal tumor bed boost dose may be delivered using once-daily, standard-fractionated mega-voltage photon- or proton-based therapy at 1.8 Gy per fraction, with multi-beam, 3-dimensional conformal or intensity modulated therapy.

7.9 Outcomes

7.9.1 Follow-Up Guidelines

Patients should be followed with serial neuraxis MRI imaging and CSF sampling initially every 2 months for the first year, every 3–4 months for years 2–3, every 6 months for year 4, then annually from years 5 and beyond, or sooner as clinically warranted. Patients should also undergo evaluation for endocrinologic, ophthalmologic, audiometric, and neurocognitive function at least annually following completion of therapy.

7.9.2 EFS, PFS, OS

As highlighted in the previous sections, outcomes of patients with SPNET have been shown to vary with tumor location (pineal vs. non-pineal), M stage, extent of resection, and patient age. The results of the SPNET cohorts from the various prospective studies highlighted above are summarized in Table 7.1 for older patient cohorts and in Table 7.2 for the younger patient groups.

Table 7.1 Summary of prospective studies of SPNET with older patient cohorts

Study [ref.]	Age (y)	# Pts	% M0	% GTR	RT Dose (CSI/Total Gy)	% LF (#LF/#Any F)	% EFS or PFS[a]	% OS[a]
CCG-921 (Cohen et al. 1995)	1.5–22	44	82	30	23.4–36/54	NR	45	57
Non-pineal		*27*	*81*	*37*			*30*	*NR*
Pineal		*17*	*82*	*18*			*61*	*73*
HIT 88/89,91 (Timmermann et al. 2002)	3–18	63	73	33	35.2/55.2	89 (34/38)	39	48
Non-pineal		*52*						
Pineal		*11*						
Milan (Massimino et al. 2006)	3–18	15	87	40	31.2–39/ 59.7–60[b]	83 (5/6)	54	61
Non-pineal		*12*		*42*				
Pineal		*3*		*33*				
PNET 3 (Pizer et al. 2006)	3–16	68	21[c]	31	35/55	83 (29/35)	57	61
Non-pineal		*54*					*41*	*44*
Pineal		*14*					*93*	*93*
Multi-institution (Chintagumpala et al. 2009)	3–21	16	69	38	23.4–39.6/55.8	50 (2/4)	68 *(5y)*	73 *(5y)*
Non-pineal		*11*		*45*			*78 (5y)*	*78 (5y)*
Pineal		*7*		*14*			*54 (5y)*	*67 (5y)*

Abbreviations: *#* number, *CSI* craniospinal radiotherapy, *EFS* event-free survival, *F* failure, *GTR* gross total resection, *Gy* gray, *LF* local failure, *M0* non-metastatic, *NR* not reported, *OS* overall survival, *PFS* progression-free survival, *pts* patients, *ref.* reference, *RT* radiotherapy, *y* year

[a]At 3 years, unless otherwise indicated

[b]BID

[c]Confirmed, excludes 39 patients with M0 by imaging only (no CSF sampling)

Table 7.2 Summary of prospective studies of SPNET with younger patient cohorts

Study [ref.]	Age (y)	# Pts	% M0	% GTR	RT Dose (CSI/Total Gy)	% LF (#LF/#Any F)	% DFS or EFS[a]	% OS[a]
COG-921 (Hong et al. 2005)	<1.5	19	74	58[b]	Optional[c]	57	NR	NR
Baby POG (Duffner et al. 1993)	<3	36	NR	27	35.2/54, if CR: 24/50	NR	19	21
POG 9233/34 (Strother et al. 2014)	<3	38	76	26	27–34.5/48–55.2 (M0)	NR	40 (3y GTR)	50
					3–4 added to CSI (M+)		15 (3y STR)	25
							10 (3y M+)	20
HIT 2000 (Friedrich et al. 2013)	<4	17	65	41	24/56.4, if CR: optional	85 (11/13)	24 (5y)	40 (5y)
Non-pineal		*9*		*44*			*ND*	*ND*
Pineal		*8*		*38*			*ND*	*ND*
SFOP (Marec-Berard et al. 2002)	<5	25	68	36	None	100 (24/24)	4	29
Non-pineal		*20*						
Pineal		*5*						
Multi-institutional (Mason et al. 1998)	<6	14	NR	50	None	67 (4/6)	43	64
Non-pineal		*11*						
Pineal		*3*						
Head Start I/II (Fangusaro et al. 2008)	<6 (I)	43	81	49	23.4/55.8 if >6y and/or residual	92 (23/25)	39 (5y)	49 (5y)
	<10 (II)							
Non-pineal		*30*					*48 (5y)*	*60 (5y)*
Pineal		*13*					*15 (5y)*	*23 (5y)*

Abbreviations: *#* number, *CR* complete response, *CSI* craniospinal radiotherapy, *EFS* event-free survival, *F* failure, *GTR* gross total resection, *Gy* gray, *LF* local failure, *M0* non-metastatic, *M+* metastatic, *ND* no difference, *NR* not reported, *OS* overall survival, *PFS* progression-free survival, *pts* patients, *ref.* reference, *RT* radiotherapy, *y* year

[a]At 2 years, unless otherwise indicated

[b]Includes patients with >90% tumor resected

[c]Physicians' discretion involved field RT after 2 cycles of chemotherapy or CSI at 1 year; most received no RT (Geyer et al. 1994)

7.9.3 Toxicities

Since SPNET may occur anywhere within the brain above the tentorium cerebelli, the OARs and, consequently, toxicities following therapy will vary. Anticipated acute sequelae of RT include alopecia, dermatitis, headache, nausea/vomiting, fatigue, and bone marrow suppression. Late effects of RT may include impaired neurocognitive, neuroendocrine, ophthalmologic and audiometric function, altered skeletal growth, and small, increased risk of secondary tumors (benign and malignant). These toxicities are discussed in more detail in Part VIII of this book.

7.10 Future Directions

As more information is gained about the molecular subtypes of both supra- and infratentorial PNET, studies investigating novel targeted agents, either alone or in combination with standard multimodality therapy, may allow for reduced doses of chemotherapy and/or RT, with opportunity for improved tumor control and QOL outcomes in this vulnerable, young patient population.

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Atypical Teratoid Rhabdoid Tumors (AT/RT) and ETMR

8

Susan L. McGovern

Contents

Abstract

Atypical teratoid/rhabdoid tumors (AT/RT) and embryonal tumors with multilayered rosettes (ETMR) are embryonal tumors of the CNS that occur most commonly in infants and young children. AT/RT occurs sporadically or in a familial pattern due to mutation of *SMARCB1* and is diagnosed by the loss of INI1 nuclear staining. ETMR includes embryonal tumors with abundant neuropil and true rosettes (ETANTR), ependymoblastomas, and medulloepitheliomas and is characterized by LIN28A positivity and amplification of the *C19MC* miRNA cluster. Staging for both AT/RT and ETMR includes MRI of brain and spine with CSF

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analysis, and initial therapy is typically maximal safe resection. Postoperative therapy may include chemotherapy and radiation, depending on the age of the patient and spread of the tumor. Detailed roles for surgery, chemotherapy, and radiation will be reviewed in this chapter, with an emphasis on the use of radiation to treat AT/RT and ETMR of the CNS.

8.1 Epidemiology

Atypical teratoid/rhabdoid tumors (AT/RT) and embryonal tumors with multilayered rosettes (ETMR) are uncommon embryonal tumors primarily occurring in infants and young children. On average, 363 cases of AT/RT are diagnosed each year in the United States. Of these, 330 cases are in patients age 0–4 years with an incidence of 0.33 per 100,000 (Ostrom et al. 2014). ETMR occurs rarely and includes embryonal tumors with abundant neuropil and true rosettes (ETANTR), ependymoblastomas, and medulloepitheliomas (Paulus and Kleihues 2010).

8.2 Predisposing Factors

Loss of function of the *SMARCB1/INI1/SNF5/BAF47* gene on chromosome 22q11.2 is found in the majority of AT/RT cases (Versteege et al. 1998). Approximately one-third of AT/RT patients have a germline alteration in *SMARCB1* resulting from mutations, deletions, or intragenic insertions (Eaton et al. 2011). The development of ETMR is uniquely associated with amplification of the C19MC miRNA cluster at 19q13.42 (Korshunov et al. 2014; Spence et al. 2014).

8.3 Presenting Symptoms

AT/RT can develop anywhere in the central nervous system (CNS); about half of cases occur in the posterior fossa. About 20% of patients have disseminated disease at diagnosis (Hilden et al. 2004). In a series of 97 cases of ETMR, the primary site was supratentorial in 70% and infratentorial in 30%, with 20% of evaluable patients having metastatic disease at diagnosis (Korshunov et al. 2014).

Because AT/RT and ETMR are aggressive, rapidly growing tumors, symptoms develop fairly quickly, over days or weeks. Symptoms depend on the location of the tumor. For primary sites in the posterior fossa, patients may present with nausea, vomiting, and/or headaches due to hydrocephalus.

8.4 Radiographic Findings

There is marked variability in the imaging features of AT/RT. Generally, intracranial AT/RT tends to present as a large mass, with supratentorial tumors larger than infratentorial tumors (Warmuth-Metz et al. 2008). On CT imaging, AT/RT is

hyperdense compared to gray matter, likely reflecting the high cellular density of these tumors. Calcifications may or may not be present. On MRI, T1 and T2 signal intensity is variably hyper-, iso-, or hypointense relative to gray matter. Contrast enhancement is inconsistent; in a series of 32 cases, 16% had no enhancement, 37% had medium enhancement, and 63% had strong enhancement (Warmuth-Metz et al. 2008). The presence of calcification, hemorrhage, necrosis, cysts, or edema is also variable (Parmar et al. 2006). An example of an MRI of a supratentorial AT/RT is shown in Fig. 8.1.

Some authors have suggested that the presence of wavy, band-like enhancing zone surrounding an area of necrosis may be an imaging marker of AT/RT (Warmuth-Metz et al. 2008; Arslanoglu et al. 2004). Au Yong et al. reviewed 61 pediatric supratentorial tumors and found that the presence of a thick, wavy enhancing wall around a central area of necrosis had a negative predictive value of 95% and a positive predictive value of 63% for AT/RT (Au Yong et al. 2013).

Imaging features of ETMR are less defined, particularly given the histologic variety of these molecularly unified tumors. One recent work reviewed cases from the German HIT studies and compared imaging characteristics of 22 cases each of ependymoblastoma, ependymoma, and CNS-PNET NOS (Nowak et al. 2015). Compared to ependymoma, ependymoblastoma occurred in younger patients, with hypointense instead of isointense T1-weighted imaging with more clearly defined tumor borders and more homogenous enhancement. Large cysts greater than 1 cm diameter were more frequent in ependymoma. Compared to CNS-PNET NOS tumors, ependymoblastoma occurred in younger patients with larger tumors. All of the ependymoblastoma cases, 89% of the CNS-PNET NOS cases, and 80% of the ependymoma cases showed restricted diffusion, suggesting that diffusion-weighted imaging may be useful to discriminate between these high-cellularity tumors and lower-cellularity tumors such as low-grade gliomas.

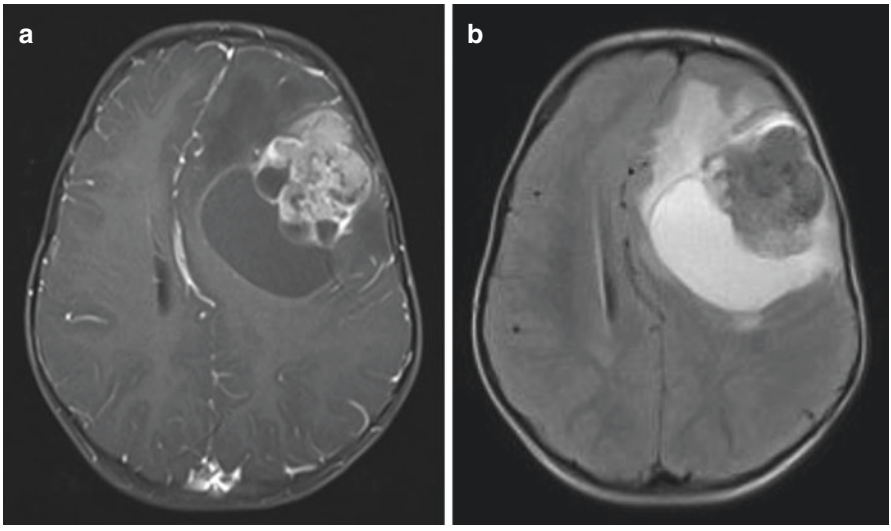

Fig. 8.1 MRI of supratentorial AT/RT in a 19-month-old boy. (**a**) Axial T1 with contrast. (**b**) Axial T2 FLAIR sequence

8.5 Workup

Because patients often present with the rapid onset of symptoms, initial evaluation usually prompts an urgent CT head that identifies a hyperdense mass, with or without additional metastatic sites. Acute management may include steroids to lessen edema and surgical placement of a shunt to address increased intracranial pressure due to obstructive hydrocephalus.

Surgical resection is both diagnostic and therapeutic, as it allows for pathologic diagnosis and also alleviates the mass effect of the tumor on the surrounding tissue. Depending on the clinical scenario, the initial diagnosis of AT/RT may be made after biopsy only or a maximal safe resection of the primary mass.

Histologically, AT/RT is characterized by the presence of rhabdoid cells and development along divergent pathways including neuroectodermal, mesenchymal, and epithelial lines. The defining diagnostic marker of AT/RT is loss of INI1 nuclear staining, which distinguishes AT/RT from other CNS tumors (Dunham 2010).

Correct diagnosis is critical for accurate therapy. Retrospective review of a Children's Cancer Group study of children less than 3 years old with brain tumors revealed that 10–15% had AT/RT on further pathologic study (Packer et al. 2002). These patients were enrolled prior to mandatory immunohistochemical analysis of tumor samples. In another series, only 12 of 22 patients were correctly diagnosed as having AT/RT based on their initial pathology review; ten patients were initially given other histologic diagnoses and were treated according to protocols for other tumor types (Slavc et al. 2014). Notably, three of those incorrectly diagnosed cases were initially diagnosed as ependymoblastomas.

One-third of AT/RT patients have germline abnormalities of *SMARCB1* that can cause rhabdoid tumors outside of the CNS, often in the kidney; these tumors are called malignant rhabdoid tumors (Eaton et al. 2011). The occurrence of two or more rhabdoid tumors in separate sites, such as the brain and kidney, should prompt referral for genetic testing (Eaton et al. 2011). Genetic abnormalities in *SMARCB1* are not specific for rhabdoid tumors; they can also be found in choroid plexus carcinoma, sarcomas, and primitive neuroectodermal tumors (Eaton et al. 2011). A family history of schwannomatosis should also trigger genetic evaluation due to its association with germline *SMARCB1* alterations (Boyd et al. 2008; Hulsebos et al. 2007; Swensen et al. 2009). These genetic alterations can also give rise to a variety of phenotypic findings, including developmental delay and heart defects (Jackson et al. 2007). Therefore, a detailed family history and clinical evaluation at the time of initial diagnosis of AT/RT are critical to identify patients and families that may be affected by these genetic abnormalities.

Combined LIN28A immunohistochemistry and FISH analysis of the 19q13.42 locus for amplification of the *C19MC* miRNA cluster are recommended as diagnostic markers for ETMR (Korshunov et al. 2014). LIN28 expression also occurs in gliomas and AT/RT (Deisch et al. 2011; Mao et al. 2013).

After initial diagnosis, complete evaluation includes an MRI of the total spine with and without contrast as well as cerebrospinal fluid (CSF) analysis to determine if disease has disseminated outside of the primary site. Both AT/RT and ETMR have

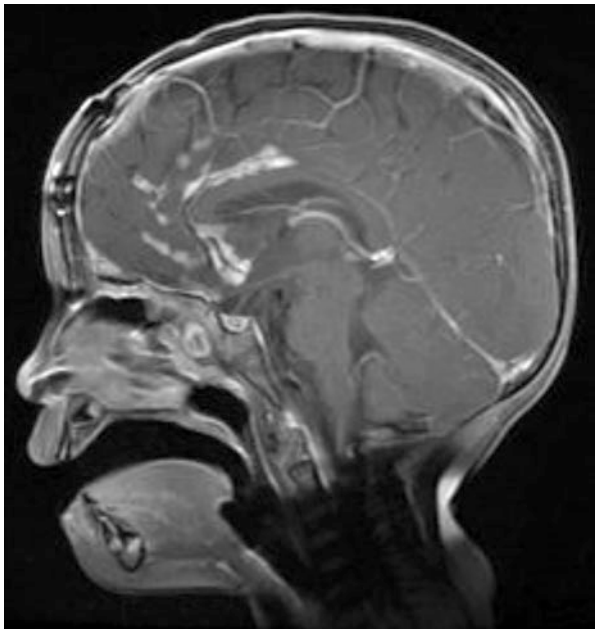

Fig. 8.2 Sagittal T1 with contrast imaging showing leptomeningeal spread of ETANTR in a 3-year-old girl

a propensity to spread within the neuroaxis; leptomeningeal spread of an ETANTR is shown in Fig. 8.2. The MRI spine should be obtained preoperatively, within 48 h postoperatively, or at least 2 weeks postoperatively. CSF should be obtained from a lumbar puncture performed at least 2 weeks postoperatively. Based on these results, the extent of disease spread is usually described using a modified Chang staging. Briefly, M0 is no disease outside of the primary site, M1 is microscopic spread to the CSF only, M2 is gross tumor deposits in metastatic sites within the brain, and M3 is gross tumor deposits in the spine (Chang et al. 1969).

8.6 Treatment

8.6.1 Surgery

Resection of AT/RT is diagnostic and therapeutic, and the extent of resection correlates with long-term survival outcomes. On the prospective Dana-Farber trial, the 2-year overall survival (OS) for patients undergoing a gross total resection (GTR) was 91%. The median OS for patients with less than a GTR was 18 months (Chi et al. 2009). Similarly, the AT/RT registry found that of 20 patients undergoing GTR, median survival was 20 months compared to 15.25 months for the 22 patients who received partial resection or biopsy alone (Hilden et al. 2004). Based on these data, second-look surgery was encouraged on the COG ACNS0333 protocol for AT/RT patients with tumors that became resectable after induction chemotherapy. Results from that trial are expected to inform future decisions

regarding the role of surgery. In the interim, maximal safe resection is the standard of care for AT/RT.

Small case series suggest that extent of resection also correlates with outcomes in ETMR. In a review of 11 cases of ependymoblastoma treated on the prospective HIT trials, the three patients in continuous complete remission all underwent GTR (Gerber et al. 2011). Similarly, in a review of eight patients with medulloepitheliomas, the two long-term survivors both had GTR, with one of those patients undergoing repeat GTR at the time of tumor recurrence (Molloy et al. 1996). Based on these small numbers, maximal safe resection is recommended for ETMR, consistent with treatment of other embryonal tumors.

8.6.2 Chemotherapy

Early approaches to ATRT were based on the third Intergroup Rhabdomyosarcoma Study (IRS-III) protocol for parameningeal rhabdomyosarcoma, Regimen 36. Using this multidisciplinary approach, Weinblatt and Kochen reported on one of the first AT/RT patients with a long-term remission (Weinblatt and Kochen 1992). Similarly, Olsen et al. described three patients treated similarly who also had prolonged survival (Olson et al. 1995). Investigators from the Dana-Farber Cancer Institute (DFCI) then described four patients, two with newly diagnosed disease and two with relapsed disease, treated according to a modified IRS-III protocol that were without evidence of disease at a median of 3 years 1 month after treatment (Zimmerman et al. 2005).

These encouraging results led to the first prospective study in AT/RT, a phase II study led by the DFCI (Chi et al. 2009). After maximal safe resection, patients received pre-irradiation induction chemotherapy, concurrent chemoradiation, post-irradiation induction chemotherapy, maintenance therapy, and continuation therapy. The IRS-III chemotherapy backbone included vincristine, dactinomycin, cyclophosphamide, cisplatin, doxorubicin, and imidazole carboximide (DTIC). On the DFCI protocol, temozolomide was used instead of DTIC because of its ability to penetrate the CNS. The DFCI protocol also included intrathecal chemotherapy with methotrexate, cytarabine, and hydrocortisone. Evaluation prior to radiation therapy yielded a chemotherapy response rate of 58% in 12 evaluable patients. Overall, this aggressive 51-week regimen yielded encouraging results, with a 2-year progression-free survival (PFS) of 53% and OS of 70%.

For children less than 3 years of age, several efforts have been made to avoid or delay radiotherapy. The POG 9233/34 study included 36 patients with AT/RT that were randomized to receive standard or dose-intensified cyclophosphamide and vincristine (Strother et al. 2014). These patients all died of disease, with a median survival of 6.7 months (Ginn and Gajjar 2012). On the CCG-9921 study, children less than 36 months old were treated with vincristine, cisplatin, cyclophosphamide, or etoposide vs. vincristine, carboplatin, ifosfamide, and etoposide. Patients with residual tumor or metastatic disease received delayed radiation; patients without residual tumor did not receive radiation until progression. Of 28 patients with

rhabdoid tumors, the 5-year event-free survival was 14% (Geyer et al. 2005). Notably, on both the POG and CCG studies, the diagnosis of AT/RT was made based on the histologic appearance of the tumor, not on molecular testing.

Given these results with conventional chemotherapy, high-dose chemotherapy (HDC) with stem cell rescue (SCR) has been pursued to intensify therapy while still avoiding or delaying radiation. On the Head Start I, postoperative patients underwent five cycles of induction with cisplatin, vincristine, cyclophosphamide, and etoposide. This was followed by consolidation with carboplatin, thiotepa, and etoposide with SCR. Head Start II was similarly designed with the addition of high-dose methotrexate to each cycle of induction chemotherapy. (Gardner et al. 2008). All six patients on Head Start I died of disease. Three of seven patients treated on Head Start II were alive without disease, yielding a 3-year EFS of 43%. These results support a role for methotrexate in the treatment of AT/RT.

On Head Start III, cisplatin and high-dose methotrexate alternated with temozolomide for five cycles of induction chemotherapy that also included cyclophosphamide, vincristine, and etoposide. This was followed by second-look surgery and consolidation with HDC with SCR. Patients 6–10 years old or with residual tumor prior to consolidation received radiation after consolidation. Of 19 patients enrolled, five died from toxicity during induction. Only four patients completed the five planned cycles of induction therapy, and three of those patients completed HDC with SCR. One of those patients had a continuous complete response, and two had partial responses. The 3-year EFS and OS were 21% and 26% (Zaky et al. 2014).

Based on the results described above, the COG study ACNS0333 includes two cycles of intense induction chemotherapy, similar to the POG9923 and CCG-9921 approaches, with systemic methotrexate as in Head Start II. Consolidation includes three cycles of HDC with carboplatin and thiotepa with SCR, based on results from CCG 99703. The COG study is currently closed to accrual and results are anticipated to direct development of the next generation of systemic therapies for AT/RT.

The optimal chemotherapy approach for ETMR remains unknown. From an analysis of 36 patients with PNET of the CNS with C19MC amplification and LIN28 positivity, Spence et al. found that patients receiving chemotherapy with or without radiation had a median survival of 13 months compared to 0.06 months for patients receiving no therapy ($p = 0.004$) (Spence et al. 2014). In published case report in the literature, patients have generally been treated according to CNS-PNET protocols or protocols designed for infants with malignant brain tumors such as CCG 99703 (Lafay-Cousin et al. 2014). From a review of 11 patients with ependymoblastoma treated on the HIT protocols, one patient survived after HDC without radiation, one patient had a response after conventional chemotherapy, and four patients had early relapses during induction chemotherapy prior to RT. Based on these observations, the authors suggest that at least for patients with residual disease after surgery, induction chemotherapy should be relatively short (Gerber et al. 2011). There is also a case report of transient maturation of ETMR after chemotherapy delivered according to CCG 99703 (Lafay-Cousin et al. 2014). Although the patient subsequently developed recurrent disease, her overall survival from diagnosis was 21 months, which is encouraging.

8.6.3 Radiation Therapy

Because of the young age of most AT/RT patients, the use of radiation for this tumor has been controversial (Squire et al. 2007). Early efforts focused on approaches that delayed radiotherapy, based on results from medulloblastoma that chemotherapy can delay radiation until after 3 years of age (Duffner et al. 1993). One of the earliest series in AT/RT came from a registry that followed 42 patients. Of 13 patients who received radiation, eight were alive without evidence of disease at least 19 months from diagnosis (Hilden et al. 2004). In a review of the St. Jude's experience, ten children treated with chemotherapy and radiation had a 2-year OS estimate of 90% vs. 12% for 21 children treated without radiation (Tekautz et al. 2005).

A recent review of 12 publications describing 332 children and adolescents with AT/RT found that initial radiotherapy was associated with improved RFS and OS (Schrey et al. 2016). Of 238 patients with radiation data, 118 had received either focal, cranial, or craniospinal radiation. The median RFS of patients who received radiation was 12.1 months, compared to 4 months for patients not receiving radiation ($p < 0.001$). Similarly, the median OS of patients receiving radiation was 23 months vs. 10 months for patients treated without initial radiation ($p < 0.001$). The association of upfront radiation with significantly improved RFS and OS was upheld on multivariate analyses including intrathecal chemotherapy, extent of surgery, and HDC with SCR. Based on emerging evidence supporting a role for radiation in AT/RT, the use of radiation has increased from 22.3% of cases diagnosed between 1973 and 2004 to 38.4% of cases since 2005 (Lau et al. 2015).

The optimal use of radiation in ETMR is unknown. In a literature review by Alexiou et al., 17 of 72 patients received radiation and had a better median OS compared to patients who did not receive radiation, 16 months vs. 11 months ($p = 0.029$) (Alexiou et al. 2013). Mozes et al. reviewed cases of seven children with recurrent ETANTR and found that the four patients who received radiation had better mean OS than the three who did not, 31.5 months vs. 24.0 months (Mozes et al. 2016). Based on these results, a role for radiation in ETMR is emerging, but clearly more data are needed.

8.6.4 Radiation Fields and Doses

Optimal radiation treatment fields for ATRT remain unknown. In the initial DFCI report, patients with M0 disease at presentation received local radiation, and patients older than 3 years with M+ disease received CSI (Chi et al. 2009). CSI was delivered to 36 Gy and local fields were treated to 54 Gy. All patients received intrathecal chemotherapy although it is unclear if intrathecal chemotherapy can substitute for CSI.

On the COG study ACNS0333, patients with M0 disease at least 6 months old with an infratentorial tumor or at least 12 months old with a supratentorial tumor received focal RT after two cycles of induction chemotherapy. Younger M0 patients received focal RT after completing induction and consolidation chemotherapy.

Patients with M+ disease at enrollment were encouraged but not mandated to receive age-adjusted CSI after induction and consolidation chemotherapy. For patients with M0 disease younger than 36 months, local fields were treated to 50.4 Gy, and for patients older than 36 months, local fields were treated to 54 Gy. Patients with M+ disease younger than 36 months were treated with CSI to 23.4 Gy and patients older than 36 months were treated with CSI to 36 Gy. All treatment was delivered at 1.8 Gy/fraction, one fraction per day.

Patients at least 3 years old were eligible for SJMB03, on which all ATRT patients received CSI after surgery. Patients with M0 disease and less than 1.5 cm^3 residual tumor were classified as average risk and treated with CSI to 23.4 Gy followed by a boost to the tumor bed to 55.8 Gy. Patients with M+ disease or more than 1.5 cm^3 residual tumor were classified as high risk and received 36–39.6 Gy CSI. After a 6-week rest period, all patients received four cycles HDC with peripheral blood stem cell support.

Results from ACNS0333 and SJMB03 are awaited to better define optimal radiation fields for ATRT, especially for M0 patients. In our retrospective review of our experience treating 31 patients with ATRT with proton therapy, one patient failed on the margin of the radiation field and seven patients failed in the neuroaxis but outside of the high dose volume (McGovern et al. 2014). These results demonstrate the efficacy of radiation in AT/RT, but especially in very young patients the risk of radiation exposure must be balanced against the long-term effects of radiation. Proton therapy may alter this toxicity equation by decreasing radiation dose to normal tissues. Results from MD Anderson (McGovern et al. 2014), the Paul Scherrer Institute (Weber et al. 2015) and Massachusetts General Hospital (De Amorim et al. 2013) show that proton therapy for AT/RT in young patients is well tolerated with acceptable short-term side effects; longer follow-up is clearly needed in this population.

Radiation fields and doses for ETMR are not defined but are typically based on those for PNET or AT/RT. In our institutional review of seven patients with ETMR treated with proton therapy, the median age at radiation start was 42 months (range, 17–58 months). Two patients received local fields only to 50.4 or 54 Gy(RBE) and five received CSI to 36 Gy(RBE) followed by a tumor bed boost to 45–55.8 Gy(RBE).

8.7 Outcomes

After completion of therapy, surveillance of patients with AT/RT or ETMR is similar to that for patients with PNET. Follow-up should include MRI of the brain and spine every 3 months for the first 1–2 years after therapy, then every 6–12 months thereafter. Patients are at risk for early and late recurrence in the CNS. Progression prior to initiation of radiation is well documented and portends a poor prognosis (Chi et al. 2009; McGovern et al. 2014). In addition to the risk of recurrence, patients are at risk for the sequelae of treatment and should be followed for specific toxicities including neurocognitive, endocrine, auditory, and visual deficits. Guidelines for long-term follow-up for pediatric survivors of CNS tumors have been published by the COG (Group CsO 2014).

Historically, survival in AT/RT has been bleak, typically less than 1 year (Burger et al. 1998). In the most recent CBTRUS analysis of SEER data from 2007 to 2011, OS in ATRT was 48.1%, 27.5%, and 26.0% at 1, 5, and 10 years (Ostrom et al. 2015). Radiation may contribute to improved outcomes in more recent studies. On the DFCI 02-0294 study, in which 15 of 20 evaluable patients received radiation, the 2-year PFS and OS were 53% and 70% (Chi et al. 2009). As detailed above, a recent literature review of 332 cases of AT/RT also found that initial radiation was associated with improved RFS and OS (Schrey et al. 2016). Results from ACNS0333 and SJMB03 are awaited for additional prospective survival data.

Patients with familial AT/RT tend to have worse outcomes than those with sporadic disease. In a retrospective review of 20 patients with AT/RT, children with familial AT/RT were diagnosed at a median age of 4.8 months and had a median OS of 4.5 months. This was markedly worse than patients with sporadic AT/RT, who were diagnosed at a median age of 13 months and had a median OS of 21 months (Bruggers et al. 2011). The younger age of children with familial disease limits therapeutic options and likely contributes to their bleak outcomes.

Outcomes for ETMR tend to be worse than for classic supratentorial PNET. Of 11 children with ependymoblastoma treated on the prospective German HIT trials, 5-year PFS was 36.4% and 5-year OS was 30.3% (Gerber et al. 2011). The four survivors in this group had either craniospinal radiation and/or HDC-SCR, suggesting that multi-modality therapy may contribute to better outcomes for these patients. Preliminary data from a literature review from our institution identified 178 reported cases of ETMR with a median OS of 10 months from diagnosis. Eighteen of these patients were long-term survivors, with a median survival of 77.2 months from diagnosis; 17 of the 18 long-term survivors received radiation.

8.8 Toxicities

The aggressive multi-modality therapy used to treat patients with AT/RT and ETMR can cause long-term effects, affecting a variety of body systems. Because of the very young age of most patients, neurocognitive outcomes are a primary concern. Even in the absence of radiation therapy, long-term survivors of AT/RT can have neurocognitive deficits, as demonstrated in a cohort of 11 patients in the Canadian Registry (Lafay-Cousin et al. 2015). This observation was upheld in a larger study of 224 patients from St. Jude's, which found that long-term survivors of pediatric CNS tumors had neurocognitive impairment compared to normative national data, even in patients that received no radiation. The degree of impairment varied with the volume of radiation exposure. For instance, in a measure of long-term memory, 11% of survivors with no cranial radiation showed impairment compared to 25% of patients treated with focal cranial RT and 36% exposed to CSI (Brinkman et al. 2016). Long-term survivors who have received radiation are also at risk for pulmonary, endocrine, cardiovascular, and gastrointestinal dysfunction, especially after CSI (Huang et al. 2014; Saha et al. 2014).

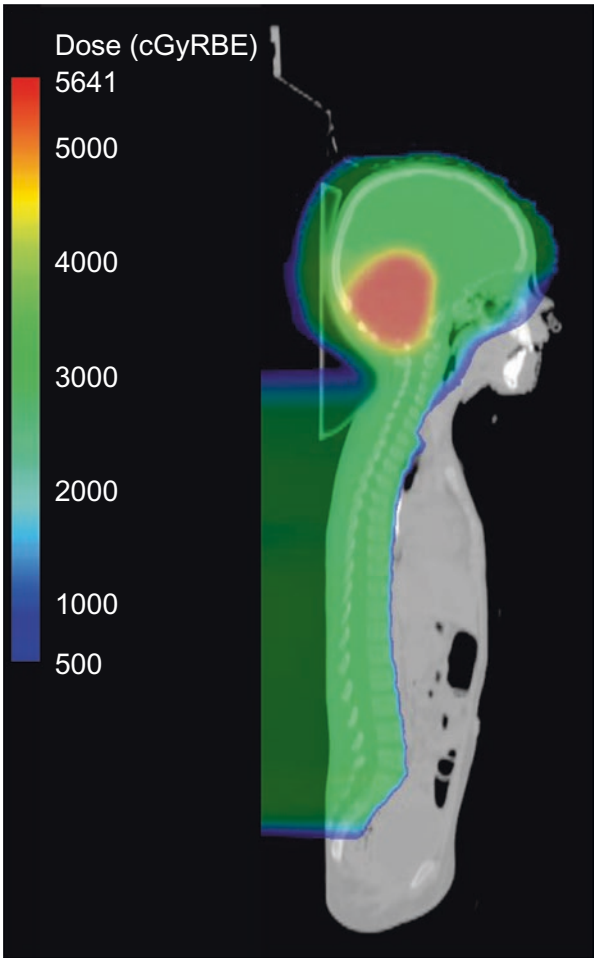

Fig. 8.3 Craniospinal and boost plan with proton therapy for a 4-year-old girl with M0 AT/RT of the posterior fossa. The craniospinal axis was treated to 30.6 GyRBE and the tumor bed was boosted to 54 GyRBE

Ongoing research into proton therapy for treating pediatric malignancies offers one avenue for decreasing the long-term toxicity of treatment. For instance, proton therapy may improve neurocognitive outcomes compared to photon therapy (Kahalley et al. 2016), which would be especially beneficial for young patients with AT/RT and ETMR. It may also decrease the risk of systemic toxicities (Yock et al. 2016) by decreasing dose to anterior structures for patients receiving CSI (Fig. 8.3).

8.9 Future Directions

Although multi-modality treatments are effective against these aggressive CNS tumors, the late effects of therapy can be substantial. Therefore, research into the biology and pathophysiology of AT/RT and ETMR continues, with the goals of

improving our understanding of these entities and ultimately of providing more targeted therapy for the young children affected by them.

The basic biology and pathology of ETMR is still emerging. As the nature of this tumor is better defined, it is hoped that more focused treatments will emerge from this knowledge. Although AT/RT is better understood than ETMR, ongoing research aims to understand the genetic and epigenetic disruptions that lead to the development of these tumors, with the goal of identifying patients that would benefit from more or less aggressive therapy, and ultimately developing more specific treatments (Bourdeaut et al. 2014; Fruhwald et al. 2016). Due to the rarity of AT/RT, progress depends on multi-institutional and often multinational cooperation. For instance, by combining molecular and clinical features, an international collaboration identified three distinct clinical risk groups in AT/RT, including a group with long-term radiation-free survival (Torchia et al. 2015). A German consortium has identified three distinct epigenetic subgroups of AT/RT tumors; each subgroup offers potential therapeutic targets (Johann et al. 2016). It is hoped that such Herculean scientific efforts will ultimately lead to the development of new therapies for these lethal tumors.

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Part III

Glial Tumors

Ependymoma

9

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Abstract

Childhood ependymoma is an aggressive malignant brain tumor that affects a vulnerable group of patients. Young age at presentation, tumor and surgery related morbidity, and tumor association with critical normal tissue structures create a formidable challenge for the pediatric radiation oncologist. The use of advanced methods of radiation therapy in clinical trials during the past 20 years has improved disease and functional outcomes for these patients and provided an example for the treatment of other tumors that affect children in a similar manner. An improved understanding of the biology of ependymoma may impact future treatment decisions and the sequencing of irradiation as well as radiation dose and volume.

9.1 Introduction

Ependymoma (EPN) is a neuroepithelial tumor that typically arises from the ependymal lining of the ventricular system or central canal of the spinal cord (Smyth et al. 2000). Approximately 90% of pediatric EPNs are intracranial, with most involving the ependymal lining of the fourth ventricle. The most common location for EPN is the posterior fossa (PF) (Smyth et al. 2000; Vaidya et al. 2012). Up to 30% of intracranial EPNs are located in the supratentorial (ST) compartment arising from the lateral or third ventricle or as intraparenchymal lesions remote from the ventricular system (Smyth et al. 2000; Reni et al. 2007). Spinal cord EPNs (occurring in <10% of pediatric patients) (Reni et al. 2007) are common in the central canal of the cervical-thoracic spinal cord and appear rarely as myxopapillary tumors in the filum terminale, conus medullaris, or cauda equina (Teo et al. 2003; Zacharoulis and Moreno 2009) (Fig. 9.1).

EPN accounts for 6–10% of brain tumors in children. At presentation, current standard initial treatment for children with EPN consists of maximally safe surgical resection, with the goal of gross total resection (GTR), and postoperative standard fractionated radiation therapy (RT) for microscopic residual tumor (Hoffman et al. 2014). By using this approach, 5-year overall survival (OS) and event-free survival (EFS) of 86% and 55%, respectively, have been achieved (Gajjar et al. 2013). EPN can spread locally into adjacent structures or via the cerebrospinal fluid (CSF) throughout the subarachnoid space (drop metastasis) (Paulino et al. 2002), especially in the case of high-grade tumors. "Sugar coating" of the meninges does not constitute metastatic disease and is likely an inflammatory process. EPN metastases most often appear to be nodular (Fig. 9.2).

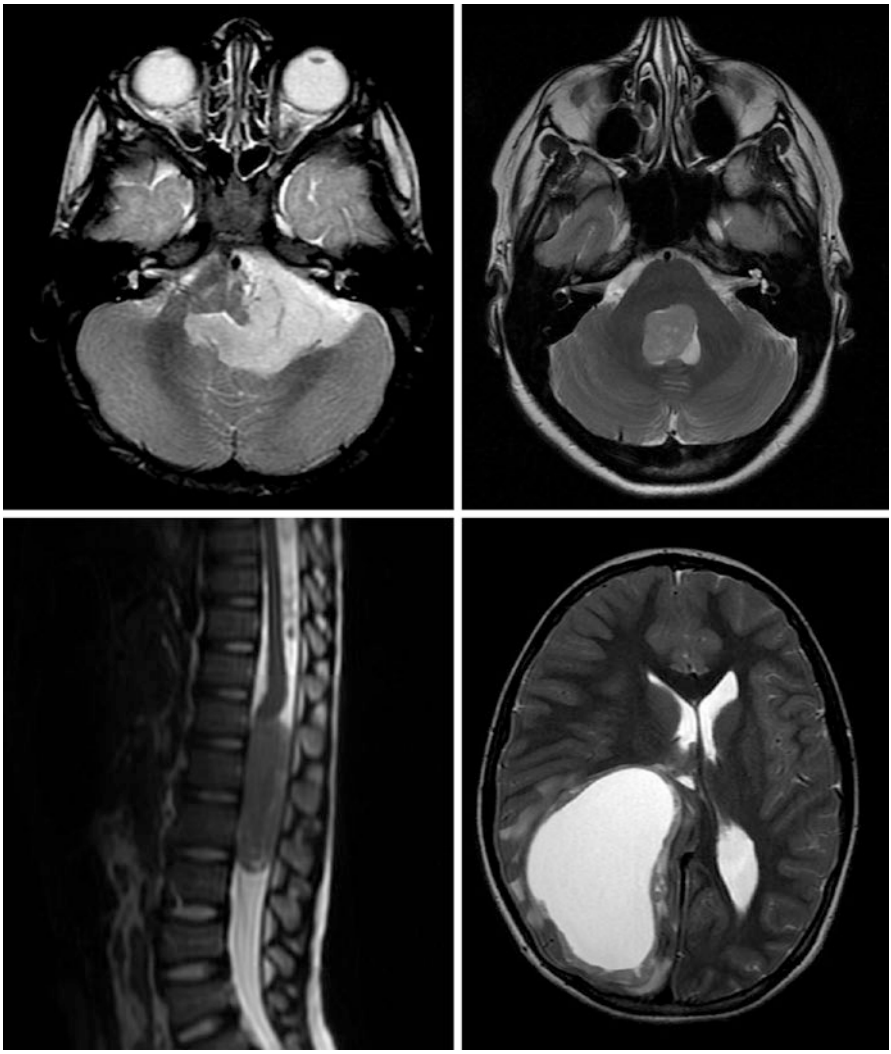

Fig. 9.1 Left cerebellopontine angle ependymoma (*upper left*), IVth ventricle ependymoma (*upper right*), spinal cord ependymoma (*lower left*), and right fronto-parietal ependymoma (*lower right*)

The clinical behavior of ependymal tumors is highly variable, and approximately 40% of patients might not be cured because of the paucity of effective and easily available treatment options (Merchant 2009). Surgical resection is the first line of treatment. Several studies have shown the benefits of adjuvant radiotherapy although the ideal volume of irradiation remains controversial. The role of chemotherapy, however, is uncertain, with little evidence supporting its use (Vaidya et al. 2012).

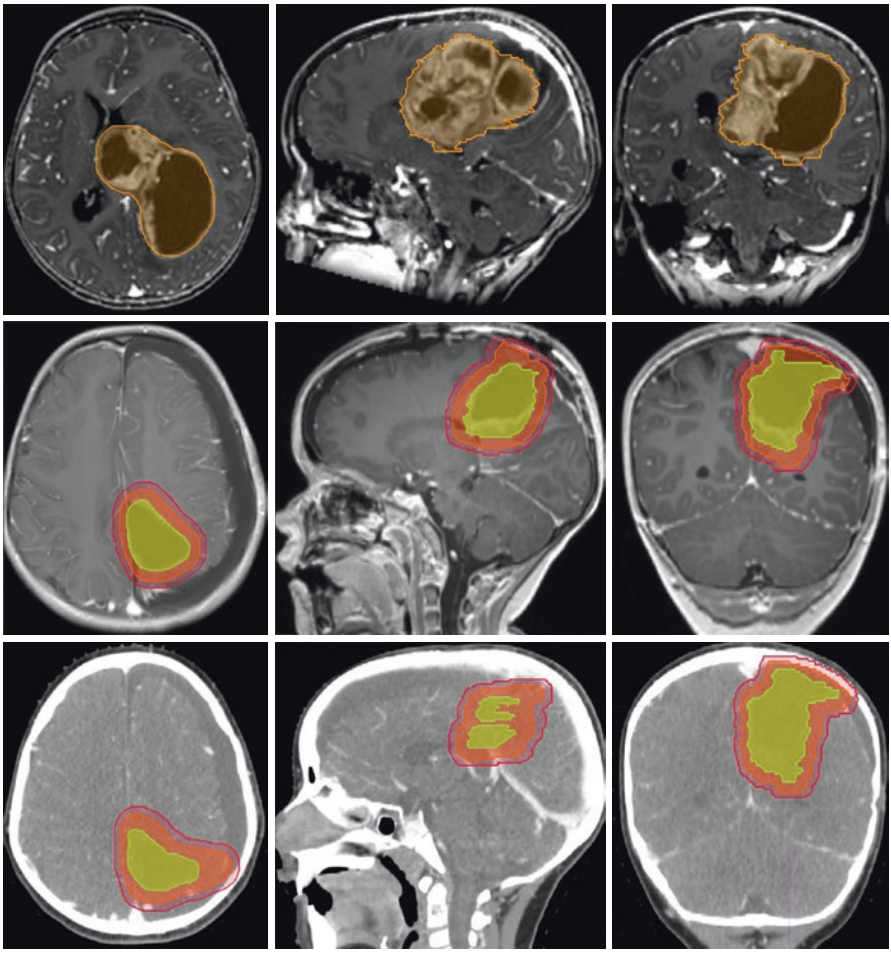

Fig. 9.2 Supratentorial ependymoma preoperative (*upper row*) MR images; postoperative (*middle row*) MR images showing gross-tumor volume (*yellow*), clinical target volume (*orange*), and planning target volume (*red*); postoperative contrast-enhanced treatment planning CT (*lower row*) showing target volumes as outlined on MR

The prognosis for pediatric EPN remains poorer than that for other brain tumors. Definitive prognostic factors include extent of tumor resection, presence of metastases at initial diagnosis, and age at presentation (Reni et al. 2007; Shim et al. 2009). The significance of factors such as tumor location and histopathologic grade and the role of adjuvant therapy remain unclear (Reni et al. 2007; Shim et al. 2009). Research is currently focused on the molecular subtyping of EPN to define diverse subgroups and more accurately predict the expected behavior of each subgroup (Vaidya et al. 2012).

9.2 Prognostic Factors

9.2.1 Age at Presentation

Most studies on pediatric EPN have reported younger age at presentation as an adverse prognostic factor. In three studies, the 5-year OS was 22–42% in children aged 3 years or younger compared with 69–75% for those older than 3 years (Paulino et al. 2002; Perilongo et al. 1997; Pollack et al. 1995). Delay in diagnosis due to nonspecific signs or symptoms (Tamburrini et al. 2009), more aggressive tumor biology (Nazar et al. 1990), delay or avoidance of irradiation (Duffner et al. 1998), and lower radiation doses (Duffner et al. 1998) can affect results in younger children.

9.2.2 Extent of Surgical Resection

The extent of resection is the single most important prognostic factor for EPN (Paulino et al. 2002; Perilongo et al. 1997; Pollack et al. 1995; Duffner et al. 1993; Massimino et al. 2004; Merchant et al. 2009; Robertson et al. 1998; Rousseau et al. 1994). Advances in surgical techniques, such as operating microscopes and image-guided resection, have led to improvement in patient outcomes. A study reported that the 5-year progression-free survival (PFS) was 51–79% for patients who underwent complete resection compared with 9–44% for those who underwent subtotal resection (STR) (Vaidya et al. 2012). The fact that more than 90% of tumor recurrence occurs locally highlights the importance of complete resection (Nazar et al. 1990; Chiu et al. 1992).

9.2.3 Site of Primary Tumor

The ability to resect a tumor is highly dependent on the tumor site within the central nervous system (CNS). In a review of ten studies reporting 307 patients, complete resection was achieved in 53% of 128 patients with ST-EPN (Bouffet et al. 1998). Complete resection was achieved in only 29% of the 179 children with infratentorial lesions. Spinal cord tumors, however, were excised without affecting function in only 27–45% of patients. This disparity arises because surgical resection is more difficult for PF-EPNs because of frequent involvement of the brainstem and multiple cranial nerves (Tamburrini et al. 2009). Higher rates of complete resection for ST-EPNs likely explain the better prognosis and disease-free survival rates for children with these tumors (Vaidya et al. 2012).

The current standard of care for EPN includes maximal safe surgical resection, followed by focal radiotherapy (Merchant 2009; Merchant et al. 2009). Several reports indicate that there was no tumor recurrence in a subset of patients with completely

resected ST tumors even in the absence of adjuvant therapy (Venkatramani et al. 2012), which underscores the need for better stratification of patients. Furthermore, although adjuvant chemotherapy continues to be a part of many trial protocols, especially in young children for avoiding or delaying RT, several clinical trials have found no survival benefit of adding chemotherapy at the time of primary diagnosis or at recurrence (Duffner et al. 1993; Bouffet et al. 2009; Bouffet and Foreman 1999).

9.2.4 Histopathologic Grade

Accurate histopathologic diagnosis according to the World Health Organization (WHO) classification for CNS tumors (Ellison et al. 2011; Louis et al. 2007; Pajtler et al. 2015) is challenging for ependymal tumors. Distinction between grade II EPN and grade III anaplastic EPN is often difficult, with poor interobserver reproducibility, even if performed by experienced neuropathologists (Ellison et al. 2011). Grade I EPN, or myxopapillary (occurring in the spine) and subependymomas (SEs; occurring across all compartments), generally have more readily distinguishable histopathologic characteristics. However, the grading of EPNs can be complicated because many tumors show isolated areas, each representing distinct grades, which presents a challenge to predict which tumor component will influence the overall biologic behavior (Pajtler et al. 2015).

The role of histopathologic grade as a prognostic factor remains contradictory. A review reported that the 5-year OS was 10–47% for patients with anaplastic EPN and 55–87% for those with low-grade tumors (Reni et al. 2007). Contrary to this, some studies have reported no differences in survival—or even an opposite survival trend—for patients with anaplastic EPN or low-grade tumors. Two studies reported a 5-year PFS of 78% and 46% for patients with anaplastic tumors and a 5-year PFS of 17% and 57% for those with low-grade tumors (Robertson et al. 1998; Rousseau et al. 1994). Classification of EPN tumors by molecular subtype is likely to obviate the need for conventional histopathologic classification in the coming years.

9.2.5 Molecular Prognostic Factors

Despite the histopathologic similarities among variants of EPN at different anatomic sites, the molecular biology of EPN remains heterogeneous and is associated with distinct genetic and epigenetic alterations as well as diverse transcriptional programs (Carter et al. 2002; Dyer et al. 2002; Korshunov et al. 2010; Mack et al. 2014; Mendrzyk et al. 2006; Parker et al. 2014; Wani et al. 2012; Witt et al. 2011). Functional cross-species studies reveal that these molecular differences reflect regionally discrete cells of origin (Parker et al. 2014; Johnson et al. 2010; Taylor et al. 2005). An association between neurofibromatosis type 2 (i.e., germline mutations in the *NF2* gene) and sporadic mutations in *NF2* has long been known as a hallmark genetic aberration in spinal EPN (Ebert et al. 1999; Rubio et al. 1994).

Other immunohistochemical markers have not adequately reflected the biologic heterogeneity of EPN and cannot reliably distinguish between histologic grades and

subgroups of EPNs. The only molecular marker that has been consistently associated with unfavorable outcome is gain of chromosome arm 1q (Korshunov et al. 2010; Mendrzyk et al. 2006; Godfraind et al. 2012; Kilday et al. 2012; Modena et al. 2012), particularly in childhood PF-EPN. Homozygous deletion of the CDKN2A/B locus is another marker associated with inferior prognosis, mainly in ST-EPN (Korshunov et al. 2010).

Recent large-scale genomic and epigenomic studies have revealed the first driver genes in ST-EPNs. Fusions between *RELA*, which encodes an NF-kB component, and the poorly characterized gene *C11orf95* resulting from chromothripsis (local chromosome shattering) on chromosome 11 occur in more than 70% of patients with ST-EPNs (Parker et al. 2014). Strikingly, the *C11orf95–RELA* fusion alone can drive tumorigenesis when aberrantly expressed in neural stem cells (Parker et al. 2014).

For PF-EPNs, two distinct molecular subgroups were consistently identified in two independent studies that used different methods and nonoverlapping patient cohorts (Wani et al. 2012; Witt et al. 2011). These subgroups [provisionally termed PF Group A (PFA) and PF Group B (PFB)] are associated with distinct transcriptomic, genetic, epigenetic, and clinical features and are much more informative than WHO grading alone (Archer and Pomeroy 2011).

In 2015, Pajtler et al. used genome-wide DNA methylation patterns to identify nine distinct molecular subgroups of ependymal tumors across all age groups (three subtypes in each anatomic compartment of the CNS) (Pajtler et al. 2015):

- Spine (SP), with subtypes SE, MPE, and EPN (with NF2 association), all associated with excellent OS and PFS
- PF, with subtypes SE, EPN-A, and EPN-B
- ST, with subtypes SE, EPN-YAP1, and EPN-*RELA*

These molecular subgroups are genetically, epigenetically, transcriptionally, demographically, and clinically distinct. Whether they also have different cells of origin, as suggested by Johnson et al. (2010), remains to be proven in further functional studies. A biologic classification might help researchers and clinicians to better understand the heterogeneity of this disease as compared with the epigenetic subgroups of medulloblastoma (Kool et al. 2012). For example, Pajtler et al. showed that patients in the PF-EPN-A and ST-EPN-*RELA* (*C11orf95–RELA* fusion) subgroups had dismal outcomes with current treatment approaches. These patients were in the high-risk category, with a 10-year OS of approximately 50% and a 10-year PFS of approximately 20% (Pajtler et al. 2015).

9.3 Radiation Therapy

9.3.1 Radiation Dose

There is sufficient evidence to show that adjuvant postoperative RT, when compared to surgery alone, improves local control and is associated with a more favorable

prognosis. Although data from prospective randomized trials are scarce largely due to rarity of the tumor, multiple retrospective studies have demonstrated that adjuvant RT improves local control as well as OS in patients with EPN. Thus, RT is currently considered to be standard adjuvant therapy after the resection of intracranial EPN (Chan and McMullen 2012; Stuben et al. 1997). The total dose varies from 45 to 54 Gy to the tumor bed in 1.5–1.8 Gy/fraction. Boost doses of approximately 10Gy have been recommended for macroscopic disease in some studies (Reni et al. 2007; Stuben et al. 1997). Two studies showed that higher radiation doses can improve outcomes in intracranial EPN: the 5-year OS for patients given a dose of >50 Gy was 58% and 51%, compared with 33% and 18% for those given a dose of ≤50 Gy (Chiu et al. 1992; Goldwein et al. 1990). Dose escalation to 66Gy by using hyper-fractionated RT was safe but was not associated with an improvement in outcome (Conter et al. 2009).

A total dose of 54 Gy is widely considered as the minimum dose required for local tumor control with gross residual and tumor bed concentrations of microscopic disease. Higher doses are considered to be more efficacious based on the first principles of RT and our understanding that local failure is a dominant component of first failure. The standard RT dose for patients without residual disease is 54–59.4 Gy in 1.8 Gy/fraction, and a more recent series used 59.4 Gy at 1.8 Gy/day for all patients except those under the age of 18 months who underwent GTR and had been treated with a dose of 54 Gy.

9.3.2 Irradiation Volume

A controversial aspect in the RT management of pediatric EPN is determining the appropriate field size and volume for irradiation [local field or craniospinal irradiation (CSI)]. CSI involves prophylactic irradiation of the entire craniospinal axis, with additional focal boost to tumor sites (Merchant and Fouladi 2005).

Previous studies showed that EPN had a predilection for leptomeningeal failures with high rates of metastatic seeding (32%) (Nazar et al. 1990; Merchant et al. 1997; Salazar et al. 1975). Consequently, CSI was the standard RT approach used for EPN for many years. These earlier studies had flaws and biases, including autopsy findings of seeding in patients who died because of local disease. Another problem was that these studies were largely conducted before the introduction of magnetic resonance imaging (MRI), when the extent of disease was not accurately known. The improvement in imaging techniques to adequately stage the craniospinal axis and modern patterns of failure studies has shown that isolated spinal failures for intracranial EPN are rare even in the absence of CSI (Perilongo et al. 1997; Rezai et al. 1996; Taylor 2004). More recent studies have reported seeding rates of only 3–10% (Pollack et al. 1995; Merchant et al. 1997; Vanuytsel and Brada 1991; Wallner et al. 1986). Therefore, the majority of spinal failures will occur in patients with pre-existing local failure (Rezai et al. 1996; Sutton et al. 1990). Reviews have confirmed that patients with localized disease do not require prophylactic CSI irradiation, because more than 90% of the recurrence occurs locally (Nazar et al. 1990;

Table 9.1 Clinical target volume margins by clinical trial

Clinical trial (sponsor)	CTV margin	Month/year of activation and identifier (clinicaltrials.gov)
ACNS0121 (COG)	Post-op tumor bed +1.0 cm	August 2003
		NCT00027846
SJYC07 (St. Jude)	Post-op tumor bed +0.5 cm	November 2007
		NCT00602667
ACNS0831 (COG)	Post-op tumor bed +0.5 cm	March 2010
		NCT01096368

Abbreviations: *CTV* clinical target volume, *COG* Children's Oncology Group, *post-op* postoperative, *St. Jude* St. Jude Children's Research Hospital

Chiu et al. 1992) and the additional morbidity associated with CSI cannot be justified. Even for anaplastic and infratentorial EPN, which are associated with a poor prognosis, prophylactic CSI has not resulted in a survival benefit (Timmermann et al. 2005). Thus, local-field RT has become the standard treatment volume for intracranial EPN (Chan and McMullen 2012).

Defining the clinical target volume (CTV) for local-field RT in EPN has been the subject of intense debate. A large study by Merchant et al. established that a 1-cm CTV margin around the tumor cavity to account for the microscopic extent of disease is sufficient to achieve high levels of local control in the setting of GTR (Merchant et al. 1999). This 1-cm margin was the established CTV margin used in the recent Children's Oncology Group (COG) trial ACNS0121. Interestingly, patterns of failure and treatment effects data from St. Jude Children's Research Hospital (St. Jude) indicate that a smaller CTV margin can likely allow adequate local control and possibly reduce neurocognitive late effects (Merchant et al. 2002a). The COG trial ACNS0831 is investigating a further reduction in treatment volume to a 5 mm CTV to 54Gy and no CTV expansion for the final boost treatment to 59.4 Gy (Chan and McMullen 2012) (Table 9.1).

9.3.3 Imaging and Treatment Planning

EPN can exhibit heterogeneous enhancement (i.e., portions of the gross tumor might not show enhancement). Both T1 and T2 MRI might be required to adequately establish the full extent of the target. Given the significant anatomic distortion after surgery for EPNs, particularly those in the PF, proper definition of the resection cavity must include review of preoperative and postoperative MRI to include the full extent of the initial disease within the gross target volume (Chan and McMullen 2012).

The combination of computed tomography planning and MRI has some limitations in the PF, and some common artifacts in that region can lead to misinterpretation of the target definition. Alignment of the spinal cord can be problematic when diagnostic images are acquired in a position different from that used for treatment. MRI to identify the target should be performed in the same simulation position to improve the quality of image fusion and target delineation.

9.3.4 Very Young Children

The treatment of very young children with primary brain tumors is particularly challenging. For example, in very young patients with medulloblastoma, standard management is chemotherapy to delay CSI until the patient reaches 3 years of age. The same approach has been applied to EPN. However, a delay in RT, even in the presence of chemotherapy, tends to increase the risk of tumor recurrence. The St. Jude RT-1 trial showed that patients who received pre-radiation chemotherapy had a poorer 3-year PFS than those receiving immediate adjuvant irradiation (49% vs. 84%, respectively) (Merchant et al. 2002b). Patients with EPN who are younger than 3 years can be treated with RT at an early age without severe toxicity (Merchant et al. 2005). EPN has a more limited treatment volume and tends to occur in the PF, thus allowing the sparing of most structures involved in higher cognitive function. In the recently completed ACNS0121 trial, patients aged 1 year and older could receive upfront conformal RT (Chan and McMullen 2012).

The need for adjuvant RT in patients with completely resected ST-EPN is also under investigation. Published series of spinal EPNs show that complete resection alone is often sufficient to achieve long-term local control (Ferrante et al. 1992; Hanbali et al. 2002). In contrast to fourth ventricular EPN where GTR challenging due to the proximity of the lower cranial nerves and adjuvant RT likely helps sterilize microscopic residual disease, ST tumors, except for those involving eloquent brain regions, the anatomic constraints of surgery are fewer and GTR rates are much higher. A small series from the Beth Israel Medical Center, New York, suggested that long-term local control can be achieved by GTR alone (Hukin et al. 1998). In the ACNS0121 trial, patients with completely resected low-grade ST-EPN were assigned to the observation arm (no RT). Preliminary results from 11 patients in the observation arm showed that 2 patients had relapses within the first 12 months, both of whom were salvaged with surgery and RT and remain disease free (ACNS0831 Protocol 2011. (https://members.childrensoncologygroup.org/Prot/ACNS0831/ACNS0831DOC.pdf). Accessed 04/22/2016. Children's Oncology Group 2011). This strategy has been retained in the ACNS0831 trial.

9.3.5 Spinal Ependymoma

The epidemiology, pathologic characteristics, and behavior of spinal EPN are distinct from those for cranial EPN. Myxopapillary ependymoma (MPE) is the predominant histologic variant in spinal EPN. These tumors appear to be less common in children than in adults. In the pediatric population, MPE is usually seen in adolescents. MPE represents 13% of ependymal tumors (Chao et al. 2011).

MPE was first recognized as a distinct histologic variant of EPN by Kernohan (1932). The designation "myxopapillary" is based on the histologic appearance of MPE. MPEs produce mucin and, because of their branching vasculature, form tumor cells arranged in papillae (Pica et al. 2009; Sonneland et al. 1985). MPEs are categorized as grade 1 tumors by the WHO and are considered benign tumors

characterized by slow, indolent growth and a long disease course (Al-Halabi et al. 2010). In general, MPEs arise in the lumbosacral spine, specifically in association with the conus medullaris, cauda equina, or filum terminale (Chao et al. 2011; Bagley et al. 2007). MPEs rarely arise at other sites in the spinal cord or outside the neuroaxis (Akyurek et al. 2006). Most patients with MPE are male, and MPEs are diagnosed in the third or fourth decade of life (Bagley et al. 2007).

MPEs are also capable of distant spread. One third of treatment failures occur at distant sites with or without a primary site failure (Akyurek et al. 2006). MPEs are rare but more aggressive in children. They are associated with higher incidences of intracranial and spinal dissemination (Pica et al. 2009; Sonneland et al. 1985; Bagley et al. 2007; Akyurek et al. 2006; Merchant et al. 2000). A study from St. Jude reported a higher-than-expected rate of subarachnoid dissemination at presentation in patients with MPEs, which resulted in the use of craniospinal RT rather than involved-field radiation in three of four patients (Merchant et al. 2000).

Maximal safe resection is considered the standard of care for MPE. Currently, there is no clearly defined role for adjuvant RT although it has been recommended after STR. Some studies recommend adjuvant RT for all patients after surgery, regardless of the extent of resection (Al-Halabi et al. 2010; Akyurek et al. 2006). Other studies advocate adjuvant RT for patients receiving piecemeal GTR as opposed to en-bloc resections, based on the increased rates of local recurrence (Volpp et al. 2007). In general, it is very difficult to determine the extension of resection at this site. Because of the rarity of MPE in children, most studies have been limited to retrospective analysis. The primary treatment is GTR, with no clearly defined role for adjuvant RT. Conservative management without the use of adjuvant RT in pediatric patients with a high risk of craniospinal dissemination can sometimes result in the need to give RT with a more extended field.

In a recent retrospective study by the Johns Hopkins Hospital, all children with spine EPN who underwent either GTR or STR were evaluated. All patients receiving RT were treated at the involved site with a median dose of adjuvant RT of 50.4 Gy (range, 45–54 Gy). After a median follow-up of 7.2 years, local control rates at 5 and 10 years were 62.5% and 30%, respectively, for the group undergoing surgery alone versus 100% at both time points for those undergoing surgery and adjuvant RT. In addition, 50% of patients receiving surgery alone had local failure. Local failure occurred in all patients receiving STR compared with 33% of patients receiving GTR alone. One patient in the surgery and adjuvant RT group had recurrence at a distant site 1 year after diagnosis (Agbahiwe et al. 2013).

9.3.6 New Radiotherapy Modalities

In a phase II trial, 88 pediatric patients receiving three-dimensional conformal RT (77 receiving a dose of 59.4 Gy and 15 patients under the age of 18 months receiving a dose of 54 Gy) showed a higher 10-year PFS (69%) (Merchant et al.

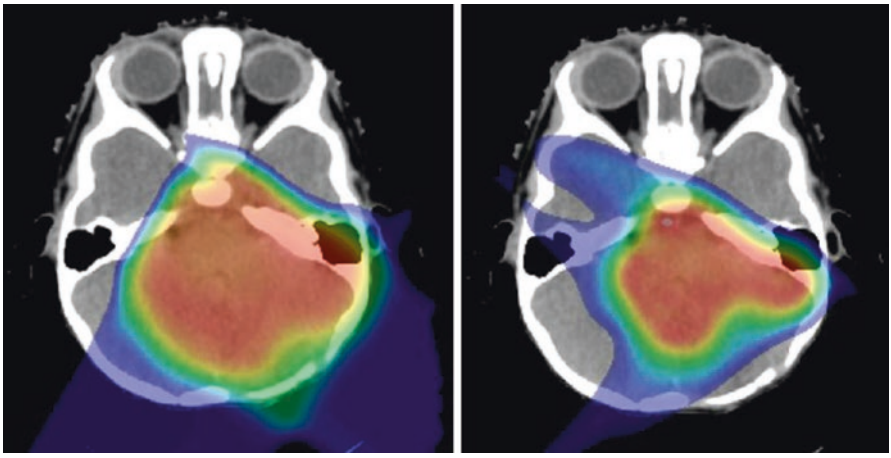

Fig. 9.3 Treatment planning CT with dose display (>10 Cobalt-Gray Equivalent) for proton therapy plans using passively scattered (*left*) and pencil-beam scanning methods (*right*)

2004) than that reported in older studies for patients receiving conventional RT (31–46%). A potential bias in the phase II study, however, was the high (84%) rate of GTR. The study also reported better preservation of neurocognitive function in those receiving conformal RT than in those treated with conventional radiation therapy (Figs. 9.3 and 9.4). A study evaluating adjuvant fractionated stereotactic RT in 80 patients (mean total dose 52.2 Gy, range 50.4–58 Gy) reported a high 5-year PFS of 87% (Combs et al. 2006). However, radiosurgery has not yet been established as a standard adjuvant therapy for EPN (Chan and McMullen 2012).

9.3.7 Intensity-Modulated Radiation Therapy

Recent studies show that treatment of a local field does not compromise local control and survival in patients with EPN. Intensity-modulated radiation therapy (IMRT) has been used over the last 12 years to treat EPN in an effort to spare surrounding normal tissues from high doses of radiation. Given that the volume adjacent to the target receives less radiation, there are concerns that IMRT might compromise local control. However, the local control and survival rates for patients receiving IMRT are comparable with those for patients who received previous therapies that used larger treatment volumes (Schroeder et al. 2008). All failures have been reported within the high-dose region, suggesting that IMRT does not diminish local control (Merchant et al. 2002a; Schroeder et al. 2008).

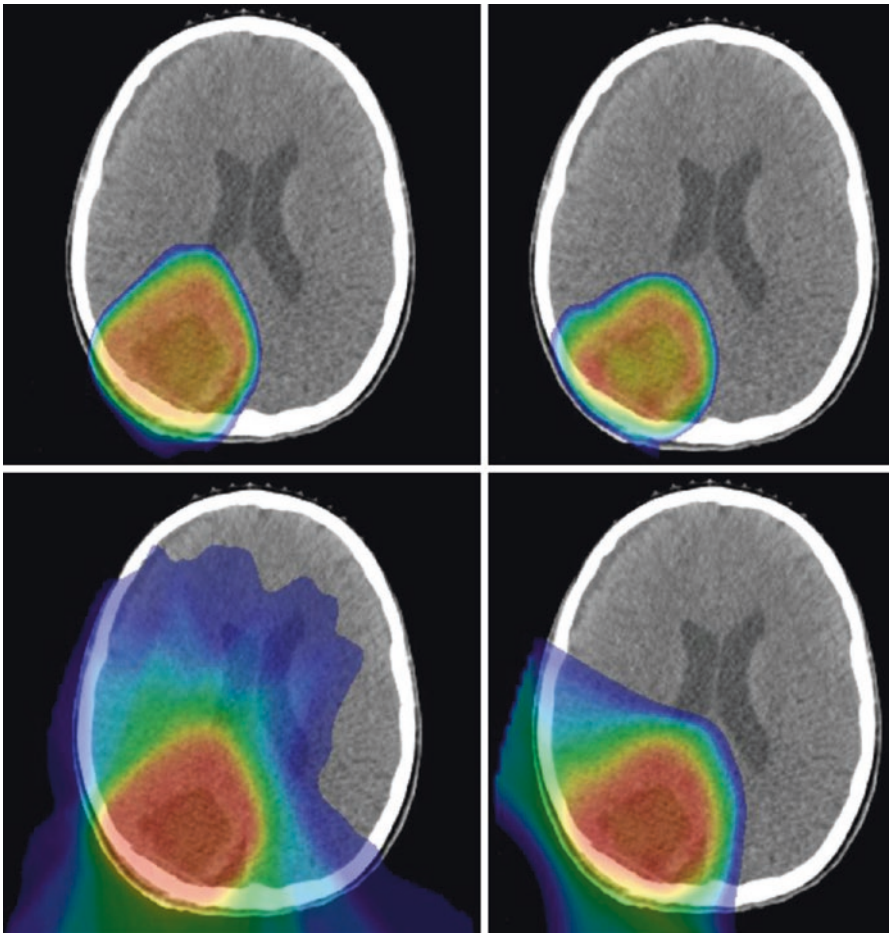

Fig. 9.4 Intensity-modulated photon (*left, top, and bottom*) and proton (*right, top, and bottom*) therapy plans displaying dose distributions greater than 40 (*top row*) or 10 (*bottom row*) Gray or Cobalt-Gray Equivalent, respectively

9.3.8 Proton Therapy

Approximately 66% of intracranial childhood EPNs occur in the PF, arising along the lining of the fourth ventricle (Smyth et al. 2000). These tumors often extend to the cerebellopontine angle through the foramina of Luschka or dorsally through the foramen of Magendie, thus placing the tumor in close proximity to critical structures such as the brainstem, cranial nerves, cochlea, and temporal lobes. Proton therapy appears to offer a better sparing of surrounding critical structures (e.g., optic chiasm, cochlea, hypothalamus, pituitary gland, and pharynx) than does IMRT (MacDonald and Yock 2010; Timmermann et al. 2007). For ST-EPNs, proton therapy appears to spare the more eloquent and cognitive areas. Proton therapy offers the advantage of lower radiation doses to organs at risk (MacDonald and Yock 2010; Timmermann et al. 2007).

9.3.9 Neurologic, Endocrine, and Cognitive Effects

The potential late effects of irradiation have led to past and present decisions about the indications for RT in the treatment of EPN and the need to question its use in some patients. Recovery of neurologic impairment after aggressive neurosurgery is not impeded by RT although whether the rate of improvement can be higher without the use of RT remains open to question (Merchant et al. 2010; Morris et al. 2009). Hearing loss is uncommon with the use of RT alone and can be prevented by using advanced RT methods (Hua et al. 2008). Given the relatively common PF location of EPN avoiding the hypothalamic pituitary axis in treatment planning has become easier, leading fewer cases of growth, thyroid, adrenal, and gonadotropin deficiency. Nevertheless, collateral irradiation of the hypothalamic pituitary axis, even with very low RT doses, can over many years result in the development of hormone deficiency (Merchant et al. 2011) and therefore, should be monitored.

Although 20 years have passed since the St. Jude RT1 trial that enrolled very young children with EPN and frontline postoperative irradiation being adopted by pediatric cooperative groups in later trials on the basis of published data and personal experiences, there remain gaps with regard to cognitive function in this group of children, especially those who were very young at the time of treatment. Findings from the St. Jude series thoroughly cover the first 5 years after RT through the assessment of global intelligence, memory, behavior, learning, adaptive function, and academic achievement (Conklin et al. 2008; Di Pinto et al. 2010; Netson et al. 2012). However, there is an opportunity to study and learn more about the overall function and quality of life of this group of long-term survivors.

9.3.10 Necrosis, Vasculopathy, and Secondary Brain Tumors

The most challenging and rare complications of RT are necrosis, vasculopathy, and secondary brain tumors. Necrosis most often occurs 3–6 months after frontline treatment and manifests itself by asymptomatic imaging changes such as prolongation of T2 and parenchymal enhancement on MRI scans. Although it is often possible to review a particular case of necrosis and identify the attributing factors, such as mass effect from tumor, tumor- and surgery-related ischemia, site-specific neurologic injury, increased intracranial pressure from hydrocephalus, CSF shunt failure, and history of infectious or chemotherapy-related toxicity, there remain cases in which necrosis clearly arises from the irradiation of normal tissues of patients who do not have other predisposing factors. The St. Jude series, which assessed more than 100 children with PF-EPN, reported a cumulative incidence of necrosis of approximately 2.5% measured at any time after 1 year (Merchant et al. 2009). Necrosis was seen in three patients and occurred during the first year. Vasculopathy, a rare complication of irradiation, was reported in one patient in this series. Clearly, irradiation of the central vasculature is required for vasculopathy to develop, which can be avoided in the majority of cases. Finally, secondary brain tumors such as malignant gliomas are a devastating complication of irradiation. The brainstem is

most often involved, and all cases are fatal. In the St. Jude series, the incidence of malignant brain tumors at 7 years was approximately 2.3% (Merchant et al. 2009).

9.4 Chemotherapy

Chemotherapy has a limited role in the treatment of EPN. Phase II trials of chemotherapy suggest that platinum agents have the highest efficacy against EPN (Duffner et al. 1993). Objective response rates as high as 48% have been reported for patients receiving platinum-based chemotherapy (Bouffet and Foreman 1999). However, for patients with gross residual disease, complete responses are rare and are achieved in approximately 10% of patients receiving platinum-based regimens (Duffner et al. 1993). A higher response rate is achieved with combination therapy than with single-agent therapy.

Chemotherapy has been assessed in several clinical scenarios, including adjuvant treatment, as bridging therapy to postpone RT in infants, as neoadjuvant therapy before second-look surgery, and as high-dose aggressive therapy delivered with stem cell transplantation (Chan and McMullen 2012). However, there is no conclusive evidence of benefit to patients in any of these indications. A study reported that high-dose chemotherapy followed by stem cell transplantation was associated with toxicity-related death in 33% of patients with intracranial EPN (Mason et al. 1998). Children's Cancer Group (CCG) 942, the only randomized trial comparing the use of adjuvant chemotherapy after conventional surgery and RT, found no improvement in outcomes when chemotherapy was used (Evans et al. 1996). The CCG 921 trial found no improvement with the eight-drugs-in-1-day regimen compared with the CCNU–vincristine–prednisone adjuvant therapy (Robertson et al. 1998). Both these CCG trials do not represent ideal conditions, because CCG 942 did not use cisplatin-based chemotherapy and CCG 921 was not randomized. The role of adjuvant chemotherapy will be assessed in the upcoming COG ACNS0831 trial, in which patients will be randomized to receive four cycles of maintenance chemotherapy or be observed after receiving standard therapy (Chan and McMullen 2012).

Baby POG-1 was a seminal study in which patients younger than 3 years with brain tumors of different histologies received chemotherapy to postpone RT until they were older (Duffner et al. 1993). As a result, the use of chemotherapy to postpone or even eliminate adjuvant radiotherapy has been evaluated for EPN. The St. Jude RT-1 trial, which included 48 children under the age of 3 years, demonstrated that using chemotherapy to delay RT actually worsened the likelihood of disease recurrence. Furthermore, patients receiving upfront radiotherapy, even those younger than 3 years, had excellent functional outcomes (Merchant et al. 2002b).

Another indication for patients to receive chemotherapy is in case of tumors that are not completely resectable at the time of first surgery. In this situation, chemotherapy has been proposed as a means of inducing a response that can improve the resectability of the tumor, thereby allowing a second-look surgery. This approach was originally used by a group from the Bristol Royal Hospital for Children, United Kingdom, who reported that three of four children with residual disease after initial

surgery were able to undergo complete resection after chemotherapy, followed by a second-look surgery (Foreman et al. 1997). The efficacy of this approach was investigated in the ACNS0121 trial, with early data indicating acceptably low rates of surgical morbidity. As such, this strategy has remained a part of the ACNS0831 protocol, which is also investigating the role of adjuvant chemotherapy.

The role of chemotherapy in the management of EPN remains uncertain. There is scant evidence that adjuvant chemotherapy improves outcome or gives a survival advantage (Vaidya et al. 2012). Thus, the efficacy of chemotherapy in EPN warrants further study. Although there is evidence that chemotherapy can induce a partial or complete response in some patients, there are no convincing findings showing that it improves OS.

9.5 Tumor Recurrence

Many EPNs can recur despite aggressive first management, often early during the disease course. The outcomes of patients with tumor recurrence are very poor (5-year OS 10–27%) (Bouffet et al. 1998). Despite a high rate of failure, there is no standard of care for recurrent EPN. Given the prognostic significance of GTR in the primary setting and the efficacy of RT in some patients, a similar therapeutic approach, though with different radiation techniques, is often used for patients at relapse (Hoffman et al. 2014). Chemotherapy, though potentially effective, does not offer sustained response at relapse (Gajjar et al. 2013; Bouffet et al. 2009).

The majority of failures are seen within the high-dose region. In this situation, one should consider only re-irradiation of the site of recurrence with tight margins. In contrast, distant recurrence in the spine or brain may warrant irradiation of the entire craniospinal space. This situation can be challenging, since the posterior fossa would have already received high-dose irradiation during the primary treatment. Patients treated in the St. Jude (Memphis) and Hospital for Sick Children (Toronto) have had the best OS with salvage therapy, which can be attributed to the acceptance of re-irradiation with an effective dose of irradiation or a new course of at least 54 Gy (Bouffet et al. 2012; Merchant et al. 2008; Stafford et al. 2000).

9.5.1 Re-irradiation

The technique used for re-irradiation depends on the site involved. Some studies support the efficacy of single-fraction radiosurgery (Merchant et al. 2008; Stafford et al. 2000; Hodgson et al. 2001; Kano et al. 2010; Stauder et al. 2012), whereas others report that it is associated with significant and unacceptable toxicity (Merchant et al. 2008; Hodgson et al. 2001). The St. Jude series reported radiation necrosis in all the six patients treated with radiosurgery, of whom one patient died due to radiation necrosis of the brainstem (Merchant et al. 2008). Merchant et al. (2008) recommend fractionated RT to treat relapsed EPN. A study by Hoffman et al. (2014) in which fractionated stereotactic radiosurgery was administered in

three fractions of 8 Gy to 12 patients reported a median EFS of 3.4 years. Although the treatment was fractionated in this series, radiation necrosis was seen in 6 of 12 patients. Of these six patients, three were asymptomatic and no patient died from the treatment.

The use of advanced technology is essential in salvage therapy to decrease the risk of major complications. IMRT is strongly recommended to spare the organs at risk. In some settings, proton therapy can offer a dosimetry advantage and preserve the brainstem, especially when there is recurrence in the PF when the target volume is adjacent to brainstem and/or spinal cord.

Conclusion

The search for the cure of EPN remains a challenge in pediatric oncology. Many patients continue to die from their disease, which may be related to access to experienced neurosurgeons and radiation oncologists. Newer RT methods have improved the survival and quality of life of patients and reduced complications associated with normal tissue irradiation. The identification of different subtypes of EPN, each with a distinct behavior, necessitates the validation of these subtypes in the setting of existing and newer treatments in order to improve the outcomes of children diagnosed with this tumor.

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Low-Grade Glioma

10

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Abstract

Local tumour control is the cornerstone in the general management of childhood low-grade glioma. Treatment traditionally consists of surgery and biopsy in areas not amenable to resection. Non-surgical treatment is usually performed upon progression. Although chemotherapy is increasingly used as first non-surgical treatment, radiotherapy remains standard as salvage treatment or as primary treatment in selected cases in which surrounding normal tissue can be optimally preserved. The effects of chemotherapy on improving the clinical, neurological, visual and endocrinological function deserve further investigation. Recent improvements in radiotherapy treatment and delivery techniques allow better coverage of target volume and assure maximal tumour control while sparing as much normal tissue as possible to reduce the risk of toxicity secondary to treatment. Additionally, the implementation of modern imaging technologies including functional imaging permits a better identification of the tumour site and neighbouring normal tissue or organs at risk thereby further reducing the risk for late adverse effects. Intensity-modulated radiotherapy (IMRT), stereotactic high precision technologies and the introduction of proton therapy may further improve treatment outcome. Brachytherapy, or in rare cases radiosurgery, is a treatment option in low-grade glioma; however, clinical data are scarce and require more research. The role of targeted therapies is currently under investigation in clinical trials. New information on molecular genetic patterns in low-grade glioma may also have an impact on the selection and sequencing of radiotherapy.

10.1 Epidemiology/Predisposing Factors

About 30–40% of all paediatric primary brain tumours are low-grade gliomas. Their annual incidence is calculated as 10–12 per 1,000,000 children under the age of 15 years in western countries (Kaatsch et al. 2001). There is a striking association of specific variants of low-grade glioma and heritable diseases such as neurofibromatosis type I (NF-1), tuberous sclerosis and Li-Fraumeni syndrome (Listernik et al. 1997). In NF-1, as many as 5–15% of cases have low-grade gliomas of the optic tract and the hypothalamus.

Low-grade gliomas in children predominantly arise along the visual pathway with or without involvement of the hypothalamus, followed in frequency by the cerebral hemispheres and the posterior fossa. Their biological behaviour varies greatly: even small chiasmatic tumours may display an aggressive, malignant growth pattern causing rapid visual deterioration, progressive neurological deficits and diencephalic syndrome, whereas larger tumours may remain quiescent for years.

10.2 Histology

Their histological grade corresponds to Grade I or II according to the revised system of the WHO of 2000 (Louis et al. 2007). For clinical purposes, some of the mixed glioneuronal tumours are included as well, if their glial component appears most relevant for

biologic behaviour. Grade I tumours include pilocytic astrocytoma, subependymal giant cell astrocytoma, dysembryoplastic neuroepithelial tumour and desmoplastic infantile ganglioglioma while Grade II tumours include pilomyxoid astrocytoma, pleomorphic xanthoastrocytoma, oligodendroglioma, oligoastrocytoma and diffuse astrocytoma (fibrillary, protoplasmic and gemistocytic). Gangliogliomas can be Grade I or II.

10.3 Molecular Genetic Profiles

Molecular genetic markers are increasingly investigated with the aim to stratify treatments according to the individual profiles. Notable abnormalities in the *RAS/MAP* kinase pathway such as *NF-1* loss or *BRAF* activation and *mTOR* activation have been described in pilocytic astrocytoma and childhood WHO Grade II tumours. Recent identification of activating rearrangements in *c-MYB* and *MYBL1* in paediatric diffuse astrocytoma also provides candidates for therapeutic intervention. Targeting these molecularly identified pathways may permit an individualized approach to improve outcomes (Raabe et al. 2013). Few but promising data are available for the interaction between radiotherapy and chemotherapeutic agents and molecular genetic markers. Several targeted inhibitors with radiation are currently under investigation in both translational bench research and early clinical trials (Dasgupta et al. 2013). *BRAF* rearrangements and *BRAF V600E* point mutations are recurring events in paediatric low-grade gliomas. Horbinsky found that a high *MIB1* proliferation index trended toward worse response to adjuvant radiotherapy is compared to *BRAF*-rearranged, *p16*-intact tumours. On multivariate analysis, the two most consistently powerful independent adverse prognostic markers were midline location and *p16* deletion. Tumours with *BRAF V600E* found at supratentorial sites had a strong trend toward an increased risk for progression, whereas those with *BRAF* rearrangement had a milder trend toward reduced risk (Horbinski et al. 2012). Dasgupta found a combinatorial additive activity between radiation and *PLX4720* (analogue to vemurafenib) in *BRAF V600E*-mutated cell lines, but not in the *BRAF WT* line (Dasgupta and Haas-Kogan 2013). Further research in this field is necessary to develop novel radiotherapy approaches using combination treatments with the aim to improve outcome.

10.4 Presenting Symptoms

Clinical signs and symptoms evolve gradually in most cases, reflecting the generally low proliferative potential of low-grade astrocytic tumours. Focal neurologic signs can be seen according to the location of the primary tumour with intractable seizures. Symptoms and signs of increased intracranial pressure (ICP) with headache upon awakening, associated with vomiting have been described and include papilledema, blurred vision and enlargement of blind spots and visual field cuts. Nonspecific findings in the very young include irritability and difficulty feeding with subsequent bulging fontanels, sun-set phenomenon and an enlarged head circumference with split sutures. One may find developmental retardation or even loss of

developmental milestones. In older children, changes of mood and personality can occur. Impaired consciousness is an alarming final stage, which can be accompanied by signs of brainstem compression such as slowing of the respiratory rate, elevation of the blood pressure and tachycardia as well as bradycardia.

10.4.1 Low-Grade Midline, Supratentorial Tumours

The clinical presentation depends upon the tumour site. For optic nerve gliomas, proptosis and some degree of visual loss and turning-in of the eye (strabismus) have been described. When there is chiasmatic involvement, decreased visual acuity in one or both eyes and visual field loss as well as nystagmus have been seen. Growth or other endocrinologic disturbances, including precocious puberty can be seen in suprasellar tumours. In very young children with hypothalamic involvement, the 'diencephalic syndrome' manifested by failure to thrive despite apparent adequate caloric intake, emaciation and euphoria can occur. Unilateral thalamic involvement may lead to alterations in the level of consciousness, hydrocephalus due to obstruction of third ventricular cerebrospinal fluid outflow while bilateral thalamic involvement may be associated with bilateral motor impairment, including dystonic posturing if the tumour has infiltrated into the basal ganglionic region. For hemispheric lesions, unilateral motor deficits on the site contralateral to the main tumour bulk and sensory deficits can be seen.

10.4.2 Cerebellar Tumours

Symptoms of increased intracranial pressure (ICP) due to obstruction of the fourth ventricle and focal neurological deficits have been described with infratentorial tumours.

10.5 Radiographic Findings

MR (magnetic resonance) imaging is essential and allows a detailed delineation of the tumour site and spread. Most commonly, low-grade gliomas show features of abnormal areas of signal intensity (increased signal on T2-weighted MR images) with mild or absent enhancement. The degree of contrast enhancement is variable and the presence does not suggest a higher grade lesion. Pilocytic astrocytomas typically enhance and show a central cystic area, mimicking high-grade glioma.

10.6 Work-Up

Aside from MR imaging, other work-up include EEG if seizures are a prominent finding. Preoperative definition of the focus is essential for the planning of the surgical procedure. Neuroophthalmological examination to assess visual acuity and field

and endocrinological work-up to assess initial deficits in tumour with suprasellar or hypothalamic involvement are helpful for follow-up in the case of tumour progression or as a baseline prior to radiotherapy. Cerebrospinal fluid cytology is often not recommended as leptomeningeal spread is rare.

10.7 General Management

Surgery, radiotherapy and recently chemotherapy are the primary treatment options with the aim to improve survival and preserve or improve the functional status. Recent approaches focus on chemotherapy as first-line non-surgical therapy to obviate radiation-induced late effects, while radiotherapy is increasingly reserved for progressive disease when chemotherapy has failed.

10.7.1 Surgery

Initial treatment is based on resectability. Hemispheric and cerebellar low-grade gliomas are amenable to resection in the majority of cases. Extent of resection is the factor associated most strongly with progression-free survival favouring complete tumour removal. Pollack and colleagues observed no disease progression in 21 patients who underwent a complete tumour resection, compared to 2 of 12 (17%) undergoing nearly complete resections and 11 of 37 (30%) undergoing subtotal resection (Pollack et al. 1995). In a recent large retrospective series including 351 consecutive paediatric patients that were diagnosed between 1970 and 2009 gross tumour resection and radiotherapy were important prognostic factors. On multivariate analysis, improved progression-free survival was significantly associated with gross total resection and postoperative radiation therapy. In those undergoing less than gross total resection, progression-free survival was improved with radiotherapy, with almost the same rates as patients receiving complete resection. On multivariate analysis, higher overall survival was significantly associated with complete resection and pilocytic histology (Youland et al. 2013). The infiltrating growth pattern and involvement of functionally significant areas in tumours of the supratentorial midline tumours may result in progressive loss of vision and hypothalamic damage precluding radical surgery. Biopsy should be attempted with the exception of tumours of the optic chiasm and optic nerve. Histological confirmation may not be necessary if course of disease and imaging provide evidence for diagnosis.

10.7.2 Chemotherapy

More recently, upfront chemotherapy has increasingly been used as non-surgical treatment. Investigation of chemotherapy treatment strategies initially focused on young children under 5 years of age to avoid early radiotherapy, especially for those with visual pathway gliomas. Early reports produced evidence that cytotoxic drugs

are active against low-grade astrocytic tumours and that they may delay or obviate the need for radiation therapy. Reports upon the effectiveness of chemotherapy in low-grade glioma have included newly diagnosed and relapsed patients, treated with single agents or drug combinations for variable lengths of time. It is difficult to compare the tumour response rates and ultimately long-term results reported by the various trials on childhood low-grade glioma. Characteristics of the patient population, the indication to start therapy, the criteria defining response as well as the timing of tumour response assessment vary between the studies (Gnekow et al. 2012). The chemotherapy agents most commonly used are carboplatin, vincristine, thioguanine, procarbazine and lomustine. In the COG A9952 protocol, the 5-year event-free survival and overall survival rates for all patients were 45% and 86%, respectively (Ater et al. 2012). In the HIT-LGG 96 trial, the 10-year progression-free survival was 62% following radiotherapy and 44% following chemotherapy indicating a higher efficacy for radiotherapy (Gnekow et al. 2012). Monotherapy with carboplatin can be equally efficient as multiagent chemotherapy (Dodgshun et al. 2016). New concepts based on targeted therapies are promising and currently investigated in prospective trials (Chalil and Ramaswamy 2016).

10.7.3 Radiation Therapy

Radiation therapy has traditionally been the treatment of choice in non-completely resected low-grade glioma and is highly effective in tumour control and preservation or improvement in visual function (Kortmann et al. 2003a, b). Modern mono-institutional series introduced 3D conformal radiotherapy and IMRT technologies with the aim of providing a reliable coverage conformed to the individual shape of the tumour while optimizing the preservation of surrounding normal tissue.

Progression-free and overall survival rates are excellent with definitive radiotherapy (Table 10.1). In the series of Merchant, 5- and 10-year event-free survival rates of 87.4 or 74.3%, respectively, were achieved. The corresponding overall survival rates were 98.5 and 95.9%, respectively (Merchant et al. 2009). The Boston group treated 81 children with fractionated stereotactic conformal radiotherapy with a margin of 2 mm and achieved an 8-year progression-free survival of 65%. Six local relapses within the treatment fields were observed (Marcus et al. 2005). Paulino used intensity-modulated radiation therapy in 39 patients. The 8-year progression-free and overall survival rates were 78.2% and 93.7%, respectively (Paulino et al. 2013).

In the only prospective multicentre HIT-LGG 96 trial, 117 patients with pilocytic astrocytoma underwent radiation therapy. The 5- and 10-year progression-free survival rate after external fractionated radiation therapy was 76% with a 10-year overall survival rate of 97%. Disease progression was not influenced by gender, neurofibromatosis type 1 status, tumour location, age or prior chemotherapy (Mueller et al. 2013) (Table 10.1).

Table 10.1 Recent series in childhood low-grade glioma using modern, fractionated radiotherapy technologies

Author	Technology and dose prescription	*N*	Results			Follow-up
Debus et al. (Debus et al. 1999)	Median 52.4 Gy/1.6–2.0 Gy Margin: 7 mm	10	5-year PFS: 90%			12–72 mos
			5-year OS: 100%			
			No acute toxicities			
Saran et al. (Saran et al. 2002)	Median	14	3-year PFS: 87%,			33 mos
	50–55 Gy/30–33 fractions		3-year OS: 100%			
	Margin: 5–10 mm		1 relapse within GTV			
Hug et al. (Hug et al. 2002)	Protons	27		Local control	survival	3.3 years
	50.4–63.0 CGE/1.8 Gy		Hemispheric	71%	86%	
			Diencephalon	87%	93%	
	Margin: no data		Brainstem	60%	60%	
Marcus et al. (Marcus et al. 2005)	Stereotactic technique median	81	5/8-year PFS: 82.5%/65%			6.9 years
	52.2 Gy/1.8Gy		5/8-year OS: 97.8%/82% 6 local relapses			
	Margin: 2 mm		All within field			
Combs et al. (Combs et al. 2005)	3D conformal RT	15	3/5-year PFS: 92%/72%			97 mos
	Med. 52.2 Gy/1.8Gy		5-year OS: 90%			
	Margin 5 mm					
Merchant et al. (2009)	3D conformal RT	78	5/10-year EFS: 87.4%/74.3%			89 mos
	Median		5/10-year OS: 98.5%/95.9%			
	54 Gy/1.8 Gy		13 relapses			
	Margin: 15 mm		(8/13 within PTV)			
			(1/13 marginal)			
			(4/13 CNS metastatic)			
Paulino et al. (2013)	IMRT	39	8-year EFS/OS: 78.2 and 93.7%			81 mos
	45–60 Gy		7/7 failures in field			
	5–10 mm					
Muller et al. (2013)	Conventional/3D planning	75	Pilocytic astrocytoma			8.4 years
	Median 54 Gy/1.8 Gy		5/10-year PFS: 76.5%			
	Margin 1–2 cm		5/10-year OS: 96.2%			
			Relapse pattern: N/A			

EFS event-free survival, *PFS* progression-free survival, *OS* overall survival, *mos* months, *N* number of patients, *N/A* not available, *GTV* gross tumour volume, *PTV* planning target volume, *CNS* central nervous system

10.7.3.1 Response of Tumour to Treatment

Only a few series indicate the response of low-grade glioma to radiotherapy with respect to tumour size and clinical symptoms (Bakardjiev et al. 1996; Fisher et al. 1998). Increase in tumour size after radiotherapy may be seen and often not accompanied by clinical signs and symptoms. This increase in size or pseudoprogression might nevertheless be misleading and misinterpreted as recurrent disease.

10.7.3.2 Radiotherapy Following Chemotherapy

Chemotherapy is associated with a high rate of early progression. In the HIT-LGG 96 trial, the 5- and 10-year progression-free survival rates following the start of treatment were 47 and 44% after a median observation time from diagnosis of 10.4 years (Gnekow et al. 2012). It appears that this subset of patients represents a cohort with biologically more aggressive tumours, and the additional question of whether chemotherapy renders the tumours more radioresistant needs to be considered. In the series of Janss et al., 46 children under the age of 5 years received first-line chemotherapy (Janss et al. 1995). Subsequently, 17 children received radiotherapy because of progressive disease; 7 of 17 children who required radiation after chemotherapy have incurred a third progression and the second progression-free survival was 29% at 10 years. Paulino treated 9 children with IMRT who failed initial chemotherapy and 30 children with radiotherapy as first-line treatment (Paulino et al. 2013). The 8-year progression-free survival rates for children who did and did not receive prior chemotherapy were 50 and 88.4% ($p < 0.03$). In the prospective HIT-LGG 96 trial, no difference was found regarding the use of previous chemotherapy. The 10-year PFS was 75% in 17 patients having received primary chemotherapy as compared with 77.6% in 58 patients after primary radiotherapy (Mueller et al. 2013).

10.7.3.3 Dose Response Effects

The optimum dose for radiation therapy in childhood low-grade glioma has not been well established. In children, no prospective randomized studies of radiotherapy dose response have been performed. The selection of dose prescriptions is strongly influenced by patient age, extent and site of tumour with a tendency to use a lower dose in younger children with larger tumours (larger treatment portals). The recommended and generally accepted dose prescription ranges between 45 and 54 Gy in 1.8 Gy fractions depending on age at treatment, extent of disease and location of tumour. Retrospective data, however, indicate that a dose of 50.4 Gy is equally effective as 54 Gy. In the HIT-LGG 96 trial, no differences were observed. In the retrospective series from Houston patients receiving 50.4 Gy or below had an 8-year PFS of 73.8% as compared with 90.9% after dose prescriptions of above 50.4 Gy, without statistically significant difference (Paulino et al. 2013) (Table 10.2).

10.7.3.4 Proton Therapy

The major advantage of proton therapy over conventional radiation techniques is the high degree of dose conformity around the tumour that can be achieved as well as reduction of low dose radiation region to surrounding brain and other critical

Table 10.2 Radiotherapy dose response and progression-free survival in children and adults with low-grade glioma

Author	*N*	Total radiotherapy dose	Fraction size	PFS (5 years)	PFS (10 years)	*p*-value
Montgomery et al. (1977)			N/A	Overall	N/A	N/A
	7	≤42 Gy		43%		
	9	≥50 Gy		100%		
Sung (1982)			N/A	Relapse rate: 11/13	N/A	N/A
	13	35–45 Gy				
	29	50–60 Gy		8/29		
Alvord and Lofton (1988)	52	>45.0 Gy	N/A	80%	65%	N/A
	62	<45.0 Gy		65%	55%	
Flickinger et al. (1988)	12	>45.0 Gy	Calculation according nominal standard dose	100%	N/A	$P = 0.045$
	12	<45.0 Gy		75%		
Kovalic et al. (1990)	3	<40.0 Gy	N/A	0	0%	<0.0001
	30	>40.0 Gy		90%	79%	
Garcia et al. (1990)	8	<40 Gy	N/A	4/8 recurred	N/A	N/A
	17	≥40 Gy		2/17 recurred		
Jenkin et al. (1993)	19	>50.0Gy	N/A	88%	88%	0.37
	15	<50.0 Gy		72%	57%	
Grabenbauer et al. (2000)	9	44–45 Gy	1.6–2.0 Gy	87%	36%	0.04
	16	45.1–60 Gy		90%	85%	
Paulino et al. (2013)				5 years	8 years	0.37
	29	≤50.4 Gy	1.8 Gy	73.8%	95.2%	
	10	>50.4 Gy		90.9%	88.9%	
Muller et al. (2013)	13	≤50.4 Gy	1.8Gy	77%	77%	0.941
	52	>50.4 Gy		77%	77%	

n.s. not significant, *N/A* not available, *PFS* progression-free survival, *N* number of patients

structures. The working group of Loma Linda treated 27 paediatric patients with progressive or recurrent gliomas at various sites (Hug et al. 2002). Target doses were between 50.4 and 63.0 Cobalt Gray Equivalent (CGE) at 1.8 CGE per fraction. At a mean follow-up period of 3.3 years, six patients experienced local failure and four died of disease. Dennis et al. compared proton therapy plans with IMRT plan for dosimetric differences to surrounding tissue. Proton therapy effectively reduces the dose to surrounding normal tissues as compared with IMRT. The authors concluded that the benefit of proton therapy over IMRT may be more substantial in patients with tumours in proximity to critical structures. (Dennis et al. 2013). In a series from Boston, 32 children received a median radiation dose of 52.2 CGE. The

6- and 8-year rates of progression-free survival were 89.7% and 82.8%, respectively, with an 8-year overall survival of 100%. There were no significant declines in full-scale intelligence quotient. However, some significant decline in neurocognitive outcomes for young children (<7 years) and those with significant dose to the left temporal lobe/hippocampus were observed. The incidence of endocrinopathy correlated with a mean dose of ≥40 CGE to the hypothalamus, pituitary or optic chiasm. Stabilization or improvement of visual acuity was achieved in 83.3% of patients (Greenberger et al. 2014).

10.7.3.5 Brachytherapy

The purpose of interstitial brachytherapy is to deliver a focal necrotizing radiation dose within the tumour while sparing normal surrounding tissue. There is a steep dose gradient at the periphery thereby leaving a high cumulative dose around the implanted radioactive seeds, most commonly Iodine-125. Two major German series investigated the temporary iodine and permanent iodine implantation in 94 and 147 patients, respectively. Progression-free and overall survival were excellent (Table 10.3). In the series of Ruge, the neurological status at last follow-up was improved in 57.8% and unchanged in 23% of patients. Fifteen (11.3%) of 132 patients had no symptoms and 4 (3%) presented with treatment induced permanent deterioration of their neurological status (Ruge et al. 2011). It seems that small, circumscribed tumours with a diameter of less than 4 cm in locations other than the optic nerve and chiasm are preferred cases for interstitial brachytherapy. Prospective data on neurocognitive function are not available.

10.7.3.6 Radiosurgery

Clinical data on radiosurgery for paediatric low-grade glioma are scarce. Weintraub et al. reported on 15 patients with pilocytic astrocytomas. The median maximum dose was 36 Gy while the median marginal dose was 15 Gy (Weintraub et al. 2012). For the total cohort, 83% of patients were progression free at a median of 74 months. No case of radiation-induced necrosis was reported. Tumour volume <2 mL was significantly associated with an improved progression-free survival. Kano et al. treated 50 patients with pilocytic astrocytoma. Median age was 10.5 years with a median marginal dose of 14.5 Gy. The 1-, 3- and 5-year progression-free survival rates were 91.7%, 82.8% and 70.8%, respectively. A target volume less than 8 mL was significantly associated with a better progression-free survival. Five of 20 patients experienced adverse radiation effects with necrosis and symptomatic oedema requiring supportive treatment (Kano et al. 2009). The Karolinska working group treated 16 patients with radiosurgery for residual tumour after surgery. In 85%, a moderate tumour volume reduction was observed after radiosurgery. Adverse radiation effects were seen in 25% (Boëthius et al. 2002). Hadjipanayis treated 49 patients with radiosurgery, with 37 patients harbouring a pilocytic astrocytoma. Tumour volumes ranged between 0.42 and 45.1 mL. The median dose ranged between 9.6 and 22.5 Gy. Of the 49 patients, 45 were alive after a median follow-up of 32 months post-radiosurgery (Hadjipanayis et al. 2003). In the series of Heppner (n = 49),

Table 10.3 Outcome after interstitial brachytherapy in childhood low-grade glioma using modern treatment technologies

Author	Technique	Tumour size	Patients	Outcome
Herrera et al. (2007)	Temporary I-	<4 cm	*n* = 12	OS: 83.3%
	125 seeds		age range: 8–17 yrs	
	60 Gy		(median: 8.7 yrs)	
			Pilocytic astrocytoma only	
Peraud et al. (2007)	Temporary I-	<4 cm	*n* = 11	Initial volume: 14.9 mL
	125 seeds			
	54 Gy		age: 11 mos to 16 yrs	CR: *n* = 4
				PR: *n* = 7
			(median: 6.8 yrs)	OS: 100%
			Grade I: *n* = 6 Grade	
			II, *n* = 5	
Korinthenberg et al. (2011)	Temporary I-	<5 cm, spherical shape	*n* = 94	5- and 10-yr OS:
	125 seeds		age range: 1–19 yrs	97 and 92%
	Median dose 60 Gy		median age: 9 yrs	
	Mean treatment time 28d		Grade I and II	
Ruge et al. (2011)	Permanent I-	<4–5 cm,	*n* = 147	5-, 10- and 15-yr PFS:
	125 seeds. Median 50–65 Gy	Demarcated lesions	age: 1.2–19.9 yrs,	
			Median:10.7 yrs Grade I and II	92, 74 and 67%
				5-, 10- and 15-yr OS:
				98, 93 and 82%
Mueller et al. (2013)	Permanent and temporary I-		*n* = 42	5- and 10-yr PFS: 65 and 58%
	125 seeds			5- and 10-yr OS: 97 and 97%

I Iodine, *yrs* years, *n* number of patients, *OS* overall survival, *PFS* progression-free survival, *CR* complete response, *PR* partial response

the median clinical progression-free survival was 44 months while the median radiological progression-free survival was 37 months. The 5-year clinical progression-free survival was 49% (Heppner et al. 2005).

The major criticisms and shortcomings of the retrospective series are limited patient numbers, short follow-up intervals, and cohorts including high-grade glioma

and brainstem glioma, adults and children without specifically addressing pilocytic astrocytomas or Grade II tumours in childhood.

10.7.3.7 Radiotherapy in Grade II Astrocytoma

Grade II astrocytomas in children are rare. In the European childhood low-grade glioma series of Stokland and Gnekow, 5.9 and 4.5% out of a total of 1940 cases, respectively, presented as Grade II diffuse astrocytoma (Gnekow et al. 2012; Stokland et al. 2010). According to genomic and transcriptomic analyses, paediatric astrocytoma Grade II carry distinct genetic signatures (Jones et al. 2011). Mutations of *IDH 1/2* and *TP 53* and *MGMT* methylation are common in adult but rare in Grade II astrocytomas (Jones et al. 2011). Data on survival for protoplasmic and fibrillary astrocytomas showed a 10-year survival rate of 81.2% for age <20 years ($n = 100$) vs. 39.2% for age 20–44 years ($n = 221$) ((Jones et al. 2011), CBTRUS). The outcomes of Grade I and II tumours have been conflicting, with some having better results with Grade I while others having equivalent results (Table 10.4). Stokland et al. noted a significantly better PFS for Grade I tumours (5-year PFS, 72% for pilocytic astrocytoma as compared with 43% for Grade II tumours). Fouladi observed a 5-year PFS of 68% for Grade I tumours vs. 52% in Grade II tumours (Fouladi et al. 2003). For overall survival, the studies by Fisher et al. and Fouladi et al. saw a significantly superior outcome for Grade I tumours (95% in both series at 5 years as compared with 48% and 64%, respectively, for Grade II tumours). The report by Packer et al. did not see a significant difference (Packer et al. 1997). The large series of Gnekow et al. observed a 10-year EFS for 59 patients with Grade II tumours of 40% as compared with 50% in 671 patients with pilocytic astrocytoma histology. While the EFS were statistically significantly different, the overall survival did not differ significantly (94% for pilocytic astrocytoma and 87% for diffuse astrocytoma) (Gnekow et al. 2012). The extent of resection is an important prognostic factor for Grade II astrocytomas. In the series by Mishra et al., the 5-year PFS rates were 79% for patients treated with gross tumour resection (GTR), 60% for those with subtotal tumour resection (STR) and 46% for those with biopsy alone. The corresponding 5-year overall survival rates were 100% after GTR, 88% for those with STR and 89% for biopsy alone (Mishra et al. 2006). The cohort was analysed for the impact of early or delayed radiation therapy irrespective of extent of resection. The 5- and 10-year PFS rates were 50 and 43% for those not receiving early radiation therapy as compared with 61 and 43% for the early radiation therapy group. The 5-year and 10-year overall survival rates were 97% and 92%, respectively, for those receiving no radiation at diagnosis as compared with 84 and 74% for those receiving radiation therapy upon progression (Mishra et al. 2006). An analysis of 24 patients that were included in the German HIT-LGG 96 and 2004 outcome was poor after salvage radiotherapy for progressive disease (Mueller et al. 2012). With a median follow-up of 2.0 years, 11 patients (45.8%) experienced progression and 8 patients (33.3%) died. The 3- and 5-year progression-free survival rates were 56% and 28%, respectively, and the 5-year overall survival was only 63%.

Table 10.4 Outcome of childhood low-grade glioma according to grade

Author	N	Median age	5-yr PFS	5-yr OS
Fouladi et al. (2003)	Grade I: 19	7.7 yrs	Grade I: 68%	Grade I: 95%
	Grade II: 34		Grade II: 52%	Grade II: 48%
			$p < 0.05$	$P < 0.05$
Fisher et al. (2008)	WHO Grade I: 135	9.1 yrs	3-yr PFS	3-yr OS
	WHO Grade II: 27		WHO Grade I: 63%	WHO Grade I: 96%
			WHO Grade II 40%	WHO Grade II: 48%
			$p = 0.007$	$P < 0.001$
Stokland et al. (2010)	Grade I: 407	6.7 yrs	Grade I: 71.5%	Grade I: 97.3%
	Grade II: 38		Grade II: 42.6%	Grade II: 76.5%
			$P < 0.001$	$P \leq 0.001$
Merchant et al. (2009)	Grade I: 67	8.9 yrs	5- and 10-yr EFS	N/A
			Grade I: 87 and/77%	
	Grade II: 11		Grade II: 91 and/64%	
			p = n.s.	
Jones et al. (2011) CBTRUS 2004–2006	0–19 yrs: 100	Children versus adults	n/a	WHO II only
	20–44 yrs: 221			0–19 yrs: 81.2%
				20–44 yrs: 39.2%
Mishra et al. (2006)	Early RT: 52	9 yrs	Grade II only	Grade II only
	Delayed RT: 38		5- and 10-yr EFS	5- and 10-yr OS
			Early RT: 61 and 43%	Early RT: 84 and 74%
			Delayed RT: 50 and 43%	Delayed RT: 97 and 92%
Mueller et al. (2012) (ISPNO)	24	2.0 yrs	3- and 5-yr PFS: 56 and 28%	5-yr OS: 63%

N number of patients, *yrs* years, *RT* radiation therapy, *PFS* progression-free survival, *EFS* event-free survival, *OS* overall survival, *ISPNO* International Society of Pediatric Neurooncology, *N/A* not available, *WHO* World Health Organization, *n.s.* not significant

10.7.3.8 Other Rare Histological Subtypes

The general management usually follows concepts used in pilocytic and Grade II tumours with surgery as the primary treatment. There are often only case reports or small series which include treatment with radiotherapy or chemotherapy. In the German HIT 96 study ($n = 1031$), 15 patients with pleomorphic xanthoastrocytoma Grade II were registered. Other subtypes included ganglioglioma Grade I and dysembryoplastic neuroepithelial tumours (DNET) ($n = 92$), oligoastrocytoma ($n = 5$),

oligodendroglioma (n = 10) and subependymal giant cell astrocytoma (SEGA) (n = 15). Outcome could not be meaningfully analysed as only 20 patients out of this cohort received either chemotherapy or radiotherapy.

SEGA typically develops in 10–15% of patients with tuberous sclerosis. They are slow-growing, and general management typically involves observation with surgical resection is the primary treatment. The role of radiotherapy in SEGA is unknown. One case report showed effective tumour control after radiosurgery in four of six patients, with progression-free periods ranging from 9 to 66 months (Kyung-Jae Park et al. 2011). Recent studies showed that rapamycin (mTOR inhibitors) can induce partial regression of SEGA (Jóźwiak et al. 2013).

In a retrospective series of children with oligodendroglioma, the 5-year PFS and OS were 66.4 and 93.4%, respectively, in 37 children. Mixed histology was associated with worse overall survival compared to patients with pure oligodendroglioma. Neither postoperative chemotherapy nor radiation therapy correlated with improved outcome. The series showed that less than gross tumour resection was associated with an increased risk for progression (Creach et al. 2012).

Pilomyxoid astrocytomas, previously diagnosed histologically as pilocytic astrocytoma, show a more aggressive course marked by multiple recurrences. Disease control is rarely achieved with single treatment modality as opposed to typical pilocytic astrocytoma. While PFS might be worse, overall survival may be the same as pilocytic astrocytoma. In one study, the overall survival of the pilomyxoid group was not statistically different from the pilocytic tumours (Bhargava et al. 2013).

10.7.3.9 Radiotherapy in Leptomeningeal Dissemination

The frequency of dissemination in childhood low-grade glioma varies between 4 and 12% (von Hornstein et al. 2011), Chemotherapy is often used. The multicentre study HIT-LGG 1996 accrued 1181 children and adolescents with low-grade glioma, of which 61 patients (5.2%) had tumour dissemination, with 2.8% being present at diagnosis. Chemotherapy achieved objective and overall response rates of 25 and 79% of the primary tumour and a similar response rate for disseminated lesions. Clinical stabilization or improvement was achieved in the majority of patients during chemotherapy, with local radiotherapy employed in some cases. However, 20 of 24 patients experienced further progression and 5-year PFS was 28% (Table 10.4). Given the rarity of dissemination, the appropriate treatment for LGG patients with metastatic disease is poorly defined. Data showing a positive impact of craniospinal irradiation (CSI) on survival are still missing; CSI may be a viable treatment option, especially when chemotherapy has failed (Mazloom et al. 2012). In the report of Pollack et al., 3 of 76 patients were found to have disseminated disease either at presentation or during the course of the disease (Pollack et al. 1994). All three patients had a pilocytic astrocytoma. In one child, craniospinal irradiation was administered. Thirty months after treatment no evidence of recurrence or persistent tumour was detectable on MRI. The patient's endocrine function was normal and school performance remained excellent at 5½ years of age. The two other children received various treatments consisting of chemotherapy and involved field irradiation. At last follow-up they were all in continuous complete remission. Late effects were acceptable. Mishima et al. reported a case of a 6-year-old boy who underwent

surgery followed by radiotherapy to the affected regions of the brain and spinal canal (Mishima et al. 1992). The child was free of recurrence at a follow-up of 6 years after treatment.

In the SIOP-LGG 2004 trial, two patients underwent craniospinal irradiation (35.2–36 Gy) and showed stable disease after 6 and 8 months, respectively. Bian et al. assessed six children with metastatic pilocytic astrocytomas (Bian et al. 2013). Four patients underwent craniospinal radiation therapy, one to the spine only and one to a supratentorial local field. With a median follow-up of 24 months after radiation therapy, five of six patients were alive, four with stable disease and one with progressive disease.

10.8 Radiotherapy Treatment Planning

Local failure is the predominant feature in progressive or recurrent disease while leptomeningeal spread is uncommon and seen is less than 5% of cases (Pollack et al. 1994, 1995). When using high precision radiotherapy including modern imaging for treatment planning, the margins for clinical target volume and planning target volume can safely be restricted without an increase failure rate close to the tumour site (Table 10.1). Especially in pilocytic astrocytomas, a sharply demarcated contrast enhancing lesion is often seen on imaging. These tumours only rarely infiltrate normal surrounding tissue, and it can be anticipated that macroscopic tumour is precisely delineated.

A precise tailoring of the necessary dose to the tumour is a prerequisite to reduce the dose to normal brain tissue. Past series used a safety margin between 1.5 and 2 cm. Debus et al. used three-dimensional conformal external beam radiotherapy to treat ten patients (Debus et al. 1999). The clinical target volume included the visible tumour in CT and MRI plus 5 mm; the planning target volume consisted of the clinical target volume plus 2 mm safety margin. With these restricted treatment volumes, the median target volume was 14.7 cm^3. No treatment failure was observed suggesting that limiting the high dose volume did not cause an increase in marginal or out-of-field failure rate. Merchant et al. used a margin of 15 mm; 8 of 13 relapses were within the PTV, 1 at the field margin and 4 patients developed CNS metastases. Paulino added a 1 cm margin to GTV to create the CTV in one group and 5 mm in another group. All failures were in-field failures (Paulino et al. 2013). Marcus et al. used a stereotactic convergence technique and applied 52.2 Gy with 1.8 Gy fractionated dose with a margin of 2 mm and observed only 6 local relapses all within field (Marcus et al. 2005). Saran used a margin between 5 and 10 mm and observed one relapse within PTV. The observed failure rates when using restricted field margins indicate that especially in pilocytic astrocytoma the margin for CTV can safely be restricted to 5 mm.

10.9 Radiotherapy Target Volume Definition

When aiming to reduce possible acute and late sequelae, it is necessary to reduce the volume of normal tissue exposed to a high RT dose. Use of 3D-conformal treatment techniques including IMRT and proton therapy will help to reduce

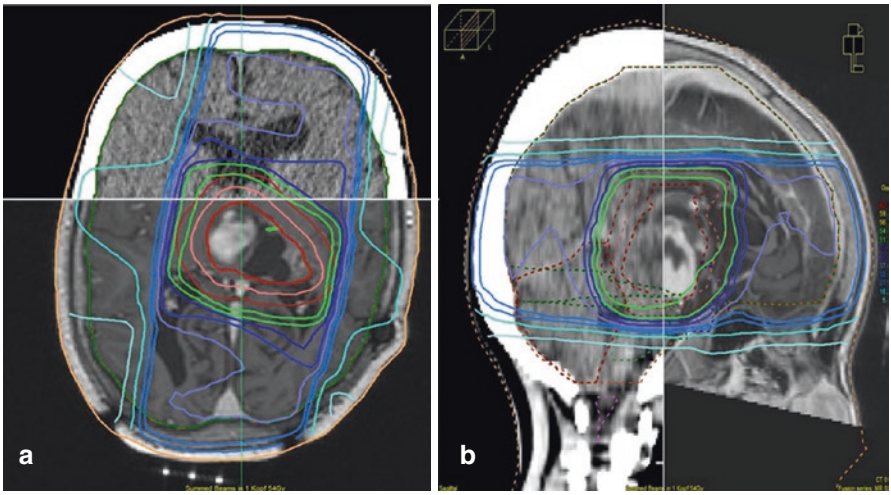

Fig. 10.1 A 10-year-old boy with pilocytic astrocytoma s/p biopsy, treated with three-dimensional conformal radiotherapy. The gross tumour volume (GTV) is outlined in *red*, clinical target volume (CTV, 5 mm) in *pink* and planning target volume (PTV, 5 mm) in *magenta*. (**a**) Transverse slice (**b**) Sagittal slice. Image fusion with T-1 weighted, contrast-enhanced MRI was performed. (**a**) Transverse slice (**b**) Sagittal slice. The 51.3 Gy isodose line (*outer green*) encompasses the entire PTV

irradiation of normal tissue. In addition, the dose to critical organs needs to be recorded. Image fusion with T2 or Flare and T1 contrast MRI sequences is recommended. Target volumes will be defined according to the ICRU 50 and 62. The clinical target volume (CTV) encompasses the visible tumour as seen on MR (T2 weighted images) with an additional margin of 0.5 cm. If surgery was performed, postoperative delineation of residual disease will be used for treatment planning (Fig. 10.1a, b). The preoperative scans are used to identify regions of possible tumour infiltration. It is not necessary to entirely encompass areas of cerebral oedema. The planning target volume (PTV) encompasses the CTV with an additional margin according to the precision of treatment technique (0.1–0.3 cm if rigid head fixation and 0.5 cm if a conventional face mask/head shell is used) depending on the department's policy. When defining the clinical target volume, anatomical borders must be considered. For Grade II tumours, no detailed recommendations can be made. Due to their infiltrative growth, the CTV margin can be defined as much as 1–1.5 cm to the GTV visible on high signal T2 or flare imaging (Fig. 10.2).

10.10 Late Effects

Although radiation therapy is highly effective in tumour control, adverse late effects mainly a decline in neurocognitive function is frequently observed (Merchant et al. 2002). Data on late effects, however, are based on small patient numbers, heterogeneous treatments spanning decades with varying dose prescriptions, treatment

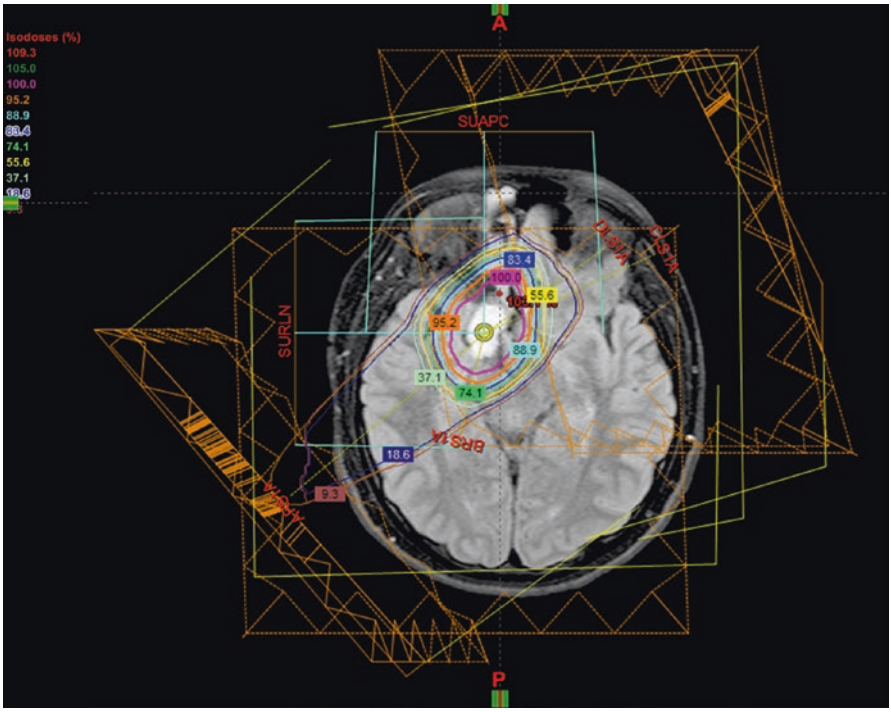

Fig. 10.2 A 15-year-old boy with pilocytic astrocytoma of the right optic pathway s/p subtotal resection and multiple chemotherapy regimens with progression. A passive-scatter proton therapy treatment plan was chosen to deliver 50.4 CGE (100% isodose line, *pink*) to the progressive tumour. In this case, a 5 mm margin for clinical target volume was used and 3 mm margin for planning target volume. He is receiving daily image-guided radiotherapy

technologies and retrospective in nature (Kortmann et al. 2000). Late effects are caused by several factors including tumour-induced dysfunction, the presence of NF 1, hydrocephalus, surgery, chemotherapy and radiotherapy. The contribution of radiotherapy is unknown and controversially discussed. In the series by Merchant, cognitive effects following conformal radiotherapy (CRT) correlated with patient age, neurofibromatosis type 1 status, tumour location and volume, extent of resection and radiation dose. The effect of age exceeded that of radiation dose; patients younger than 5 years experienced the greatest decline in cognition. Before radiotherapy, growth hormone secretion abnormality was diagnosed in 24% of tested patients, and 12% had precocious puberty. The 10-year cumulative incidence of growth hormone replacement was 48.9%; thyroid hormone replacement, 64.0%; glucocorticoid replacement, 19.2%; gonadotropin-releasing hormone analogue therapy, 34.2% (Merchant et al. 2009). In contrast, radiotherapy was only in part associated with a decline in function in a large retrospective cohort analysed by Armstrong et al. which included patients receiving radiotherapy and chemotherapy as sole adjuvant therapy. Among 240 patients who survived more than 5 years, the 5-, 10- and 15-year cumulative incidence of adverse outcomes included blindness: 10, 13 and 18%; hearing loss: 8, 14 and 22%; obesity: 18, 35 and 53%; hyperinsulinism: 1, 5 and 24%; growth hormone deficiency:

13, 27 and 29%; thyroid hormone deficiency: 16, 28 and 33%; and adrenocorticotropic hormone (ACTH) deficiency: 12, 22 and 26%. Multivariable models demonstrated radiation therapy to be a significant independent predictor of hearing loss, growth hormone deficiency, abnormal thyroid function and ACTH deficiency. Their findings indicate a progressive loss of endocrine function beyond 10 years after treatment. Diencephalic location was a statistically significant independent risk factor for blindness, growth hormone deficiency, abnormal thyroid function and ACTH deficiency. Among the 182 5-year survivors assessed for intellectual function, intelligence quotient (IQ) below average (<85) was associated with younger age at diagnosis, epilepsy and shunt placement but not radiation therapy. Their findings indicate a complex pattern of late effects caused my multiple different co-factors among which radiotherapy is one of the contributors (Armstrong et al. 2011).

10.11 Follow-Up

Table 10.5 summarizes the recommended follow-up recommendation for children with low-grade glioma.

Table 10.5 Recommended follow-up investigations

	Year 1–3	Years 4–5	Years 6–10
Physical examination and neurological examination, including anthropometric measurements	Every 3 months	Every 6 months	Annually
Ophthalmological examination	Year 1: 3 monthly Year 2: 3–6 monthly Year 3: 6 monthly	Every 6–12 months	Annually, except for optic pathway tumours (every 6 months)
Contrast-enhanced cerebral and spinal (if indicated) MRI	Every 6 months	Every 6 months	Annually
[a]Audiogram—pure tone where possible age 3 years or over, otherwise free field testing or otoacoustic emissions	Every 6 months	Not indicated if previously repetitively normal	–
[a]Glomerular filtration rate (GFR)	6 months after chemotherapy, then yearly, if not indicated otherwise	Not indicated if previously repetitively normal	–
Endocrinologic investigation and, if indicated, bone age and hypothalamic-pituitary functioning test	Yearly, if not indicated otherwise	As indicated by stage of growth and puberty and previous chemo- or radiotherapy	As indicated by stage of growth and puberty and previous chemo- or radiotherapy

[a]If chemotherapy was given

10.12 Future Directions

Modern radiation therapy technologies are intended to deliver the appropriate dose to the target and minimize dose to surrounding normal tissues. While most studies in the literature have reported that a safety margin of 5 mm would suffice for pilocytic astrocytoma, there is a possibility that the margins can be reduced further. The impact on the reduction of late effects with radiation volume and dose reduction are, however, unknown with respect to endocrinological and neurocognitive function. Radiation-induced endocrinological disorders and structural changes of brain parenchyma depend on a dose–volume relationship and the corresponding integral dose distribution (Merchant et al. 2009; Jalali et al. 2010; Steen et al. 2001). Future studies may allow dose and volume calculations to predict and reduce the risk for endocrinological disorders and/or neurocognitive dysfunctions. Proton therapy might offer an advantage both in coverage of tumour and reduction of dose to non-target tissue. Brachytherapy is a valuable treatment option in selected cases, but its availability is only restricted to a few institutions. Reliable prospective data on late effects after proton therapy and brachytherapy, however, are scarce and still missing. Radiosurgery has been applied in few cases and need further study. The effects of chemotherapy on improving the actual clinical and neurological function, the visual and endocrinological function for supratentorial midline tumours, and ultimately on health status and quality of life deserve further investigation.

The role of chemotherapy is currently in flux with the advent of integrated genomics and next generation sequencing. Targeted therapies with different agents are currently being investigated in clinical trials. Information on molecular genetic patterns in low-grade glioma may also have an impact on the selection and sequencing of radiotherapy.

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Optic Pathway Glioma

11

Julie A. Bradley, Ronny L. Rotondo, and Daniel J. Indelicato

Contents

Abstract

Pediatric optic pathway gliomas share common clinicoradiographic characteristics and are typically World Health Organization grade I/II astrocytomas. Management of these tumors presents a therapeutic challenge based on host age as well as anatomic location. Radical excision is limited to tumors with unilateral optic nerve involvement and irretrievable ipsilateral vision loss. Subtotal resection is reserved for tissue diagnosis and acute symptom relief. Chemotherapy is

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infrequently curative but may effectively delay radiotherapy, allowing critical neurocognitive and neuroendocrine development in young children. For most lesions, radiotherapy offers the best option of local control but carries a range of risks related to adjacent normal tissue exposure.

11.1 Epidemiology

Optic pathway gliomas (OPGs) occur predominantly in the pediatric population. Fewer than 10% of cases arise in those older than 19 years of age; 75% of cases are found in children in their first 10 years of life (Dutton 1994). OPGs constitute approximately 5% of all pediatric intracranial tumors (Halperin et al. 2013). An overall predilection for males or females is not seen; however, tumors confined to the optic nerve alone have been reported more frequently in females (Jahraus and Tarbell 2006).

11.2 Predisposing Factors

The etiology of most OPGs remains unknown; however, neurofibromatosis type I (NF-1) has a genetic mutation in the neurofibromin 1 gene on chromosome 17q11.2, which encodes the protein neurofibromin that is expressed by Schwann cells, oligodendrocytes, neurons, astrocytes, and leukocytes (Petrak et al. 2015). NF-1 has a strong association with OPGs. Of patients with OPGs, the incidence of NF-I is at least 30% (Dutton 1994). OPGs are the most common central nervous system (CNS) tumors in those affected by NF-1 (Bikowska-Opalach and Jackowska 2013).

11.3 Presenting Symptoms

Children commonly present to their pediatrician with loss of visual acuity in one or both eyes. Proptosis may also be apparent. On physical examination, optic nerve atrophy, nystagmus, and strabismus can be detected. These tumors can also be associated with macrocephaly due to hydrocephalus at a young age, precocious puberty due to interference with gonadotropin pathways, and developmental delay (Jahraus and Tarbell 2006). Presence of hydrocephalus at diagnosis is not necessarily a poor prognostic factor (Jenkin et al. 1993). In NF-1 patients, the optic tumors may be asymptomatic but can be found on screening (Listernick et al. 2007).

11.4 Radiographic Findings

On magnetic resonance imaging (MRI), tumors are predominantly solid but occasionally can have a cystic component, which is more common in those without NF-1 (Kornreich et al. 2001; Gower et al. 1990). OPGs are hypointense on T1 and

hyperintense on T2 (Jahraus and Tarbell 2006). They typically enhance after contrast administration (Fig. 11.1). These tumors can be multilobulated and can track along the optic pathway (Fig. 11.2). Calcifications can be present (Fig. 11.3).

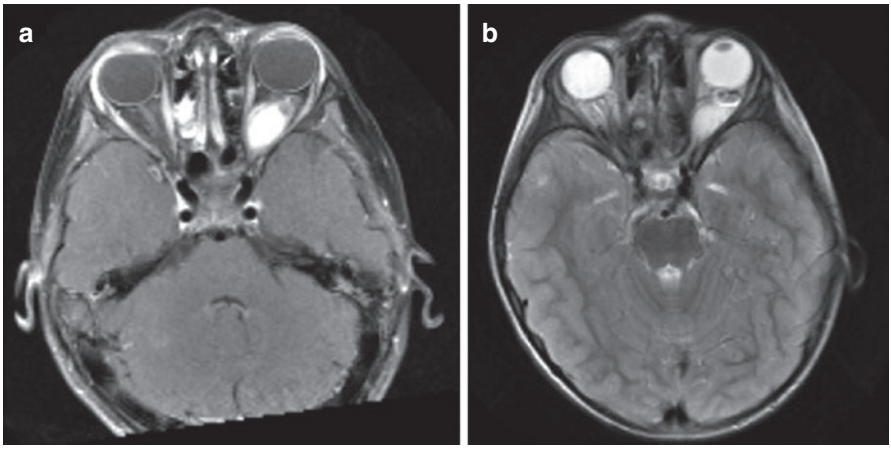

Fig. 11.1 Left optic nerve glioma (**a**) enhancing on contrast-enhanced T1-weighted magnetic resonance sequence and (**b**) hyperintense on a contrast-enhanced T2-weighted magnetic resonance sequence

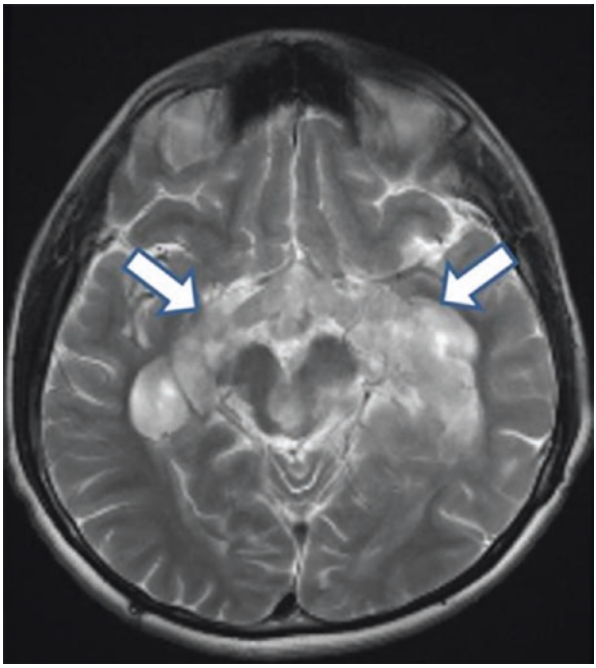

Fig. 11.2 Bulky extension of a chiasmatic optic pathway glioma posteriorly along the left and right optic tracts

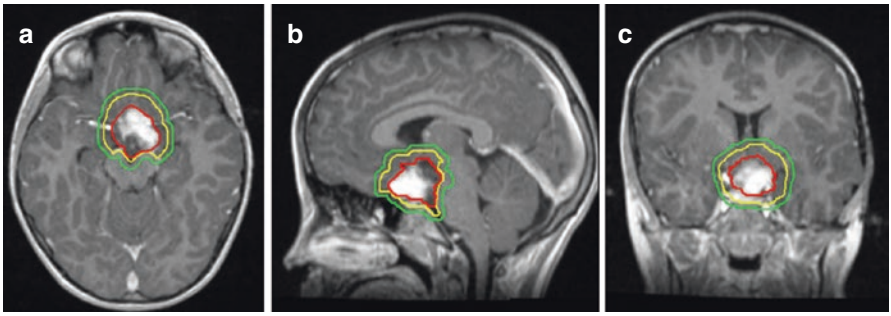

Fig. 11.3 Chiasmatic optic pathway glioma outlined for radiation treatment delivery on (**a**) axial (**b**) sagittal and (**c**) coronal views. The gross tumor volume is in *red*, the clinical target volume is in *yellow* (5 mm edited from the brainstem), and the planning target volume is in *green* (3 mm)

Kornreich et al. found that tumors in NF-1 patients arise most commonly in the optic nerve and chiasm (66% and 62%, respectively), compared to 91% arising in the chiasm in non-NF-1 patients (Lopez Ibor 1975). Of the non-NF-1 patients, 68% have visible radiographic extension beyond the optic pathway, which is significantly less frequent in the NF-1 group at 2% (Kornreich et al. 2001).

In 1958, Dodge et al. published a classification system for OPGs (Dodge et al. 1958). Type I involves a single optic nerve, type II involves the optic chiasm and unilateral or bilateral optic nerves, and type III involves the hypothalamus or adjacent structures (Cappelli et al. 1998). A modified Dodge classification was published in 2008 and includes NF status among other factors (Dotson et al. 1991).

11.5 Workup

MRI of the brain with and without contrast is important to define tumor origin, extent, and imaging characteristics that may differentiate OPGs from other primary CNS tumors. Due to the small gauge of the pediatric optic nerves, a high-resolution MRI at 1- to 2-mm slice thickness may be necessary to capture the full extent of tracking along the optic pathway. Although the risk of CNS dissemination is rare (Perilongo et al. 2003) a complete spinal MRI is recommended for thorough staging (McCowage et al. 1996).

Today, a biopsy is often obtained to confirm the diagnosis of OPG, unless it is associated with NF-1 (Walker et al. 2013). However, if a biopsy could result in a high risk of morbidity, the diagnosis can be made based on the characteristic tumor location and imaging appearance. On pathologic analysis, tumors are most commonly low grade (Dutton 1994). The majority are pilocytic astrocytomas, a World Health Organization grade 1 tumor (Jahraus and Tarbell 2006).

All patients should undergo complete ophthalmologic evaluation. Neuroendocrine laboratory tests can be obtained to assess baseline levels of thyroid hormone, growth hormone, cortisol, and estrogen or testosterone, as these can be affected by the tumor at diagnosis or by treatment (Fouladi et al. 2003). Like endocrine function,

neurocognitive function can be affected by the tumor itself, hydrocephalus, or prior therapy (Sutton et al. 1995; Fouladi et al. 2003; Carpentieri et al. 2003). Baseline neurocognitive function testing by a neuropsychologist can be performed for children old enough to participate (typically >3 years old). Newly diagnosed patients should be screened for NF-1.

11.6 Acute Management

For cases of rapid deterioration in vision, urgent treatment is needed to prevent blindness. Once the visual deficit has developed, it is often irreversible (Awdeh et al. 2012). Steroids can be used to decrease edema and are usually prescribed as a temporizing measure before definitive therapy, but their efficacy in restoring vision is unclear (Awdeh et al. 2012).

For tumors resulting in compression of the third ventricle, often accompanied by symptoms, hydrocephalus can be rapidly relieved by shunt placement (Goodden et al. 2014).

11.7 Treatment

The treatment approach for OPGs must be individualized based on the tumor size, tumor extent, and patient age. Treatment may include surgery, chemotherapy, radiation therapy, or a combination of these. In some cases, surveillance may be appropriate, especially for asymptomatic tumors in NF-1 patients (Shamji and Benoit 2007; Goodden et al. 2014; Jenkin et al. 1993).

Historically, surgery was the initial treatment of OPGs. Curative radical surgery may still have a role when tumors are located anteriorly and confined to one optic nerve, particularly when no useful vision remains in that eye, or when tumors are exophytic from the optic chiasm (Jenkin et al. 1993; Wisoff et al. 1990; Tenny et al. 1982). Surgery for posterior lesions with diffuse involvement of the optic chiasm or hypothalamus is less commonly performed due to the morbidity of bilateral loss of vision, vascular damage, and endocrinopathy (Sutton et al. 1995). The 2011 consensus conference for pediatric neurosurgery does not recommend primary surgical management of low-grade hypothalamic/chiasmatic tumors except for select cases (Walker et al. 2013). The value of a subtotal resection is debatable, with some studies showing benefits (Goodden et al. 2014) while others do not (Silva et al. 2000; Jenkin et al. 1993). Beneficial debulking operations are those that offer immediate decompression, which can maximize the chance of vision preservation, release extreme proptosis, or relieve obstructive hydrocephalus (Tenny et al. 1982; Medlock and Scott 1997).

Chemotherapy can be used to delay tumor progression in order to allow childhood growth and development. The landmark Children's Cancer Group (CCG) study A9952 enrolled children under 10 years old with low-grade astrocytomas of all sites from 1997 to 2005. Five-year event-free survival for all patients was 45%, with a

non-statistically significant improvement in the 6-thioguanine, procarbazine, lomustine, and vincristine (TPCV) arm compared to the carboplatin and vincristine (CV) arm at 52% versus 39%, respectively ($p = 0.10$) (Ater et al. 2012). A retrospective review of adolescents with OPGs showed 12 of 15 patients had stable disease at a mean follow-up of 52.9 months (Chong et al. 2013). Other modern chemotherapy options include vinblastine (Bouffet et al. 2012), carboplatin monotherapy (Aquino et al. 1999), and vincristine with etoposide (Pons et al. 1992).A lack of consensus exists for the age at which chemotherapy should be used to delay radiation and therefore varies by institution, frequently ranging between less than age 6 years to less than age 10 years (Merchant et al. 2009). In the USA, for example, protocols such as ANCS 0221 investigating radiotherapy for pediatric low-grade gliomas (any site of origin) required patients less than 10 years of age to have received one or more courses of chemotherapy prior to enrollment. For European multi-institutional protocols for pediatric low-grade gliomas, such as HIT-LGG-1996, chemotherapy was recommended over radiotherapy for children less than 5 years of age (Gnekow et al. 2012).

The role of radiation therapy in definitive treatment of OPG was described in 1956 (Taveras et al. 1956) and served as an impetus to consideration of radiation therapy as primary therapy in OPGs. Radiation therapy is more commonly recommended for older children and when surgery would threaten visual or endocrine function. Radiation is utilized relatively less in NF-1 patients due to concern for radiation-induced secondary tumors and increased risk of vasculopathy (Listernick et al. 2007; Grill et al. 1999).

11.8 Target Delineation

Accurate target and organ-at-risk (OAR) delineation are critical steps in effective and safe radiotherapy delivery. The gross tumor volume (GTV) is defined as the gross residual disease. Fusion of a contrast-enhanced high-resolution MRI is recommended to improve accuracy of the target and OAR contours. If radiation is being delivered for tumor progression after surgery, chemotherapy, or both, the previous MRIs throughout the time course of the tumor should also be fused and the extent of disease reviewed. The clinical target volume (CTV) encompasses the GTV and the adjacent area at risk for microscopic spread of disease. This margin should extend 5–10 mm beyond the GTV to encompass regions at risk for tumor infiltration, such as the proximal and distal optic nerves and the prechemotherapy tumor extent. The CTV margin should be expanded further as necessary to encompass the tumor bed and any surfaces in contact with the tumor prior to surgery and/or chemotherapy. The CTV is edited from anatomical boundaries, such as bone and tentorium. A planning target volume (PTV) is then added to account for set-up uncertainty, typically 3–5 mm if daily image guidance is used (Fig. 11.2).

These tumors develop among numerous critical intracranial structures, including the uninvolved optic apparatus, hypothalamus, pituitary, cochlea, brainstem, lacrimal gland, retina, lens, and temporal and frontal lobes. All structures should be identified and used to optimize planning.

The standard prescription dose is 50.4–54 Gy at 1.8 Gy per fraction. Improved overall survival (OS) and progression-free survival (PFS) are associated with doses over 43.2 Gy (Flickinger et al. 1988), but the dose effect beyond 50 Gy is unclear (Jenkin et al. 1993).

Fractionated external-beam radiotherapy with photons or protons is the most common treatment technique and radiation may be delivered through three-dimensional (3D) conformal or intensity-modulated techniques. Intensity modulation offers a dosimetric advantage compared to 3D conformal therapy by increasing the conformality of the high-dose region. However, multifield intensity-modulation techniques typically expose more intracranial tissue to a low radiation dose. Early reports of proton therapy using 3D conformal techniques are encouraging (Indelicato et al. 2012), but longer follow-up is needed to clarify the magnitude of clinical benefit. Radiosurgery or other means of hypofractionation are not typically recommended based on the heightened sensitivity to large dose-per-fraction regimens observed in late-responding tissue of the pediatric brain, brainstem, and optic nerves.

11.9 Outcomes

Following surgery, chemotherapy, or radiotherapy, an MRI of the brain is obtained typically every 3 months for this first 2–3 years, then every 6 months through year 5, and then annually. Due to its low grade and thus low-proliferation rate, radiographic regression following radiotherapy is slow. Tao et al. found a median time of 31.7 months to reach a ≥25% radiographic response rate and 62 months to achieve ≥50% tumor reduction rate (Tao et al. 1997). The radiographic response continued for years after the completion of radiotherapy. For four patients, a complete response by imaging occurred more than 10 years later. In 19 patients receiving vincristine and carboplatin, 58% experienced radiographic progression, 21% stability, and 21% regression (Shofty et al. 2011). The extent of tumor response does not seem to correlate with improvement in vision (Cappelli et al. 1998; Shofty et al. 2011; Kalin-Hajdu et al. 2014).

Treatment-related toxicity surveillance includes routine ophthalmologic evaluation, including visual acuity and visual field testing. Given the age and potential of each treatment modality as well as the tumor itself to contribute to cognitive dysfunction (Carpentieri et al. 2003), neurocognitive testing under the direction of a neuropsychologist is recommended on a regular basis. Magnetic resonance angiogram should be considered due to the risk of vasculopathy caused by the tumor, surgery, and radiotherapy (Kestle et al. 1993).

Outcomes after surgery vary based on tumor extent. Jenkin et al. reported a 10-year relapse-free survival rate ranging from 58–81% (Jenkin et al. 1993). The highest control rates occurred when the tumor was confined to one optic nerve, with a 20-year OS rate of 90%. In contrast, the OS rate decreased to 58% for posterior tumors (Jenkin et al. 1993). Outcomes following chemotherapy are more modest: Janss et al. reported on 46 pediatric patients with OPG ≤5 years old (Janss et al.

1995). With a median follow-up of 72 months, the OS rate was 93%. For initial management, 32 of the 46 patients underwent chemotherapy, with only 28% achieving sustained disease control. Chemotherapy did, however, defer other treatment until after age 5 years in over 70%. For tumors that extend beyond a single optic nerve, radiation offers the most durable disease control. In a study from the prechemotherapy era, in which 78% of the cohort received radiotherapy at diagnosis or after progression, Cappelli et al. reported an OS rate of 83% and a PFS rate of 65% at 10 years (Cappelli et al. 1998). Vision stabilized or improved in nearly 70%. In 29 patients with chiasmatic gliomas treated with salvage radiotherapy, the 10- and 15-year freedom from progression rates were 89% and 82% and the OS rates were 100% and 85%, respectively (Tao et al. 1997). Of these 29 patients, 4 had disease progression 1–60 months after radiotherapy, and all were salvaged with chemotherapy. In a study of 36 patients, radiotherapy increased the local control rate to 86%, compared to 45% without radiotherapy (Wong et al. 1987). The 10-year OS, PFS, and cause-specific survival rates were 79, 77, and 88% in 33 patients primarily treated with definitive radiotherapy with a mean follow-up of 13.6 years (Erkal et al. 1997). Tenny et al. reported lower mortality rates in patients who received radiotherapy compared to those who did not: 36% versus 80% (Tenny et al. 1982).

In a study of 73 patients with OPGs (Fouladi et al. 2003), 50% underwent observation after diagnosis and 50% underwent active treatment: 15 with radiotherapy, 20 with chemotherapy, and 1 with chemotherapy then radiotherapy. The median age of the irradiated patients was 7.2 years compared to 2 years for the chemotherapy patients and 4 years for the observed patients. Ninety percent of the chemotherapy administered was cisplatin or carboplatin based. The 6-year PFS rate was 69% with radiotherapy compared to 12% with chemotherapy and 37% with observation. There was no difference in OS between the three cohorts. Chemotherapy delayed the need for additional treatment for a median of 2 years, but children were subjected to dual-modality therapy and the risk of vision loss upon tumor progression. With all outcome series, careful attention must be paid to the length of follow-up for treatment-related deaths, regardless of treatment modality since disease progression can occur more than 20 years after therapy for this low-grade tumor (Alvord and Lofton 1988).

OPGs in children with NF-1 typically take a more indolent course compared to sporadic OPGs. Janss et al. report a significant difference in PFS, with rates higher in children with NF-1 (Janss et al. 1995). Other studies report no difference in OS or PFS between these two groups (Tao et al. 1997).

Select studies on outcomes after treatment of OPGs are summarized in Table 11.1.

Table 11.1 Literature review of outcomes studies on the treatment of optic pathway gliomas

Study and years	No. of Pts	Pts with NF-1 (%)	Initial treatment (No. or % of Pts)	Follow-up	Overall survival	PFS	Endocrine	Vision	Neurocognitive	Cerebrovascular	Second malignancy
Jenkin et al. (1993) 1958–1990	87	44	Observation, 23; surgery, 26; RT, 28; surgery + RT, 10	Median, 11.5 years	84% at 10 years	10 years 68%	Not reported	With RT, 13% improved, 70% stabilized, 17% worsened	Not reported	Not reported	5/48 irradiated, 4 central nervous system tumors, 1 lymphoma; 0/49 nonirradiated
Tao et al. (1997) 1971–1993	29	41	All received RT for progressive disease, with or without prior surgery or chemo	Median, 9 years	85% at 15 years	15 years 82%	72% with new endocrinopathy after RT	24% improved, 48% stabilized, 17% worsened	$n = 20$ required special education ($n = 11$ required this prior to RT)	3%	1 glioblastoma
Erkal et al. (1997) 1973–1994	33	18	STR, 22; biopsy, 7; All received RT	Mean, 13.6 years	79% at 10 years	10 years 77%	39% with abnormalities	36% improved, 52% stabilized, 12% worsened	not reported	0%	Not reported

(continued)

Table 11.1 (continued)

Study and years	No. of Pts	Pts with NF-1 (%)	Initial treatment (No. or % of Pts)	Follow-up	Overall survival	PFS	Endocrine	Vision	Neurocognitive	Cerebrovascular	Second malignancy
Sutton et al. (1995) 1976–1991	33	12	Biopsy/STR then RT, 9; and/or chemo, 18	Mean, 10.9 years	5 deaths overall	3 deaths from tumor progression	57% on replacement medication	82% with functional vision	Required special education, 12	Not reported	Not reported
Janss et al. (1995) 1977–1990	46	33	Chemo, 32; surgery, 3; RT, 5	Median, 6 years	93% at 5 years	5 years 19%	59%	Four became blind	10 of 17 required special education	Not reported	Not reported
Cappelli et al. (1998) 1980–1992	69	58	Observation, 16; RT, 39; Surgery, 14	Median, 7 years	83% at 10 years	10 years 66%	83% on replacement medication	With RT, 33% improved, 54% stabilized, 13% worsened	"Major scholastic failure," 18	17%	2 (1 glioblastoma and 1 out-of-field Ewing sarcoma)
Fouladi et al. (2003) 1981–1999	73	38	Biopsy/STR, 58%, followed by observation, 37; RT, 16; chemo, 20	Median, 6.3 years	86% at 6 years	6 years 36%	71% with ≥ endocrinopathy	Not reported	No difference between baseline and post-treatment IQ	Not reported	Not reported

Goodden et al. (2014) 1998–2011	42	45	Surgery, 12; surgery + RT, 5; surgery + chemo, 4; observation, 21	Median, 6.4 years	93%	$n = 1$	38%	74% stabilized, 21% worsened	Not reported	5%	Not reported
Indelicato et al. (2012) 2007–2014	40	5	All received RT	Median, 2.7 years	2 deaths	4 progressions	Not reported	2.5% worsened	Not reported	Not reported	None

Chemo chemotherapy, *NF-1* neurofibromatosis type I, *PFS* progression-free survival, *Pts* patients, *RT* radiation therapy, *STR* subtotal resection

11.10 Treatment Toxicity

In pediatric OPGs, both the tumor location and average patient age contribute to the risk of treatment toxicity. Vision is often affected by the tumor itself and fortunately some patients experience vision stabilization or improvement following treatment (Jahraus and Tarbell 2006). However, surgery can result in planned or unplanned blindness in one or both eyes as well as visual field deficits. Radiation therapy carries a risk of injury to the optic nerves and chiasm, resulting in decreased visual acuity or complete vision loss. Radiation can also cause retinopathy, corneal ulceration, cataract formation in the lens, and permanent dry eye that not only is symptomatic but contributes to the risk of other eye injuries. With radiation therapy, stabilization of vision is achieved in 50–80% of patients, with improvement in 10–40% and deterioration in 0–20% (Flickinger et al. 1988; Horwich and Bloom 1985; Rodriguez et al. 1990; Tao et al. 1997; Erkal et al. 1997). In contrast, in 19 patients treated with chemotherapy alone, 73% experienced decline in vision, with stable vision in 21% and improved vision in 5% (Shofty et al. 2011). Of the 38 eyes in the 19 patients, vision degraded to legal blindness in 10. Awdeh et al. similarly report worse visual outcomes in children treated with chemotherapy and salvage radiotherapy compared to radiotherapy alone (Awdeh et al. 2012). Limited surgery before radiotherapy resulted in improved visual acuity compared to radiotherapy alone.

Due to the tumor proximity to the pituitary and hypothalamus, surgery and radiation can result in neuroendocrine dysfunction. After definitive radiotherapy, 72% of patients developed a new diagnosis of hypopituitarism; 21% of these cases were panhypopituitarism (Tao et al. 1997) and growth hormone is most commonly impaired (Tao et al. 1997; Brauner et al. 1990; Adan et al. 2001). Surveillance with neuroendocrine labs is recommended long term, as the incidence of hypopituitarism increases with time (Tao et al. 1997).

Neurocognitive dysfunction can be caused by the tumor, surgery, radiation, hydrocephalus, neurofibromatosis, radiation, hypopituitarism, and disordered sleep. The degree of dysfunction varies in severity depending on patient age and extent of prior interventions (Padovani et al. 2012). Carpentieri et al. found moderate neurocognitive dysfunction, including motor function, verbal memory, and visuospatial organization, following surgery and prior to radiotherapy in 106 children with brain tumors (Carpentieri et al. 2003). Cappelli et al. (1998) report that after radiotherapy 65% of survivors had "normal scholastic function," defined as <2 years behind their age category. For those with cognitive dysfunction, mean age at the time of radiotherapy was 4 years old. Sutton et al. also found an increased need for special learning needs in young children (Sutton et al. 1995). In their cohort, 57% attended regular school (mean age at diagnosis, 7.2 years) and 43% required special education (mean age at diagnosis, 4.5 years).

Intracranial vasculopathy can develop after radiation therapy for OPGs. This vessel injury can manifest as a stroke which may result in irreversible neurologic deficit. Management includes anticoagulation and/or neurosurgical intervention for revascularization (Kestle et al. 1993). Of 54 patients treated with radiotherapy at the

Institut Gustave Roussy (Paris, France), 9 developed cerebrovascular complications (Cappelli et al. 1998). Of these patients, eight had NF-1. The median time to a vascular event was 2.5 years (range 6 months to 6 years). Another study reported an incidence of 19%, with a median time to cerebrovascular abnormality of 36 months, and with NF-1 patients affected more often (Grill et al. 1999). Vascular abnormalities can develop in patients with NF-1 independent of radiation or other therapies (D'Arco et al. 2014). Surgical resection carries a risk of injury to the carotid arteries and Circle of Willis, likewise resulting in permanent neurologic deficits.

Second malignancy is a possible late toxicity of radiation therapy. Jenkin et al. report 5 new malignancies in 48 patients treated with radiotherapy, with 3 in the brain, 1 in the cervical spine, and 1 elsewhere (Hodgkin lymphoma) (Jenkin et al. 1993). These tumors developed a median of 13 years after diagnosis of OPG (range, 9–29 years). Limiting the irradiated volume can reduce this risk (Moteabbed et al. 2014; Chung et al. 2013).

11.11 Future Directions

Improvements in systemic therapy are under investigation, with biologically targeted agents generating particular interest as a means to individualizing care and improving the therapeutic ratio (Brossier and Gutmann 2015). For example, BRAF duplication and MAPK activation have been reported as frequent findings in low-grade gliomas, including OPGs, and targeted agents to these pathways are in development (Rodriguez et al. 2012). Proton therapy should reduce the late side effects of radiation therapy, particularly neurocognitive dysfunction and second malignancy (Greenberger et al. 2014; Merchant et al. 2008). Advances in imaging, including intraoperative MRI and tractography, may likewise improve surgical management of OPGs (Goodden et al. 2014). Finally, more insight into the natural history of OPGs might aid our ability to select patients for observation alone.

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High-Grade Glioma

12

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Contents

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Abstract

High-grade gliomas are defined as tumors of glial origin with a very low incidence rate in infants and young children. They form part of the spectrum of primary intrinsic CNS and spinal cord tumors of children although their proportionate frequency of all primary CNS and spinal cord tumors is significantly lower compared to the adult population. The overwhelming number of newly diagnosed cases are sporadic primary tumors presenting with either signs of raised intracranial pressure, seizures, or other more nonspecific neurological symptoms. The initial management is aimed at restoring CSF flow, alleviation of existing mass effect, and establishing a pathological diagnosis. Ideally, the primary surgical approach is aimed at achieving a macroscopic complete excision without postoperative severe and permanent neurologic deficits. While primary chemotherapy is the preferred mode of adjuvant treatment in infants under the age of 3 years, the standard of care in all other patients is the use of combined focal radiotherapy and chemotherapy. Long-term outcome remains poor albeit appears generally slightly better than their adult counterparts.

12.1 Epidemiology

Pediatric high-grade gliomas (HGG) are defined as tumors of glial origin with a grade III or IV histology, according to the World Health Organization (WHO) histological grading system (Louis et al. 2007). The most common pediatric HGG are the anaplastic astrocytoma (AA, WHO grade III) and glioblastoma (GBM, WHO grade IV). Diffuse intrinsic pontine glioma will be discussed separately in this chapter. Other less frequently encountered subtypes include anaplastic oligodendroglioma, anaplastic oligoastrocytoma, anaplastic ganglioglioma, anaplastic pilocytic astrocytoma, anaplastic pleomorphic xanthoastrocytoma, giant cell glioblastoma, and gliosarcoma (MacDonald et al. 2011).

Whereas 40–50% of all pediatric central nervous system (CNS) tumors are gliomas, HGG represent approximately only 6–15% of all pediatric CNS tumors (Pollack 1994; Kaatsch et al. 2001; Broniscer and Gajjar 2004). The distribution between males and females is relatively equal (Fangusaro 2012). Unlike their adult counterparts, HGG comparatively are rare in the pediatric population. According to the Central Brain Tumor Registry of the United States between 2007 and 2011, the average annual incidence of HGG (including anaplastic astrocytoma, anaplastic oligodendroglioma, glioblastoma, and malignant glioma NOS) was 0.89 per 100,000 individuals aged 0–19 years (Ostrom et al. 2014). This translates into an incidence of approximately two cases per million children/adolescents annually.

Notwithstanding, despite advances in the field of neuro-oncology, the prognosis of HGG remains dismal. Overall the most important clinical determinants of

outcome for pediatric HGG are extent of resection and histological grade (Broniscer and Gajjar 2004; MacDonald et al. 2011; Fangusaro 2012).

Patients undergoing complete or near-complete resection fare better than those for whom a lesser degree of tumor debulking is achieved (Sposto et al. 1989; Finlay et al. 1995; Wolff et al. 2002), with 5-year progression-free survival (PFS) rates of 14–17% following <90% resection vs. 39–49% following ≥90% resection (Finlay et al. 1995). With regard to histology, children with GBM fare worse than those with AA; the 5-year survival rates range between 5 and 15% for children with GBM and 20 and 40% for those with AA (Phuphanich et al. 1984; Sposto et al. 1989; Marchese and Chang 1990), whereas HGG other than AA and GBM are associated with a more favorable outcome (Finlay et al. 1995). More recently, ACNS0126 demonstrated a 3-year event-free survival and overall survival in over 100 patients treated in the current era of 11 ± 3% and 22 ± 5% (Cohen et al. 2011).

12.2 Predisposing Factors

12.2.1 Etiology

The cause of the majority of pediatric HGG is unknown. A well-established predisposing factor for HGG is the exposure to ionizing radiation, typically following treatment of a previous oncologic condition, such as acute leukemia (Relling et al. 1999; Carret et al. 2006). Other suspected environmental factors such as pesticides, dietary nitrites, and some parental occupational exposures have not consistently shown a statistically significant association with pediatric brain tumors (McKean-Cowdin et al. 2013).

12.2.2 Genetic Issues

Some rare genetic disorders predispose to the development of HGG. Most of these are inherited defects in the regulation of cell proliferation and apoptosis, typically caused by germline mutations, such as neurofibromatosis type I, Li–Fraumeni syndrome and, less frequently, Turcot's syndrome, tuberous sclerosis, and von Hippel–Lindau disease (Melean et al. 2004; Fangusaro 2012). Although these genetic disorders represent only a small percentage of children with HGG, they have contributed greatly to the understanding of tumor biology.

Pediatric HGG are histopathologically indistinguishable from their counterpart in adulthood. However, there is increasing evidence indicating biological differences that suggest distinct molecular paths to gliomagenesis in children and adults (Rickert et al. 2001; Qu et al. 2010; Paugh et al. 2010; Bax et al. 2010; Miele et al. 2014; Sturm et al. 2014). Molecular pathways known to be involved in the process of gliomagenesis include the epidermal growth factor (EGF) ligand and receptor

pathway; the p53 pathway; the retinoblastoma tumor-suppressor pathway; the phosphatidyl-inositol 3-kinase (PI3K) pathway; and the DNA repair pathway, particularly involving the methylguanine methyltransferase (MGMT) protein and mismatch repair (MMR) enzymes (Broniscer and Gajjar 2004; Wu et al. 2014).

Compared to its adult counterpart, pediatric GBM has a much lower frequency of EGFR amplification (Bredel et al. 1999; Sung et al. 2000; Pollack et al. 2006), a relatively higher frequency of p53 overexpression (Sung et al. 2000; Pollack et al. 2002; Batra et al. 2014), and a higher frequency of focal amplification of platelet-derived growth factor receptor α (PDGFRα) (Paugh et al. 2010) and microsatellite instability resulting from deficient DNA mismatch repair (Leung et al. 1998; Alonso et al. 2001). In addition, pediatric HGG show more frequently 1q gain and loss of 1p, 4q, 8p, and 16q, and have a considerably lower frequency of chromosome 7 gain and 10q loss, a defining feature of adult HGG (Rickert et al. 2001; Qu et al. 2010; Paugh et al. 2010; Bax et al. 2010; Barrow et al. 2011). In contrast, there is a subset of pediatric HGG that displays isocitrate dehydrogenase 1 (IDH1) gene mutations, a typical feature of HGG in adults of younger age, usually associated with secondary HGG. IDH1 mutations have also been found in HGG of adolescents, but not in younger children (De Carli et al. 2009; Paugh et al. 2010; Pollack et al. 2011).

IDH1 mutations are mutually exclusive with mutations in the H3F3A gene, encoding the histone H3.3 (Sturm et al. 2012). Recurrent somatic H3F3A mutations have been identified in two critical amino acids (K27 and G34) of histone H3.3 in approximately 50% of pediatric GBM (Schwartzentruber et al. 2012; Sturm et al. 2012; Bender et al. 2013). H3F3A mutations induce deregulation of epigenetic control mechanisms by altering histone modifications, DNA methylation, and gene expression, constituting major drivers towards gliomagenesis (Sturm et al. 2012, 2014; Bender et al. 2013; Wu et al. 2014).

Furthermore, another particular hallmark of GBM is its intratumoral heterogeneity. On a molecular level, this phenomenon translates the presence of different areas with specific chromosome aberrations, mutations, and gene expression patterns within a single tumor. Intratumoral heterogeneity entails major clinical implications, such as the potential for sampling bias over space and time and the prospect of combined targeted approaches to tackle the mosaic of molecular drivers (Sturm et al. 2014).

Comprehensive molecular profiling studies have greatly broadened our knowledge of the underlying genomic and epigenomic aberrations associated with GBM (Sturm et al. 2014; Wu et al. 2014). Based on recurrent combinations of genomic and/or epigenomic features with distinct patient characteristics, GBM across all ages is being dissected into meaningful biological subgroups which are likely to guide future clinical trials (Sturm et al. 2012, 2014).

12.3 Presenting Symptoms

Presenting symptoms of HGG are common to other CNS tumors. These symptoms are often due to raised intracranial pressure, including persistent headaches, behavioral changes, early morning nausea/vomiting, diplopia, and papilledema, or due to

compression/infiltration of adjacent structures, including focal motor deficits, pyramidal tract findings, or cerebellar signs depending upon the localization of the tumor (Broniscer and Gajjar 2004; Fangusaro 2012). Seizures in the setting of a HGG are surprisingly not a common feature at the initial presentation, but often occur following subsequent invasion of the temporal lobe (Fangusaro 2012). Infants and very young children often present with nonspecific findings, such as failure to thrive, lethargy, nausea/vomiting, and macrocephaly, frequently making a rapid/early diagnosis difficult (Reddy and Wellons 2003). In contrast to low-grade gliomas, the typical duration of symptoms prior to presentation is often much shorter in children with HGG (Reulecke et al. 2008; Fangusaro 2012).

12.4 Radiographic Findings

Childhood supratentorial HGG are commonly polar hemispheric tumors, although 20–30% are midline, deep-seated lesions (Pollack 1994). Classically, HGG are hypo-intense on T1 and hyper-intense on T2-weighted sequences, but no specific MRI findings can distinguish them from other pediatric CNS tumors. Nevertheless, some characteristics may help the differential diagnosis, such as irregular borders, mass effect on surrounding brain structures, significant edema on fluid attenuation inversion recovery (FLAIR) images, and nodular enhancement (Panigrahy and Blüml 2009). Although contrast enhancement is commonly seen in supratentorial HGG, the amount and degree of enhancement does not always correlate to tumor grade (Fangusaro 2012).

12.5 Workup

The first diagnostic tool of choice in children suspected of having an intracranial process is a computerized tomography (CT) scan. This imaging technique is quick, convenient, and locally easily available, and identifies cases that may require urgent intervention, such as hydrocephalus or acute CNS hemorrhage (Fangusaro 2012). However, CT as an imaging modality has been superseded by magnetic resonance imaging (MRI) as the routine imaging modality of choice to characterize the tumor type, anatomic location, relationship to adjacent structures, and extent of pediatric CNS tumors (Fangusaro 2012). HGG rarely present with leptomeningeal spread (Broniscer and Gajjar 2004; Fangusaro 2009). However, many clinicians will obtain a complete spinal MRI in addition to the brain at diagnosis as a baseline or whenever focal symptoms warrant further assessment (Fangusaro 2012).

Advanced MRI techniques, such as diffusion-weighted, perfusion-weighted and MR spectroscopy, as well as different PET modalities, can provide valuable information on cellularity, tissue ultrastructure, metabolism, and vascularity. These techniques can aid diagnosis, provide noninvasive prognostic biomarkers, help treatment planning, and monitor the clinical outcome. However, these techniques are currently not incorporated into routine clinical practice and robust data obtained from multicenter clinical trials are yet required to further define their role (Peet et al. 2012).

12.6 Acute Management

The acute management of pediatric high-grade glioma centers on the management of cerebrospinal fluid (CSF) and mass effect.

12.6.1 CSF

Hydrocephalus is seen in over 50% of patients at presentation; in the majority of cases (>90%), this hydrocephalus is communicating (Wong et al. 2011). CSF diversion can be achieved in several ways. A primary tumor resection or targeted debulking can alleviate raised intracranial pressure in it's own right without the need for CSF diversion; however it may not be feasible in all patients. In particular, those patients with an intrinsic tumor of the basal ganglia, bithalamic gliomas, or other deep structures may benefit from an endoscopic ventriculostomy to provide rapid symptom relief. Insertion of a ventriculoperitoneal shunt is a more definitive procedure. Its insertion carries small risk, including that of infection albeit there is some evidence that the use of antibiotic impregnated shunts may reduce this risk (Kandasamy et al. 2011).

12.6.2 Mass Effect

Mass effect can be managed by surgical or medical means. A macroscopic complete resection is possibly the best way to relieve intracranial pressure. However, even those patients in whom a macroscopic complete resection cannot be achieved, debulking surgery offers frequently the best option of rapid reduction of local mass effect and lasting symptom improvement. In addition, medical management of local mass effect can be achieved through high-dose steroid therapy, usually dexamethasone. Osmotic diuretics, such as mannitol, may be used but due to a possibility of the "rebound phenomenon," their role is in the acute setting only and steroids remain the first pharmacologic port of call in the management of mass effect (Roth et al. 2013).

12.6.3 Steroid Use

Steroids are used to alleviate the symptoms and signs of peritumoral edema. There have been no randomized, blinded trials but historically dexamethasone has been the glucocorticoid of choice. It has a long half-life, minimal mineralocorticoid effects and can be delivered orally. It is used at the time of presentation to control symptoms and is generally used also in the postoperative period. Steroid administration is associated with side effects including weight gain, proximal myopathy, and diabetes amongst others and hence the aim is to maintain the patient on as low a dose as possible.

12.7 Treatment

12.7.1 Evolution to Current Treatment

Treatment for pediatric HGG in the latter half of the 20th century has evolved from surgery alone, towards integrated multi-modality therapy combining surgery, radiotherapy, and chemotherapy. Oncological management initially focused on whole brain radiotherapy, which was also the standard of care in the adult population. Chemotherapy was introduced to the management of children with high-grade gliomas (HGG) in 1976, with the initiation of the Children's Cancer Group (CCG) phase III study, CCG-943. This combined involved-field irradiation with or without chemotherapy. Involved-field irradiation was a deviation from the standard practice in adults at the time. The chemotherapy regimen combined prednisone, CCNU, and vincristine as vincristine and CCNU had demonstrated activity in those with recurrent tumors. It demonstrated an improved event-free survival (46%) in those in the combination therapy arm as compared to those in the radiation alone arm (18%) and led to the inclusion of chemotherapy in treatment regimens for pediatric HGG. Further CCG trials since then have combined varying cytotoxic chemotherapies to further refine the optimal treatment. Regional field irradiation was demonstrated to have comparable rates of local control in CCG-943 and whole brain radiotherapy is no longer clinically acceptable.

12.7.2 Role of Surgery

Surgery has a role in both symptom management and in improving prognosis. In the adult setting, the extent of tumor resection (EOR) has been demonstrated to have a prognostic impact (Grabowski et al. 2014) and a macroscopic complete resection is the primary goal at surgery if this can be achieved safely. In the pediatric setting, it has also been demonstrated to have prognostic significance (Wisoff et al. 1998; Wolff et al. 2010). Extent of resection is a prognostic factor for glioblastoma with greatest influence on long-term survival with a 5-year PFS of >35% when EOR is >90%, but only 17% when EOR is <90% (Campbell et al. 1996; Wisoff et al. 1998).

Given the appreciated impact of gross total resection on outcome, pediatric neurosurgical teams increasingly apply adjunctive pre- and perioperative technologies over and above direct visual intraoperative techniques. This will increase the percentage of patients with postoperative radiologically confirmed gross total resections. These may include among other approaches: intraoperative ultrasound or MRI, cortical mapping/stimulation, awake craniotomies, and more recently the use of 5-aminolevulinic acid (5-ALA, Gliolan) (Stummer et al. 2014).

In addition, in the era of molecularly targeted therapy, surgery plays a crucial role in providing an adequate tissue sample for both histopathological diagnosis and subsequent molecular analysis.

12.7.3 Role of Chemotherapy

Chemotherapy has become part of the management in pediatric HGG following the publication of the CCG-943 study in many centers across both the USA and Europe. (Sposto et al. 1989) In those patients under the age of 3 years, chemotherapy is given in order to avoid or delay radiotherapy. This is due to the broad range of adverse effects, to which those under 3 are more susceptible. In those over 3, it may be added to surgery and radiotherapy to improve outcomes. Since the publication of CCG-943, there have been several studies of combination chemotherapy. Included amongst these is ACNS0126, a cooperative group study which combined radiotherapy and temozolomide (Cohen et al. 2011). Temozolomide is an oral alkylating agent which has demonstrated improved survival in adult glioblastoma (Stupp et al. 2005). ACNS0126 study demonstrated a 3-year event-free survival of 11 ± 3%, and a 3-year overall survival of 22 ± 5%. This was significantly worse than outcomes in CCG-943 but may be explained by a large population of low-grade gliomas in the latter; a 30% reclassification rate was seen in CCG-945 and similarly is likely to have been present in CCG-943 (Boyett et al. 1998). In ACNS0126, this rate was less than 10%. The current UK's Children's Cancer and Leukemia Group (CCLG) guidelines recommend treatment with chemoradiotherapy and adjuvant temozolomide, with treatment continuing for up to 12 months of temozolomide. However, the benefit of extending adjuvant temozolomide chemotherapy beyond 6 month remains unproven. A further large single center series using combined postoperative radiotherapy and temozolomide chemotherapy was recently published by the group from the TATA Memorial Hospital (Jalali et al. 2015). The data suggest a close correlation between the ability to achieve a macroscopic complete resection and outcome as previously demonstrated but no obvious predicative role for the mGMT methylation status. Patients under the age of 3 years are treated according to a modified version of the HIT-SKK regimen, originally used to treat patients with medulloblastoma (Rutkowski et al. 2005). This regimen combines methotrexate, carboplatin, cyclophosphamide, and vincristine. If, after three cycles, there is residual tumor, second-look surgery is recommended due to reports of dedifferentiation of such tumors to a lower grade following treatment (Jeibmann et al. 2009).

12.7.4 Role of Radiotherapy

Radiotherapy (RT) for HGG has been in use for several decades (Bloom et al. 1990). Definitive evidence that RT for HGG improves survival was first demonstrated by the NCI Brain Tumor Study Group studies in the 1970s, which included both children and adults (Walker et al. 1978; Bloom and Bessell 1990; Gorlia et al. 2008). Traditionally, primary or postoperative adjuvant RT for HGG was delivered using parallel pairs of opposed beams covering the whole brain, due to the highly infiltrative nature of these tumors (Bloom 1975) Irradiation of the whole neuraxis is reserved for the very small number of patients with leptomeningeal disease dissemination at presentation. The CCG-943 study introduced involved-field brain radiotherapy, treating the gross tumor and associated peritumoral edema with a defined margin followed by a focal boost, and this has approach to brain RT since become

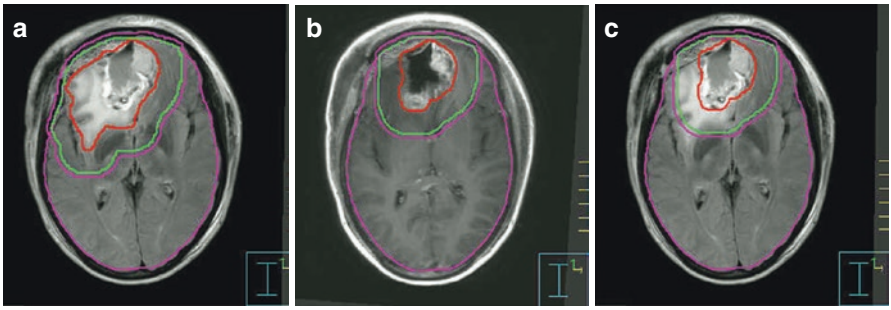

Fig. 12.1 (**a**) The target volume definition for glioblastomas according to the CCG-943 study and most commonly used in US centers. The *red line* depicts the extent of the primary postsurgical tumor bed and associated edema (gross tumor volume, GTV) on the appropriate sequence of a dedicated volumetric planning MRI scan. This target volume is then increased by an institutional three-dimensional margin of 2–2.5 cm (*green line*) limiting/editing the volume by any barriers of natural spread (clinical target volume, CTV). Finally a margin of 0.3–0.5 cm (*pink line*) is added to form the final planning target volume (PTV) which takes into account spatial variations of the target volume due to setup uncertainties during a course of daily radical radiotherapy. This PTV receives usually a total dose of 45–46 Gy. (**b**) Using a shrinking field technique (according to the CCG-943 guidelines) following 45–46 Gy patients receive a boost to the primary postoperative tumor bed and/or any areas of visible macroscopic contrast enhancing tumor (GTV, *red line*) outlined on a fused post-contrast T1-weighted volumetric sequence. This target volume is then increased by an institutional three-dimensional margin of 2–2.5 cm (*green line*) limiting/editing the volume by any barriers of natural spread (clinical target volume, CTV). Finally a margin of 0.3–0.5 cm (*pink line*) is added to form the final PTV. The PTV receives a further dose increase to the final prescription dose of 54–60 Gy depending on local institutional protocols. In contrast to many US sites this GTV/CTV/PTV is used in most European centers as the primary target volume using a single phase approach to the prescription dose of 54–60 Gy. At our own institution we have been using for more than two decades—compared to the published literature—smaller margins without detriment to clinical outcome. Our institutional GTV to CTV margin for high-grade gliomas is 1.7 cm and the CTV to PTV margin 0.3 cm and are depicted in (**a**)–(**c**). (**c**) This figure depicts the target volumes as defined in (**b**) transferred to the fused MRI planning sequence visualizing the tumor bed, postoperative changes and remaining peri-tumoral edema. It is highlighting that a target volume definition as used in many European centers does cover most of the remaining edema within the defined CTV/PTV albeit not completely. It is unlikely that any future clinical trials will prospectively assess the potential differences between these two different radiotherapeutic approaches either with respect to local control or toxicity. Thus the choice of the target volume definition used for glioblastomas will remain at the discretion of local services

the standard of care for HGG in the USA (Sposto et al. 1989). Most European centers use a single phase primary target volume definition as recently recommended by a multinational working group (Niyazi et al. 2016, Fig. 1). HGG with an oligodendroglial component may be more responsive to RT and chemotherapy (Donahue et al. 1997; van den Bent 2007).

12.7.4.1 Sequencing of Radiotherapy and Chemotherapy

The use of RT for children under 3 years requires careful evaluation on an individual basis, and is generally avoided in this age group of patients. The therapeutic ratio of brain RT for HGG is considered to be unfavorable for patients less than 3 years due to unacceptable neurocognitive toxicity, possibly as a result of incomplete

myelination of brain white matter (Duffner et al. 1985; Ellenberg et al. 1987; Packer et al. 1989; Jannoun and Bloom 1990; Glauser and Packer 1991; Mulhern et al. 1992). Patients with HGG aged less than 3 years may be treated with surgery followed by prolonged chemotherapy, with the aim of deferring brain RT until the patient is older, and thereby reducing the risk of RT-induced morbidity (Duffner et al. 1993).

Limited data on effect of delaying RT after surgery for HGG are available from three studies. The Pediatric Oncology Group's "Baby POG" study included 18 patients with HGG aged less than 3 years. Nine of these patients had an unclassified malignant glioma, six had GBM, and three had AA. Children less than 2 years received 24 months of chemotherapy (vincristine, cyclophosphamide alternating with cisplatin, etoposide), and those children between the ages of 2 and 3 years received chemotherapy for 12 months. Following chemotherapy, all children were recommended to receive brain RT. In addition, if any child developed progressive disease during chemotherapy, repeat surgery followed by RT was recommended. The 5-year PFS was 43%± and the 3-year and 5-year OS were both 50%±. The families of four children refused radiation after completion of 24 months of chemotherapy, and each of these four patients was alive and well at 43+ to 84+ months after diagnosis (Duffner et al. 1996). The CCG-945 study included 39 children younger than 2 years with HGG: 9 with GBM, and 20 with AA. Children received combination chemotherapy (the 8-in-1 regimen) for a maximum of ten cycles, amounting to up to 15 months of chemotherapy. The CCG-945 study protocol specified involved-field brain RT for all children following completion of chemotherapy, but only four patients received RT, and in two of these RT was given at the time of relapse. The 3-year PFS estimate for all patients was 31% ± 8%, and the OS at 3 years was 51% ± 8%. The 3-year PFS estimate for patients with AA and GBM was 44% ± 11% and 0, respectively (Geyer et al. 1995) [Geyer et al., Cancer 1995]. A chemotherapy only approach delivering 16 months of combination chemotherapy (the so-called BBSFOP regimen) was investigated in a multi-institutional French study that included 21 patients less than 5 years treated with postoperative chemotherapy following maximal surgical resection, with RT delayed until disease progression or recurrence. Consistent with the "Baby POG" results, this approach achieved a 5-year PFS of 35% ± and a 5-year OS of 59% ± (Dufour et al. 2006). Taken together, the results of these three studies suggest that HGG in younger patients has different biology and more favorable clinical behavior to HGG in older children and adults.

There are very few data on the use of chemotherapy before RT in children older than 3 years with HGG and the utility of this approach in this patient group is unclear. In a more contemporaneaous study, patients aged between 3 and 17 years with HGG were randomized between chemotherapy before RT (neoadjuvant) and chemotherapy during and after RT (concomitant and maintenance) (Wolff et al. 2002) Neoadjuvant chemotherapy consisted of alternating cycles of ifosfamide and etoposide, methotrexate, and cisplatin and cytarabine; RT started at week 17. Maintenance chemotherapy consisted of weekly vincristine during RT, and eight cycles of vincristine, lomustine, and cisplatin following RT. Although analysis of the subset of patients with gross total resection showed significantly improved survival for patients assigned to neoadjuvant chemotherapy compared to those

who received concomitant and maintenance chemotherapy, more than one-third of patients with incompletely resected disease who received neoadjuvant chemotherapy experienced early tumor progression. Therefore, there is a concern that initial treatment with ineffective chemotherapy regimens and the delay of RT may worsen the outcome of children with macroscopic residual disease. Currently, involved-field RT is indicated for all children with HGG older than 3 years.

12.7.4.2 Radiotherapy Dose

The radiation tolerance of the normal brain parenchyma and its vascular and supporting structures are dose limiting for external beam brain RT. The risks of acute and long-term sequelae increase with increasing brain RT doses. Aside from the neurocognitive decline associated with brain RT, other well-recognized late effects include endocrinopathy, RT-induced tumors (benign and malignant), and vasculopathy. The risk and severity of these effects depend on patient age, the total volume of the planning target volume (PTV), and the proximity of PTV to critical organs at risk. The current standard RT dose for patients with HGG is 54–60 Gy delivered in daily fractions of 1.8–2.0 Gy over a period of 6 weeks. Since the overwhelming number of failures occur within the high-dose region of the RT volume, RT dose escalation has been investigated in several trials, but without evidence of benefit for doses greater than 60 Gy (Fulton et al. 1992; Packer et al. 1993). However, RT doses above 60 Gy are associated with significant long-term adverse normal tissue toxicity in long-term survivors (Werner-Wasik et al. 1996; Lawrence et al. 2010). Combined photon-proton therapy explored in a phase II trial at Massachusetts General Hospital—90CGE was delivered using accelerated fractionation, but there was no evidence of improved survival with 3-year OS of 18% (Fitzek et al. 1999). Alternative radiotherapy techniques such as hyper- and hypo-fractionation have not consistently proven to be statistically beneficial in children with HGG and should not be utilized outside of a clinical trial setting (Fallai and Olmi 1997). The failure of intensified RT to improve outcomes for HGG suggests that improved brain-directed therapies are needed.

12.8 Target Delineation

12.8.1 Radiotherapy Tumor Target Volumes

Involved-field RT for HGG delivers a therapeutic radiation dose to not only the postoperative tumor cavity and any residual tumor, that is the gross tumor volume (GTV), but must also include an additional circumference of brain tissue considered to be at risk of microscopic disease extension, which forms the clinical target volume (CTV). The GTV to CTV margin also allows for any uncertainties in tumor definition to be accounted for. A further circumferential margin is added to the CTV to allow for variations in daily treatment setup, to create the planning target volume (PTV). The ICRU 50 report provides formal definitions of the GTV, CTV, and PTV concepts and these are followed in RT planning for HGG. Specific normal tissue structures may be defined and identified as organs at risk (OARs), and each OAR may be given a surrounding safety margin to create a planning at risk volume (PRV) as defined by ICRU

50. The primary tumor should be treated, using a suitable technique that allows for the least amount of normal brain tissue and organs to be at risk from exposure to high-dose irradiation. Suitable techniques include 3D conformal RT, fixed field IMRT, and dynamic arc IMRT. 6MV photons are typically used to deliver RT. No therapeutic advantage from the use of particle therapy relative to megavoltage photon therapy has been demonstrated for treatment of pediatric HGG, with reported results being equivalent (McAllister et al. 1997). Dose variations across the PTV should be within +7% and −5% of the prescription dose according to ICRU 50 and 62 recommendations.

The GTV is defined by co-registering a volumetric (3D) MRI scan with the RT planning CT scan within the RT treatment planning system (TPS). The MRI needs to be obtained as close to time of RT planning as possible. Three-dimensional imaging data (CT ± MRI) are acquired with the patient in the treatment position with a slice thickness of ≤2.5 mm. Three-dimensional treatment planning software is used to determine beam arrangements and dosimetry. Image data are used to delineate and reconstruct a GTV, CTV, PTV, and organs at risk (OAR) in three dimensions. Pre- and post-op MRI images should be co-registered to the planning CT and available within the TPS at the time of contouring.

Two somewhat different philosophies towards tumor target volume definition for HGG have developed in North America and Europe, as illustrated by outlining guidelines within study protocols from Children's Oncology Group (COG) and the European Society of Paediatric Oncology (SIOP-Europe). American technical approaches, for example, frequently use a two-phased approach (shrinking field technique). GTV1 is defined as the volume encompassing the contrast enhancing tumor tissue and all high signal changes as seen on T2-weighted imaging. GTV2 is defined as the volume encompassing only any residual contrast enhancing tumor elements/tumor bed as seen on postoperative MRI. Marginal expansion for GTV1 is an anatomically confined 2 cm margin to form CTV1, and the marginal expansion for GTV2 is 1 cm to form CTV2. Bone and dura act as barriers to disease infiltration, and so CTV1 and CTV2 are manually edited following marginal expansion to reside within the skull vault and to avoid crossing dural planes unless there is definite radiological evidence of disease. The CTVs may also be manually modified to avoid crossing midline and to avoid critical structures including the optic apparatus, pituitary, and brainstem. The CTVs are expanded to form the PTVs by means of an isotropic expansion without regard to anatomy—the margin applied is dependent on the patient positioning and immobilization systems used and is therefore institutional dependent, but in practice will typically be between 0.3 and 0.5 cm. The PTV1 dose is 54 Gy, and an additional dose of 5.4 Gy is prescribed to PTV2.

The HGG tumor volume definitions in use in most European centers are most commonly using a single phase approach. GTV is defined as the enhancing tumor as seen on gadolinium contrast enhanced MR at the time of RT planning (postoperatively) together with the entire surgical cavity if patient has been able to undergo either a debulking procedure or a gross total resection. The GTV must take into account any anatomical shift or other tissue changes after surgery. The CTV includes an additional margin of 2.0–2.5 cm in directions of potential tumor spread, and is edited to avoid crossing anatomical boundaries to tumor dissemination as per the COG guidelines (Vern-Gross et al. 2014). The PTV is generated from the CTV by the

addition of an isotropic margin according to department policy (usually 0.3–0.5 cm). The standardly prescribed PTV dose is ranging between 54 and 60 Gy in conventional fractionation over a period of 6 weeks although there remains controversy if a dose increase from 54 Gy to 60 Gy in this patient population is critical for outcome.

12.8.2 Radiotherapy Organs at Risk

The following organs at risk (OARs) are frequently defined on the treatment planning system (TPS): supratentorial brain (left and right hemispheres); hippocampi (left and right); cochlea (left and right); pituitary; optic globes (left and right); lenses (left and right); optic nerves (left and right); optic chiasm; brainstem and cervical spinal cord (foramen magnum to C2). The lenses of the eyes should be excluded from primary beams unless a primary intensity modulated arcing technique is employed.

Cochleae. Each cochlea is contoured on the RT planning CT, viewed using bone-windows, as a circular structure within the petrous portion of the temporal bone anterior to internal acoustic meatus (IAM). The contour should appear on at least two successive axial CT slices. The aim is for the cochlea dose to be no more than D50% < 35.00 Gy for hearing preservation (Bhandare et al. 2010).

Optic Globes. Each eye is separately contoured on the RT planning CT from the most superior to inferior aspect. Effort should be made to avoid direct treatment of the anterior chamber of the eye to protect the lenses. Dose to the entire eye should be kept to the minimum possible, without compromising PTV coverage. If the COG tumor target definitions are used, then in the event that the optic globe dose constraints cannot be met, as a result of treatment of PTV2, then it may be preferable to compromise PTV2 coverage. Dose to the optic globes should be constrained to D50% < 20.00 Gy and D10% < 54.00 Gy (Mayo et al. 2010).

Optic Nerves and Chiasm. The optic nerves and optic chiasm may be contoured on the RT planning CT, or on a co-registered T1-weighted MRI. The optic chiasm is most readily identified on coronal images prior to outlining on axial images on the TPS. The right and left optic nerves are contoured separately, starting from the posterior globes to their exit from the optic canals. The optic chiasm is contoured as a single structure consisting of pre- and post-chiasmal nerves and a central body. The pre-chiasmal nerves start at the optic canals and terminate at the anterior body of the chiasm; the post-chiasmal nerves start from the posterior body of the chiasm and run posteriorly to enter the thalami. The incidence of radiation-induced optic neuropathy (RION) is uncommon with a Dmax <55 Gy at fraction sizes of <2 Gy. The RION risk increases to 3–7% for doses in the region of 55–60 Gy with fraction sizes of 1.8–2.0 Gy (Mayo et al. 2010). SIOP-E protocols specify optic apparatus dose constraints of D50% < 56.00 Gy and D10% < 60.00 Gy. Efforts should be made to avoid direct treatment of the optic nerves and chiasm—without compromising target volume coverage during treatment of PTV1. In the event that the recommended constraints provided in this section would be exceeded as a result of treatment of PTV2, the treating radiation oncologist may use their discretion to reduce target volume coverage.

Hypothalamus/Pituitary. The hypothalamus and pituitary may be contoured as a single composite structure on the RT planning CT. Guidance on the definition of this

volume is available from contouring atlases produced for clinical trials, such as COG ACNS0331 (http://www.qarc.org/cog/ACNS0331Atlas.pdf Michalski J). Retrospective data from a cohort of childhood cancer survivors treated with cranial radiotherapy for a variety of diagnoses found that compared with total RT doses <22 Gy, doses of 22 Gy to 29.9 Gy were associated with GH deficiency; doses ≥22 Gy were associated with LH/FSH deficiencies; and doses ≥30 Gy were associated with TSH deficiency and ACTH deficiency (Chemaitilly et al. 2015) The aim is to keep the hypothalamus and pituitary dose D50% < 20.00 Gy, but never at the expense of PTV coverage, which should always take priority.

Hippocampus. The hippocampal structures are best contoured on a T1-weighted MRI co-registered with the RT planning CT, according to the Radiation Therapy Oncology Group (RTOG) hippocampal outlining atlas (Gondi V et al.). Retrospective data from the Childhood Cancer Survivor Study (CCSS) demonstrate an increased risk for memory difficulties with RT doses above ≥30 Gy to the temporal lobe region (Armstrong et al. 2010). Effort should be made to minimize dose to the hippocampi but without compromise to PTV coverage, which always takes priority.

Brainstem. The brainstem is contoured directly on the RT planning CT. The volume includes the midbrain, pons, and medulla. The cranial boundary is inferior to the third ventricle and optic tracts. The caudal boundary of the brainstem is taken as the foramen magnum. For supratentorial HGG, the brainstem can usually be excluded from the CTV. The entire brainstem may be treated to 54 Gy using fraction sizes of ≤2 Gy with a low risk of irreversible neurological toxicity (Mayo et al. 2010; Merchant et al. 2010). Smaller volumes of the brainstem (1–10 cc) may be irradiated to a maximum dose of 59 Gy at dose fractions of ≤2 Gy, but the risk of neurological toxicity increases markedly at doses beyond 64 Gy (Mayo et al. 2010).

Spinal Cord. For supratentorial HGG, spinal cord dose constraints do not typically pose difficulties for RT planning. With conventional fraction sizes of ≤2 Gy, total doses of 50 Gy and 60 Gy to the full spinal cord cross section are associated with a risk of myelopathy of 0.2% and 6% respectively (Kirkpatrick et al. 2010). SIOP-E guidelines specify spinal cord dose constraints of D50% < 50.00 Gy and D10% < 55.80 Gy. The spinal cord (not the spinal canal) is contoured on the RT planning CT using suitable window settings. The spinal cord begins where the brainstem ends, at the inferior border of the foramen magnum.

12.9 Outcomes

12.9.1 Follow-Up Guidelines

CNS tumors are the leading cause of morbidity in survivors of childhood tumors/cancers. They require dedicated follow-up clinics with access to all aspects of the multidisciplinary team, including endocrinology and psychology. The CCLG guidelines are a good reference for the organization of a follow-up clinic.

12.9.2 EFS, DFS, OS

Historical data is somewhat clouded by the contamination of trials by low-grade gliomas, rather than true high-grade tumors. The ACNS0126 trial (with fewer than 10% of tumors reclassified as low grade) demonstrated a 3-year EFS of 13 ± 6% for those patients with an anaplastic astrocytoma (AA) and 7 ± 4% for GBM.

12.9.3 Toxicities

Depending upon the treatment paradigm used, toxicity patterns differ. In the acute period, common toxicities whilst on chemotherapy include myelosuppression (with the resulting risk of infection), nausea, hair loss, etc. For those on radiotherapy, hair loss, skin changes, headaches, and seizures are seen. Long-term toxicities are more problematic; however, given the poor long-term survival rates, they are not as pressing an issue as they are in low-grade glioma, for example. Medium- and long-term toxicities can be broadly grouped into those caused by chemotherapy and those caused by radiotherapy. Chemotherapy may lead to sensorineural hearing deficits, infertility, and peripheral neuropathy. Long-term toxicity data from radiotherapy pertains to historic techniques and, as such, may differ from those expected with modern techniques. Toxicities are related to the organs at risk and their respective radiotherapy doses. Endocrine function must be monitored. Longer term, there is a potential risk of second malignancies and stroke.

12.10 Future Directions

Despite advances in many other areas of oncology, improvements in outcomes for patients with pediatric high-grade glioma remain poor. Improvements in surgical resection techniques through the use of aides, such as cortical mapping and 5-ALA fluorescence, may improve macroscopic complete resection rates. Combination regimens of traditional cytotoxic chemotherapies have not provided the improvements expected.

In the era of personalized medicine, next generation sequencing and whole exome sequencing of tumor samples have led to the identification of potential molecular targets. These include mutations within the phosphatidylinositol-3-kinase pathway (PI3K), the sonic hedgehog (SHH) pathway, and the RAS/RAF/MEK pathway. Molecules targeting these mutations are already in clinical trials; we await results. The heterogeneity of mutational profiles will need to be incorporated even more into clinical trials. Already in the adult setting, it is recognized that molecular characteristics may be more significant than histological classification; undoubtedly, pediatric glioma is similar. The increasing incorporation of "basket" design studies will facilitate further investigation of targeted therapies.

Immune modulation is an area of intense interest across many oncological specialties; neuro-oncology is no exception. Studies in pediatric gliomas have focused

on vaccines, deriving antigens from the tumor itself. These studies are ongoing and their results are awaited.

Another novel strategy under investigation in a new cooperative study is the combination of multi-agent chemotherapy with a randomization to maintenance valproic acid as a cell differentiating agent.

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Brainstem Tumors

13

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Abstract

Brainstem tumors are of several distinct types that can be broadly classified as either focal or diffusely infiltrating. Most focal tumors are low grade gliomas for which the treatment of choice is surgery. If not feasible, or if and when progression occurs after surgery, chemotherapy, and radiotherapy may be considered, typically chemotherapy for children less than 10 years of age or children of any age with NF-1 and radiotherapy for all others. Although patients may need more than one, and frequently several, interventions (including repeat surgery) over time, the prognosis is very good with an overall survival of approximately 95% at 10 years. This is not the case for diffusely infiltrating pontine tumors for which surgery is not an option and chemotherapy has not proved useful and so these tumors are typically treated with radiotherapy alone. While radiotherapy is a useful treatment for DIPG, in most patients leading to early complete neurological recovery, time to progression is only 5–6 months and median survival is less than 1 year. For both focal and diffusely infiltrating brainstem tumors, new insights into the tumor biology hold promise for new therapeutic targets, potentially reducing risk associated with treatment (surgery, radiotherapy, and/or chemotherapy) for the former and improving tumor control and survival for the latter.

13.1 Introduction

Approximately 10–15% of all CNS tumors in the pediatric age group arise in the brainstem. They are of several distinct types that can be broadly classified as either focal or diffusely infiltrating (Donaldson et al. 2006; Farmer et al. 2001; Fisher et al. 2000). Presenting symptoms and signs and imaging characteristics as well as management and prognosis are very different for the two groups. Patients with neurofibromatosis type 1 who have lesions in the brainstem, not all of which are tumors, should be managed as a group apart and are not discussed further here.

13.2 Focal Tumors

Focal tumors are low grade tumors of several types, each with rather distinctive growth patterns (Epstein and Farmer 1993). *Intrinsic focal tumors* are seen mostly in the midbrain and medulla oblongata. Patients typically present with a long history of localizing symptoms and signs, e.g., an isolated cranial nerve deficit and contralateral hemiparesis, or with hydrocephalus as a result of aqueductal distortion in the case of midbrain tumors. On MRI, the tumor is by definition well circumscribed with no infiltration of surrounding tissues and no edema. Most are juvenile pilocytic astrocytomas (JPA) and, like JPA in other locations, usually enhance brightly with gadolinium injection and often have an associated cystic component. *Cervico-medullary tumors* arise in the upper cervical cord and grow rostrally

beyond the foramen magnum. Axial growth is limited by the pyramidal decussations located ventrally at the junction of the cervical cord and medulla such that the tumor becomes exophytic posteriorly at the obex. Patients may present with lower cranial nerve deficits, sleep apnea and feeding difficulties in younger children, long tract signs, and/or torticollis. Most cervico-medullary tumors are also JPA although a significant proportion of tumors in this location are gangliogliomas. Finally, *dorsal exophytic tumors* arise from the floor of the IVth ventricle. They are often large, filling the ventricle, but do not invade the brainstem. Patients present insidiously with failure to thrive in younger children and symptoms and signs of raised intracranial pressure in older patients. Cranial nerve deficits are seen in about half of the patients. On MRI, these tumors appear sharply delineated. They are hypointense on T1-weighted images and hyperintense on T2-weighted images and enhance uniformly and brightly with gadolinium injection. Most are JPA.

13.2.1 Treatment

General principles of treatment of focal brainstem tumors are similar to those for low grade gliomas (LGG) in other locations. Surgery is the treatment of choice if feasible, meaning that the tumor is accessible, i.e., exclusively exophytic or extending toward the surface of the brainstem laterally or at the floor of the IVth ventricle. Radiotherapy and/or chemotherapy are reserved for patients that are not operable or who have progressive disease after surgery.

13.2.2 Surgery

Surgery for tumors involving the brainstem requires a high level of expertise and a skilled pre-/intra-/post-op team, as well as all modern accessories including fiber tractography and a multimodality monitoring team (motor evoked, sensory evoked, and auditory evoked responses, and spontaneous EMG monitoring for cranial nerves V (motor), VII, XI, and XII). Good clinical judgment is essential, with attention to the location and growth pattern, and any erosion of the floor of the fourth ventricle or the location of the facial colliculus if there is no erosion. It is important too that there is no peritumoral hypodensity that would be suggestive of more invasive/higher grade disease. Patients with involvement of the medulla who have lower cranial nerve deficits are at particular risk for serious permanent sequelae.

When complete resection is achieved, the outcome may be very good. In the St. Jude series, 48% of 52 patients with focal brainstem tumors had surgery alone. At 10 years, event-free survival for the patients who underwent gross total resection was 75%. Event-free survival was much less satisfactory for patients who underwent lesser degrees of resection: 25.7% at 5 years for patients who underwent near total or subtotal (>90%) resection and 33.3% for those that had <90% resection (Klimo et al. 2013). In a series from the Hospital for Sick Children in Toronto,

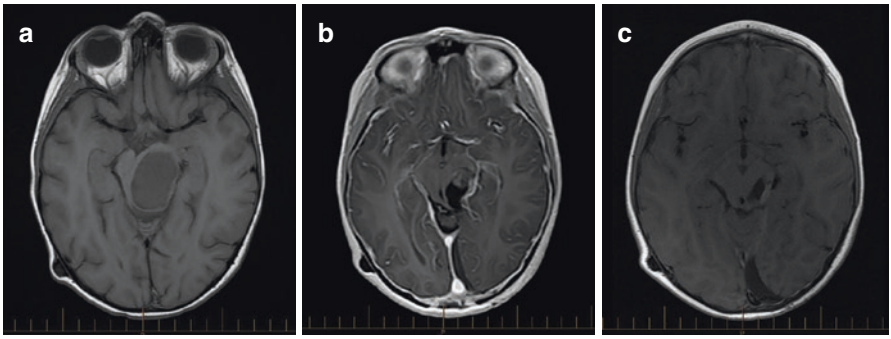

Fig. 13.1 (**a**) A midbrain JPA in a 6-year-old boy who presented with a right VI nerve deficit and a right hemiparesis. (**b**) Macroscopic residual disease following initial surgery was resected at a second surgery 2 months after the first. (**c**) MRI 2 months after the second surgery shows residual signal abnormality in the tumor bed interpreted as possible residual tumor vs. early gliosis. He will continue to be followed with MRI Q3–4 months. If and when there is evidence of progressive tumor, further surgery or systemic chemotherapy would be considered as the next step. Radiotherapy would not normally be considered the best option at this age

results for the 42 patients that had a partial resection or biopsy alone were somewhat better than this: 5-year progression-free survival was 50 ± 6% (Fried et al. 2012). The message from both of these relatively large, single institution series is that, as for low grade gliomas in other locations, not all patients who have undergone less than complete resection will progress. Also as for low grade gliomas at other locations, overall survival is very good. In our own study (Farmer et al. 2001), 20/22 patients with focal tumors were alive at 5 years with surgery alone or surgery and radiotherapy at the time of progression. Consequently, observation following surgery, even if there is residual tumor, is an acceptable option (Fig. 13.1).

13.2.3 Chemotherapy

As for LGG at other locations, chemotherapy has become the treatment of choice in North America for patients less than 10 years of age with a focal brainstem tumor with symptomatic inoperable disease or disease progressive after surgery (Ater et al. 2012; Bouffet et al. 2012; Gururangan et al. 2002, 2007, 2014; Laithier et al. 2003; Packer et al. 1988, 1997, 2009; Prados et al. 1997; Reddy and Packer 1999). Three regimens—vincristine/carboplatin, thioguanine/procarbazine/lomustine/vincristine (TPCV), and weekly vinblastine—have been prospectively assessed in chemotherapy-naïve LGG. Response rates range from 13–70% but event-free survival (PFS), defined as the need to consider another intervention to control tumor progression, does not exceed 50% at 5 years. For children who fail first-line therapies, other drugs including temozolomide, oral etoposide, and VP-16 have been used in small numbers of patients with variable benefit. A regimen combining a chemotherapeutic agent irinotecan and an anti-angiogenic agent bevacuzimab that targets the vascular

proliferation often present in these tumors has also been used with some success: a recent phase II study showed an 85% response rate at 6 months, albeit with a similar PFS of 47.8% at 2 years. Many children will have several lines of therapy over the course of their disease. The excellent survival rate of over 95% at 10 years calls into question the benefit of such interventions and underscores the need for a long-term strategy for this patient population, the goal of which would be to minimize risk associated with treatment (not only chemotherapy but also surgery and radiotherapy) and maximize neurological and functional outcomes and quality of life.

13.2.4 Radiotherapy

Radiotherapy may be considered at the time of progression following surgery or chemotherapy or for a tumor inoperable because of location. Guidelines for radiotherapy (target volumes, technique, dose, and fractionation) are as for low grade gliomas in other locations. The probability of tumor control is at least 50–70% (Combs et al. 2009; Merchant et al. 2009) and the risk of long-term morbidity, including neurocognitive sequelae, should be lower now than in the past using modern radiotherapy treatment techniques with image guidance and smaller safety margins.

13.2.5 Evolution of Practice and Future Directions

Surgical resection is more commonly used now than in the past, and chemotherapy has become accepted as a useful and often now the favored approach for patients with progressive inoperable disease. However, radiotherapy should always be considered an option for patients with focal brainstem tumors progressive after surgery or chemotherapy. Like surgery and chemotherapy, radiotherapy practice is evolving. Safety margins are smaller than those used in the past and this, as well as improved techniques and new modalities such as protons that allow better sparing of surrounding uninvolved tissues, reduces the risk of long-term sequelae associated with radiotherapy. Recent molecular breakthroughs using next generation sequencing technologies have shown that JPA have a single oncogenic hit affecting the MAPK pathway and implicating the BRAF oncogene, a key regulator of the MAPK pathway, and the AKT/mTOR pathway. This has opened up promising new avenues for targeted therapy and many agents are now under investigation.

13.3 Diffuse Intrinsic Pontine Gliomas

Diffuse intrinsic pontine gliomas (DIPG) account for approximately half of all tumors arising in the brainstem. The median age at presentation is approximately 7 years. Boys and girls are approximately equally affected. There are no known genetic associations or predisposing factors.

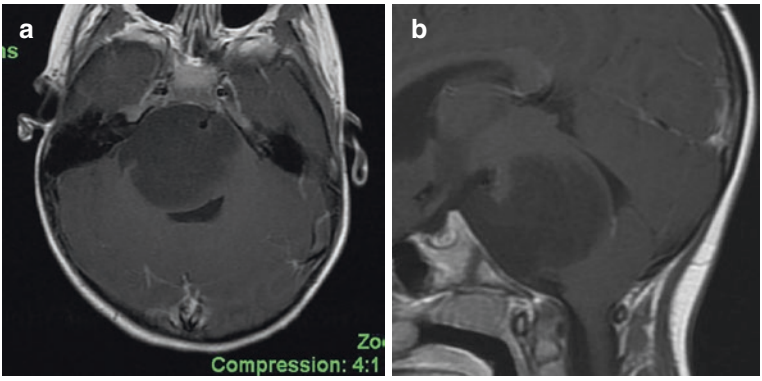

Fig. 13.2 (**a** Axial, **b** sagittal) A typical DIPG in a 4½-year-old girl with a 1-week history of facial asymmetry. Note diffuse enlargement of the pons and exophytic growth surrounding the basilar artery. The tumor is hypointense on T1-weighted sequences, hyperintense on T2, FLAIR, and shows no enhancement with gadolinium

Patients usually present with symptoms of short duration—classically defined as less than 6 months but more usually much shorter—consisting of multiple, often bilateral, cranial nerve deficits (especially cranial nerves VI and VII), long tract signs, and ataxia. MRI is the imaging modality of choice and findings are very characteristic. With the epicenter in the pons with axial and/or exophytic growth in about two-thirds of patients, the classic description is of a tumor that causes diffuse enlargement of the brainstem, often encases the basilar artery, and appears hypointense on T1-weighted sequences and hyperintense on T2, FLAIR without enhancement with gadolinium injection (Fig. 13.2). However, a Pediatric Brain Tumor Consortium study found enhancement in 62% of cases, albeit small volume with a median enhancing volume of 1.28 cc (Poussaint et al. 2011), and a European multinational study that included 316 patients reported ring enhancement in 36% of patients at diagnosis (Jansen et al. 2015). There may be cystic necrosis within the tumor and/or intratumoral hemorrhage. Atypical clinical and/or imaging findings should prompt consideration of other tumor types that are occasionally seen in the brainstem such as atypical teratoid/rhabdoid tumor or PNET and of biopsy for confirmation of diagnosis.

13.4 Workup

In addition to MRI of the brain, patients with any symptoms concerning for spinal metastases should have an MRI of the spinal axis to rule out leptomeningeal spread that is seen at diagnosis in about 5% of cases. It is not necessary, and in fact potentially risky, to perform a lumbar puncture for CSF cytology, and, outside the context of a clinical trial with particular requirements, it is not necessary to perform any other studies except routine blood work.

13.5 Acute Management

Steroids will usually be started at presentation and typically result in some improvement in the symptoms and clinical findings. Hydrocephalus is present at diagnosis in less than 10% of patients but if present CSF diversion may be necessary.

13.6 Treatment

In the context of a classical presentation and typical imaging findings, biopsy is not considered necessary for diagnosis—even though now associated with only a low risk of complications—and there is no role for more aggressive surgery. Most commonly, patients are referred on a semi-urgent basis for radiotherapy which is the mainstay of treatment for DIPG.

13.6.1 Radiotherapy

Patients are usually treated supine in a custom-made immobilization device. All patients should undergo CT simulation and for all patients the diagnostic MRI should be co-registered with the CT images. The target volume for radiotherapy is then contoured on MRI. The gross target volume is almost always best defined on T2-weighted or FLAIR MRI (maximum extent of disease). The margin for the clinical target volume is 1–1.5 cm, anatomically constrained by bone and sometimes too by the tentorium. The planning target volume will be technique- and institution specific. Although these days more sophisticated techniques such as IMRT are commonly used, 2D or 3D techniques may also be very acceptable, especially if to do so reduces the preparation time and so the delay to the start of treatment. The radiotherapy dose is typically 54–55.8 Gy given in 30–31 daily fractions of 1.8 Gy over 6 weeks. Alternative fractionation schedules have been extensively investigated in patients with DIPG. *Hyperfractionated radiotherapy* using fraction sizes of 1–1.26 Gy given twice a day to higher total doses of up to 78 Gy in an attempt to improve tumor control was tested in series of studies in North America in the 1980s and 1990s. There was no evidence of benefit and at the highest doses levels of 76–78 Gy considerable morbidity such as protracted use of steroids and vascular events was observed (Freeman 1996). *Accelerated radiotherapy* using conventional fraction size of 1.8 Gy given twice a day to total doses of 48.6–50.4 Gy over a shorter overall treatment time of approximately 3 weeks theoretically reduces the opportunity for tumor repopulation. While outcome in a British study was not improved, treatment was well tolerated and considered advantageous in that the patient and family spends less time in/near to the hospital (Lewis et al. 1997). *Hypofractionated radiotherapy* has been given with the goal of achieving equivalent tumor control with fewer hospital visits. When compared with conventional radiotherapy in previously

treated patients and in one prospective randomized study, hypofractionated radiotherapy using doses of 39–45 Gy given once daily with fraction sizes of 3 Gy appeared safe and equally effective and thus could be considered an acceptable option given the shorter overall treatment time of less than 3 weeks and lesser burden for patients and families (Janssens et al. 2013; Negretti et al. 2011; Zaghloul et al. 2014).

13.6.2 Chemotherapy

Chemotherapy has no established role in the treatment of newly diagnosed DIPG. Two randomized phase III trials as well as many phase I/II studies using chemotherapy and/or biological agents concurrent with standard radiotherapy, e.g., cisplatinum, VP-16, temozolomide, topotecan, gadolinium texaphrin, have all failed to show any improvement in outcome (Hargrave et al. 2006). Nimotuzumab, an anti-EGFR monoclonal antibody, appears somewhat more promising with a very high response rate of 96% and a median time to progression of 8.5 months when given in combination with Vinorelbine and radiotherapy (Massimino et al. 2014).

13.7 Treatment Outcomes

The majority of patients tolerate radiotherapy very well, without acute side effects such as headache, nausea, or vomiting. Most patients (~80%) show early clinical improvement during radiotherapy, and it may be possible to begin to taper dexamethasone during the second or third week of radiotherapy and to discontinue it altogether before completion of treatment. However, longer term outcomes are very poor, with a median time to progression of only ~6 months and a median survival time of only ~10–11 months. Survival at 2 years is only ~10%. The prognosis appears to be slightly better for patients age <3 years as well as for patients with symptoms of longer duration, while ring enhancement at diagnosis appears to be an unfavorable finding (Broniscer et al. 2008).

13.8 Follow-Up After Radiotherapy

Complete neurological recovery before the end of treatment is not at all unusual. Any skin reaction in the radiotherapy field will settle down within the first week or two following radiotherapy. Most patients will remain well after treatment for a few months during which time there may or may not be some improvement on MRI that is typically repeated at 1 month post radiotherapy and every 3–4 months thereafter (Fig. 13.3). At progression, symptoms and clinical findings as well as MRI findings are usually very similar to those at presentation although in some cases there may be evidence of intralesional necrosis or a change in enhancement pattern.

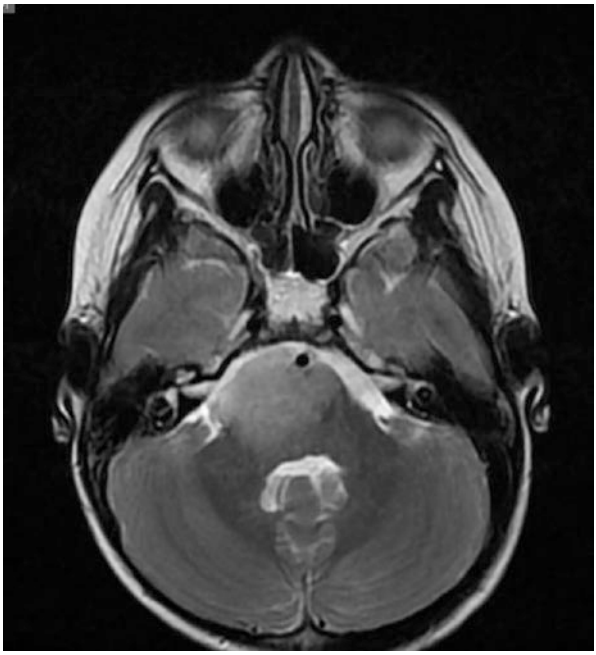

Fig. 13.3 Same patient as in Fig. 13.2 at 2 months post radiotherapy at which time she was clinically well and off all medication

13.9 Treatment at Progression

At progression, steroids may be re-introduced for symptom control and patients may be offered chemotherapy or other systemic agents, preferably on a clinical trial. Re-irradiation may also be considered, especially if the progression-free interval has been relatively long (at least 6–9 months). Based on pilot data showing that a dose of 20 Gy in 10 daily fractions may result in clinical improvement and several more months during which the patient is relatively well (Fontanilla et al. 2012; Wolff et al. 2012), re-irradiation was built into an Italian study using nimotuzumab in combination with Vinorelbine and radiotherapy. In the 11 patients that received re-irradiation to a dose of 19.8 Gy in 1.8 Gy fraction at progression, median survival following re-irradiation was 6 months (range: 14 weeks to 14 months).

13.10 Evolution of Practice and Future Directions

There has been essentially no improvement in outcome for patients with DIPG despite 30 years of intensive study within the North American and European co-operative groups, focused first on hyperfractionated radiotherapy and, over the past decade or so, chemotherapy and biological agents combined with conventional radiotherapy. However, it is now known that more than 80% of DIPG are specified by a recurrent somatic gain of function mutation in histone 3 genes that lead to an amino-acid substitution in lysine 27 to a methionine (K27 M). This mutation is associated with TP53 alterations and/or mutations in growth factor receptors involved in brain development

and targeting these mutations or downstream effects is the focus of several labs. Because of the potential for the development of much-needed alternate therapies for DIPG, there is renewed interest in performing a biopsy at diagnosis to obtain tissue for molecular and other studies. Off study, the standard of care remains conventional radiotherapy alone to a dose of 54 Gy in 30 daily fractions although the use of a hypofractionated regimen could also be considered in discussion with the parents.

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Part IV

Germ Cell Tumors

Central Nervous System Germinoma

14

Yuta Shibamoto and Shinya Takemoto

Contents

Abstract

Central nervous system (CNS) germinoma, occurring most often in teenagers, is a highly curable tumor. Germinomas have typical clinical and radiological findings; they can have slight elevation of β-human chorionic gonadotropin levels in the serum and/or cerebrospinal fluid and often respond quickly to radiotherapy or chemotherapy. Until recently, radiation therapy has been the standard treatment for CNS germinoma. Germinomas 4 cm or less in diameter can be cured with

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radiation doses of 40–45 Gy. Regarding the treatment volume, the clinical target volume covering the ventricular system is recommended if no cerebrospinal fluid (CSF) dissemination is present and CSF cytology is negative. Recently, systemic chemotherapy with reduced radiation doses (24–30 Gy) appears to have gained success, but longer follow-up is necessary to draw conclusions regarding the superiority of this treatment over standard-dose radiation therapy. When using a combined approach, whole ventricular irradiation should still be employed.

14.1 Epidemiology

Central nervous system (CNS) germinoma is a rare neoplasm. It is, however, more common in East Asian than in Western countries. Its incidence among all childhood brain tumors is 0.1–2% in Western countries, whereas it is 1.4–6% in East Asia (Keene et al. 2007). According to the Brain Tumor Registry of Japan (The Committee of Brain Tumor Registry of Japan 2009), 1258 patients were reported from 1984 to 2000 which represented 1.9% of all primary brain tumors in children and adults. In a more recent report from the same registry, 200 pure germinomas (1.5%) and 35 HCG-producing germinomas (0.3%) were documented during 2001–2004 (The Committee of Brain Tumor Registry of Japan 2014). This tumor registry includes about 30% of all primary brain tumors occurring in Japan.

14.2 Predisposing Factors

Germinomas occur most often in teenagers, followed by young adults aged 20–29 years. For germinomas of the pineal region and basal ganglia, male preponderance is seen, but for neurohypophysial (supra- and para-sellar) germinomas, the male to female ratio is near unity. Table 14.1 shows the tumor site and gender in our series of 163 patients with CNS germinoma where this trend is clearly seen. Etiology and genetic issues have not yet been clarified. A recent study demonstrated that high expression of KIT mRNA was associated with the presence of KIT/RAS alterations and severe chromosomal instability in pure germinomas (Fukushima et al. 2014).

Table 14.1 Distribution of male and female patients with CNS germinoma according to tumor site (Shibamoto 2009)

Site	Total	%	Male	Female	Male/female
Pineal	73	45	68	5	14
Neurohypophyseal	52	32	26	26	1
Pineal + neurohypophyseal	17	10	15	2	7.5
Basal ganglia, thalamus	21	13	20	1	20
Total	163	–	129	34	3.8

14.3 Presenting Symptoms

Presenting symptoms depend on tumor location. In patients with pineal germinomas, Parinaud sign (upward gaze palsy and pupillary light-near dissociation) is seen when the tumor becomes large. Accordingly, patients may complain visual disturbance including diplopia. In patients with a large tumor, hydrocephalus and associated symptoms could develop. In neurohypophysial germinomas, diabetes insipidus is the most common symptom. With tumor enlargement, deficits of hormones from the anterior lobe of the pituitary gland, visual field defects, and visual disturbances could develop. In germinomas of the basal ganglia, hemiparesis, change in mental and neurocognitive status, and/or loss of higher brain functions can be presenting symptoms.

14.4 Radiographic Findings

Germinoma shows homogenous density on CT and homogenous signal intensity on T1-weighted MR images (Fujimaki et al. 1994). It is slightly hyperdense and hyperintense on CT and T1-weighted MRI, respectively. Typically, it shows homogenous and striking contrast enhancement, but slightly inhomogenous contrast enhancement does not exclude the possibility of germinoma. Inhomogeneity of the density, signal intensity, and contrast enhancement indicate the possibility of a non-germinomatous germ-cell tumor; however, germinoma often contains cysts, so the differential diagnosis is often not easy. Findings of subependymal spread and intraventricular dissemination are sometimes observed.

14.5 Workup

When germinoma is suspected on MRI, tumor markers, i.e., β-human chorionic gonadotropin (HCG), α-fetoprotein (AFP), and carcinoembryonic antigen (CEA), in the serum and/or cerebrospinal fluid (CSF) should be checked. A recent development in immunohistochemistry enables the detection of very low levels of HCG, especially its β-subunit, using an ultrasensitive kit. In one study, use of this ultrasensitive assay showed that elevation of β-HCG levels in the serum or CSF was seen in most CNS germinoma patients (Katakami et al. 2003). Elevation of β-HCG over 1000 mIU/mL or 200 ng/mL would indicate the presence of pure or mixed non-germinomatous germ-cell tumors, especially choriocarcinoma, but low levels of elevation below 10 mIU/mL or 2 ng/mL would suggest that the tumor is pure germinoma. It should be noted that elevation of β-HCG levels may be observed in craniopharyngioma (Suzuki et al. 1985). On the other hand, elevation of AFP or CEA levels indicates the presence of non-germinomatous germ-cell tumors or their component. Placental alkaline phosphatase (PLAP) is also known as a marker for germinoma (Ono et al. 1991). Although the usefulness of PLAP does not seem to be

well established, the true- and false-positivity rates are reported to be about 50% and 1.6%, respectively, in testicular seminoma (Koshida et al. 1996).

Investigation of CSF dissemination is important, and CSF cytology should be performed. Germinoma frequently shows the "two-cell pattern" that was considered to be almost pathognomonic (Sano 1976), but later, it was realized that other diseases can also show similar cytological patterns. So, CNS germinoma cannot be diagnosed by the CSF cytological findings alone although it is helpful in diagnosing CSF dissemination (Shibamoto et al. 1994a, b). Whole spinal MRI should also be performed.

14.6 Acute Management

When hydrocephalus is observed, CSF drainage needs to be considered. However, one may avoid placement of a shunt tube because tumor shrinks quickly in response to treatment and hydrocephalus can soon be ameliorated. Mass effect is unusual, so debulking operation and administration of steroid are usually unnecessary.

14.7 Treatment

Until recently, the standard treatment for CNS germinoma has been radiation therapy alone. Germinoma can be cured with a total dose of 40–50 Gy. The vast majority of patients treated with radiation therapy live a normal life, but long-term adverse effects in adolescents were feared, particularly hormonal insufficiency and decline in neurocognitive function (Duffner et al. 1985; Roman and Sperduto 1995). In the late 1980s, systemic platinum-based chemotherapy was employed, and its efficacy was recognized. However, treatment with chemotherapy alone was found to be associated with a high recurrence rate of 50–60% (Farng et al. 1999; Kumabe et al. 2002; Balmaceda et al. 1996). Although germinoma recurring after primary chemotherapy can be salvaged with radiation therapy (Shibamoto et al. 1999), the high recurrence rate was considered unacceptable and the chemotherapy alone trials were regarded as a failure. Thereafter, systemic chemotherapy with reduced-dose radiation was investigated and reasonably high cure rates comparable to those obtained by standard radiotherapy have been reported. Thus, systemic chemotherapy with reduced-dose radiation appears to be gaining popularity although treatment with radiation alone remains an option for patients.

14.7.1 Surgery

Surgical resection is usually unnecessary for this tumor.. The role of surgery is limited to establishing histological diagnosis. With improvements in modern diagnostic imaging modalities and tumor marker measurements, the authors think that histological diagnosis may not be mandatory in every patient. This is rather controversial

as the standard approach in North America is to have histological confirmation of the tumor. Even with the advances in neurosurgery, the authors argue that the probability of complications from a biopsy exists, and any complication associated with brain surgery becomes a serious problem for the patient. From the clinical and radiological findings, it is often not difficult to predict a diagnosis of germinoma even before any treatment. In addition, pure germinoma is known to quickly respond to radiation and chemotherapy. The lesions less than 3 cm in diameter usually disappear after 20 Gy of radiation therapy ("radiodiagnosis"). Marked shrinkage is also observed following systemic chemotherapy. With the typical clinical and radiological findings, mild elevation of β-HCG levels and quick response to treatment, the diagnosis of germinomas is usually confirmed. Therefore, the authors believe that avoiding a biopsy is an option in cases with typical clinical and radiological findings. Of course, there exist germinomas that do not possess above-mentioned characteristics, and biopsy should be considered for such patients. Some pure germinomas do not respond so quickly to treatment, and one of the reasons for this is considered to be the presence of granulomatous components (Utsuki et al. 2006).

14.7.2 Radiotherapy

When treating germinoma with radiation alone, the treatment volume is a controversial issue. Since germinoma can develop CSF dissemination in up to 10% of patients, irradiation of the entire cerebrospinal axis was historically the recommended treatment. (Shibamoto et al. 1988, a) reported treatment results according to the irradiated volume. Depending on the era of treatment, germinoma patients were irradiated to the primary tumor site plus a margin or to the cerebrospinal axis regardless of the clinical and radiological findings. There was no significant difference in overall survival between patients receiving craniospinal irradiation and those receiving focal radiation; the 10-year survival rate was 95% for 38 patients receiving craniospinal irradiation and 88% for 33 patients receiving focal radiation therapy. In a comprehensive review of the existing literature, (Rogers et al. 2005) found that the recurrence rate was 7.6% after whole-brain or whole ventricular radiotherapy plus boost compared with 3.8% after craniospinal radiotherapy. Since the incidence of CSF dissemination beyond the ventricular system is below 10%, the routine use of craniospinal irradiation appears to be overtreatment for most patients, and hence treatment with whole ventricular irradiation followed by a boost has gained popularity. It is now recommended to treat the whole cerebrospinal axis only when CSF cytology is positive or CSF dissemination is present.

Previously, the standard dose for pure germinoma was 50 Gy in 1.8–2.0 Gy daily fractions. (Shibamoto et al. 1994a, b, 2001) conducted a prospective study to investigate dose reduction for germinoma. Using a daily dose of 1.8 Gy (focal radiation) or 1.6 Gy (craniospinal radiation), the total dose was 36 Gy after macroscopic total tumor removal, 40 Gy for tumors less than 2.5 cm, 45 Gy for tumors between 2.5 and 4 cm, and 50 Gy for larger tumors. An individualized approach was employed to determine the treatment volume. After a median follow-up of 120 months, the

10-year relapse-free survival rate for 38 patients treated with this policy was 95%; this cure rate was considered to be equivalent to that obtained using a policy of uniformly giving 50 Gy. Therefore, the dose of 40–45 Gy appeared to be sufficient to cure CNS germinoma with a diameter 4 cm or less. The German Society for Pediatric Oncology and Hematology also conducted a prospective study to reduce total radiation doses, and they found no local recurrence after a dose of 45 Gy (Bamberg et al. 1999).

The optimal dose for cerebrospinal axis prophylaxis has not yet been clarified. Considering the high radiosensitivity of germinoma, (Shibamoto et al. 1988, 1994a, 2001) used 20–24 Gy in 13–15 fractions, and obtained a favorable outcome. In the dose-reduction study stated above (Shibamoto et al. 2001), the authors used craniospinal doses around 20 Gy for patients with negative or equivocal CSF-cytology findings and 24 Gy for patients with positive CSF cytology or CSF dissemination; one patient in the latter group developed CSF dissemination. Therefore, doses of 20 and 24 Gy were recommended for CSF dissemination-negative and positive cases, respectively. The German Society for Pediatric Oncology and Hematology also attempted at reducing the craniospinal radiation dose from 36 to 30 Gy and found no difference in the outcome of patients in both groups (Bamberg et al. 1999).

14.7.3 Chemotherapy and Reduced-Dose Radiation

Systemic chemotherapy in combination with a reduced dose of radiation has been tested by several groups (Allen et al. 1994; Bouffet et al. 1999; Matsutani et al. 2001). The dose has been reduced to 24–40 Gy, and excellent results have been reported as compared with the results obtained by chemotherapy alone. (Matsutani et al. 2001; Matsutani 2009) carried out a multi-institutional study in which three courses of carboplatin (450 mg/m^3) and etoposide (150 mg/m^3 × 3 days) were given before 24 Gy with a focal radiation field or an extended local field encompassing the tumor site, the third and lateral ventricles, and the sellar and pineal regions. The 5-year overall survival rate in 123 patients was 98%, and the disease-free survival was 88% (Matsutani 2009). The recurrence rate was 6% in patients treated by an extended local field, whereas it was 28% in patients treated with a limited local field with a margin of less than 2 cm. Thus, it was suggested that the radiation treatment volume should involve the whole ventricular system.

The French Society for Pediatric Oncology (SFOP) conducted a study combining chemotherapy (alternating courses of etoposide/carboplatin and etoposide/ifosfamide up to four courses whenever possible) with 40-Gy focal irradiation (CNS GCT-96) (Bamberg et al. 1999; Alapetite et al. 2005). They treated 60 patients and the 8-year overall and event-free survival rates were 98% and 83%, respectively. The SFOP group also found an excess of periventricular relapses when the focal radiation field was used in the combined treatment of germinoma, and they recommended the use of ventricular field radiation (Alapetite et al. 2010).

The International Society of Paediatric Oncology (SIOP) conducted a prospective non-randomized comparison study of craniospinal irradiation (24 Gy) plus

focal tumor boost (16 Gy) vs. the SFOP CNS GCT-96 chemotherapy regimen followed by focal radiation therapy to the tumor (40 Gy) (Calaminus et al. 2013). There were no differences in 5-year overall and event-free survival between patients treated with radiotherapy alone ($n = 125$) and those treated with combined therapy ($n = 65$), but there was a difference in progression-free survival in favor of the radiotherapy alone approach (97% vs. 88%, $P = 0.04$). Again, patterns of relapse suggested inclusion of the entire ventricles in the radiation field. The use of lower dose irradiation (24–30 Gy) was not investigated in the SFOP and SIOP studies.

There are more studies that have investigated systemic chemotherapy combined with reduced-dose irradiation (Shim et al. 2013; Lim et al. 2014). At present, the Japanese studies suggest that such treatment is promising; however, further investigations with more patients and longer follow-up are warranted to establish the combined therapy with reduced-dose radiation as the standard treatment.

14.8 Target Delineation

Currently, chemotherapy with reduced-dose irradiation appears to be gaining popularity. In this treatment approach, whole ventricular irradiation is recommended based on excess ventricular relapses when chemotherapy and focal tumor irradiation alone were given. The definition of the whole ventricular irradiation field is somewhat controversial. Figure 14.1 shows an example of the clinical target volume (CTV) for whole ventricular irradiation. The primary tumor sites and lateral, third, and fourth ventricles are included, but the level of the lower border below the fourth ventricle and inclusion of the prepontine, interpeduncular, and chiasmatic cisterns are controversial (Mailhot et al. 2012). The entire ventricular walls should be delineated and PTV margins of 3–5 mm may be sufficient when image-guided radiation therapy is employed.

To deliver whole ventricular irradiation, intensity-modulated radiation therapy (IMRT) or proton therapy is highly recommended; dose distributions of

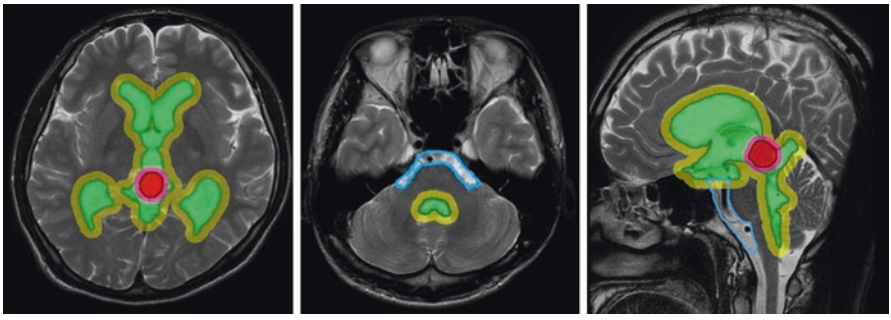

Fig. 14.1 Example of the clinical target volume for whole ventricular irradiation (*green*). Primary tumor (*red*) may be boosted simultaneously. The *blue line* indicates the part that should be included case by case. Planning target volume margins are 3 mm (*pink*) or 5 mm (*yellow*) (color online)

conventional radiotherapy using parallel-opposed fields, conventional radiotherapy using the 4-field box technique, and IMRT are shown in Fig. 14.2. With IMRT, the dose to the basal ganglia and thalamus can be lowered. A total dose of 24–25 Gy in 12–14 fractions may be reasonable. In addition, the authors prefer to give simultaneous integrated boost (SIB) to the primary tumor site with IMRT; 30 Gy in 12–14 fractions is usually planned when chemotherapy is used. This SIB plan is recommended for pineal region tumors because there is less concern against radiation-induced hormonal deficiency. In neurohypophysial tumors, the use of SIB depends on patient age, hormonal status, and tumor response to chemotherapy.

When evident CSF dissemination is present, irradiation to the cerebrospinal axis needs to be considered. The CSF space should be delineated with 5 mm margins, with the lower border of the CSF space confirmed using the spinal MRI. In irradiating the whole cerebrospinal axis, the use of proton radiotherapy is gaining wide acceptance. In patients receiving photons, tomotherapy seems to be an excellent treatment option (Sugie et al. 2011). Figure 14.3 shows an example of dose distribution for craniospinal irradiation using a helical tomotherapy and a linear accelerator. With tomotherapy, uniform doses are delivered with no gaps that are unavoidable with conventional craniospinal irradiation using a linear accelerator. Unnecessary doses to midline thoracic and abdominal organs are markedly reduced.

Germinomas are known to occur in both the pineal and neurohypophysial regions. As shown in Table 14.1, the incidence seems to be around 10% of all germinomas. It has been a common question whether to treat this bifocal germinoma as localized or disseminated. The current literature suggests that the bifocal germinoma should be treated as localized disease, and these patients do not need CSI unless there is CSF dissemination (Weksberg et al. 2012; Al-Mahfoudh et al. 2014).

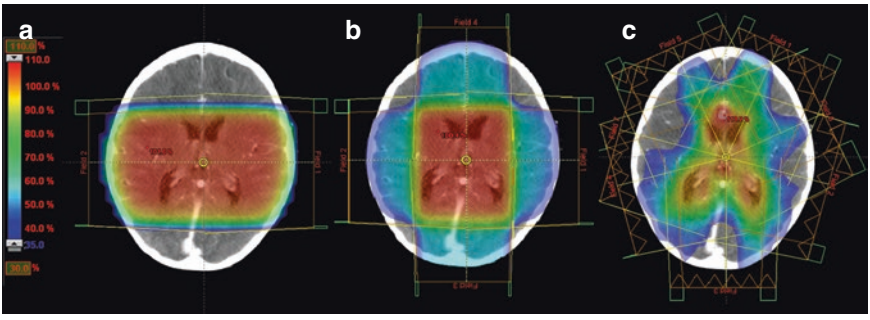

Fig. 14.2 Dose distribution for whole ventricular irradiation using photons by (**a**) parallel-opposed beams, (**b**) 4-field box technique, and (**c**) intensity-modulated radiation therapy

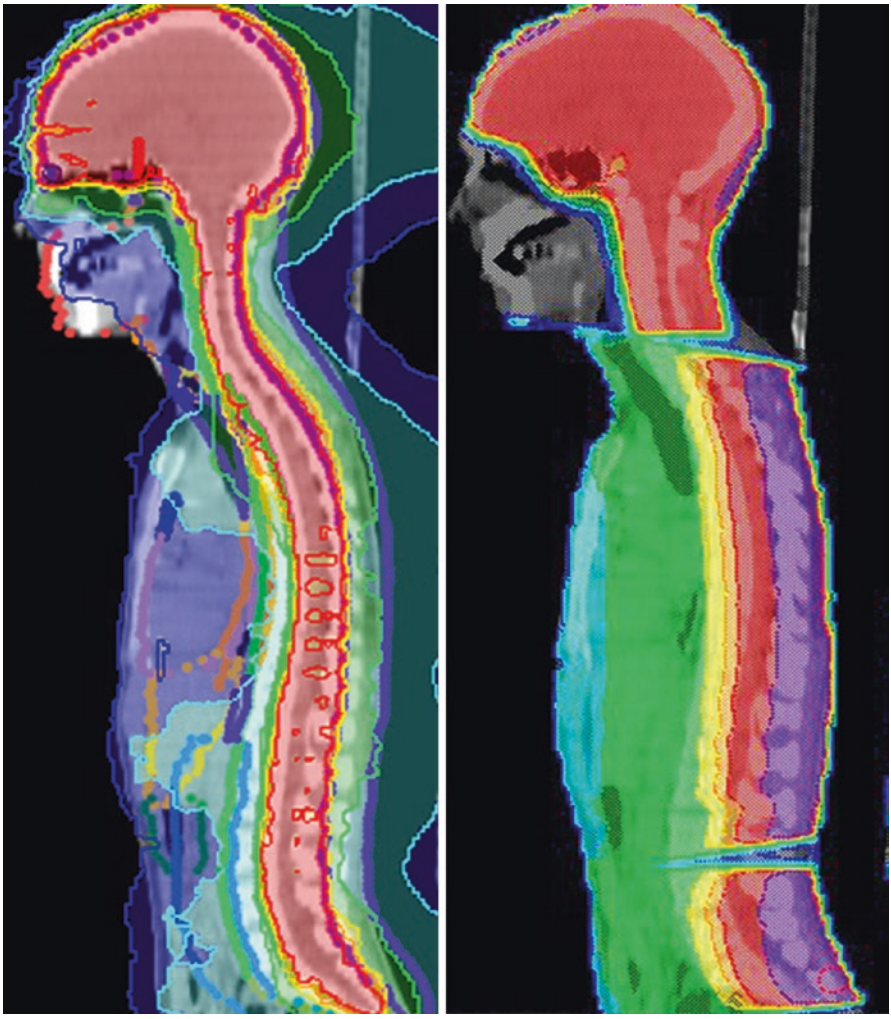

Fig. 14.3 Dose distribution for craniospinal irradiation by helical tomotherapy (*left*) and linear accelerator (*right*)

14.9 Outcomes

Recurrence of germinomas is most commonly observed a few years after treatment, so follow-up examinations should be initially performed three to four times a year, and twice a year after 4–5 years. MRI of the brain and β-HCG examinations are recommended.

CNS germinoma can be cured with a high probability over 90%. A small proportion (5–10%) of the tumors recur; recurrence may be more often seen at distant sites (i.e., as meningeal dissemination) rather than at the primary tumor site after

standard-dose radiotherapy. With systemic chemotherapy and reduced-dose radiation, local or marginal recurrence is sometimes observed. Although rare, metastasis to the abdomen can also develop in patients harboring a ventricular-peritoneal shunt tube with no filter.

The influence of slight HCG level elevation in the serum or CSF on prognosis has been controversial. Some studies have reported a worse prognosis in patients with an elevated HCG level (Uematsu et al. 1992; Utsuki et al. 1999), while others indicate similarly good prognosis in patients with normal and elevated HCG levels (Shibamoto et al. 1997; Ogawa et al. 2004; Ogino et al. 2005). If the prognosis of patients with an elevated HCG level is worse, treatment intensity should be increased for such patients, and this was indeed done in a Japanese study (Matsutani et al. 2001). However, the same group later found that the HCG level does not influence the prognosis, and hence have abandoned the intensified treatment approach.

With the use of lower dose radiation, late adverse events of radiation therapy are expected to be less. After standard doses of radiation, hormonal deficiency, especially growth hormone deficiency, is seen. Radiation necrosis, leukoencephalopathy, and secondary CNS malignancy are rare complications. With the combined use of systemic chemotherapy and reduced-dose irradiation, more attention should be paid to late effects of chemotherapy, including secondary malignancy.

14.10 Future Directions

The combination of systemic chemotherapy and reduced-dose radiation seems to be a promising treatment approach for intracranial germinoma. In the future, it should be clarified whether the long-term cure rate obtained by this treatment is identical to that obtained by standard-dose radiation therapy. Also, long-term follow-up is needed to determine the late complications of chemotherapy, including the incidence of secondary cancers.

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Central Nervous System Nongerminomatous Germ Cell Tumors

15

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Abstract

Intracranial nongerminomatous germ cell tumors (NGGCT) encompasses a heterogeneous group of germ cell tumors of various histology which occur in the brain. Various criteria for prognostic categorization have been used in different parts of the world with varying treatment strategies. Systemic chemotherapy is an essential part of the multimodal treatment of NGGCT. Survival rate of patients with NGGCT is 60–70% with use of combined chemoradiotherapy. From the published literature, craniospinal radiotherapy (CSI) combined with cisplatin-based chemotherapy with or without second-look surgery tends to provide the best treatment outcome for NGGCT. Intracranial NGGCT requires high radiation dose >50 Gy to the primary site, however, the optimal volume of radiotherapy is still debatable. Whole ventricular irradiation is currently being adopted for localized intracranial NGGCT to minimize late neurocognitive toxicity. A Children Oncology Group study is currently underway to test whether the dose and volume of radiotherapy can be adapted according to the tumor response to chemotherapy. The role of surgery in treatment of NGGCT is both diagnostic and therapeutic. In Europe and North America, delayed surgery for persistent disease after chemotherapy is preferred, while in Japan, more aggressive and upfront resection is advocated for better therapeutic design. Use of intensity-modulated radiotherapy (IMRT) or proton beam therapy (PBT) is expected to translate to an improved neurocognitive outcome after treatment.

15.1 Epidemiology

Intracranial germ cell tumors (ICGCT) are uncommon in North America and Europe, accounting for 2–4% of brain tumors that occur in children and adolescents under 19 years of age (Arora et al. 2009; Ostrom et al. 2013; Wohrer et al. 2009). In contrast, it is the most common type of brain tumor in Japan, Taiwan, and Korea, accounting for 11–15% of brain tumors in the same age group (Committee of Brain Tumor Registry of Japan 2003, 2009; Lee et al. 2010; Wong et al. 2008). The biological factors responsible for the different ethnic incidence of ICGCT and high male-to-female ratio are poorly understood. Several novel and rare germline variants are suggested to play a role in the development of ICGCT (Wang et al. 2014); however, further studies are needed to unravel the etiology of ICGCT.

15.2 Biology of Intracranial Germ Cell Tumors

The origin of ICGCT is considered to be the primordial germ cells of the embryo (Glenn and Barkovich 1996). Human primordial germ cells from the yolk sac endoderm migrate along the dorsal mesentery of the hind-gut to the genital ridges

for incorporation into developing gonads during week 4 of embryogenesis. Failure to initiate migration, abnormal migration, abnormal termination of migration, and entrapment during the migration are observed in midline extragonadal areas in chick, human, and mouse embryos and appears to coincide with the occurrence of extragonadal germ cell tumors (GCT), including ICGCT (Glenn and Barkovich 1996). Studies of molecular and cytogenetic characteristics of ICGCT are limited because of the infrequency of surgical biopsy and the small size of biopsy specimen. As shown in methylation and comparative genomic hybridization studies, both germinoma and nongerminomatous germ cell tumors (NGGCT) originate from primordial germ cells (Schneider et al. 2001; Sievers et al. 2005). *Oct-4*, a transcription factor encoded by the *POU5F1* gene, is involved in the initiation, maintenance, and differentiation of pluripotent and germline cells during normal development, but is absent in all differentiated somatic cell types. *Oct-4* is considered to be a highly sensitive and specific and immunohistochemical marker for primary ICGCT (Cheng et al. 2007; Hattab et al. 2005). In the few studies on genome-wide analysis of ICGCT, 53% of tumors harbor somatic mutations in at least one of the genes involved in *KIT/RAS* or *AKT/mTOR* pathways (Fukushima et al. 2014; Terashima et al. 2014; Wang et al. 2010). By whole-exome sequencing, significant enrichment of novel and rare germline variants in *JMJD1C*, which encode a histone demethylase and a coactivator of the androgen receptor, have been discovered (Wang et al. 2014). Expression microarrays reveal high *JMJD1C* and *AR* (androgen receptor) expression levels, indicating a strong association between *JMJD1C* variants and the risk of developing ICGCT (Wang et al. 2014).

Although many analysis of ICGCT samples reveal that the overall pattern of genomic aberration is similar in germinoma and NGGCT (Wang et al. 2014; Terashima et al. 2014), there are some findings which indicate the presence of more specific genomic profile for NGGCTs compared to germinomas. For example, *KIT* is mutated in intracranial germinomas but not in any NGGCT cases. *KIT* is also over-expressed in the majority of pure germinomas but rarely in NGGCTs. *KRAS* or *NRAS* are mutated in 19% of IGCT cases. The *KRAS/NRAS* and *KIT* mutations are mutually exclusive genetic events in IGCTs (Wang et al. 2014; Fukushima et al. 2014). There is no significant difference in the average mutation rate between pure germinomas and NGGCTs, however, the mutation rates vary dramatically among the subtype of NGGCTs (Wang et al. 2014). DNA microarray analysis and hierarchal cluster analysis for ovarian dysgerminomas versus ovarian endodermal sinus tumors which is counterpart of CNS germinoma and NGGCT, respectively, show a differential expression of the genes in the *Wnt/β-catenin* signaling pathway. *B-catenin* expression is observed in all of endodermal sinus tumors and immature teratomas, whereas there is no expression in other types of ICGCT. Especially, nuclear expression of *β-catenin* are observed in 50–70% endodermal sinus tumor and immature teratoma compared to those in dysgerminoma, embryonal carcinoma, and choriocarcinoma (Fritsch et al. 2006), suggesting activation of *Wnt/β-catenin* signaling pathway in these tumors. Studies also reveal a high expression of small RNAs which are differentially expressed in different subtypes of ICGT, questioning

the possibility of future use of microRNAs as diagnostic biomarkers for subclassification of intracranial GCTs and also to monitor treatment response (Gillis et al. 2007; Murray et al. 2011; Palmer et al. 2010).

15.3 Presenting Symptoms

Symptoms and signs at presentation of ICGCT are dependent on the size of the tumor and the sites of involvement. There is no specific difference between germinoma and NGGCT in clinical presentation because typical locations of both tumor types are the pineal and suprasellar, with at least 15% of the tumors occurring at multiple sites (Bromberg et al. 2013; Matsutani et al. 1997; Phi et al. 2013). The vast majority of patients in the pineal region presents with intracranial hypertension, Parinaud's syndrome, and/or diplopia. Patients with suprasellar tumors frequently present with visual disturbances or symptoms of hypothalamo-hypophyseal insufficiency such as diabetes insipidus. As the tumors develop along the third ventricular area, obstructive hydrocephalus is frequently observed in the patients with an ICGCT. Progressive hydrocephalus can produce headache, vomiting, and altered consciousness. If not timely managed, a catastrophic hydrocephalic fit can develop and a dismal prognosis is expected for such patients (Phi et al. 2012).

15.4 Radiographic Findings

The majority of intracranial NGGCT develop in pineal and suprasellar regions. Pineal NGGCT outnumber those arising from the suprasellar location in some studies (Matsutani et al. 1997; Phi et al. 2005; Kim et al. 2012), but not in other reports (Sawamura et al. 1998). GCT arising from the basal ganglia are predominantly germinoma, but NGGCTs can also develop in this location (Phi et al. 2010). Multifocal tumors are more often germinomas than NGGCT. Sometimes, fat granules are dispersed in the ventricles if spontaneous rupture of a teratoma cyst occurs. NGGCT is a heterogeneous group including several subtypes of GCTs. Mature and immature teratoma are most common component of NGGCT individually. However, germinoma and teratoma is the most common type of combination in NGGCTs.

Magnetic resonance images (MRI) of NGGCTs typically show a large mass with heterogeneous signal. Teratomas usually contain fat tissues and high signal intensity of the fat tissue in T1-weighted images is characteristic (Reis et al. 2006). Teratomas exhibit a mixed cystic and solid structure. The signal intensity of cystic contents is variable depending on the nature of the cystic fluid. Extensive multi-cystic architecture (honeycomb appearance) is characteristic of immature teratoma and growing teratoma syndrome (Kim et al. 2011). On computed tomography (CT), NGGCTs display both low attenuation due to fat contents and dots/clumps of high attenuation due to calcification (Fig. 15.1).

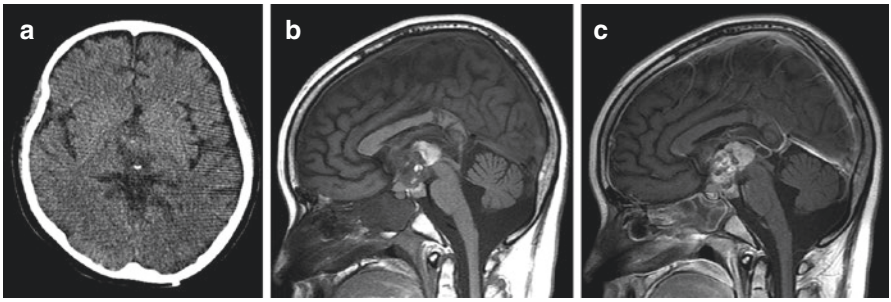

Fig. 15.1 Immature teratoma arising from the suprasellar area in a 13-year-old boy. (**a**) CT scan shows a mass in the third ventricle with low attenuation. Minute dots of high attenuation are observed in the mass, indicating the presence of calcification. (**b**) Areas of high signal intensity are found in the tumor in a T1-weighted image which represent fatty tissues in the tumor. (**c**) The tumor is well enhanced in gadolinium-enhanced T1-weighted image

15.5 Workup

Accurate diagnosis and staging is required to guide therapy. Diagnosis is based on the combination of clinical symptoms, tumor markers, neuroimaging characteristics as well as cytological and histological confirmation. CT scan and/or magnetic resonance imaging (MRI) scan of the brain and spine with Gd-DTPA should be performed. Leptomeningeal spread is not uncommon at diagnosis (Aoyama 2009; Calaminus et al. 2005). Many studies with large patient numbers include both germinoma and NGGCT (Matsutani et al. 1997; Sawamura et al. 1998; Aoyama et al. 1998; Sano et al. 1989), and the exact rate of leptomeningeal spread specifically for NGGCT is not readily available in these studies. In the studies with relatively small number of patients, screening for detection of leptomeningeal disease is inconsistently performed (Kim et al. 2012; Ogawa et al. 2003; Robertson et al. 2014). According to a recent report which used modern MRI imaging for spinal leptomeningeal spread, it is reported to be as high as 22% (Korean Society of Pediatric Neuro-Oncology group study, unpublished data). Lumbar puncture for examination of human chorionic gonadotropin-beta (β-hCG) and α-fetoprotein (AFP) should be performed along with cerebrospinal fluid (CSF) cytology. Examination of serum AFP and β-hCG are also required. CSF level of tumor markers are more sensitive and reliable for diagnosis than serum level. Due to the common presentation of endocrinopathies, a thorough endocrine evaluation at the time of diagnosis is highly recommended (Thakkar et al. 2013). Imaging is not reliable to distinguish germinomas from NGGCTs, and diagnosis is made either by tissue confirmation or tumor markers. Tumor markers can be more sensitive than changes in images (Jorsal and Rorth 2012) and can be used during treatment to assess tumor response. It is highly controversial whether a tissue biopsy is mandatory for ICGCT because many patients with ICGCT can be correctly diagnosed without a tissue biopsy if demographic and radiological data were combined with serum/CSF tumor markers. In the recent COG study, patients with elevation of serum or CSF β-hCG >100 IU/L or any elevation of serum and CSF AFP >10 ng/mL

are considered as NGGCT. The SIOP CNS germ cell tumor study uses >50 IU/L and >25 ng/mL as cut-off values for β-hCG and AFP, respectively, however, a biopsy is regarded as mandatory if marker levels are ≤50 IU/L (total HCG) or ≤25 ng/mL (AFP) in order to exclude the possibility of any malignant component in tumors (https://www.skion.nl/workspace/uploads/2_siop_cns_gct_ii_final_version_2_15062011_unterschrift_hoppenheit.pdf). There are pitfalls in diagnosing NGGCT on the basis of elevated tumor markers without a histologic diagnosis. Using an ultrasensitive enzyme immunoassay (EIA) method or a quantitative measurement of β-hCG mRNA in tumor tissues (Takami et al. 2015), Japanese investigators showed that some pure germinomas and at least some NGGCTs produce β-hCG. In that study, germinomas with syncytiotrophoblastic giant cells and those located other than at midline structures of the brain were associated with higher β-hCG levels. There are occasional patients with biopsy-proven germinoma who initially presented with mild elevation of AFP below reference level and recur with a mixed malignant component. Patients with mildly elevated AFP need to be carefully watched particularly if biopsy was not performed at the time of diagnosis. More emphasis is now being given in taking tissue biopsy before treatment starts. More standardized cut-off value needs to be adopted for diagnosis of NGGCT especially with serum and CSF β-hCG. When treatment is completed, routine physical and neurologic examinations are carried out every 3–6 months after treatment. Follow-up MRI is generally carried out every 6 months for the initial 5 years after treatment or more frequently for tumors which do not show complete response to treatment, and then once a year.

15.6 Acute Management

Obstructive hydrocephalus is frequently observed in the patient with ICGCT. Diagnosis of accompanying hydrocephalus and its management is the initial step in the treatment of patients with ICGCT. Intravenous mannitol can alleviate symptoms of increased intracranial pressure (ICP). Although corticosteroids are commonly used for the management of brain edema associated with tumors, they are less helpful for ICGCT because brain edema is less prominent for intraventricular tumors than for parenchymal tumors. If obstruction of the CSF pathway is evident in MRI and/or CT, surgical diversion of the CSF is required after initiation of mannitol and corticosteroid administration. For tumors located in the pineal area, endoscopic third ventriculostomy (ETV) is the treatment of choice to relieve the increased ICP. ETV can be performed simultaneously with an endoscopic tumor biopsy. For suprasellar tumors, ETV is rarely attempted because the tumor mass blocks the third ventricular floor. If a large suprasellar GCT occludes both foramina of Monro and causes severe hydrocephalus, an endoscopic septostomy is recommended with tumor biopsy. The procedure should be followed by a temporary extraventricular drainage (EVD) if surgical resection is planned (as is common for NGGCTs), or by a permanent ventriculoperitoneal shunt if chemotherapy or radiation therapy is scheduled (as is common for germinomas) for definite treatment of the tumor. If only one foramen of Monro is occluded, an endoscopic septostomy with tumor biopsy may be sufficient.

15.7 Treatment

15.7.1 Chemotherapy

Systemic chemotherapy is an essential part of the multimodal treatment of NGGCT. The use of neoadjuvant chemotherapy with radiation therapy results in a very high rate of response with acceptable toxicity and excellent outcomes. Survival rate of patients with NGGCT increased to 60–70% by use of combined chemoradiotherapy (Kim et al. 2012; Robertson et al. 1997, 2014; Goldman et al. 2015) compared with 20–40% when only RT (Dearnaley et al. 1990; Hoffman et al. 1991) or only chemotherapy (Balmaceda et al. 1996; Baranzelli et al. 1998; Chang et al. 1995) was given . Most of the patients are treated with cisplatin or carboplatin in combination with other agents. Cisplatin and etoposide (PE), carboplatin and etoposide (CARB-VP) combination treatment are commonly used. Ifosfamide has been added to PE or CARB-VP for patients at higher risk for recurrence (Calaminus et al. 2005; Robertson et al. 2014; Goldman et al. 2015). Vincristine and cyclophosphamide also have been used (Thakkar et al. 2013; Ogawa et al. 2004). For patients with an immature teratoma component (Japanese intermediate prognosis group, Table 15.1), an approach which includes surgical resection, radiotherapy, and chemotherapy leads to the best treatment outcome (Matsutani et al. 1997; Sawamura et al. 1998). Patients with a serum AFP level >1000 ng/mL and age <6 years are categorized as high risk group in the phase II Society of International Pediatric Oncology (SIOP) CNS germ cell tumor trial, and high dose chemotherapy with peripheral stem cell transplant is attempted for this subset of patients and who show residual unresectable tumors after three cycles of chemotherapy. The current COG study (ACNS1123) also tests whether dose escalation of chemotherapy would increase event-free survival in patients with higher risk for recurrences based on

Table 15.1 Classification of intracranial germ cell tumors by prognosis (Matsutani classification) (Matsutani et al. 1997)

Good prognosis
Pure germinoma
Mature teratoma
Intermediate prognosis
Germinoma with syncytiotrophoblastic giant cells
Immature teratoma
Teratoma with malignant transformation
Mixed tumors mainly composed of germinoma or teratoma
Poor prognosis
Choriocarcinoma
Yolk sac tumor
Embryonal carcinoma
Mixed tumors mainly composed of choriocarcinoma, yolk sac tumor, or embryonal carcinoma

serum/CSF AFP using high dose cisplatin, etoposide, ifosfamide (PEI), and peripheral stem cell transplant (Calaminus et al. 1997, 2012). The current study of the Japanese CNS germ cell tumor study group adopts concomitant radiochemotherapy for NGGCT patients with histologic diagnosis of choriocarcinoma, embryonal carcinoma, yolk sac tumors, or tumors with mixed histology. Adjuvant chemotherapy is also given after completion of radiotherapy (personal communication, Masao Matsutani, Saitama International Medical Center, Hidaka, Japan).

15.7.2 Radiotherapy

15.7.2.1 Radiotherapy Volume and Dose

NGGCT is less radiosensitive than germinoma. Radiation doses higher than 50 Gy given to the primary tumor site is associated with superior survival rates (Matsutani et al. 1997; Kim et al. 2012; Sawamura et al. 1998; Aoyama et al. 1998; Schild et al. 1996) than those with less than 50 Gy. Regarding the volume of radiation therapy, the studies using craniospinal irradiation (CSI) tend to give the best survival outcome; however, it has not yet been determined whether CSI should be used in all patients with NGGCT. In the SIOP phase II trial, focal radiotherapy was adopted on the basis of the results of their preceding trials (Calaminus et al. 1997, 2012), which showed that focal irradiation was sufficient for local tumor control in localized disease if >50 Gy was delivered. All SIOP patients with localized NGGCT receive focal radiotherapy, and 30 Gy CSI is given only to the patients >6 years old with disseminated disease (multiple masses and/or positive cytology) with 24 Gy boost to the gross tumor. In the SIOP study, patients in the high risk group (serum AFP level >1000 ng/mL and age <6 years) are treated with focal radiotherapy, whereas the Japanese CNS germ cell tumor study group uses 30.6 Gy CSI with a 30.6 Gy tumor bed boost for high risk group (AFP level >2000 ng/mL and/ or a serum β-HCG level >2000 IU/L). In the Japanese protocol, the rest of the patients with localized tumors receive whole ventricular irradiation (WVI). The COG ACNS1123 study is currently underway to test whether the dose and volume of radiotherapy can be adapted according to the tumor response to six cycles of carboplatin/etoposide alternating with ifosfamide/etoposide chemotherapy. In this protocol, CSI is avoided when the response to chemotherapy is good. The patients are given 30.6 Gy of WVI with a boost dose of 23.4 Gy to the primary site if the patients showed complete response (CR) to chemotherapy or showed partial response (PR) with normalization of tumor markers. The patients who showed less than PR with negative tumor markers undergo second-look surgery. If second-look surgery converts the patient to CR or PR, then the patients get 30.6 Gy WVI followed by a 23.4 Gy primary site boost.

There are studies which support the use of CSI in intracranial NGGCT. The results of a phase II multi-institutional study which used WVI for patients with localized disease and for patients who showed CR to four cycles of neoadjuvant chemotherapy showed that there was a relatively high frequency (25%) of relapse outside the initial RT volume despite the use of high dose chemotherapy and

second-look surgical resection (Robertson et al. 2014). In a multi-institutional study by Aoyama et al. (1998), spinal canal recurrence was observed in 37.8% (3/8) of patients in the poor prognosis group who did not have CSI. None of the 5 patients in the same group who received CSI experienced spinal recurrence. Matsutani et al. (1997) also reported a 21.7% (5/23) rate of spinal recurrence in the poor prognosis group patients treated primarily by whole brain radiotherapy without spinal irradiation.

15.7.2.2 Radiotherapy Technique

Adoption of radiotherapy techniques which can minimize radiation doses to the normal tissue is important in treatment of patients with NGGCT. Comparison of the dose–volume histograms (DVH) of intensity-modulated radiotherapy (IMRT) and three dimensional-conformal radiotherapy (3D-CRT) for WVI showed that IMRT reduced the irradiated volume receiving radiation doses of 20, 30, and 40 Gy by 7.5%, 12.2%, and 9.0%, respectively, compared with 3D-CRT (Chen et al. 2010). Proton beam therapy (PBT) can further reduce radiation dose to the normal tissue because of its physical characteristics with the absence of dose beyond target tissue. The use of PBT for CSI also significantly reduces hematological toxicity (Barney et al. 2014; Brown et al. 2013; Song et al. 2014) as well as decreases the risk of late effects such as secondary malignancy (Miralbell et al. 2002; Yoon et al. 2011). In addition, using PBT for WVI brought the volume of the cerebral cortex receiving $\leq$10 and $\leq$15 Gy down to two-third to a half of the dose achieved with 3D-CRT and IMRT, respectively (Fig. 15.2) (Kim and Park 2015). In tumors arising in the pineal gland, suprasellar area, or basal ganglia, PBT was shown to deliver lower mean radiation doses to the cochlea, pituitary gland, and temporal lobes (Fig. 15.3) (Park et al. 2015). PBT significantly differs from photon therapy in the volume of brain parenchyma that receives doses of 5–20 Gy, and the volume of temporal lobes that receives doses of 5–30 Gy when a total of 30.6 Gy was delivered to the primary tumor (Park et al. 2015). Whether this extent of dose reduction would translate into better neurocognitive function remains to be seen.

15.7.3 Surgery

The roles of surgery in the management of NGGCTs are as follows: (1) management of hydrocephalus, (2) tissue biopsy, (3) primary resection, (4) delayed (second-look) resection. Endoscopic tumor biopsy is the most commonly applied procedure because of the versatility and safety. Bleeding from the tumor during the procedure is a potential complication. Tumor bleeding can be managed successfully with water tamponade, direct coagulation, and EVD. Open craniotomy for bleeding control is rarely required. Stereotactic biopsy is reserved for deep-seated NGGCTs in the basal ganglia or brainstem. The management of hydrocephalus is discussed above. Even when a radical surgical resection is planned for NGGCTs, management of hydrocephalus should be considered first.

Primary surgical resection is the only treatment option for mature teratoma. After complete resection, the prognosis of mature teratoma is excellent. However, for NGGCTs other than mature teratoma, the situation is more complex because these malignant tumors can rarely be cured by surgery alone. Currently, the majority of treatment protocols adopt neoadjuvant chemotherapy, radiation therapy, followed by a delayed, "second-look" surgery. Delayed surgery is commonly recommended

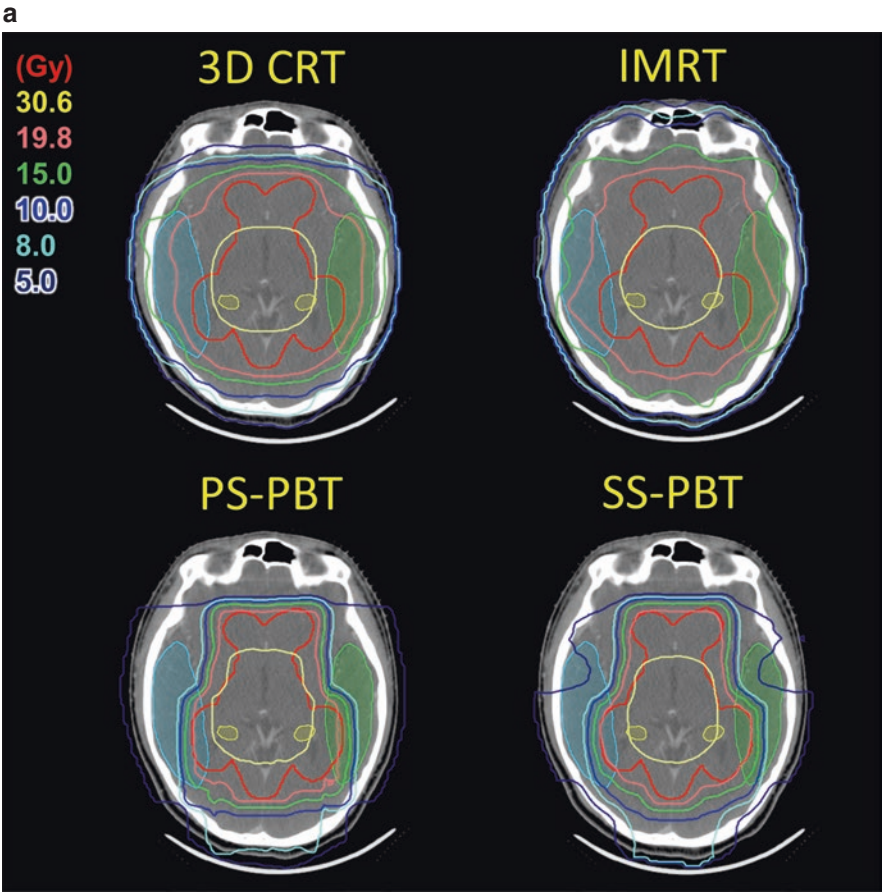

Fig. 15.2 (**a**) Dose distribution for whole ventricle irradiation. Comparison of 3D-conformal radiotherapy (3D-CRT), intensity-modulated radiotherapy (IMRT), passive scattering proton beam therapy (PS-PBT), and spot scanning proton beam therapy (SS-PBT). *Thick red lines* and *thick yellow lines* are combined planning target volume (PTV) for the whole ventricle and tumor bed boost for pineal tumor. *Blue*, *green*, *pink,* and *yellow lines* represent 10, 15, 19.8, and 30.6 Gy isodose lines, respectively. Both temporal lobes and hippocampi are contoured. (**b**) Dose volume histogram (DVH) of normal brain and both temporal lobes in the whole ventricular irradiation including the pineal gland tumor bed. Prescribed dose are 19.8 Gy at 95% volume of whole ventricular PTV and 10.8 Gy boost to the pineal gland boost PTV (Calaminus et al. 2012)

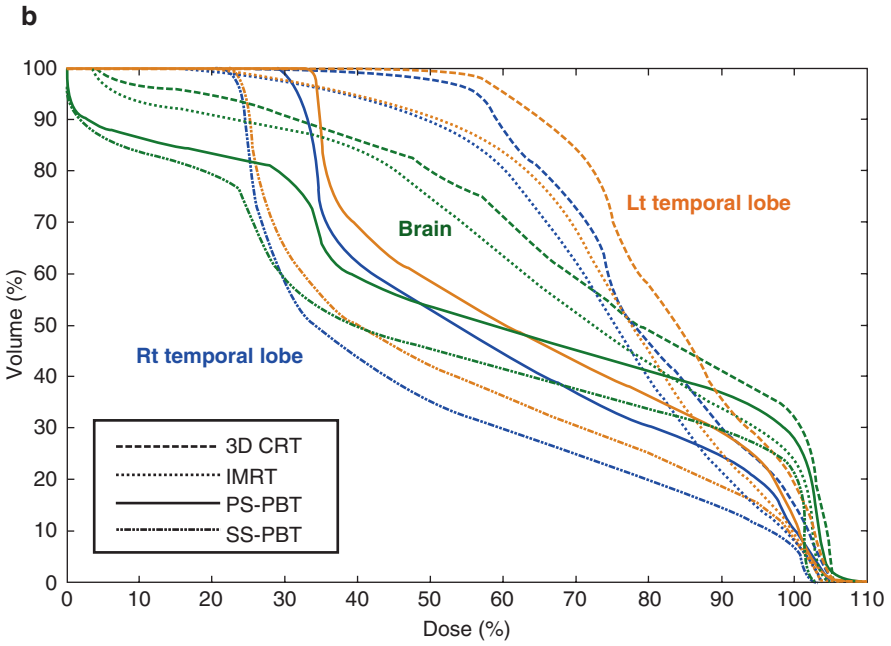

Fig. 15.2 (continued)

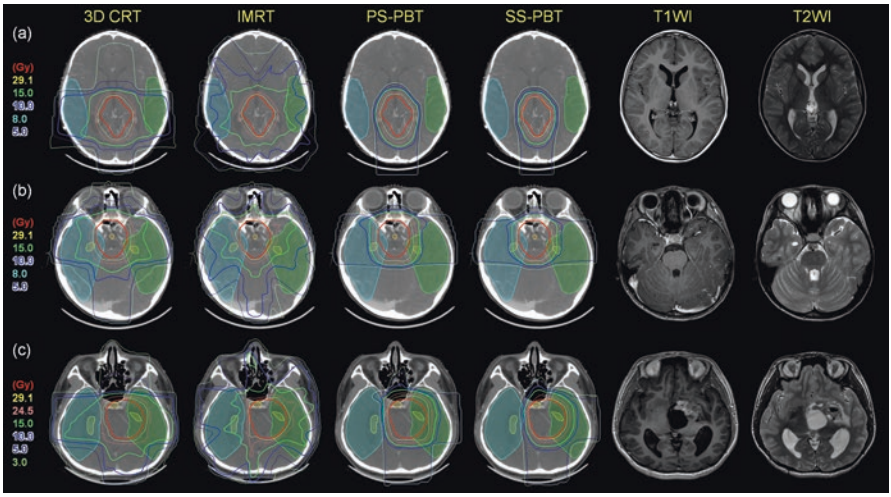

Fig. 15.3 Dose distributions of primary site boost irradiation to pineal gland, suprasellar, and basal ganglia tumors with their pre-chemotherapy MRI images. *Thick red lines* are primary site PTV. *Thick blue lines* represent 10 Gy, and *green lines* represent 15 Gy isodose line. Prescribed dose is 30.6 Gy at 95% volume of PTV. Tumors arising in the (**a**) pineal gland (**b**) suprasellar area (**c**) left basal ganglia (Calaminus et al. 2012)

for the patients who show residual tumors after chemotherapy and radiotherapy are completed. However, some authors advocate surgery after a few cycle of chemotherapy before the patients undergo radiotherapy for the tumors which show minimal response. The tumors thus resected were mostly mature teratomas (Goldman et al. 2015; Ogiwara et al. 2015). Delayed surgical resection of NGGCTs confers several advantages to patients. First, neoadjuvant therapies can reduce the tumor burden and make the surgery easier to accomplish. Second, neoadjuvant therapies also reduce tumor vascularity and delayed surgical resection enforces less blood loss of the patient. Third, generally, malignant components of NGGCTs are more susceptible to neoadjuvant therapies than teratoma components. After neoadjuvant therapies, tumor is devoid of highly vascular malignant tissues and the potential risk of tumor dissemination during surgery is also diminished. Finally, many patients with NGGCTs may not need delayed surgical resection if tumors disappear after chemotherapy and/or radiation therapy. In a recent clinical trial assessing the outcome of neoadjuvant chemotherapy for NGGCTs, six cycles of chemotherapy yielded CR or PR in 69% of patients (Goldman et al. 2015). Therefore, at present, neoadjuvant chemotherapy is considered a reasonable initial treatment for NGGCTs except for mature teratomas. However, surgical resection of NGGCTs should be undertaken in some situations. Immature teratomas and mixed GCTs composed predominantly of teratoma components often grow rapidly during neoadjuvant therapies, causing a mass effect and increased ICP (Vaughn et al. 2009). This phenomenon is known as growing teratoma syndrome (GTS) in which the mature teratoma component, especially multiple cystic structures, expand rapidly (Kim et al. 2011). GTS is a definite surgical indication and delaying surgery can be fatal in some patients.

The validity of the "second-look" surgery for a residual mass after neoadjuvant therapies is also under debate (Weiner et al. 2002). Weiner et al. reported the result of second-look operations for 10 patients with NGGCTs. Second-look surgery was performed after chemotherapy, and pathological examination revealed that 5 patients had mature or immature teratomas and 5 patients had scar tissue. The authors advocated second-look surgery for any residual lesions after chemotherapy. Ogiwara et al. (2015) also supported the role of second-look surgery early after a short course of chemotherapy because mature teratoma was found in 5 out of 7 patients in their series. However, Souweidane et al. (2010) suggested that with an asymptomatic residual lesion that is stable or diminishing with normalized tumor markers, avoiding delayed surgery would be preferable because the lesion is most likely scar tissue. Therefore, second-look surgery should be considered in selected patients. The development or possibility of GTS is the major indication for the procedure.

15.8 Target Delineation

The target delineation for NGGCT is quite similar to germinoma patients. For WVI and primary tumor target delineation, please refer to the intracranial germinoma Chap. 14. For CSI target delineation, please refer to Chap. 27 on craniospinal irradiation techniques.

15.9 Outcomes

The published survival rates of patients with intracranial NGGCT range from 30 to 90% (Matsutani et al. 1997; Kim et al. 2012; Goldman et al. 2015; Matsutani and Japanese Pediatric Brain Tumor Study Group 2001) depending on histology and treatment. The largest study of intracranial NGGCT which included 153 patients treated between 1960s and early1990s showed that the 3-year survival rate for the patients who have purely malignant GCTs (choriocarcinoma, yolk sac tumors, and embryonal carcinomas) was 27.3% with a 1-year survival rate of 0%, 33.3%, and 80%, respectively, for each histology (Matsutani et al. 1997). In that study, 3- and 5-year survival rates were less than 10% for patients with purely malignant GCTs, whereas the survival rates of patients with small component of malignant GCT cells mixed with germinoma and/or teratoma was 52.5% (Matsutani et al. 1997). More recent reports tend to show improved survival rates, however, reports about the survival rates of the patients in different histologic subgroups are rare. In a single institutional study with 32 patients with NGGCT, the 10-year relapse-free and overall survival rates were 77.6% and 74.6%, respectively (Kim et al. 2012). The subset of patients with pure malignant germ cell tumors in this study showed 10-year recurrence-free survival rate and overall survival rates of 61.1% and 66.7%, respectively. About 58% of the patients had upfront surgical resection followed by chemotherapy and radiotherapy, and multivariable analysis revealed that the use of CSI was associated with a superior overall survival rate. The Korean Society of Pediatric Neuro-Oncology (KSPNO) group study on intracranial NGGCT delivered CSI after four cycles of carboplatin, cyclophosphamide, etoposide, and cisplatin chemotherapy for 88 patients with NGGCT; they reported 3-year progression-free and overall survival rates of 81.8 and 93.6% at median follow-up of 41 months (Murray et al. 2013). In this study, there were 30 patients who were diagnosed as NGGCT solely on the basis of increased serum β-hCG >50 IU/L, which some would have considered as germinoma when different criteria of tumor markers are applied. In the COG phase II study of the neoadjuvant chemotherapy with or without second-look surgery, the authors achieved high response rates and excellent survival outcome. A total of 102 patients received six cycles of neoadjuvant chemotherapy, carboplatin 600 mg/m^2 on day 1 plus etoposide 90 mg/m^2 on days 1 through 3 (cycles 1, 3, and 5) alternating with ifosfamide 1800 mg/m^2 on days 1 through 5 and etoposide 90 mg/m^2 on days 1 through 5 (cycles 2, 4, and 6). Sixty-nine percent of patients achieved complete response or PR with neoadjuvant chemotherapy. The 5-year event-free and overall survival rates of 84 and 93% are excellent; however, like in KSPNO study, a significant number of patients were coded as NGGCT solely based on serum or CSF β-hCG >50 IU/L, suggesting that many β-hCG secreting germinomas might have been included (Goldman et al. 2015).

Most relapses of CNS NGGCT occur within 5 years; late recurrence beyond 5 years is less common compared to pure germinomas (Alapetite et al. 2010; Cho et al. 2009; Hu et al. 2012; Jensen et al. 2010; Kamoshima et al. 2008) because many patients with NGGCT who fail to achieve CR at the primary tumor site progress rapidly. Leptomeningeal seeding with failure at the primary site is not

uncommon (Matsutani et al. 1997; Kim et al. 2012; Aoyama 2009). The impact of surgical resection on local control in immature teratoma and the lower incidence of spinal metastasis than other NGGCT make the survival rate of patients with immature teratomas higher than other types of malignant germ cell tumors (Matsutani et al. 1997; Kim et al. 2012; Aoyama 2009).

15.9.1 Toxicities

ICGTs are usually diagnosed after puberty, and hence, the influence of radiotherapy tends to be less problematic than for younger patients with other brain tumors (Aoyama 2009; Calaminus et al. 2005; Merchant et al. 2000). Most neurological and neuropsychological deficits observed at later time points are associated with preexisting symptoms before treatment is given. Endocrinopathies are almost always associated with tumors located at suprasellar location by tumor invasion or surgical intervention of hypothalamic-pituitary axis. However, insufficient growth is often observed in patients with ICGCT, and the need for hormonal replacement is not limited to patients with tumors located at neurohypophyseal location (Sawamura et al. 1998; Ogawa et al. 2004). Because radiation and intensive chemotherapy are needed to control the primary tumors and disease at the neuraxis for patients with NGGCT, efforts need to be made to minimize late toxicity of treatment. Meticulous baseline and follow-up evaluation of endocrinopathies and neurocognitive function is needed for all patients.

15.10 Future Directions

Improving the survival rate especially in the pure malignant tumors is a major goal in the management of CNS NGGCT. Diverse treatment strategies have been developed by pediatric and medical oncologists, radiation oncologists, and neurosurgeons to improve survival outcomes and to decrease the morbidity of treatment. An international consensus is needed for the use of tumor markers in diagnosing and individualizing treatment in intracranial NGGCT. Results from on-going multi-institutional trials are awaited to ensure improved survival rates and quality of life of patients. From the radiotherapy aspect, efforts need to be given to reduce treatment-related morbidities by actively integrating newer radiotherapy techniques and also by investigating whether further RT volume and dose reduction is possible.

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Part V

Miscellaneous Tumors

Craniopharyngioma

16

Andrew J. Bishop and David R. Grosshans

Contents

Abstract

Craniopharyngiomas are rare, histologically benign tumors that arise in the suprasellar space. As noted by Harvey Cushing as early as 1932, these lesions while benign in nature are frequently adherent to adjacent critical structures, which makes complete surgical resection challenging. Because a microscopic gross total resection is rarely obtained, adjuvant radiotherapy plays an important role in the management of these lesions. However, given the proximity of critical

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normal tissues adjacent to or even within target volumes, radiation therapy may be associated with adverse effects. Both surgical- and radiation-induced adverse effects are compounded by the frequent presence of morbidities arising from the tumor itself. While morbidities are frequent, patients with craniopharyngioma have excellent survival outcomes. Thus, practitioners of all specialties must take great care in treatment planning and survivorship in order to optimize post-treatment outcomes.

16.1 Epidemiology

Craniopharyngiomas are uncommon, suprasellar, histologically benign tumors that have an incidence of about 1.3 per million person years without a clear preponderance based on gender or race (Bunin et al. 1998). In the United States, craniopharyngiomas constitute about 1–3% of all brain tumors with an estimated 350 new cases per year (Bunin et al. 1998; Jane and Laws 2006). However, in other parts of the world, craniopharyngiomas may be more common, with the relative incidence reportedly 11.6% in Africa compared to 3.9% in Japan (Izuora et al. 1989; Stiller and Nectoux 1994).

There is a bimodal age distribution for patients with craniopharyngioma. The first peak incidence is in children between 5 and 14 years with craniopharyngiomas representing about 4–6% of all pediatric brain tumors. The second peak is among older adults aged 65–74 years, which represents 1–4% of adult brain tumors (Bunin et al. 1998; Samii and Tatagiba 1997; Moore 2000). Histologic type also differs by age with adamantinomatous craniopharyngiomas most commonly found in the pediatric patients and papillary-squamous in adults (Muller 2014).

16.2 Predisposing Factors: Etiology and Genetics

Currently, there are no known genetic or environmental risk factors that predispose to the development of craniopharyngiomas. Rather, it is believed craniopharyngiomas arise spontaneously from the squamous-cell remnants of Rathke's pouch, along a line from the nasopharynx to the diencephalon (path of the primitive craniopharyngeal duct and adenohypophysis) (Sughrue et al. 2010; Petito et al. 1976).

As mentioned, there are two histologic subtypes of craniopharyngioma. Adamantinomatous is the most frequent and is commonly cystic with pockets of dark brown, "crank-case oil-like" fluid. Histologically, this subtype has epithelial lobules and palisading epithelium, which resemble tooth-forming tissues. The cyst fluid is rich in cholesterol that accumulates from membrane lipids, as well as keratin that comes from the top layer of desquamated keratinized squamous cells, which can often calcify. The second type of craniopharyngioma is the papillary-squamous subtype that exhibits well-differentiated, non-keratinizing squamous epithelium with papillary projections; these rarely calcify (Muller 2014; Sughrue et al. 2010).

A metaplastic origin to the papillary subtype from the adenohypophyseal cells has been suggested but remains controversial (Sughrue et al. 2010).

Newer data suggests the two histologic subtypes have different molecular aberrations. Activation of the WNT signaling pathway appears to drive the development of adamantinomatous craniopharyngiomas. Buslei and colleagues showed that this subtype contains mutations in *CTNNB1*, the gene that encodes β-catenin (Buslei et al. 2005). In contrast, the papillary subtype contains mutations in the *BRAF* oncogene (Brastianos et al. 2014; Sekine et al. 2002; Marucci et al. 2015). Targeted genotyping has identified *CTNNB1* mutations in nearly all adamantinomatous (96%) craniopharyngiomas and *BRAF* mutations in nearly all papillary subtypes (95%) (Brastianos et al. 2014). Such insights will hopefully lead to the development of new therapeutic approaches in coming years.

16.3 Presenting Symptoms

Craniopharyngiomas are slow growing tumors that can reach rather large sizes before diagnosis. Retrospectively, symptoms attributable to the tumor are often apparent at least months, if not years, prior to diagnosis (Muller 2008, 2013). Patients can experience a wide range of symptoms that are largely dependent upon the exact location of the tumor and subsequent compression of nearby critical structures including the optic chiasm, optic nerves or tracts, pituitary stalk, or hypothalamus. However, the initial clinical symptoms may also be commonly related to nonspecific signs of intracranial pressure, including headaches (Fig. 16.1). Moderate to severe daily headaches are found in approximately 50% of patients at presentation, with etiologies related to obstructive hydrocephalus, meningeal irritation, or traction on pain-sensitive structures (Khan et al. 2013).

Visual symptoms or endocrine abnormalities are more specifically attributable to suprasellar tumors, like craniopharyngiomas. The presentation and severity of symptoms range based on the tumor location. For instance, pressure on the optic chiasm may result in temporal quandrantanopias. However, a variety of visual symptoms are possible based on the particular growth pattern of the tumor and include: diplopia, blurred vision, decreased acuity, or in severe cases sometimes unilateral blindness. Visual symptoms tend to be the presenting sign more common in adults (~80%) than children (~20–60%) (Sughrue et al. 2010; Muller 2013).

Endocrine deficiencies are also common due to disruption of the hypothalamic-pituitary axis. At diagnosis, up to almost 90% of patients present with at least one hormone deficit, most commonly growth hormone (GH) (75%), followed by gonadotropins (40%), adrenocorticotropic hormone (ACTH) (25%), and thyroid-stimulating hormone (TSH) (25%) (Muller 2008; Caldarelli et al. 2005; Hoffman et al. 1992). Each hormone deficit has its own associated symptoms. For instance, GH deficiencies result in growth retardation and delayed bone age. Low gonadotropin levels interfere with pubertal changes, which may be more clinically apparent in adolescents. Low TSH levels result in hypothyroidism leading to fatigue, cold intolerance and weight gain (Rath et al. 2013; Rose et al. 1999).

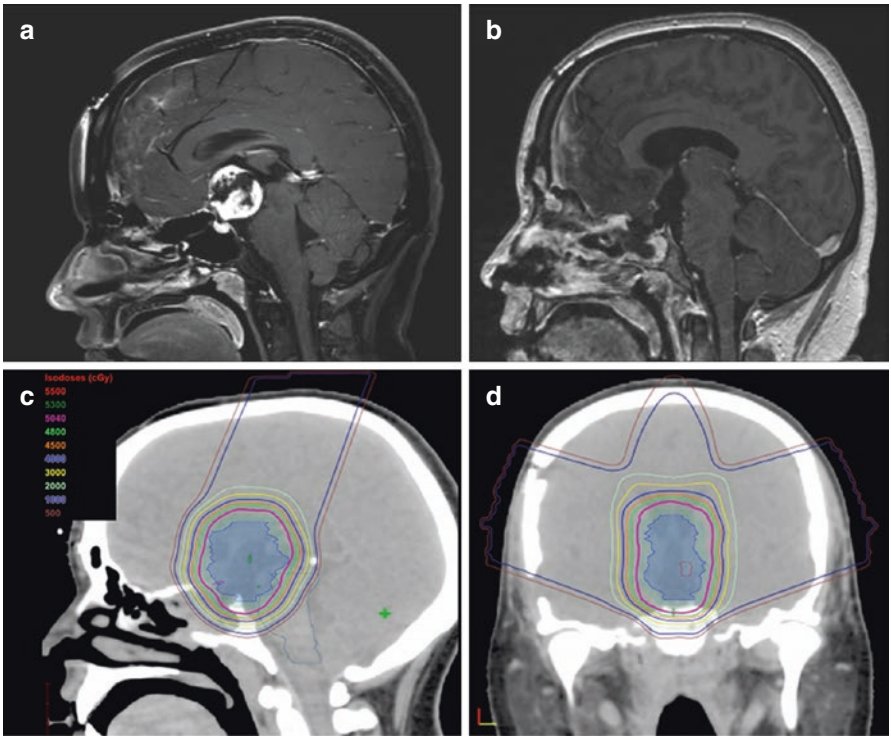

Fig. 16.1 This example depicts a 16-year-old female who presented with headaches, visual changes, and amenorrhea. On MRI (**a**), she was found to have a suprasellar mass with radiologic changes consistent with craniopharyngioma. She underwent a subtotal resection as confirmed with postoperative imaging (**b**). She then received postoperative proton beam radiation therapy to a dose of 50.4 cGE in 28 fractions using a 3-field passive scatter technique (**c**, **d**)

Overall, there is a relatively specific constellation of symptoms in patients with suprasellar tumors. Therefore, patients presenting with a combination of headaches, visual impairment, and signs of endocrine abnormalities (decreased growth rate, short stature, or polydipsia/polyuria) should be evaluated for a craniopharyngioma (Muller 2010).

16.4 Radiographic Findings

While plain radiographs are rarely used for diagnosis of this disease, several classic findings can be seen on these films. First, most patients have sellar abnormalities, including enlargement (~65%) or erosion (~44%) (Moore 2000). Second, tumor-associated calcifications can also be seen on plain radiographs, which are more common in children (up to 90%) due to the preponderance of the adamantinomatous histology (Warmuth-Metz et al. 2004).

A computed tomography (CT) scan is commonly the initial imaging obtained for workup of patients with the previously discussed symptomatology. On CT, the tumors are characteristically described as suprasellar and lobular with a central solid component surrounded by multiple, various sized, hypodense cysts. Calcifications are also best demonstrated by CT (Warmuth-Metz et al. 2004). Additional imaging is typically performed using magnetic resonance imaging (MRI); this is particularly useful for providing detailed information related to the anatomic relationship of the tumor to nearby structures. On T1-weighted images, the solid tumor component (appears isointense without contrast) and cyst rims typically enhance with contrast and the cyst fluid may appear hypo-intense. Conversely, on the T2-sequence, the tumor will typically appear hyperintense.

16.5 Workup

Initial assessment for craniopharyngiomas usually consists of obtaining adequate neuroimaging with CT brain and subsequent MRI, as discussed above. Features such as calcifications and cystic regions often help to narrow the differential diagnosis, making other lesions such as germ cell tumors less likely. Depending on the acuity and need for neurosurgical intervention to manage hydrocephalus, additional workup is warranted.

Ideally, patients with tumors that are suspicious for craniopharyngioma should receive evaluation and management by a multidisciplinary team with subspecialists from neurosurgery, radiation oncology, medical oncology, endocrinology, ophthalmology, and neuropsychology. A baseline visual acuity exam is useful in determining where there is optic pathway compression and for establishing baseline function. Additionally, since most patients have at minimum partial hypopituitarism, a complete endocrine assessment is important, especially in order to identify adrenal or thyroid dysfunction prior to surgery. Finally, despite their relatively unique appearance, imaging alone does not suffice to establish the diagnosis of craniopharyngioma, and histologic confirmation in required (Moore 2000; Sughrue et al. 2010; Muller 2010).

16.6 Treatment

The optimal therapeutic strategy for craniopharyngiomas remains controversial. The two basic approaches include either an aggressive surgical resection that attempts a gross total resection (GTR) versus a more conservative surgery followed by radiation therapy to treat residual disease. Unfortunately, the published literature and lack of randomized data have not been able to resolve the debate. Notably, biases against either strategy are based primarily on morbidities associated with historical cohorts. For instance, significant advances in neurosurgical techniques have decreased the morbidity of resections and perhaps more aggressive approaches

are warranted. Similarly, radiation therapy techniques have evolved rapidly allowing for more accurate, conformal dose deposition while minimizing radiation to nearby critical structures. Therefore, it is imperative that an experienced multidisciplinary team evaluate patients with craniopharyngiomas tumors for personalized and optimal treatment planning.

16.6.1 Surgery

Surgery is indicated in all patients in order to achieve a histologic diagnosis, allow for cyst or hydrocephalus decompression, and to minimize disease burden (Van Effenterre and Boch 2002). Some surgeons believe that an aggressive GTR is required for cure, while others believe the morbidity associated with that approach is too great and opt for cyst drainage and a subtotal resection (STR) with planned postoperative radiation therapy (Aggarwal et al. 2013; Fahlbusch et al. 1999; Merchant et al. 2002; Sanford 1994; Stripp et al. 2004; Weiner et al. 1994; Yasargil et al. 1990; Clark et al. 2013; Schoenfeld et al. 2012).

Initial surgical intervention is focused on relieving acute symptoms related to these tumors. In patients presenting with hydrocephalus, decompression of the lesion itself is the favored treatment approach to restore CSF flow (Fahlbusch et al. 1999; Choux and Lena 1979). However in severe cases, an external drain may be required to relieve pressure prior to tumor resection.

The approach to surgical resection is dependent on the location and makeup of the tumor. Historically, a common surgical approach included a right frontotemporal incision (Fahlbusch et al. 1999). Also, suprasellar tumors were also resected using a transcranial approach, while prechiasmatic tumors may be best visualized via a supraorbital craniotomy (Moore 2000). For tumors that are primarily intrasellar, an endoscopic, transsphenoidal approach may provide optimal visualization while remaining minimally invasive (Elliott et al. 2011; Zona and Spaziante 2006). More commonly, newer techniques including microsurgery, endoscopic assistance, and minimally invasive approaches have allowed neurosurgeons to improve the quality of their resections while minimizing morbidity (Sughrue et al. 2010; Muller 2008, 2013). Ultimately, the intraoperative findings will dictate the degree of resection.

16.6.2 Radiation Therapy

Factors, which most impact the choice of whether to proceed with adjuvant radiotherapy or observation, are most often the presence of residual disease and the age of the patient. For tumors arising in very young patients, a discussion is warranted regarding the appropriateness of observation since very young children are particularly susceptible to adverse radiation effects. However, because incompletely resected lesions have a high rate of local relapse without adjuvant therapy

(71–90%), postoperative radiotherapy should be recommended in patients with subtotal resection (Clark et al. 2013; Becker et al. 1999).

Numerous radiation therapy techniques exist and have been utilized with excellent outcomes in terms of disease control for these tumors. It is, however, worth noting that no prospective studies evaluating the benefits of advanced technology exist, in terms of reduced radiation adverse effects, either for photon or proton therapy. In the majority of published literature, photon-based therapies, both traditionally fractionated and hypo-fractionated stereotactic techniques have been employed (Merchant et al. 2002, 2006; Becker et al. 1999; Habrand et al. 1999, 2006; Minniti et al. 2009). Merchant and colleagues conducted a single arm prospective study of reduced margin 3D conformal radiation therapy for pediatric patients with craniopharyngioma (Merchant et al. 2006). In a total of 28 patients, the solid and cystic tumor components along with a 1 cm expansion were targeted to a dose between 54 and 55.8 Gy with acceptable rates of disease control. Greenfield and colleagues have also retrospectively evaluated the use of intensity modulated radiation therapy techniques (Greenfield et al. 2015). These investigators documented high rates of disease control but also noted a high burden of pre-radiotherapy comorbidities including endocrinopathies. More recently, dosimetric studies of volumetric arc therapy (VMAT) have been conducted and indicate that close attention to beam angles is important in order to minimize hippocampal exposure (Uto et al. 2016).

In addition to studies using common 1.8 Gy fractionation schemes, given the relatively well-demarcated tumor boundaries on imaging, radiosurgery, or hypofractionated stereotactic radiotherapy have also been explored in the treatment of these tumors. For radiosurgery, the most commonly employed platform has been gamma knife. Patients selected for gamma knife radiotherapy typically have small tumors, measuring less than 3 cm; also, there must be a safe separation (generally 3–5 mm depending on stereotactic delivery technique) between the target and nearby critical structures such as the optic chiasm in order to allow for adequate target coverage while respecting normal tissue constraints. Reported doses delivered in single fractions using gamma knife range from 12 to 14 Gy (Amendola et al. 2003; Kobayashi 2009; Mokry 1999; Chung et al. 2000). In these select patients, reported disease control rates seem acceptable and toxicities minimal (Lee et al. 2014; Park et al. 2011; Xu et al. 2011). However, patient numbers included are small and outcomes for adult and pediatric patients are frequently not separated. Given various differences in patient selection (i.e., tumor volumes, etc.), it is difficult to compare these results to traditional fractionated regimens.

As for many pediatric brain tumors, proton therapy is increasingly used in the treatment of craniopharyngiomas. Boehling and colleagues described in detail the dosimetric advantages of proton therapy including the potential for sparing of vascular structures and the hippocampus, especially with advanced proton therapy delivery modalities, namely intensity modulated proton therapy (IMPT) (Boehling et al. 2012). One of the preliminary reports by Luu and colleagues on the use of proton therapy for patients with craniopharyngiomas showed equivalent local control rates (88%) as compared to previous photon-based studies (Luu et al. 2006).

More recently, a multi-institutional study comparing proton therapy to photons, again reported comparable outcomes (Bishop et al. 2014).

16.7 Radiation Details

Currently, for traditionally fractionated therapies, doses range from 50.4 to 54 Gy delivered at 1.8 per fraction. The commonly used upper limit of 54 Gy likely represents the tolerance for structures such as the optic chiasm, which are frequently immediately adjacent to the target (Merchant et al. 2002, 2006; Bishop et al. 2014; Kiehna and Merchant 2010). Advanced photon-based therapies have improved normal tissue sparing, which includes the use of intensity modulated radiation therapy (IMRT) (Greenfield et al. 2015; Merchant et al. 2013). In a single institution series, 24 patients were treated to a dose of 50.4 Gy using IMRT, and the 5- and 10-year progression-free survival rates were consistent with those seen with 3D conformal or other photon-based therapies (Greenfield et al. 2015). Regarding target delineation, the gross tumor volume (GTV) is typically easily visualized and delineated following fusion of MR imaging with treatment planning CT. While there is some discussion of whether or not all cystic areas should be included in the GTV, tumor cells could be present in the cyst walls, which is the reason to ensure coverage with the prescription isodose line.

Some debate surrounds the appropriate clinical target volume (CTV) expansion to be utilized. Historically, larger expansions of 1–2 cm have been employed given less reliable immobilization and image-guidance. However, more recently, studies have suggested that a smaller target volume expansion of 5 mm may be safely employed (Merchant et al. 2013). This is justifiable based on the fact that craniopharyngiomas are not inherently infiltrative, unlike gliomas or other intrinsic brain tumors. Preliminary studies reporting disease control outcomes utilizing reduced margin treatments have documented good disease control outcomes (Merchant et al. 2013). However, it is important to note that the CTV should be customized for each individual patient; this includes ensuring coverage of areas of adhesion noted intraoperatively. For photon therapy planning target volume (PTV), expansions will depend on institutional practices with common values falling between 3 and 5 mm.

16.7.1 Cystic Considerations for Radiation Planning

While it has long been known that craniopharyngiomas may contain cystic components, only recently has it been appreciated the dynamic changes that occur within these structures. Investigators at the Massachusetts General Hospital were among the first to describe in detail the potential for rapid cystic changes in these tumors (Winkfield et al. 2009). A group of 24 pediatric patients, 19 with a cystic component, underwent treatment. Seventeen of the 19 patients with cysts received surveillance imaging during the course of radiation therapy. Six of these patients had

imaging evidence of cyst enlargement with 4 requiring revision of the radiation plan in order to ensure target coverage. The authors recommended routine imaging during the course of radiation therapy in patients with tumors containing cystic components (Winkfield et al. 2009). Following this initial observation, a subsequent report from the University of Texas MD Anderson Cancer Center confirmed relatively frequent cystic changes during irradiation (40%), with some patients requiring alteration to the treatment plan (20%) (Bishop et al. 2014). Therefore, when small CTV and PTV expansions are used, weekly or biweekly imaging during treatment is recommended in patients with cystic components to their tumors in order to ensure adequate tumor coverage. Additionally, close surveillance imaging is of greater importance in the setting of reduced CTV margins and/or the use of proton therapy.

16.7.2 Intracavitary Therapies

A less commonly employed treatment approach is the intracavitary injection of either β-emitting radioisotopes or sclerosing substances. The radioisotopes (Schoenfeld et al. 2012) phosphorus or ^{90}yttrium have been used both as a primary and salvage treatment for cystic craniopharyngiomas, in which they are injected into the cysts via a catheter. Once within the cyst, photons are emitted by beta decay allowing for delivery of high doses of radiation to the epithelial lining of the cyst. Several studies have reported cyst regression in 81–88% of patients (Blackburn et al. 1999; Leksell 1952; Pollock et al. 1995). Alternatively, intracystic catheters can be used to instill chemotherapeutic agents (i.e., bleomycin or interferon α) with some efficacy (Cavalheiro et al. 2010; Schubert et al. 2009).

16.8 Outcomes

There are not evidence-based guidelines or recommendations regarding a follow-up plan for patients with a history of craniopharyngioma. However, given the potential for cystic changes following treatment, a best practices approach would suggest that neuroimaging should be obtained routinely. Our institutional approach is to obtain post-radiation imaging 4–6 weeks following completion of treatment and every 3 months thereafter for 2–3 years, at which point longer intervals may be recommended. In addition to monitoring for disease relapse, a multidisciplinary team is essential to manage disease-related and iatrogenic toxicities. Endocrine function will need to be closely monitored and supplements added as indicated, especially for developing children and adolescents; the importance of close endocrine follow-up cannot be overstated. Periodic visual field testing is also important for early intervention. Other members of a multidisciplinary team (internists/pediatricians, neuropsychologists, teachers, dieticians, etc.) may be required depending on the needs of the patient.

16.8.1 Outcomes

While disease control rates are high, craniopharyngiomas are associated with decreased overall survival compared to the normal population; the 10-year survival outcomes commonly reported are between 80 and 91% (Schoenfeld et al. 2012; Bishop et al. 2014; Merchant et al. 2013; Karavitaki et al. 2006; Pereira et al. 2005; Fernandez-Miranda et al. 2012). In addition to the deaths attributable to disease progression or surgical mortality, these patients are at higher risk of cardiovascular and cerebrovascular death (Pereira et al. 2005). Notably, based on the current evidence, there does not seem to be a difference in long-term survival between patients treated with GTR versus STR and postoperative radiation therapy. However, a recent SEER study did suggest a short-term survival benefit independently associated with STR (HR 0.39) and RT (HR 0.45) on multivariate analysis (Zacharia et al. 2012).

In terms of surgical resection, GTR rates range widely (between about 30 and 75%), with recurrences most commonly reported to occur in about 8–30% of patients following a GTR (Caldarelli et al. 2005; Fahlbusch et al. 1999; Sanford 1994; Stripp et al. 2004; Shi et al. 2008; Gardner et al. 2008). Conversely, the rate of recurrence following a STR alone is unacceptably high (40–75%) without RT (Fahlbusch et al. 1999; Karavitaki et al. 2005; Villani et al. 1997). However, direct outcome comparisons are difficult given the variable median follow-up and differing definitions of disease progression.

Patients that receive STR and postoperative radiation therapy appear to have similar control rates to GTR with disease relapse occurring in 0–12% of patients (Schoenfeld et al. 2012; Bishop et al. 2014; Merchant et al. 2013). Several studies have also differentiated solid from cystic tumor progression. Immediately following radiotherapy many patients experience transient cyst growth before they regress (Bishop et al. 2014; Shi et al. 2008). Shi and colleagues reported cyst enlargement in 11 of 21 patients following radiation therapy. Similarly, Bishop and colleagues observed a third of patients to have evidence of cyst growth within 3 months of completing treatment. However, in the majority of cases, growth was transient and followed by subsequent shrinkage of the cystic component. Reported 3-year recurrence rates of the solid tumor component were 5% versus 24% for cysts (Bishop et al. 2014). Cyst growth is appreciably more challenging to control, but its biologic significance is undefined.

If tumors recur, management is increasingly difficult primarily because surgical resection of recurrent tumors is more challenging. The recurrent tumors are commonly more adherent to surrounding tissue with poorly defined tissue planes, which is evidenced by the lower rate of resection (13–53%) achieved at the time of recurrence (Fahlbusch et al. 1999; Villani et al. 1997; Duff et al. 2000). For patients that recur, surgery alone is unlikely to provide durable control. In a study by Kalapurakal and colleagues, the 10-year progression-free survival after surgery and radiation therapy for recurrent tumors was 82–83% compared to 0% for surgery alone (Kalapurakal et al. 2000). However, withholding radiation in the definitive treatment setting in order to reserve it for use at the time of salvage is not justified based

on available evidence. In fact, a recently published study by Bishop and colleagues showed that recurrent cyst growth was associated with poorer visual outcomes and hypothalamic obesity; furthermore, radiation therapy as salvage therapy negatively affected endocrine function (Bishop et al. 2014). Therefore, reserving radiation for salvage in the setting of STR is not advisable.

16.8.2 Toxicities

While patients may present with varying degrees of endocrine or visual dysfunction, treatment may impart additional morbidity. The rate of endocrine dysfunction increases significantly after surgical resection given the proximity, and sometimes involvement, of the tumors to the pituitary-hypothalamic axis (Caldarelli et al. 2005; Hoffman et al. 1992; Merchant et al. 2002). Diabetes insipidus is the most commonly reported postoperative endocrine complication. It occurs transiently in nearly all patients (80–100%) and permanently in 40–93% (Caldarelli et al. 2005; Hoffman et al. 1992; Merchant et al. 2002; Poretti et al. 2004). Anterior pituitary function also is often commonly compromised with several reports suggesting panhypopituitarism in up to 75–100% of patients following surgery (Fahlbusch et al. 1999; Kalapurakal et al. 2000; De Vile et al. 1996). Visual outcomes may also be influenced by surgical interventions. While some patients experience improvement in their preoperative visual deficits (41–58%) (Caldarelli et al. 2005; Elliott et al. 2011), others have further deterioration (2–66%) following resection (Sughrue et al. 2010; Fahlbusch et al. 1999; Poretti et al. 2004). Finally, another commonly underreported, yet serious toxicity associated with surgery is hypothalamic dysfunction. Symptoms include disturbed circadian rhythm, behavioral changes, obesity, or temperature/thirst regulation, and it may worsen in up to 65–80% of patients (Muller 2013; Elliott et al. 2011; Poretti et al. 2004). Other less common morbidities associated with surgery include neurologic, cerebrovascular, or cognitive complications. For example, Merchant and colleagues reported a 10-point drop in IQ scores in 15 patients treated with GTR alone (Merchant et al. 2002).

Similar to surgery, it is challenging to distinguish the long-term toxicities of radiation therapy from disease-related sequelae. The most commonly reported late toxicity associated with radiation therapy is worsening endocrine dysfunction, which is observed in 77–95% of patients (Clark et al. 2013; Bishop et al. 2014); panhypopituitarism is reportedly induced in 30–46% of patients (Bishop et al. 2014; Clark et al. 2012). Reduced visual acuity is also a potential long-term toxicity but is unusual using modern radiation techniques if normal tissue constraints are met. Hypothalamic obesity is a particular morbid treatment-related toxicity that requires specialized management; the impact of radiation therapy on this toxicity is uncertain, but the prevalence of obesity following combined modality treatment has been reported in 25–55% of patients (Muller 2008; Hoffman et al. 1992; Elliott et al. 2011; Bishop et al. 2014).

Less common toxicities associated with radiation include neurocognitive decline and cerebrovascular changes. Merchant and colleagues reported a median drop in

IQ scores of only 1.25 points in patients treated with surgery and radiation (compared to 10 points in patients receiving aggressive surgery only) (Merchant et al. 2002). Vascular changes and stroke have also been observed in patients treated for craniopharyngiomas. Mueller and colleagues suggested that the incidence of stroke is increased tenfold in patients with childhood cancers,(Mueller et al. 2013) with several studies specific to craniopharyngiomas reporting rates of late vascular accidents or moya-moya in about 10% of patients after long-term follow-up (Bishop et al. 2014; Liu et al. 2009; Lo et al. 2014, 2016). Specifically, one cross-sectional study observed vasculopathies in 32% of patients (n = 6 of 32) (Lo et al. 2016). However, modern radiation techniques may lower the rate of late toxicities compared to those reported in historical cohorts.

Conclusions

Debates regarding the appropriate management of craniopharyngiomas will continue. Debates include deciding upon the appropriate surgical intervention, whether radical resection versus limited decompression is indicated. Increasingly, there is a trend towards limited surgical resection followed by adjuvant radiotherapy. While radiation oncologists will agree there is an established role for adjuvant radiation therapy if residual disease is present following surgery, there is still debate regarding the appropriate treatment modality and/or techniques (photons vs. protons vs. stereotactic, etc.) as there is no prospective data documenting differing disease control or toxicity outcomes. Beyond neurosurgeons and radiation oncologists, other providers, particularly endocrinologists, should routinely be involved in the upfront and continued management of these patients. Given the excellent survival outcomes for craniopharyngioma patients, all practitioners should focus on minimizing and managing post-treatment morbidities, thereby improving quality of life for survivors.

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CNS Leukemia

17

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Contents

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Abstract

Pediatric acute lymphoblastic leukemia (ALL) is the most common cancer of children and now has a particularly high cure rate as there have been improvements in risk stratification, matching the intensity of therapy to prognostic factors. These factors include risk for central nervous system (CNS) involvement, immunophenotype, molecular factors, and response to induction systemic therapy. Radiotherapy (RT) to treat the CNS due to relatively poorer penetration of chemotherapy through the physiologic blood–brain barrier had an important historical role in the development of ALL therapy. But use of RT in this role has been curtailed to high-risk patients in order to limit late occurring toxicities. The other uses of RT for AML include CNS relapse, palliative therapy, and total body irradiation as part of an allogeneic stem cell transplant. Radiotherapy is used in as similar albeit even less frequently for acute myeloid leukemias (AML) and related CNS lymphomas.

17.1 Epidemiology

Leukemias account for 30% of all pediatric malignancies. The most common pediatric malignancy is acute lymphoblastic leukemia (ALL), responsible for 24% of all childhood cancers. The incidence of pediatric ALL is rising, with about 3500 new cases diagnosed each year in the United States (Siegel et al. 2014; Hunger et al. 2012). The median age at diagnosis of ALL is 4 years of age, and it is more common in boys with twice as common in white than in black children.

Aside from pediatric ALL, acute myeloid leukemia (AML) accounts for additional 20% of childhood leukemias. AML is much more common in adults, and treatments for pediatric AML have not been generally as successful as those for ALL.

17.2 Predisposing Factors

17.2.1 Etiology

Leukemias are a systemic disease with circulating immature blast cells and diffuse bone marrow involvement along with micro- or macroscopic involvement of organs—most commonly lymph nodes, spleen, and liver. ALL arises when there is arrest in maturation of lymphoid cells, leading to clonal expansion. Nearly 85% of pediatric ALL cases are mature B-cell or B-cell precursors, identified histologically by cell surface marker CD19, with the remainder T-cell precursor identified by CD7. Pediatric T-cell ALL tends to occur in older children, age greater than 10 years, and is associated with higher risk disease with extramedullary involvement (including CNS disease), higher white blood cell (WBC) count on presentation, and carries an overall worse prognosis. AML is relatively rare in children but has a classification scheme and association with particular genetic markers similar to adults.

Central nervous system (CNS) leukemia is thought to develop from perivascular leukemic infiltration of meningeal vasculature, with extension into subarachnoid space, before penetration into the brain parenchyma. Only 3–5% of pediatric ALL patients present with detectable CNS disease, although given the high rate of CNS relapse in those treated with low intensity chemotherapy alone, the CNS is considered a sanctuary site.

17.2.2 Genetic Issues

Several diseases characterized by well-defined germ line genetic abnormalities including Fanconi anemia, Bloom Syndrome, and Down syndrome are associated with an increased risk of ALL. Patients with Down syndrome have a 10–20 times higher risk of developing ALL.

17.3 Presenting Symptoms/Findings

The most common presenting symptoms of ALL are fever, bleeding, lymphadenopathy, and bone pain, the latter from infiltration of the periosteum, which can lead to aseptic osteonecrosis. Physical examination may reveal lymphadenopathy, hepatosplenomegaly, ecchymoses, and petechiae. Abnormalities of circulating blood cells are common, although if there are less than two lines of cytopenias (i.e., anemia, neutropenia, lymphopenia, and thrombocytopenia), ALL as a diagnosis is uncommon.

As mentioned, 3–5% will have clinically detectable CNS disease though the majority of ALL cases with CNS involvement are asymptomatic. Symptoms of CNS disease often occur with more advanced CNS disease, including extensive leptomeningeal involvement, which can lead to headaches, irritability, nausea, and vomiting. Cranial nerve palsies are uncommon but are otherwise diagnostic of CNS disease. The most common cranial nerves involved are CN VII followed by CN VI and CV III. More advanced CNS disease can lead to retinal infiltration and signs of increased intracranial pressure such as papilledema. Hypothalamic syndrome can result from leukemic infiltration of hypothalamus, causing unexplained weight gain (Greydanus et al. 1978).

17.4 Workup

Complete blood count (CBC) of the peripheral blood in ALL patients typically contains immature lymphoblasts and elevated WBC. In 30% of cases, WBC is 10–50,000, and in 15–20% of cases WBC is over 50,000. Bone marrow biopsy, comprehensive metabolic panel, LDH, DIC panel, uric acid and tumor lysis panel, and viral titers (EBV, CMV, HIV, Hepatitis B, VZV) complete standard serological workup. A chest X-ray is important to evaluate for mediastinal mass when

suspected, and a testicular ultrasound can be used if testicular mass is palpated. A CT chest should be considered particularly for T-cell ALL cases. A CT or MRI head is needed is patient demonstrates any neurologic symptoms.

The lumbar puncture is a critical part of workup for all pediatric ALL cases at the time of diagnosis. CNS leukemia is defined by presence in CSF of more than 5 WBC per microliter with blasts or cranial nerve palsies. Traditional stages of CNS leukemic involvement are defined as follows: CNS 1 has an absence of blasts on CSF cytospin, CNS 2 has fewer than 5 WBC in CSF but with blasts present, and CNS 3 has 5 or more WBC with blasts present in CSF, or if there is clinical evidence of cranial nerve deficits. Care should be taken during lumbar puncture since traumatic lumbar punctures have been associated with worse prognosis (Gajjar et al. 2000).

Patients are stratified into standard-risk or high-risk disease with some additional degradations depending on prognostic factors and treatment protocols. Standard-risk disease includes those between the ages of 1 and 10, peripheral blood WBC < 50,000, and B-cell lineage disease. Higher risk disease encompasses patients younger than 1 or older than 10. In the Berlin-Frankfurt-Munster (BFM) clinical studies, patients with T-cell lineage disease, BCR-ABL fusion gene or t(9;22) and CNS involvement were also designated as high risk. Further classification into risk groups is often delayed after diagnosis and initial "induction" chemotherapy, awaiting assessment of chromosomal/molecular markers and response to therapy. See Table 17.1 for one current example of ALL risk groups.

17.4.1 Cytogenetics

More than 60% of pediatric ALL cell lines have genetic abnormalities. Specific cytogenetic abnormalities have important prognostic value in ALL. Chromosomal translocations occur in approximately 15% of pediatric ALL. The oldest known is the t(9;22) BCR-ABL translocation that forms the Philadelphia chromosome. This translocation is found in up to 5% of B-cell precursor ALL and is associated with a higher risk of CNS involvement and overall poorer prognosis.

The t(12;21) translocation leads to the TEL-AML1 fusion gene and can be found in about 22% of cases. About 6% of ALL patients have the t(1;19) translocation that creates the E2A-PBX1 fusion gene. Rarer genetic abnormalities include the t(4;11) translocation associated with African-American children who have high WBC counts, the t(8;14) MYC defect in cases of mature B-cell ALL (2%), and t(11;14) associated with T-cell ALL with extramedullary involvement.

RUNX1 and ETV6 gene are juxtaposed *in utero* in TEL-AML1 containing cryptic t(12,21) translocation found in 15% of patients can lead to impaired hematopoietic differentiation. The MLL rearrangement tends to be found in infants and is associated with poor prognosis; it can arise from t(4;11), t(11;10), or t(9;11) translocations.

Twenty-five percent of ALL have hyperdiploid chromosomal changes and is associated with a more favorable outcome. The most common are trisomies 4, 10,

Table 17.1 Risk groups for pediatric acute lymphoblastic leukemia

	NCI risk (age/ WBC)	Favorable genetics	Unfavorable characteristics	Day 8 PB MRD (%)	Day 29 marrow MRD (%)	% of B-cell patients	5-year EFS (%)
Low risk	SR	Yes	None	<0.01	<0.01	15	>95
Average risk	SR	Yes	None	≥0.01	<0.01	36	90–95
	SR	No	None	<1	<0.01		
High risk	SR	Yes	None	Any level	≥0.01	25	88–90
	SR	No	None	≥1	<0.01		
	HR (age < 13 years)	Any	None	Any level	<0.01		
Very high risk	SR	No	None	Any level	≥0.01	24	<80
	HR	Any	None	Any level	≥0.01		
	HR (age ≥13 y)	Any	None	Any level	<0.01		
	SR or HR	Any	Yes	Any level	Any level		
Special group	T-cell ALL					n/a	66–80

Adapted from the Children's Oncology Group Classification of Newly Diagnosed ALL protocol, AALL03B1

NCI National Cancer Institute (consensus conference in 2003 established basic risk groups), *WBC* white blood cell, *SR* standard risk (WBC < 50,000/μL and age 1 to <10 years), *HR* high risk (WBC ≥ 50,000 μL or age ≥ 10 years [up to 13 years if treated on a COG protocol]), or overt CNS involvement, i.e., CNS3, *PB* peripheral blood, *MRD* minimal residual disease (percent blasts detected in PB or marrow at chemotherapy nadir or recovery after first induction cycle), *EFS* event-free survival

Note that chemotherapy response is defined as rapid if MRD negative at days 8 and 29 or slow if MRD positive at day 8 and negative at day 29

Favorable Genetics include: Trisomies 4, 10, or 17; TEL-AML1 fusion, Hyperdiploidy; ETV-RUNX1 fusion

Unfavorable Characteristics include: t(9;22) and/or BCR/ABL fusion; hypoploidy defined as DNA index <0.81 or <44 chromosomes; MLL translocation; induction failure

and 17. Conversely, hypodiploidy of fewer than 45 chromosomes conveys a more unfavorable outcome.

One of the most recently identified genetic abnormalities is the IKZF1 deletion found in 15% of precursor B-cell ALL cases. These are associated with older patients who have higher WBC count at diagnosis, and, as such, are also associated with a high-risk prognosis. IKZF1 deletions are also associated with higher chance of a BCR-ABL1 abnormality (van der Veer et al. 2013; Dorge et al. 2013).

Table 17.2 French-American-British (FAB) classification of acute myelogenous leukemia (AML) correlated with common cytogenetic abnormalities

FAB type	Cytogenetic finding
M0, M1 (Undifferentiated AML)	trisomy 11, t(10;11)
M2 (Acute myeloid leukemia)	t(8;21)
M3 (Acute promyelocytic leukemia)	t(15;17), t(11;17), t(5;17)
M4 (Acute myelomonocytic leukemia with eosinophilia)	inv(16)
M5 (Acute monocytic leukemia)	t(11;23)
M6 (Acute erythroleukemia)	t(3;5)
M7 (Acute megakaryocytic leukemia)	t(3;3), t(3;12)

CRLF2 overexpression and JAK mutations are also associated with IKZF1 deletion and poorer prognosis. A CRFLF2 abnormality has been found to independently confer worse prognosis (Chen et al. 2012).

AML subtypes based on hematopoietic lineage in the French-American-British (FAB) classification system still have some practical usage and have distinct molecular correlations (Table 17.2).

17.5 Acute Management

Aside from cranial neuropathies and leptomeningeal disease, pediatric CNS leukemias rarely cause medical emergencies due to mass effect in CNS space. In cases where neurologic symptoms do arise, glucocorticoids can serve an important part of acute management along with cranial radiation. The use of glucocorticoids can cause rapid leukemia or lymphoma cell lysis, which can hinder diagnostic workup in undiagnosed patients. In other parts of the body, mediastinal adenopathy can cause airway compression, and may sometimes be amenable to low-dose palliative RT (e.g., 4–6 Gy in 2–3 fractions).

AML patients can rarely develop neurologic symptoms from hyperleukocytosis. A small Robert Wood Johnson medical center study showed that whole brain radiation for 1–3 fractions to a total dose of 2–9 Gy lead to resolution of neurologic symptoms in majority of patients (Ferro et al. 2014).

17.6 Treatment

17.6.1 General Principles

Investigation into combined chemoradiation treatments for ALL began in the 1960s. The earliest chemotherapy trials led to significant improvement in survival rates but still had high CNS relapse rates. Subsequent addition of prophylactic cranial radiation significantly decreased CNS relapse. Clinical trials in the 1970s established

that prophylactic cranial irradiation (PCI) was effective in conjunction with intrathecal chemotherapies and certain systemic therapies to control leukemic burden in the entire subarachnoid space, meninges, and CNS parenchyma. RT to the entire craniospinal axis is only required in setting of high-risk CNS relapse. Overall, the evolution of ALL treatments is a paradigm for how iterations of clinical trials can over time significantly improve outcomes, particularly with attention to matching therapy to prognostic factors. Most patients with ALL no longer require PCI. Patients who still require PCI receive lower radiation doses in combination with intensification of the systemic and intrathecal therapies. PCI doses for pediatric ALL are often 12 Gy (depending on the specifics of the systemic therapy program used) while overt CNS involvement with active chemotherapy often uses 18 Gy cranial irradiation.

In the evolution of ALL therapy, the specific phases of treatment include induction (of remission), consolidation, and post-remission therapies. Consolidation therapy includes CNS-directed therapy that may involve PCI depending on risk factors and the particular treatment protocol being followed. The optimal timing of PCI is not clear, but has generally been scheduled to minimize interactions with other chemotherapy agents, particularly high-dose methotrexate. Regardless, intrathecal chemotherapy is important. Post-remission therapy may include intensification and delayed intensification therapies. In addition, there is typically a protracted phase of low intensity maintenance chemotherapy which is delivered over several years once a firm remission is established.

The mainstay of ALL treatment is induction chemotherapy with the goal of rapid complete remission. The typical regimen is: dexamethasone, vincristine, and asparaginase. Additional daunorubicin as well as targeted tyrosine kinase inhibitor for Philadelphia chromosome positive disease are sometimes also included in induction regimen. Induction therapy typically lasts 4–6 weeks and leads to complete remission in over 90% of cases. The systemic steroid of choice is dexamethasone as several studies have shown that dexamethasone reduces CNS and systemic relapse in pediatric ALL compared to prednisone due to better CNS penetration (Bostrom et al. 2003; Jones et al. 1991).

Bone marrow biopsy at 2–4 weeks of induction therapy is essential in looking for residual lymphoblast burden as a marker of prognosis, chemotherapy sensitivity, and guide for further therapy. The finding of residual blasts constitutes minimal residual disease (MRD) designation and confers a worse prognosis (van Dongen et al. 1998). An associated molecular marker for a patient's ALL improves the prognostic accuracy of MRD. Correspondingly, rapid response to induction treatment confers better prognosis compared to a slower induction of molecular remission (Gaynon et al. 1997). See Fig. 17.1.

Consolidation after remission from induction therapy is tailored to prognostic factors and most commonly used chemotherapy using methotrexate alone, or with 6-mercaptopurine, asparaginase, and etoposide (or teniposide), or a combination of doxorubicin, 6-thioguanine, asparaginase, vincristine, ifosfamide, teniposide, or etoposide, and dexamethasone. There has been a push in recent decades to strengthen post-induction intensification regimens. Indeed, COG analysis of intensification

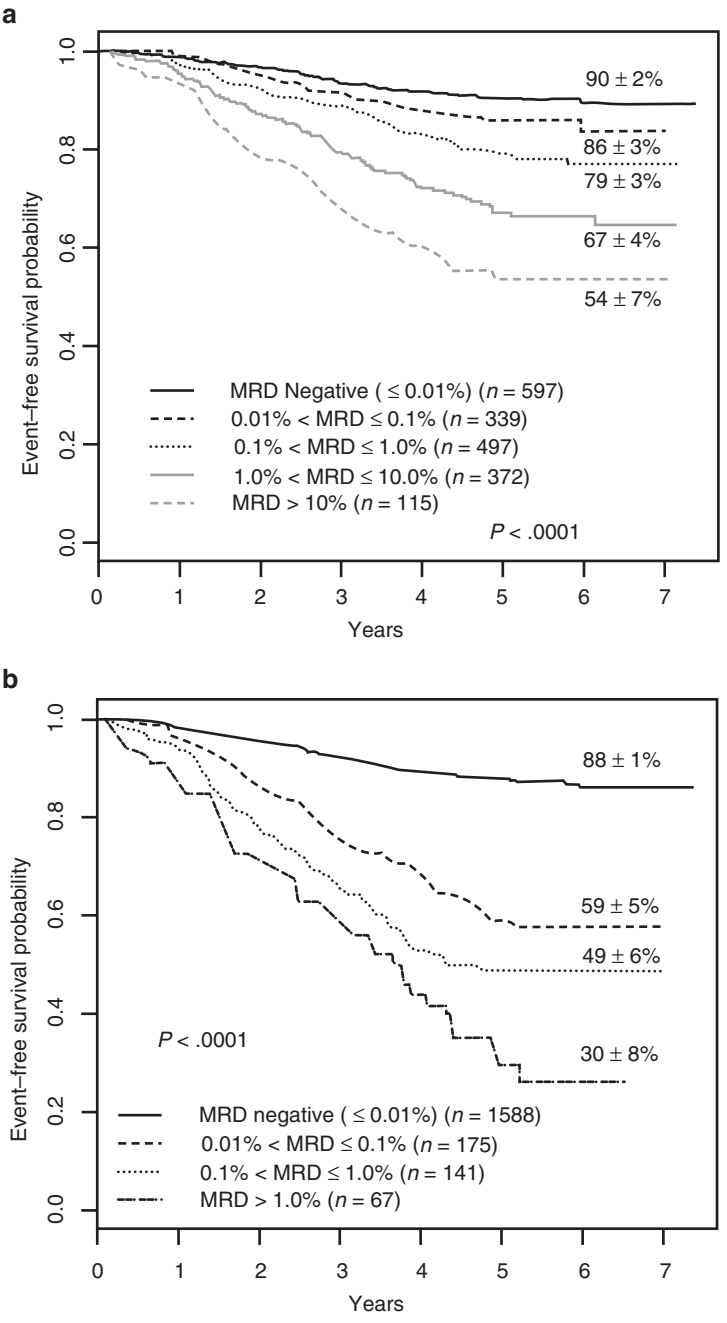

Fig. 17.1 The prognostic importance of minimal residual disease (MRD) after induction chemotherapy for ALL. From Borowitz M J et al. Blood 2008;111:5477-5485. Panel (**a**): EFS of ALL patients as a function of level of day-8 PB MRD. Panel (**b**): EFS of ALL patients as a function of level of day-29 marrow MRD

trials have considered more aggressive treatments, including Ara-C, high-dose methotrexate, or L-asparaginase and have shown selected benefits (Schrappe et al. 2000a). Some cooperative groups have showed that a delayed intensification regimen after a period of maintenance therapy leads to improved outcomes in high-risk patients (Schorin et al. 1994). A recent multinational European trial, however, showed that further strengthening of delayed intensification regimens based on risk factors did not lead to improved outcomes at 5 years (Stary et al. 2014).

Recent examples of attempts to intensify post-induction chemotherapy include a 2013 trial of 111 high-risk patients who received three new chemotherapy blocks and then received allogeneic transplantation or further chemotherapy (Marshall et al. 2013).

Maintenance therapy for 2–3 years is given to nearly all patients without mature B-cell disease and is typically weekly methotrexate and daily oral 6-mercaptopurine, with pulses of vincristine and dexamethasone, and intermittent intrathecal methotrexate as well. Some protocols also include repeat induction 4 months into continuation therapy. In general, males require longer maintenance therapy than females for reasons that are unclear.

Consideration for allogeneic stem cell transplant is taken especially with minimal residual disease or when high-risk features, such as BCR-ABL, are present. The recently published BFM prospective study of allogeneic stem cell transplant in high-risk children after achievement of remission showed those receiving grafts from HLA identical siblings had similar relapse rates and mortality but faster engraftment rates and fewer acute side effects than those receiving transplantation from HLA-matched unrelated donors (Peters et al. 2015). Total body irradiation along with cyclophosphamide is a frequent conditioning regimen prior to allogeneic transplantation.

Relapsed ALL is generally treated with a second induction chemotherapy regimen consisting of a combination including vincristine, prednisone, L-asparaginase, an anthracycline with or without MTX, VP-16 or teniposide, and cytarabine. Intrathecal chemotherapy is also given along with radiotherapy if there is evidence of CNS disease upon relapse. CNS relapse even if initially isolated is treated with systemic and intrathecal therapy with the addition of CNS radiotherapy directed at the brain and selectively at the spine as well.

Second remission is expected in 70–90% of patients, and treatment for second relapse typically then involves either allogeneic transplantation or consolidative chemotherapy. Testicular relapses are now rare with improved systemic treatments and testicular irradiation is typically only indicated in cases of testicular relapse.

17.6.2 Role of RT: Initial Therapy

Combined treatment regimens first developed in the 1960s showed effectiveness of prophylactic cranial-spinal irradiation to reduce CNS relapse (Dahl et al. 1978). The earliest St. Jude Children Research Hospital (SJCRH) trials, Total V, VI, and VII, all incorporated either prophylactic craniospinal irradiation or cranial irradiation and

lead to observation of reduced CNS relapse rates. For instance, CSI to a dose of 24 Gy in 15 fractions reduced isolated CNS relapse from 48–64% in SJCRH IV to 8% (Simone 1981). Similarly, the CNS relapse rate decreased from 67 to 4% in SJCRH studies V and VI, which utilized CSI to a dose of 24 Gy in 15–16 fractions (Aur et al. 1973). Total VI trial randomized pediatric patients after hematologic remission to CSI or salvage treatment after CNS relapse and noticed that 24 Gy CSI lead to increased event-free survival. SJCRH trial VII was the first to include intrathecal methotrexate and to directly compare craniospinal irradiation to cranial radiation only; the CNS relapse were comparable, approximately 8% (Simone 1981).

SJCRH study VIII patients received 24 Gy plus IT MTX, and then received either weekly IV MTX, oral MTX, 6-MP, or oral MTX, 6-MP, and cyclophosphamide, or everything plus Ara-C. The CNS relapse rates were 1.5–20% but 55% of patient in the weekly IV MTX and cranial radiation group developed leukoencephalopathy. Therefore, oral MTX and 6-MP after cranial irradiation along with IT MTX became the standard regimen. Furthermore, it is now accepted that intravenous MTX and cranial irradiation should not be given in close temporal proximity given concern for leukoencephalopathy (Aur et al. 1973).

The long-term side effects of prophylactic cranial RT in pediatric patients led to increasing attempt to use intrathecal chemotherapy and/or intermediate or high-dose IV MTX to replace cranial RT. Disease control in all but highest risk subsets have been comparable.

Several trials comparing cranial RT versus high-dose MTX along with IT chemotherapy have shown that patients with low- or standard-risk ALL without cranial radiation can have a CNS relapse rate roughly around 5% or less if IT MTX is used (Conter et al. 1997; Mahoney et al. 1998). A large meta-analysis in 2003 of 65 randomized trials of pediatric ALL patients showed that intrathecal MTX lead to comparable outcomes as cranial radiotherapy (Clarke et al. 2003). Furthermore, this meta-analysis saw that addition of intravenous MTX improved 10-year event-free survival from 62 to 68% and decreased rates of systemic relapse.

Dose reduction studies of cranial irradiation at 18 Gy have generally shown and equivalent outcome compared to 24 Gy (Nesbit et al. 1981). The CCSG trial 101 from the 1970s (when less intensive therapy for ALL unguided by modern prognostic factor tailoring of therapy) helped to further define volume of radiotherapy for CNS treatment. This large randomized trial showed that 24 Gy CSI with or without supplemental 12 Gy to liver, spleen, kidneys, or gonads for 12 Gy was not superior to 24 Gy cranial RT with intrathecal therapy although IT chemo alone was inferior to any CNS irradiation volume (Nesbit et al. 1982). German BFM studies have focused on optimizing cranial irradiation dose with high-dose methotrexate, including doses 0–12 or 18 Gy (Buhrer et al. 1990; Schrappe et al. 2000b). The St. Jude group has been very concerned about late effects of cranial RT in ALL patients such that their latest trials have completely removed all upfront use of PCI even for high-risk patients (Pui et al. 2009).

More modern trials have demonstrated that standard-risk ALL may be treated without prophylactic cranial irradiation. The risk factors that appear to benefit the most from cranial irradiation are T-cell ALL patients, WBC on presentation >100K

(Conter et al. 1997). Some Pediatric Oncology Group (POG) trials have treated T-cell ALL patients with poorer risk features on protocols without prophylactic cranial radiation; there was adverse CNS relapse rates, with the 3-year CNS relapse rate of 18% without cranial radiation compared to 7% with cranial radiation (Laver et al. 2000).

In the minority of patients who present with detectable CNS leukemic involvement, these patients are managed as high-risk patients and are treated with cranial radiotherapy. The historical use of cranial-spinal irradiation used a cranial dose of 24 Gy and spinal dose of 6–15 Gy. However, CSI has been generally replaced by cranial radiation with high-dose intravenous chemotherapy thought to have good brain penetration (Cherlow et al. 1996). The survival rates for patients with detectable CNS disease at presentation have improved over the decades to as high as a 5-year survival rate of 70%. Doses of cranial radiation now range typically from 18 to 24 Gy. One interesting approach to dosing was the ALL-BFM 90 trial which used age-based doses for patients with CNS-3 disease: no RT for those <1 year old age, 18 Gy for 1–2 years, and 24 Gy for older than 2 years (Schrappe et al. 2000b). Modern cooperative group trials including within the Children's Oncology Group (COG) that use a BFM-type systemic therapy generally employ 18 Gy for patients with CNS3 disease.

There have been several trials with small numbers of patients evaluating the deletion of cranial RT in CNS3 disease. The Dutch Childhood Oncology Group (DCOG) and the European Organization for Research and Treatment of Cancer (EORTC) have omitted cranial radiation by also using more high-dose methotrexate during post-induction consolidation and by an increased frequency of intrathecal chemotherapy. The SJCRH study also included higher cumulative doses of anthracycline than on COG trials, and frequent vincristine/dexamethasone pulses and intensified dosing of L-asparaginase, while the EORTC trials included multiple doses of high-dose Ara-C, during post-induction treatment phases for CNS3 patients. On the DCOG-9 trial, CNS3 patients treated without cranial radiation had a 5-year EFS of 67%. On the EORTC trial, the 8-year EFS of CNS3 patients treated without cranial radiation was 68%. The cumulative incidence of isolated CNS relapse for those patients was 9.4%. This CNS3 subgroup is relatively uncommon and further studies will be required to see if CNS irradiation can be safely eliminated contrary to current standard of care (Sirvent et al. 2011; Veerman et al. 2009; Pui et al. 2009). Arguably, CNS3 patients treated without cranial irradiation have inferior results and RT should not be deleted.

Additional considerations are cranial or cranial-spinal boost for patients undergoing TBI typically in preparation for bone marrow transplantation. A recent Stanford retrospective study found that pediatric patients undergoing TBI for stem cell transplant also tolerated sequential CSI to bring the cumulative cranial median dose of 24 Gy without significant long-term cognitive deficits (Hiniker et al. 2014).

Patients with T-cell ALL with few exceptions are considered at high risk, including risk for CNS relapse. As such, most modern ALL treatment schemes for T-cell ALL include cranial irradiation. An analysis of T-cell ALL patients treated within several Pediatric Oncology Group (POG) protocols suggested that omitting cranial

radiation had an adverse impact on CNS relapse rates. Specifically, the 3-year CNS relapse rate was 18% for those who did not receive RT compared to 7% who did (Laver et al. 2000). But in a subgroup of favorable T-cell ALL patients defined as those with young age and low WBC at initial presentation, it may be safe to omit cranial radiation (Conter et al. 1997). Most T-cell ALL patients present with high WBC counts, however. A retrospective comparison of the AIEOP-91 trial with the BFM-90 trial in which similar backbone chemotherapy was used for T-cell ALL, differed principally in the use of cranial RT. The AIEOP-91 trial omitted cranial RT albeit with more IT chemotherapy, leading to a significantly higher CNS relapse along with a 3-year event-free survival of 62% compared to 88% for the BFM-90 patients who received cranial RT. Multivariate analysis showed that WBC >100,000 in particular defined a group of T-cell ALL patients who should receive cranial RT (Conter et al. 1997).

17.6.3 Role of RT: Relapsed ALL

In decades past, CNS relapse was thought to have a poor prognosis with disease control in the 25–50% range (Kun et al. 1984). More recent trials that utilize more intensive chemotherapy as well as RT to the CNS have reported ALL 5-year survivals of 50–70% (Kumar et al. 1995; Kun et al. 1984; Ribeiro et al. 1995; Ritchey et al. 1999). There is an ongoing debate between cranial RT alone and CSI. Doses used have generally been approximately 18–24 Gy to the brain and 10–15 Gy to the spine. Most nonrandomized comparisons suggest superior outcomes with CSI. One small phase III trial did show superiority for CSI compared to cranial RT (Land et al. 1985).

Several prognostic factors have been found to be of importance in the setting of CNS relapse (Bleyer et al. 1986). Patients who were originally deemed at diagnosis to be at low risk for CNS relapse by virtue of a low initial leukocyte count (<20,000/μL), who originally did not receive cranial irradiation, or whose CNS relapse occurred at a relatively long period after the original diagnosis have a better prognosis after CNS recurrence. An isolated CNS relapse has generally been more favorable compared to combined CNS and systemic relapse. After completing chemotherapy, those children with CNS relapse have better outcomes with longer disease-free intervals. Within the Pediatric Oncology Group (POG), RT for isolated CNS relapse of ALL used a cranial dose of 24 Gy and a spine dose of 15 Gy. The 4-year event-free survival was 71%. Those patients who presented with greater than an 18-month disease-free interval prior to CNS relapse had a 4-year event-free survival of 83% compared to 46% for those with shorter initial remission durations (Ritchey et al. 1999). This led subsequent POG trials to omit RT to the spine if there is a long disease-free interval. Whether the omission of spinal RT in this favorable subgroup is detrimental is unclear. However, high-dose Ara-C has generally been added to the management of CNS relapse of ALL. One report using high-dose Ara-C reported a favorable 63% complete response rate (Morra et al. 1993). These concepts have been maintained within current COG trials for CNS relapse of ALL;

but with intensification of systemic therapy, spinal RT has been proposed to be dropped even for short disease-free intervals, while the brain is treated to 18 Gy.

17.6.4 Role of RT: AML

The role of CNS prophylaxis is not well defined for AML, particularly because CNS relapse rates are relatively infrequent (at roughly 5–10%) for this uncommon pediatric leukemia. The German-based BFM group has studied the role of prophylactic RT in combination of increased intense induction therapy with anthracycline an intrathecal Ara-C. The AML-BFM-87 study found that PCI decreased risk of CNS and bone marrow relapse. Five-year disease-free survival for patients who received cranial RT was 69% compared to 46% those not receiving RT Response to 12 Gy appeared to be similar to 18 Gy (Creutzig et al. 1993).

Other studies, however, show no clear difference in relapse rates with cranial radiation. Nevertheless, many pediatric regimens employ IT drugs such as Ara-C. Patients with a high WBC count at diagnosis or monocytic variants of AML are believed to have a higher risk for CNS relapse, which may justify both IT chemotherapy and cranial radiation in this setting. Moreover, additional follow-up of the AML-BFM-87 along with additional patient numbers showed a reduced risk for both marrow and CNS relapses when cranial RT was followed intensive induction therapy emphasizing anthracycline chemotherapy and intrathecal Ara-C chemotherapy. In a nonrandomized analysis, current data suggest that 12 Gy results in the same relapse rate as 18 Gy (Creutzig et al. 2013).

Chloromas (or myeloid/granulocytic sarcomas) are solid masses of leukemic cells that can appear in a variety of extramedullary sites, including epidural space, meninges, and extracranial site such as skin, soft tissue, and GI tract. Doses in the range of 10–20 Gy are effective although planning should take into account the possibility of future TBI.

17.7 Target Delineation

17.7.1 RT Volumes

Whole brain radiotherapy requires full coverage of the intrathecal subarachnoid space, and particular care should be taken to include the cribriform plates. The posterior globes are generally covered due to risk of relapse in the subarachnoid extension along the optic nerves. Inferior margins are typically the bottom of the first or second cervical vertebra and should include the entire vertebral body, ensuring coverage of the obex of the fourth ventricle. This may also be particularly important to help matching with any future spinal treatments. Anterior eye blocks should not be so generous to prevent irradiation of the cribriform plate and the middle cranial fossa. In all other field borders, blocks may flash over the scalp. A theoretical reason why the spine RT need not be treated in conjunction with intrathecal chemotherapy

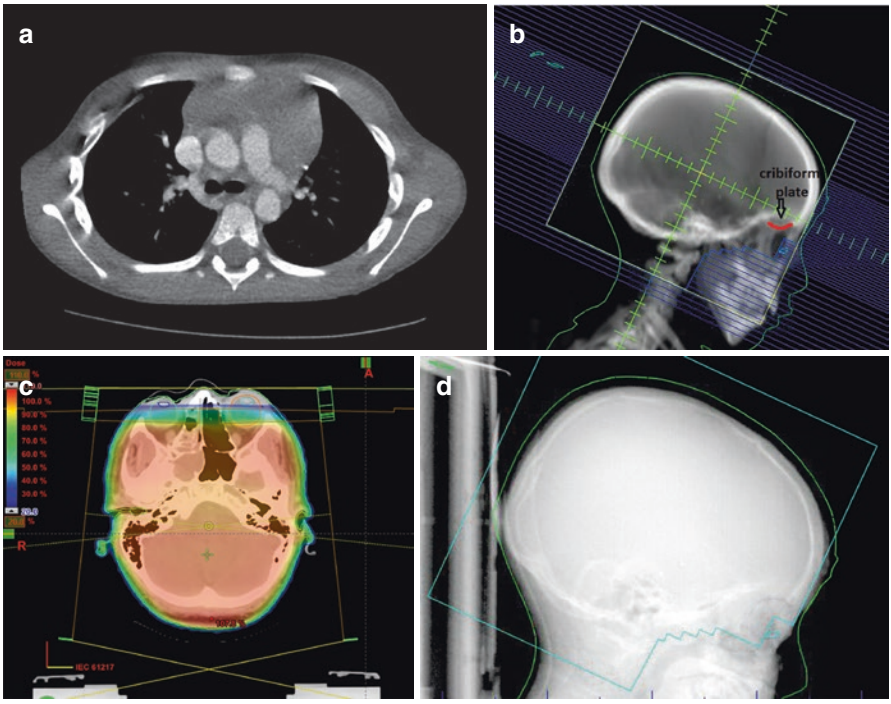

Fig. 17.2 Example of cranial RT fields for leukemia. A 6-year-old male presented with a petechial rash from thrombocytopenia along with anemia and a white blood cell count of 115,000. Chest CT scan showed an 8 cm mediastinal mass. Peripheral smear and flow cytometry showed a T-cell acute lymphoblastic leukemia. Lumbar puncture did not show any evidence of lymphoblasts though there were a few mononuclear cells. After being placed into complete remission with induction chemotherapy, the patient received cranial RT to 12 Gy in 8 fractions during consolidation phase of therapy. Standard lateral fields to the whole brain through C2 was set up with blocking and gantry angles to align the divergence of the anterior edge of the fields, so as to reduce dose to the anterior eye and lenses. There was attention in the field design to cover the cribriform plate and posterior eye. Three years later, the patient remains in remission as he is finishing up maintenance therapy. Panel (**a**) shows the presenting chest CT. Panel (**b**) is the digitally reconstructed radiograph with multileaf collimation of field edge blocking the face and anterior eye. The cribriform plate is outlined. Panel (**c**) shows the dosimetry at the level of the eye. Panel (**d**) is a port film of the patient's first fraction of radiotherapy

is the poor circulation of intrathecal drugs within the ventricles and sulci of the brain relative to the subarachnoid space in the spine (Rieselbach et al. 1962; Shapiro et al. 1975). See Fig. 17.2 demonstrating cranial RT fields used for leukemia.

Special considerations include craniospinal irradiation for overt CNS leukemic involvement or cranial boost in patients receiving TBI. Craniospinal irradiation is now rarely used in pediatric ALL cases given the evolution of intrathecal and systemic chemotherapy, as noted above, but remains justified in certain high-risk situations. The spinal field matching with cranial irradiation can be constructed by matching PA spine field divergence with opposed cranial fields, using collimator

rotation of cranial fields and couch kick of the PA spinal field. The field junction can be shifted 1–2 cm once twice to avoid dose overlap in the cervical spine. Inferiorly, the spinal field must cover the full extent of the thecal sac, which can vary greatly between L5 and S3 areas but can be visualized on MRI; there is no need to cover the sacroiliac joints. The use of specialized RT techniques such as tomotherapy or proton RT to reduce normal tissue exposures are a consideration. But, the relatively low doses of radiation for leukemia management along with resource allocation and cost considerations dictate that conventional megavoltage RT remains a standard of care currently.

Boosting to sites of relatively high risk for recurrence during total body irradiation (TBI) can be an option at the time of transplant. Additional doses to the brain in patients with ALL can be as high as 14–18 Gy. The cranial boost in these cases typically utilized opposing lateral fields. Similarly, testicular boost in males to a total dose of 16–18 Gy with en face electrons or orthovoltage X-rays can be considered.

17.7.2 Dose

The historic cranial radiation dose of 24 Gy is rarely used; dose reduction to 18 Gy, typically in 1.8–2 Gy fractions has reduced observed cognitive effects of RT. Dose de-escalation to 12 Gy, given in 1.5 Gy fractions, has become the new standard with BFM-type ALL systemic therapy. Energies greater than 6 MV should not be used given potential for under dosing the superficial meninges.

17.7.3 Techniques

Immobilization with head mask made from thermoplastic material such as Aquaplast is sufficient to ensure positional reproducibility. Reducing or preventing dose to the lenses especially given posterior globe coverage can be challenging. Downward rotation of the eyes also can reduce lens dose by theoretically move the lens outside of dose-build up region. Matching divergence of anterior fields with a slight gantry rotation can also help reduce excess dose to the anterior globe. Alternatively, the isocenter can be set immediately posterior to the lens, with the anterior portion modified by a half-beam block.

17.8 Outcomes

17.8.1 Follow-Up Guidelines

The first year after consolidation or maintenance therapy, patients are expected to have regular CBC with differential, as frequently as every 2 months. Patients with

CNS disease will need surveillance CSF studies as well. Testicular exam on follow-up physical exams are important to detect testicular relapse.

17.8.2 Cure and Survival

Overall ALL survival has been demonstrated to be in the 80–90% range. Low-risk patients have disease-free survival over 80%, with high-risk disease with disease-free survival in the 70–80% range. SJCRH Total trial XIIIB using modern treatment regimens reported a 5-year event-free survival of 81% and a 5-year CNS relapse risk of 3%, with 1.7% isolated CNS relapse risk (Pui et al. 2004).

17.8.3 Toxicities

17.8.3.1 Secondary Malignancies

Cranial irradiation is associated with low risk of secondary malignancy. Notably, the most common neoplasms include low-grade malignancies such as basal cell carcinomas and meningiomas, which also tend to become more prevalent with extended time beyond radiotherapy. Other secondary cancers include gliomas, thyroid cancers, sarcomas, and parotid gland neoplasms (Hijiya et al. 2007).

A 2007 review of over 2000 patients treated at SJCRH revealed the overall incidence of secondary malignancies to be 4.2% at 15 years and 10.9% at 30 years. Brain tumors in this study were divided equally between meningiomas and high-grade gliomas (Hijiya et al. 2007). A 1991 CCSG report of secondary cancers in nearly 10,000 pediatric ALL revealed 43 secondary malignancies at an average of 6 years of follow-up (Neglia et al. 1991). All but one of these patients were younger than age of 5 at time of ALL diagnosis, suggesting that younger patients may be more susceptible. Twenty-four of the 43 patients received 24 Gy cranial RT. The ALL-BFM 90 trial of over 2100 pediatric ALL patients showed that incidence of secondary brain tumor was 3.4% at an average of 16 years follow-up (Moricke et al. 2008). The risk of meningioma at 20 years was estimated to be 15%; these often are asymptomatic but are found on screening MRI and can be found to be multi-focal as well (Goshen et al. 2007).

17.8.3.2 Hypopituitarism

Long-term pituitary dysfunction can result in a dose-dependent fashion and pediatric patients following cranial RT, and patients need regular clinical follow-up that includes endocrine evaluation.

Growth hormone deficiency is most common, and younger patients appear to be more susceptible to growth hormone deficiency and may develop deficiency earlier (Birkebaek et al. 1998). There is empirical evidence that the incidence of growth

retardation is higher for 24 Gy compared to 18 Gy (Stubberfield et al. 1995). One study estimates between 20 and 25% of pediatric ALL survivors who had cranial RT for their initial disease will go on to have some level of growth hormone deficiency (Steffens et al. 2008).

17.8.3.3 Cognitive Dysfunction

A subject of great study and controversy has been the cognitive sequelae of pediatric ALL patients after cranial radiotherapy and/or chemotherapy. Indeed, the concern for intellectual impairment has led researches to attempt to lower or eliminate cranial RT.

The pathophysiology of long-term cognitive dysfunction is thought to be secondary to white matter damage leading to decreased information processing speed. Patients under the age of 5, particularly younger than 3 years old are thought to be most susceptible given the growth of brain, especially with myelination (Jankovic et al. 1994). Long-term follow-up of 202 pediatric ALL patients in the CALGB 7611 study of those who received intrathecal methotrexate with either cranial radiation or systemic methotrexate did reveal poorer academic achievement and poorer self-image (Hill et al. 1998).

However, another prospective study of ALL survivors showed no difference in cognitive side effects between patients with children who received 18, 24 Gy, or IT MTX along with parenteral MTX (Mulhern et al. 1991). This study did reveal a decrease in IQ across all study groups and also suggested that female patients may be more susceptible.

Another Dana Farber retrospective analysis of long-term cognitive side effects of 66 pediatric ALL who underwent IV MTX with or without CRT also showed that the reduction in IQ was possibly the result of the combination of high-dose MTX with cranial radiation (Waber et al. 1995).

Nevertheless, the contribution of chemotherapy to long-term cognitive deficits has also been considered. The aforementioned Dana Farber study showed that verbal memory impairment was independent of cranial radiation in all patients, suggesting chemotherapy played a role in cognitive changes (Waber et al. 1995). In this study, CRT by itself was not independently predictive of poorer cognitive outcomes.

Dose reduction trials have also had associated analysis of effect of dose reduction on long-term neurocognitive side effects. So far there has been inconsistent evidence whether 18 Gy results correlate with less cognitive deficits than 24 Gy. One study of 35 pediatric ALL patients observed that those who received 24 Gy had an average IQ that was 12 points lower than 18 Gy patients after an average of over 10 years (Halberg et al. 1992). However, patients in this study also were treated with varying chemotherapy regimens, which may serve as confounders.

Other studies have showed that cranial radiation for ALL does not lead to significantly different IQs compared to those who receive high-dose methotrexate

(Halsey et al. 2011). Interestingly, a 2001 Dana Farber group study showed that high-risk ALL patients after 18 Gy did not have significant higher risk of neurocognitive deficit than general population (Waber et al. 2001).

The Dana Farber group is currently studying hyperfractionated cranial radiation on a schedule of 0.9 Gy twice daily to a total of 18 Gy. So far, hyperfractionation has not led to a significantly different neurotoxicity rate (Waber et al. 2007).

17.8.3.4 Leukoencephalopathy

Debilitating leukoencephalopathy has been observed in a minority of pediatric ALL patients (Bleyer 1981). The pathophysiology of leukoencephalopathy is thought to be endothelial damage leading to cytokine release that eventually cause microinfarction and demyelination (Hong et al. 1995). Increased permeability of blood–brain barrier after radiotherapy has been theorized as one mechanism for increased neurotoxicity of systemic chemotherapies after radiotherapy (Griffin et al. 1977). The most important risk factor for leukoencephalopathy appears to be concurrent methotrexate and cranial methotrexate. However, both high-dose chemotherapy and radiation doses higher than 30 Gy are thought to be associated with dementia-like syndromes (Keime-Guibert et al. 1998). Overall, it is thought that for doses of cranial radiotherapy below 20 Gy the risk of leukoencephalopathy is low.

17.8.3.5 Somnolence Syndrome

Somnolence syndrome is characterized by a collection of symptoms including prolonged sleep, lethargy, anorexia, nausea, headaches, irritability, and sometimes low-grade fever (Freeman et al. 1973). It is reportedly found in as high as 50–80% of pediatric ALL patients often 4–6 weeks after cranial radiation and typically self resolves within 2 weeks (Mandell et al. 1989). The pathophysiology is theorized to resemble leukoencephalopathy with either increased disruption of microvasculature or myelin dysfunction after irradiation (Littman et al. 1984). Low-grade fever is among the possible symptoms although high-grade fever would require infectious workup given many patients after chemotherapy in this time range have some level of immunodeficiency. Some studies have suggested that glucocorticoid use during cranial radiotherapy can reduce the incidence of somnolence syndrome (Mandell et al. 1989; Uzal et al. 1998).

17.9 Future Directions

Some groups have continued attempts to eliminate cranial radiation. For instance, a recent St. Jude Children's Research Hospital trial eliminated prophylactic cranial radiation even in high-risk patients (Pui et al. 2009). Further delineating of subtypes, including those based on specific genetic changes, will further help guide treatments.

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Spinal Tumors

18

Natia Esiashvili, Ronica Nanda, Mohammad Khan, and Bree Eaton

Contents

Abstract

Spinal cord tumors are very rare in children. They present unique clinical challenges, and their treatment should be individualized based on the histologic type. The use of postoperative irradiation for spinal cord tumors has been controversial, and largely inconsistent. Radical surgery is the aim for low-grade astrocytic

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tumors and ependymomas. The need for adjuvant therapy most often depends on the extent of resection as well as the tumor type. While the role of postoperative radiotherapy in high-grade spinal cord tumors is widely accepted, its role in low-grade intramedullary tumors is debatable. Patients with disseminated low-grade glial tumors and ependymomas of the spinal cord may achieve long-term progression-free survival with craniospinal irradiation. The potential role of chemotherapy in the management of spinal cord astrocytoma remains to be defined.

18.1 Epidemiology

Primary spinal cord neoplasms constitute about 5% of central nervous system (CNS) tumors in children, and are usually intradural in origin. They need to be distinguished from extradural tumors (neuroblastoma, peripheral PNET, etc.), which are outside the scope of this chapter. Thirty-five percent of pediatric spinal tumors are intramedullary, higher than the 20% cited for adults (Constantini et al. 1996). The cervical spinal cord is affected slightly more frequently than the thoracic. The average lesion spans multiple segments (Reimer and Onofrio 1985) and can also result in holocord tumors as well (Epstein and Epstein 1981).

The median age at diagnosis of intramedullary spinal cord tumors (IMSCT) in children is around 10 years, with a slight male predominance (DeSousa et al. 1979, Reimer and Onofrio 1985, Zileli et al. 1996, Goh et al. 1997). Astrocytic tumors account for nearly 60% of primary spinal cord tumors in children; of which, low-grade astrocytomas, such as fibrillary or pilocytic astrocytomas (PA), constitute more than two-thirds of the cases. There are a handful of very rare cases of oligodendroglia-like and neuroepithelial tumors of spinal cord, presenting as disseminated tumors (Schniederjan et al. 2013). Another rare entity is a gliofibroma of spinal cord, which also has a propensity for leptomeningeal spread (Prayson 2013). High-grade neoplasms, including anaplastic astrocytoma and glioblastoma, represent less than 20% of the cases, are more commonly diagnosed at younger ages, and have a high propensity for leptomeningeal dissemination (Hardison et al. 1987, Cohen et al. 1989). Ependymoma is the second most common pediatric spinal cord neoplasm, yet it represents less than 5% of all ependymomas diagnosed in children. Other gliomas, like ganglioglioma and oligodendroglioma, comprise less than 10% of spinal cord tumors.

18.2 Predisposing Factors

18.2.1 Etiology

Histologically, primary spinal cord tumors are mostly indistinguishable from their brain counterparts, and likely share a common etiology. With regard to environmental risk factors, ionizing radiation has been most commonly linked with CNS tumors,

but data on its association with primary spinal cord tumors is sparse. There is no evidence of any association between chemical environmental exposures and spinal cord tumors.

18.2.2 Genetic Issues

As with brain tumors, only a very small proportion of newly diagnosed spinal cord tumors can be linked with genetic syndromes. Patients with neurofibromatosis type 1 (NF-1) have a higher incidence of developing both low- and high-grade astrocytomas in the spinal cord. Neurofibromatosis type 2 can be associated with meningiomas within the spine, as well as with intramedullary gliomas and ependymomas. Hemangioblastoma's association with von Hippel–Lindau syndrome sometimes can be manifested in the spinal cord, particularly with multifocal presentation. Of note, patients with retinoblastoma, NF-1, Li–Fraumeni syndrome, or nevoid basal cell carcinoma syndrome are at substantial risk for developing radiation-related cancers, and can be diagnosed with primary spinal tumors within the radiation field.

18.3 Presenting Symptoms

Most patients present with insidious symptoms, evolving over several months or even years (Innocenzi et al. 1996; Rossitch et al. 1990). The short duration of presenting symptoms is associated with aggressive high-grade neoplasms and poor survival (Bouffet et al. 1998). Pain is the most frequent presenting symptom, and complaints of worsened pain at night may result from venous congestion and dural tube distention caused by the recumbent position. The pain may or may not be localized to the level of the lesion; however, search for local tenderness of the spine is still important during a physical examination. The most common localizing symptoms and signs are hemiparesis, hemisensory loss, and hyperreflexia which will often correspond to the level of involved lesion (Houten and Weiner 2000). Although rare, dissemination of disease may cause neurologic dysfunction, which can make localization of tumor more challenging. Upper motor neuron signs are usually evident at presentation, and include mild spasticity and increased deep tendon reflexes. Since these tumors are usually located in the central portion of the spinal cord, cervical tumors can produce weakness and muscle wasting in the upper extremities, prior to the development of lower extremities' sensory disturbances such as dysesthesias. Dorsal column dysfunction is less common because of the central location of these masses. A partial Horner syndrome (ipsilateral ptosis, miosis, and anhidrosis) may also be present in some patients with upper cervical cord disease as a result of compromise of the descending sympathetic tracts. Torticollis commonly appears in tumors of the cervical spine prior to the development of objective neurological dysfunction. Spinal cord and cauda equina involvement may cause bowel or bladder dysfunction. Kyphoscoliosis may be seen in tumors of the thoracic spine. Hydrocephalus can be associated with intramedullary spinal cord tumors and can occur with greater frequency in pediatric than adult patients (Rifkinson-Mann et al. 1990).

18.4 Radiographic Findings

Spinal tumors should be imaged preoperatively; however when this cannot be accomplished, it is recommended to perform a baseline imaging examination at approximately 3 weeks in the postoperative period to avoid difficulty with interpretation of findings caused by postsurgical subdural blood. MRI has a significant advantage as an imaging modality for visualization of anatomical details of spinal cord tumors. It can help to readily distinguish intramedullary from extramedullary lesions and to appreciate the full extent of the tumor. Typically, sagittal T1 images of the entire spine with gadolinium are obtained with axial T1 images obtained as needed. Tumors such as pilocytic astrocytoma, high-grade gliomas, and ependymomas are typically contrast enhancing lesions (Fig. 18.1). T2 sequences can better delineate nonenhancing tumors, like fibrillary astrocytomas and gangliogliomas; however, high-grade lesions sometimes do not enhance after contrast administration (Fig. 18.2). Intramedullary astrocytomas and hemangioblastomas are sometimes associated with multiple cysts or larger confluent rostral and/or caudal cysts, which typically are lined with nonneoplastic, gliotic tissue.

In evaluating spinal cord tumors, it is important to image the entire length of the spinal canal. It is important not to miss rare, but clinically important "skip" lesions

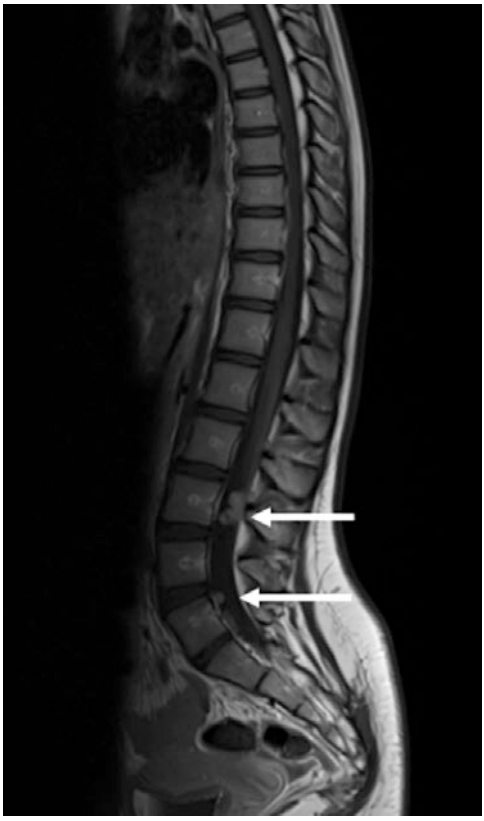

Fig. 18.1 Fifteen-year-old girl with known diagnosis of neurofibromatosis type I was incidentally found to have lesions in distal thecal sac during surveillance imaging (sagittal T1 sequence post-gadolinium administration demonstrated several enhancing masses (*arrows*)). Pathology after resection was consistent with grade II ependymoma

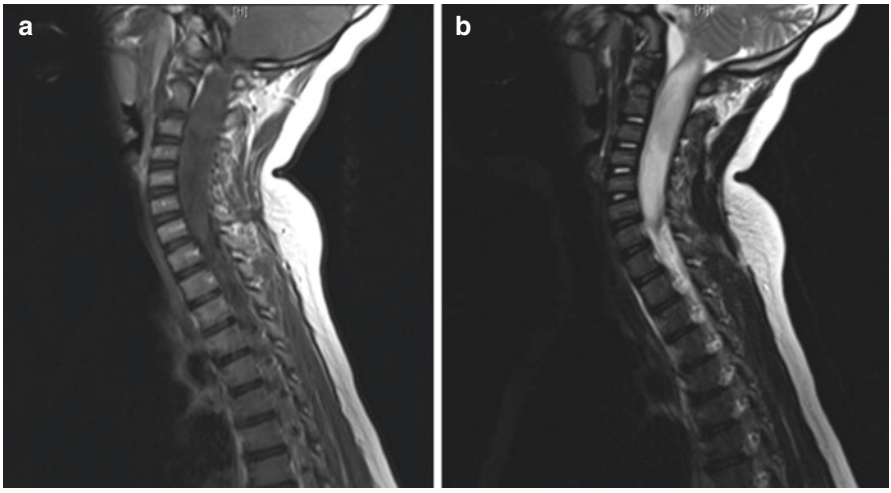

Fig. 18.2 Expansile cervical cord lesion in a 7-year-old child, nonenhancing on T1 post-contrast sagittal image (**a**) and hyperintense on T2 sagittal sequence (**b**), pathology from biopsy was consistent with anaplastic astrocytoma

sometimes seen in astrocytomas and ependymomas, and/or subarachnoid dissemination, more commonly found in malignant gliomas and ependymomas (Hardison et al. 1987; Cohen et al. 1989). Brain imaging should be performed in multifocal and disseminated cases, as there is a risk of rostral disease spread. The presence of multiple discrete tumors, along with other stigmata, is commonly associated with neurofibromatosis.

18.5 Workup

Medical history should focus on details of presenting symptoms including duration. Long-standing symptoms are more indicative of low-grade tumors while rapidly evolving ones raise concern for a more aggressive neoplasm. Additional history, including pre-existing genetic conditions and history of ionizing radiation exposure, cannot be overlooked. Inheritable genetic syndromes should be recognized in the family history. Attention during the physical examination should be directed to both upper and lower motor neuron signs, as well as sensory function. The constellation of neurological signs, such as Brown-Séquard syndrome, can help to localize the lesion. Imaging evaluation gives the best delineation of tumor process, and should include the entire neuraxis. As discussed above, MRI has become a gold standard in imaging of spinal tumors and should be considered first, when available. Cerebrospinal fluid (CSF) examination for protein levels, cytology, and infectious cultures, among other factors, can help diagnostic workup, particularly when nonneoplastic processes are still considered in diagnosis. Cytological detection of tumor cells can confirm the presence of disseminated tumor and can be complementary to spinal imaging. Ultimately, biopsy or resection, when feasible, can establish the most accurate diagnosis.

18.6 Acute Management

Spinal cord tumors commonly grow contiguously across the spinal cord and can result in significant mass effect on neurons and lead to a functional loss (Peschel et al. 1983; Reimer and Onofrio 1985; Hardison et al. 1987). Steroids are commonly prescribed to patients exhibiting symptoms from tumor mass effect, but laminectomy with or without tumor decompression is a very important intervention. Steroids should be administered carefully, as it could alter diagnosis in certain histologies such as lymphoma or other infectious agents.

18.7 Treatment

The benefit from postoperative radiotherapy in low-grade intramedullary spinal cord tumors is debatable. Data is limited to institutional case series, and there is no randomized study that has evaluated the use of postoperative radiotherapy (Nadkarni and Rekate 1999). While the extent of resection has more consistently been shown to be a significant prognostic factor in tumor control probability for low-grade lesions, tumor histology is the most important predictor of a patient's outcome (Whitaker et al. 1991, Innocenzi et al. 1996, Goh et al. 1997, Ahmed et al. 2014). A handful of studies demonstrated a trend toward improved tumor local control with the use of adjuvant radiotherapy when compared with surgical resection alone (Nadkarni and Rekate 1999, Guss et al. 2013). With regard to grade II ependymomas in children, radiotherapy is most commonly given after subtotal versus gross-total resection; this practice trend in North America has not significantly changed over the past three decades (Lin et al. 2014). There is also limited, but convincing evidence on radiation treatment achieving durable local control in patients without any surgical resection (O'Sullivan et al. 1994, Guss et al. 2013).

For high-grade spinal cord tumors, outcome overall remains dismal. Therapeutic advances in the management of high-grade gliomas of the spinal cord have been hampered by the rarity of incidence and the lack of uniform treatment. Despite the lack of evidence for improved outcome, trimodality approach including maximum safe resection, adjuvant radiotherapy and chemotherapy is commonly used (Merchant et al. 1999).

18.7.1 Role of Surgery

Surgical management plays a very important role in spinal cord tumors for establishing diagnosis while achieving maximum safe resection for improved local control. Laminectomy or laminoplasty, as appropriate, is typically performed to access the lesion. Extramedullary intradural tumors are more readily accessible and can be completely removed for diagnostic and treatment purposes (Jenkinson et al. 2006). When it comes to intramedullary lesions, intraoperative tumor resection is based on whether

a plane of dissection can be identified, which is often dependent on tumor histology. For instance, ependymomas commonly demonstrate a well-demarcated margin between tumor and spinal cord tissues, while astrocytomas can have infiltrative borders; however, for each histological type, there is considerable variability in the presence or absence of identifiable tumor planes (Garces-Ambrossi et al. 2009). The presence of identifiable tumor planes carries positive prognostic significance regardless of tumor type, suggesting that this may offer valuable prognostic information regarding biological aggressiveness and subsequent recurrence. Low-grade spinal cord astrocytomas, in spite of their infiltrative behavior, are amenable to radical surgical resection. Gross-total resection (GTR) has been associated with improved prognosis for low-grade intramedullary tumors such as ependymoma and hemangioblastoma (McCormick et al. 1990, Hanbali et al. 2002, Stephen et al. 2012, Karikari et al. 2015).

Gross tumor resection can significantly affect tumor control and survival for most types of spinal cord tumors, and should be attempted when deemed safe (Garces-Ambrossi et al. 2009). Typically, gross-total and near-total resection is reported in 6–46% of cases with a trend toward increased radical resection in more recent times (Reimer and Onofrio 1985, Allen et al. 1998, Garces-Ambrossi et al. 2009). Subtotal resection (STR) can be achieved in up to 50% of cases (Kutluk et al. 2015). Surgical complication rates are low in the hands of skilled neurosurgeons; however, preoperative functional status is a predictor of good postoperative function (Jenkinson et al. 2006). It has also been shown that significant intraoperative changes of somatosensory evoked potentials can predict postoperative deficit.

Modern surgical techniques with microscopy, intraoperative ultrasonography, and electrophysiological monitoring (sensory and/or motor evoked potentials) can greatly improve the probability to identify tumor margin and achieve total resection with less functional damage (Zentner 1991, Constantini et al. 1996, 2000, Hoshimaru et al. 1999, Houten and Weiner 2000). Intraoperative ultrasound can be used as a tool to demarcate tumor for resection. The use of electrophysiological monitoring has become common practice and can provide the surgeon with continuous intraoperative information about the integrity of the spinal tracts in order to facilitate an aggressive resection with minimal morbidity and to predict postoperative function. Somatosensory evoked potentials (SSEPs) monitor the function of the posterior columns, and its intraoperative monitoring can affect postoperative outcome (Kearse et al. 1993). Motor evoked potentials (MEPs) are a more recently developed technique using scalp and epidural electrodes to provide “real time” information about the integrity of the motor tracts.

18.7.2 Role of Chemotherapy

Experience using chemotherapy is limited. The rationale for using it is mainly based on extrapolation from similar tumors in the brain.

The standard treatment of spinal cord astrocytomas is surgery, followed by radiotherapy for incompletely resected or high-grade tumors. Owing to the major consequences of radiotherapy on the spine in childhood, alternative therapies have been

explored. The potential role of chemotherapy in the management of spinal cord astrocytoma remains to be defined. A small case series demonstrated benefit in both low- and high-grade tumors (Lowis et al. 1998). The Children's Cancer Group (CCG) 945 High-Grade Astrocytoma Committee devised a pilot study to collect natural history information and explore the benefit of an experimental multimodality treatment in children with newly diagnosed high-grade astrocytomas arising within the spinal cord (Allen et al. 1998). Patients were assigned in a nonrandom fashion to the experimental regimen of an 8-drugs-in-1 regimen consisting of vincristine 1.5 mg/m^2, lomustine 100 mg/m^2, procarbazine 75 mg/m^2, hydroxyurea 3000 mg/m^2, cisplatin 90 mg/m^2, mannitol 12 g/m^2, cytarabine 300 mg/m^2, dacarbazine 150 mg/m^2, and methylprednisolone 300 mg/m^2 for three doses (Allen et al. 1998). A centralized neuropathology review was used to confirm the diagnosis of high-grade astrocytoma in 13 of the 18 children: anaplastic astrocytoma (eight patients), glioblastoma multiforme (four patients), and mixed malignant glioma (one patient). Diagnoses were discordant in five patients. There were eight boys and five girls in the group with confirmed diagnoses, with a median age of 7 years (range 1–15 years). The extent of resection was confirmed by computerized tomography or magnetic resonance (MR) evaluation in five of 13 patients. There were six gross-total or near-total resections (>90%), four partial or subtotal resections (10–90%), and three biopsies. Six patients showed evidence of leptomeningeal metastases at diagnosis based on staging MR examinations. Eight of the 13 patients completed at least eight of the prescribed 10 cycles of chemotherapy; five received craniospinal radiotherapy and five had spinal radiotherapy. The 5-year progression-free and overall survival rates for the 13 children were 46 ± 14% and 54 ± 14%, respectively.

Eight children with unresectable or recurrent intramedullary glioma were treated on a French Society of Paediatric Oncology (BB SFOP) protocol of a 16-month chemotherapy regimen with carboplatin, procarbazine, vincristine, cyclophosphamide, etoposide, and cisplatin. Six children had progressive disease following incomplete surgery and two had a postoperative relapse. Three patients had leptomeningeal dissemination at the outset of chemotherapy. Seven of the eight children responded clinically and radiologically while one remained stable. At the end of the BB SFOP protocol, four children were in radiological complete remission. After a median follow-up of 3 years from the beginning of chemotherapy, all children but one (who died from another cause) are alive. Five patients remain progression-free, without radiotherapy, 59, 55, 40, 35, and 16 months after the beginning of chemotherapy. The efficacy of this chemotherapy in patients with intramedullary glial tumors calls for further trials in this setting, especially in young children and patients with metastases. While chemotherapy may delay the need to radiotherapy administration in low-grade glial tumors, most of the patients would need radiotherapy to achieve tumor control (Gajjar et al. 1995, Doireau et al. 1999, Merchant et al. 2000, Bian et al. 2013, Schniederjan et al. 2013). The role of chemotherapy in ependymoma, studied exclusively for intracranial tumors, has proven controversial due to mixed results (Evans et al. 1996, Timmermann et al. 2000, Garvin et al. 2012, Venkatramani et al. 2013, Strother et al. 2014); however, there is renewed interest in investigating its role for WHO grade II and III tumors.

18.7.3 Role of Radiation Therapy

The use of postoperative irradiation for spinal cord tumors has been controversial, and largely inconsistent. There may be an increased trend toward using upfront chemotherapy for low-grade spinal astrocytomas. Radiotherapy is commonly used for progression or recurrence. In some series, radiotherapy was shown to improved progression-free survival while others report no advantage (Bouffet et al. 1998, Ahmed et al. 2014).

For low-grade tumors, surgery and irradiation after incompletely resected spinal astrocytomas can result in survival rates of 50–60% at 5 years (Houten and Weiner 2000, Jenkinson et al. 2006, Ahmed et al. 2014). Although lacking conclusive data, a rational approach includes maximal surgical resection. For incompletely resected tumors, one can support observation for low-grade gliomas (pilocytic histology), especially in prepubertal children where the risk-to-benefit ratio may favor delaying radiation intervention. If one elects to observe a child with suspected or definite residual disease, it is important to commit to a later second surgery when feasible, as well as irradiation, unless the second surgery results in imaging-confirmed total resection, at the time of disease progression.

For spinal cord ependymomas, there is evidence supporting surgery alone for intramedullary tumors and for initial management of cauda equina tumors (McCormick et al. 1990). The indolent nature of myxopapillary tumors may argue for favoring observation after good resection in a young child; however, there is evidence that children with myxopapillary ependymoma experience a shorter time to recurrence and higher rates of dissemination with surgery alone (Bagley et al. 2009, Feldman et al. 2013, Bandopadhayay et al. 2016). Adjuvant radiotherapy can significantly improve local control and progression-free survival and should be considered strongly, especially after STR (Schild et al. 1998, Akyurek et al. 2006, Agbahiwe et al. 2013). Although the impact of histologic grade in ependymomas is apparent in adult studies, higher grade ependymomas of the spinal cord are uncommon in children. Extrapolation from the adult data suggests a role for postoperative irradiation for such lesions. It is evident that patients with grade II ependymoma, especially after subtotal resection, may benefit from postoperative radiotherapy (Lin et al. 2014).

Glial and ependymal tumor presenting with neuraxis dissemination at diagnosis may also benefit from radiotherapy. There is evidence to support that these patients can potentially achieve long-term progression-free survival with craniospinal irradiation (Gajjar et al. 1995, Merchant et al. 2000).

18.8 Target Delineation

18.8.1 Radiotherapy Volume

Radiation therapy target volume definitions have evolved significantly in the last two decades based on improved imaging technology. Full neuraxis imaging is

warranted, and MRI gives the best anatomical delineation of tumor extent. Tumor extent in the craniocaudal direction can be delineated based on MRI images; image registration should be employed when available to allow accurate delineation of target volumes. Localized intramedullary astrocytomas are generally treated with focal fields targeting the gross tumor and/or tumor bed, based on preoperative and postoperative MRI. Local fields are also indicated for spinal ependymomas (Akyurek et al. 2006, Agbahiwe et al. 2013). Recent studies suggest regional irradiation with a slightly more generous margin and including entire distal thecal sac. In the postoperative setting, target volume definition should start with an analysis of preoperative image sets to appreciate the full extent of disease in the craniocaudal direction; additionally, postsurgical changes should be incorporated in clinical target volume since they may extend beyond original tumor levels and commonly reflect an actual tumor plane. The additional margin for covering microscopic disease extent is created (clinical target volume or CTV); in the longitudinal direction, it is typically 2–3 cm and radially typically includes the entire spinal canal to the body edges of the vertebral body. For astrocytomas, one typically sees decompression or obliteration of the rostral and caudal cystic components after resection of the solid tumor. In such instances, it appears that radiation therapy can be limited to the solid tumor bed. Planning target volume expansion will depend on patient setup, immobilization, and onboard imaging capabilities of treating institution. Typically, the PTV ends up being 0.5–1 cm from the CTV, respecting symmetrical coverage of vertebral bodies in skeletally immature child (Fig. 18.3).

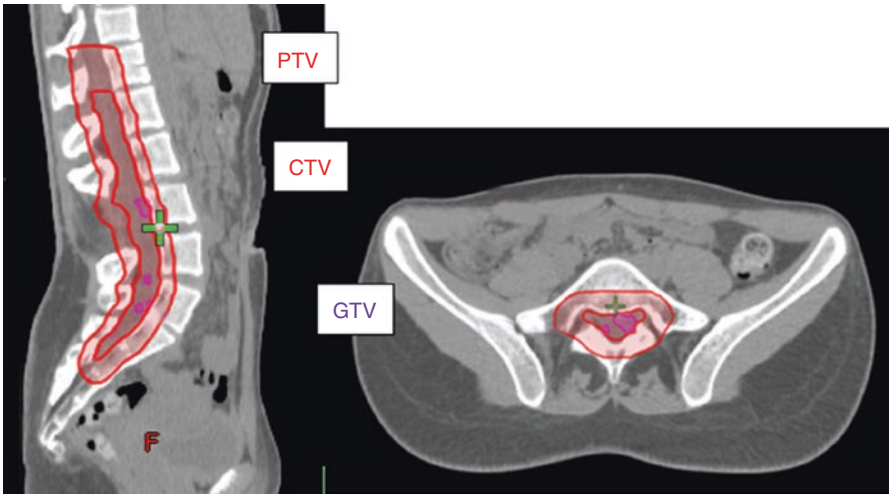

Fig. 18.3 Grade I myxopapillary ependymoma presented with tumor nodules in distal thecal sac: Gross Tumor Volume (*GTV, purple*), Clinical Target Volume (*CTV, inner red*), and Planning Target Volume (*PTV, outer red*)

Comprehensive neuraxis irradiation is given to tumors displaying dissemination (Merchant et al. 2000) and the craniospinal technique is discussed elsewhere in this book. As with brain tumors, age is a very important factor when considering full neuraxis irradiation.

18.8.2 Dose

Radiation dose typically varies from 45 to 54 Gy. These levels were based at least partially on estimated cord tolerance. Radiation dose–response has not been clearly established for spinal cord low-grade astrocytomas, although most patients are treated to a dose ranging from 45 to 50 Gy (O'Sullivan et al. 1994, Guss et al. 2013). There is evidence for better local control acheived with the dose ≥50 Gy in ependymomas (Schild et al. 2002, Pica et al. 2009). The local radiation dose for spinal cord tumors of other glial origin, including high-grade gliomas, has typically been treated to 50–54 Gy, and dose selection is mainly driven by dose constraint to the spinal cord. Daily fractions have ranged from 1.8 to 2 Gy. In cases of the disseminated disease, 36–39.6 Gy is commonly used for the initial dose targeting entire craniospinal axis, followed by focal boosts to a total primary site dose of 45–54 Gy, depending on the level of cord involvement. When prescribing a dose, special attention needs to be given to target volume dosimetry as often there is significant dose buildup from using a single posterior-anterior (PA) field.

18.8.3 Techniques

Historically, single posterior-anterior (PA), or anterior-posterior (AP) and posterior-anterior (PA) opposing fields were used for targeting spinal cord tumors. For PA fields, specific depth of dose prescription was chosen, commonly to the point of the posterior edge of the vertebral body or anterior edge of the spinal canal with the understanding that dose falloff would provide additional dose coverage to take care of setup variability. Particular attention needs to be paid to symmetrical dose coverage to the entire vertebral body in a child with growth potential. Static or dynamic wedges can be used with PA fields to compensate for an uneven body surface, commonly encountered in cervical and lumbar spine (Fig. 18.4). Lateral opposed or posterior oblique fields can be used for a tumor in cervical spine to help to reduce anterior dose exit (Fig. 18.5). Electrons have also been used in some cases; however, because of limited range and surface dose buildup, they are rarely feasible for older age patients. Current techniques have emerged based on the image-guided definition of the target volume, with 3D CRT or IMRT and VMAT approaches to achieve better dose homogeneity and limit the dose exposure to critical visceral organs in proximity to the target, like the kidneys, lung, or heart. Protons provide excellent dosimetry by sparing of tissues anterior to the spinal canal. Homogeneous irradiation of the vertebral bodies for growing children is a very important consideration for treatment planning regardless of techniques.

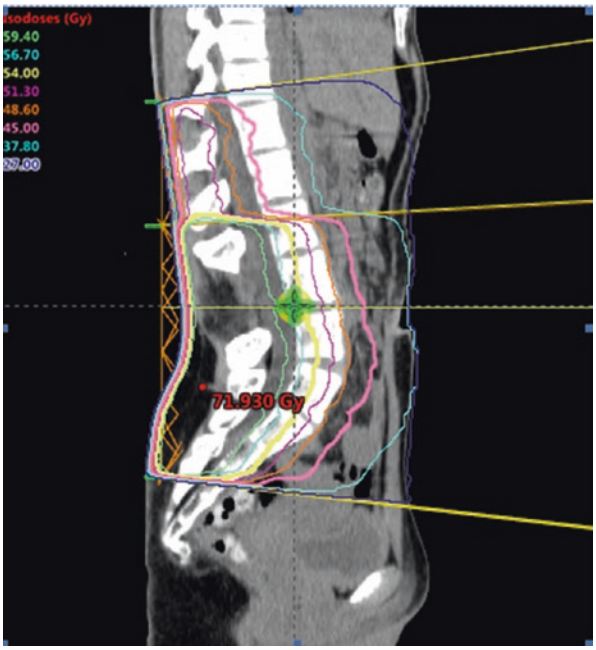

Fig. 18.4 Volumetrically modulated PA field is used to treat grade II ependymoma of a lumbar spine

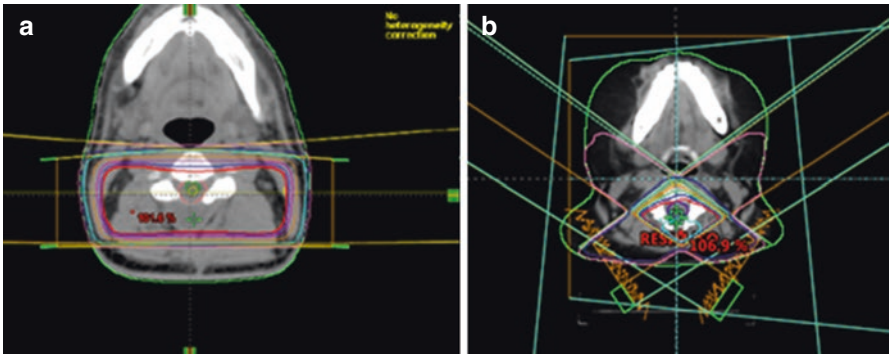

Fig. 18.5 Axial images of planning CT showing field projections and isodose lines for lateral opposed (**a**) and posterior oblique (**b**) field techniques

18.9 Outcomes

Pediatric patients have a good chance of recovery of neurological function over time (Kane, el-Mahdy et al. 1999). For all intramedullary spinal tumors, tumor histology and extent of resection have consistently been shown to be the most significant prognostic factor (DeSousa et al. 1979, Constantini et al. 2000, Houten and Weiner 2000, Ahmed et al. 2014). The histologic grade of astrocytic tumors of the spinal

cord has prognostic implications similar to those found in other central nervous system sites (Kopelson and Linggood 1982). Duration of symptoms can be an additional predictor of disease outcome (Bouffet et al. 1998), whereas the extent of resection may have a less significant effect on spinal cord low-grade astrocytoma outcome compared to ependymoma (Innocenzi et al. 1996). Postoperative radiotherapy can improve the outcome of patients with infiltrative astrocytomas, while no improvement in outcome is seen in patients with completely resected pilocytic astrocytomas (Minehan et al. 2009). Overall, the role of postoperative radiotherapy for low-grade astrocytic tumors of the spinal cord is still controversial, with a median survival time exceeding 6 years (Guidetti et al. 1981, Rossitch et al. 1990).

The prognosis of patients with spinal cord ependymoma is mainly affected by histologic grade and the extent of surgical resection. Grade I ependymoma is associated with good survival outcome; conversely, patients with grade II ependymoma have a significant risk of disease progression and death (Merchant et al. 2000). Recently published population-based study of 64 patients with grade II spinal ependymoma showed that adjuvant radiotherapy was statistically significantly more likely to be administered in cases of STR than in cases of GTR ($p < 0.001$) (Lin et al. 2014). As in other studies, resection was a strong predictor of 10-year survival (93.8% in GTR vs. 87.5% in STR). Survival estimate at 10 years for those who underwent radiation therapy was 87.4%, and for those who did not, it was 75.1%; this difference was not statistically significant. In a multivariate regression model analyzing sex, age at diagnosis, year of diagnosis, radiotherapy, and extent of resection, only female sex was found to be an independent predictor of decreased mortality (HR 0.15 [95% CI 0.02–0.94], $p = 0.04$). Myxopapillary ependymoma originating in the cauda equina has better long-term survival compared with intramedullary tumors, possibly attributable to greater resectability and potentially higher radiotherapy dose that can be applied to the level below the spinal cord.

Children with high-grade tumors of the spinal cord have a median survival time of less than 7 months (Cohen et al. 1989). The prognosis for children with primary high-grade astrocytomas of the spinal cord is dismal despite the use of trimodality therapy (Kopelson and Linggood 1982, Merchant et al. 1999). The majority of patients will either present with or develop leptomeningeal metastases, but the major treatment challenge is still local tumor control (Allen et al. 1998, Merchant et al. 1999). The effect of various clinical, radiographic, and operative factors on progression-free survival remains unknown.

While many patients with low-grade astrocytomas and ependymomas will have good survival and neurological recovery, some will suffer from permanent neurosensory deficits, such as neurogenic bladder, bowel, and scoliosis that can significantly affect quality of life (McGirt et al. 2008, Poretti et al. 2008).

18.10 Follow-up Guidelines

Posttreatment monitoring should be guided by tumor type. Low-grade ependymoma follow-up should include a clinical examination and MRI imaging every 3 months for the initial 2 years, every 6 months for an additional 3 years, annual evaluation

from 5 to 10 years after therapy, and every other year thereafter. High-grade tumors are often monitored more frequently, even though earlier detection of disease progression may not offer effective therapeutic salvage option at this time.

18.11 Future Directions

Better therapy is needed for high-grade intramedullary spinal cord tumors. Long-term damage to spinal cord function precludes significant improvement of local therapy options, such as surgery and radiotherapy. A better understanding of tumor biology may offer the most meaningful improvement in long-term outcomes via development of novel targeted and cytotoxic therapy.

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Choroid Plexus Tumors

19

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Abstract

Choroid plexus tumors (CPTs) are rare tumors of childhood and include choroid plexus papillomas (CPPs), atypical choroid plexus papilloma (aCPP), and choroid plexus carcinoma (CPC). CPTs often have mutations in TP53 and CPC is seen in patients with Li-Fraumeni syndrome. CPTs have relatively common characteristics on MRI. Management is primarily surgical for CPP, with chemotherapy and radiation generally reserved for CPTs that recur, or aCPP and CPC. Outcomes for CPP are very good with nearly all children cured with surgery. In contrast, CPC survival at 5 years ranges from 30 to 60%. Current studies are examining novel chemotherapy regimens.

19.1 Epidemiology and Histopathology

Choroid plexus tumors (CPTs) are rare in children, making up approximately 2% of all pediatric brain tumors. In a population-based Surveillance, Epidemiology and End Results (SEER) analysis of choroid plexus tumors, only 202 patients under age 20 from 1978 to 2010 were identified (Dudley et al. 2015). CPTs include choroid plexus papilloma (CPP, WHO grade I), atypical choroid plexus papilloma (aCPP, WHO grade II), and choroid plexus carcinoma (CPC, WHO grade III). aCPP was added to the WHO classification in 2007. CPCs are found more commonly in young children, with 75% seen in children less than 5 years old. CPPs are more evenly distributed throughout childhood.

The WHO classification of CPT provides histologic definitions of CPP, aCPP, and CPC (Louis et al. 2007). CPPs are similar to normal choroid plexus and have low mitotic activity (Fig. 19.1a). CPCs are malignant in appearance and demonstrate increased cellularity, abnormal papillary architecture, high mitotic activity, nuclear pleomorphism, and necrosis (Fig. 19.1b). Atypical CPP are intermediate lesions notable for increased mitotic activity.

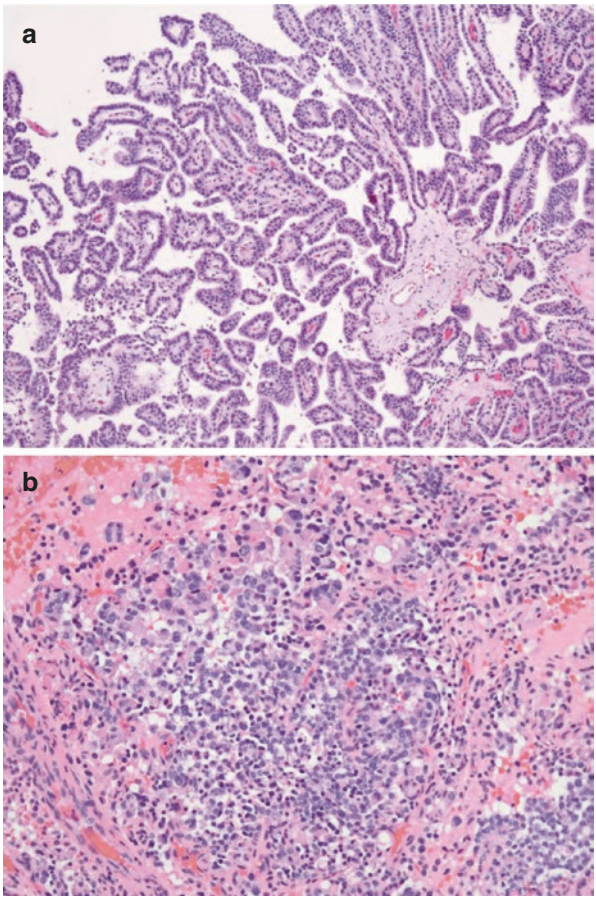

Fig. 19.1 (**a**) H&E stained histological sample of a WHO Grade I Choroid Plexus Papilloma. There is a single layer of epithelial cells overlying a fibrovascular core, resembling normal choroid plexus, although demonstrating more cellular crowding. Mitotic activity is low and there is no evidence of necrosis. (**b**) H&E stained histological sample of a WHO Grade III Choroid Plexus Carcinoma. There is a loss of the papillary organization of the tissue as well as nuclear pleomorphism and atypia. While invasion of adjacent cerebral tissue is common, it is not identified on this sample. (Pathology images courtesy of Dr. DeMasters)

19.2 Predisposing Factors

CPTs, in particular CPC, frequently have mutations in TP53. CPCs are seen in patients with Li-Fraumeni syndrome, who have germline TP53 mutations and are one of the 2009 Chompret criteria (Tinat et al. 2009). A recent multi-institutional genomic analysis of 100 CPTs shows that CPCs differ from CPPs in copy number, gene expression, and DNA methylation (Merino et al. 2015). TP53 mutations were seen in a high proportion of CPC and the number of mutated TP53 was correlated with outcome. There may also be an association between simian virus 40 (SV40) and CPT. There is in vitro data (Carruba et al. 1983, 1984) and animal data (Brinster et al. 1984; Cho et al. 1989; Enjoji et al. 1996; Small et al. 1985) that shows SV40 can induce CPT.

19.3 Presenting Symptoms

In the pediatric population, the most common location for CPTs is the lateral ventricles, followed by the fourth ventricle. As a result, presenting symptoms often relate to elevated intracranial pressure (ICP), either as a result of obstructive hydrocephalus or CSF overproduction by tumor, which overwhelms the absorptive mechanisms. Signs and symptoms of elevated ICP include a full anterior fontanelle, irritability, lethargy headache (reported by verbal children), vomiting, and changes in vision. Visual changes are exceedingly difficult to detect in the pediatric population, but a downgaze preference or failure of a baby to track objects may indicate dysfunction. Ophthalmological examination may reveal papilledema. Additional physical exam findings in infants may include rapidly increasing head size or prominent scalp veins.

19.3.1 Radiographic Findings

Diagnostic imaging for children with CPTs usually includes computed tomography (CT) and magnetic resonance imaging (MRI), although infants with a rapidly increasing head circumference may also undergo an initial cranial ultrasound. Ultrasound is both noninvasive and inexpensive. It may reveal a dilated ventricular system and/or a hyperechoic mass. On CT, CPP is usually a well-defined mass within a dilated ventricular system. The tumor often has a frondular appearance and may or may not demonstrate calcification. On MRI, CPP again demonstrates a unique frondular appearance, consistent with its derivation from the choroid plexus. On both modalities, CPP avidly enhances following contrast administration. While adjacent edema may be identified with FLAIR or T2 sequences, significant edema raises concerns for local infiltration, which is most consistent with CPC. While CPP is very discrete (Fig. 19.2), CPC usually has less well-defined borders and is more heterogeneous in appearance, including cystic changes, necrosis, or hemorrhage (Fig. 19.3).

There is limited data regarding the use of other noninvasive imaging modalities in CPT. With MR spectroscopy, the choline peak may be more elevated in CPC compared to CPP (Horska et al. 2001) and myoinositol may be elevated in CPP compared to other choroid plexus tumors (Krieger et al. 2005). There have also been descriptions of using SPECT (Shibata et al. 2008; Wolff et al. 2001) and PET (Sunada et al. 2002). MR angiography is often a useful adjunct in revealing the vascular supply of the lesion, which can guide decision-making regarding surgery or the need for angiography with tumor embolization.

19.4 Workup

These suggested pretreatment evaluations are based on the CPT-SIOP-2009 protocol. Evaluation of these children begins with a history, physical examination, and basic bloodwork. Imaging should include MRI of the brain and complete spine. In the absence of elevated intracranial pressure (ICP), a lumbar puncture should also be performed to assess for metastatic disease. In the presence of elevated ICP, this

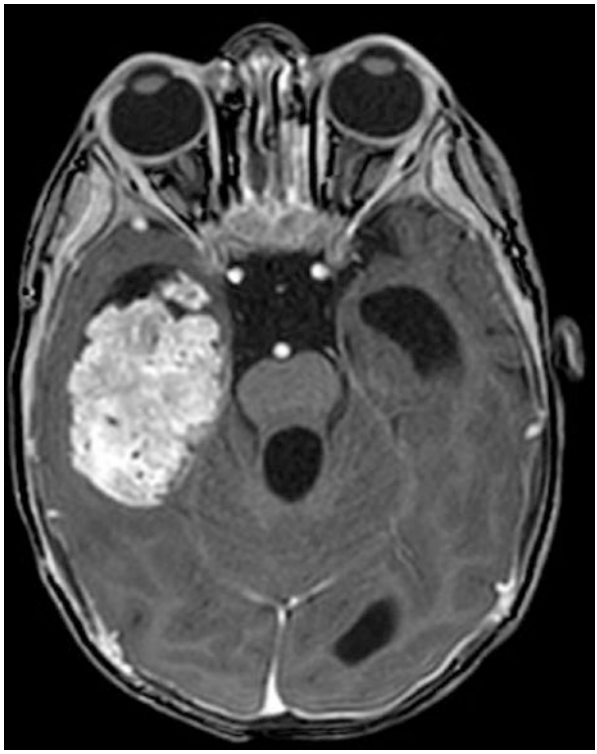

Fig. 19.2 Axial T1-weighted post-contrast MRI in a child with a CPP. The frondular tumor is located in the right temporal horn of the lateral ventricle, showing avid enhancement and no evidence of edema or infiltration involving the adjacent parenchyma

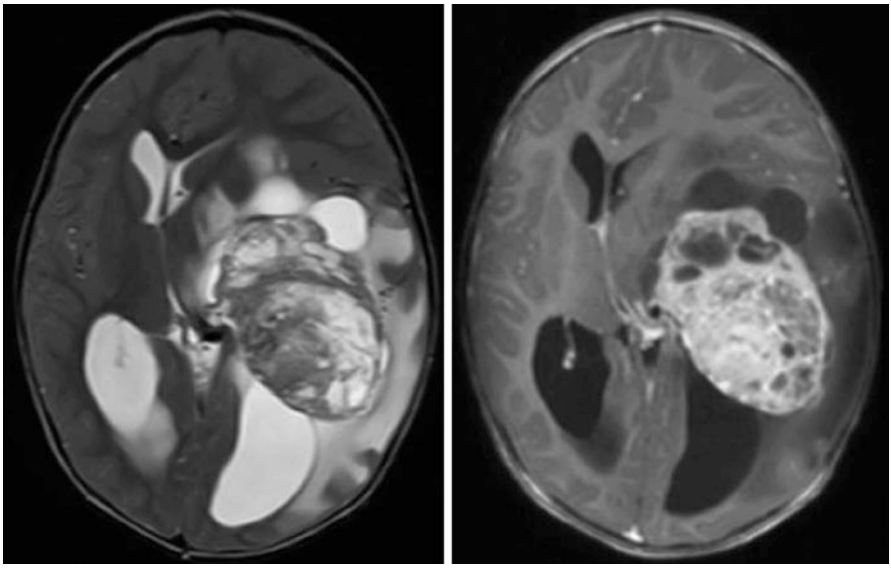

Fig. 19.3 Axial T2-weighted (*left*) and T1-weighted post-contrast (*right*) MRI in a child with a CPC. The tumor is located in the left lateral ventricle, showing less homogenous enhancement and multiple cysts. There is substantial edema in the adjacent temporal parenchyma

may be completed postoperatively. Other metastatic evaluations are not typically needed. Other recommended evaluation includes EKG and ECHO for children who will receive doxorubicin, and audiology testing for children who will receive radiation to the cochlea or cisplatin.

19.5 Acute Management/Surgical Treatment

Many children with CPTs present with symptomatic ICP elevation. As a result, initial management often focuses on this issue, including the administration of mannitol or the urgent/emergent placement of an external ventricular drain or ventricular shunt. Typically, third ventriculostomy is less effective due to overproduction of CSF. During the preoperative period, patients are commonly maintained on dexamethasone.

The goal of primary management of both CPP and CPC is maximal, safe surgical resection. As a highly vascular lesion that commonly presents in very young small children, the risk of life-threatening intraoperative blood loss must always be considered. Based on the radiographic appearance of the lesion, the clinical team determines whether preoperative angiography with embolization is indicated. While this may be challenging in the very young, embolization can substantially reduce the arterial supply of the tumor that is particularly relevant in suspected CPC.

The tumor is approached using a stereotactically guided craniotomy with a transventricular trajectory that provides early access to the tumor's arterial supply, which is then cauterized and cut. The need for stereotactic guidance and stability of the operative field during microsurgical resection may require specialized head holders to accommodate the thin skull of the very young. The risk of skull fracture and epidural hematoma must always be carefully evaluated by the neurosurgeon during operative positioning and following surgery, as the usual self-tamponade of a small epidural hematoma is lost following the removal of CSF and tumor. Close communication between the operating team and anesthesiologist is critical in order to prevent rapid and catastrophic vascular collapse as a result of intraoperative blood loss and fluid shifts. The operative approach is tailored to the location of the lesion and the vascular supply, which invariably includes choroidal vessels. Unlike the case with many intracranial tumors, internal tumor debulking is not the recommended approach for CPTs, as this could result in dramatic tumoral hemorrhage. Instead, the surgeon carefully disconnects the arterial supply with the goal of removing the tumor en bloc. Due to the vascularity of these lesions, safe tumor removal may require staged resection, especially in the case of CPC, which is more likely to be infiltrative, creating challenges for en bloc resection.

Following tumor resection, an external ventricular drain is invariably left in place. This may be weaned and removed in some cases, but permanent CSF diversion through ventriculo-peritoneal shunting is often required. Positioning of the shunt should take into account the possibility that a young child will collateralize some neurological function to the non-injured contralateral hemisphere.

19.6 Postoperative Management

Outcomes for CPP after surgery alone show excellent results. In the Canadian Pediatric Brain Tumor Consortium, all 21 children with CPP were alive after surgery alone (Lafay-Cousin et al. 2011). Extent of surgery is also correlated with improved outcomes for CPC. A meta-analysis of 347 CPC patients found 5-year overall survival (OS) of 58.1% for completely resected CPC compared to 20.9% for those with residual disease (Wrede et al. 2007). A more recent meta-analysis of 322 patients from 101 studies found similar improvements in outcomes with extent of surgery (Sun et al. 2014).

Given the low incidence of CPTs, treatment recommendations for adjuvant therapy or observation after resection are somewhat variable. Here we summarize recommendations based on SIOP-CPT-2009. For CPP, regardless of extent of resection or completely resected localized aCPP, observation is recommended. For aCPP with metastatic disease, and all CPC, adjuvant chemotherapy is recommended. In the previously mentioned meta-analysis, for CPC chemotherapy was associated with improved 5-year OS, 46.4% for those receiving chemotherapy compared to 27.6% for no chemotherapy. High dose chemotherapy with autologous stem-cell rescue has been used in the Head Start regimens (Zaky et al. 2015). In that series of 12 children, 5-year OS and PFS was 62% and 38%, respectively. CPT-SIOP-2000, which enrolled 131 patients, compared carboplatin/etoposide/vincristine to cyclophosphamide/etoposide/vincristine and found no difference. CPT-SIOP-2009 is now studying additional agents including doxorubicin, actinomycin D, cisplatin, methotrexate, temozolomide, irinotecan, intrathecal etoposide, and intrathecal cytarabine.

There is some data showing benefit for adjuvant radiation therapy for CPC. In the meta-analysis by Wrede, for CPC 5-year OS was 47.4% for those receiving radiation and 25.2% for those who did not receive radiation therapy (Wrede et al. 2007). There is also some data supporting the use of craniospinal irradiation (CSI) in CPC. A meta-analysis of 56 CPC patients found a 5-year progression-free survival of 44.2% for those who received CSI compared to 15.3% for those who received radiation to a smaller field (Mazloom et al. 2010). There were 19 patients with sufficient data regarding patterns of failure. Nine (47%) patients failed in field, 6 (32%) failed out of field, and 4 (21%) failed both in and out of field.

For CPP, radiation is only recommended at progression—local radiation for local progression and craniospinal radiation (CSI) with a boost to gross disease for metastatic progression. For localized aCPP, local radiation is recommended for residual disease or local progression and CSI is recommended for metastatic progression. For metastatic aCPP and all CPC, CSI is recommended. Since these tumors often occur in very young children, there are age guidelines—local radiation should only be given for children younger than age 3 and CSI with a boost for gross disease given for children older than 3 years. Additional chemotherapy can be given to allow children to reach these recommended ages. Suggested radiation doses are given in the table below.

	Age at the time of radiation (years)			
	≥1.5 to <2.5	≥2.5	≥3 to <5	≥5
Local (Gy)	50.4	54		
CSI + boost (Gy)			24 + 30 = 54	36 + 18 = 54

19.6.1 Radiation Planning Guidelines

19.6.1.1 Local Radiation and Boost After CSI

The Gross Tumor Volume (GTV) should include the surgical cavity and any residual tumor. The GTV can be modified to account for postsurgical or post-chemotherapy changes in the normal anatomy.

The Clinical Target Volume (CTV) will encompass potential microscopic disease involvement. The CTV is defined as the GTV + 0.5–1 cm. The CTV should be anatomically constrained. For example, the CTV should not extend across the falx, tentorium, or into the skull.

The Planning Target Volume (PTV) will reflect potential daily positioning variability and will vary based on the institutional practice and use of daily image guidance. In most cases, the PTV expansion of CTV is 0.3 cm, with the use of daily image guidance, to 0.5 cm, without daily image guidance.

At least 95% of the prescription dose should cover at least 95% of PTV. No more than 10% of PTV should exceed 110% of the prescription dose. No more than 50% of the upper spinal cord should receive more than 54 Gy. The mean cochlea dose should be limited to 35 Gy and the mean pituitary dose should be limited if possible.

An example of the local radiation planning volumes is shown in Fig. 19.4.

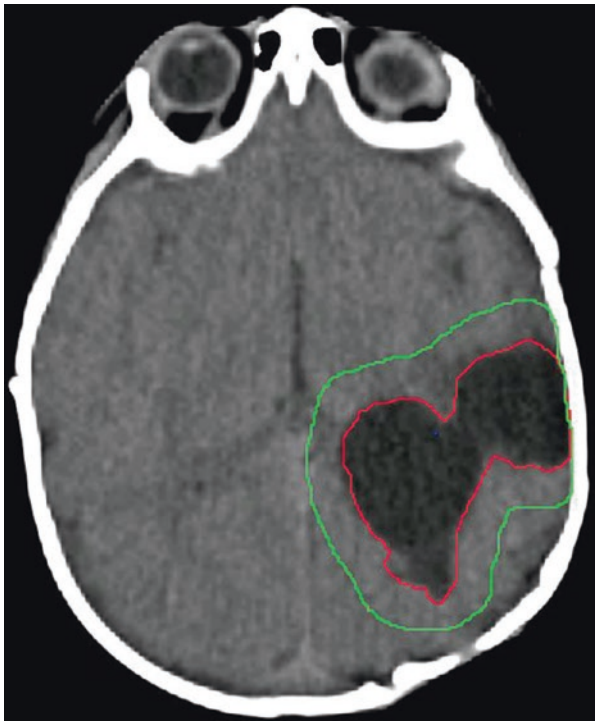

Fig. 19.4 The GTV (tumor bed) is shown in *red* and the CTV (1 cm expansion of GTV) is shown in *green*. The CTV is modified to exclude skull

19.6.2 Craniospinal Irradiation

The target volume for CSI includes the entire brain (including the cribriform plate) and spine extending down to the thecal sac. There is no consensus regarding coverage of the sacral nerve root foramina. For conventional 3D photon treatments, the cranial field is typically treated with lateral fields that are collimated to match the divergence of the spine field(s). A couch kick is used to match the inferior borders of the cranial fields and eliminate divergence into the spine field. The match between the brain and spine fields should be feathered after five fractions. A gap between the fields may be used to allow for setup variability. There are a number of other approaches for treating CSI, which include proton radiotherapy, tomotherapy, and IMRT. These techniques are discussed in Chap. 27.

19.7 Outcomes

19.7.1 Chemotherapy Toxicities

Toxicity from chemotherapy varies with the agent. Common acute toxicities include hair loss, mucositis, nausea, vomiting, diarrhea, neuropathy, and bone marrow suppression. Late term effects from chemotherapy can include injury to heart, lung, kidney, urinary bladder, auditory apparatus and development of secondary malignancies.

19.7.2 Radiation Toxicities

Acute effects from radiation to part of the brain include fatigue, hair loss, skin irritation, headache, nausea, and vomiting. With CSI, patients may also report sore throat, and bone marrow suppression. Late effects can include fibrosis and atrophy of normal tissues (including skin, muscle, bone, nerves, and vessels), permanent hair loss, cognitive dysfunction, hormonal dysfunction, hearing loss, cataracts, or secondary tumors.

19.7.3 Survival

Given the rarity of this tumor, estimates of survival outcomes are often based on small series of patients and can be quite variable for CPC. A few of larger studies of CPC are summarized in the table below.

	Type of study	Number of patients	OS 5 year (%)
Wrede J Neuoroncol 2007	Meta-analysis	347	34
Dudley J Neurooncol 2014	SEER	95	60
Lafay-Cousin Childs Nerv Syst 2010	Review of Canadian Pediatric Brain Tumor Consortium	16	31

19.8 Follow-Up

There is no standard follow-up recommendation for CPT. We suggest follow-up every 3 months for the first 2 years after diagnosis, biannual follow-up for the next 3 years, then annual follow-up for an additional 5 years, for a total of 10 years of follow-up. Each follow-up should include history, physical exam, and imaging of the primary site and any metastatic sites. Evaluation for late effects, which will depend on the therapy delivered, should occur annually.

19.9 Future Directions

For CPP, clinical outcomes are excellent with surgery alone. In comparison, outcomes for CPC are quite poor. There appears to be a benefit to radiation therapy, including CSI, but many patients are quite young which precludes the use of radiation, in particular large field radiation. Current work including CPT-SIOP-2009 is attempting to improving outcomes with acceptable toxicity for CPC, through the use of novel chemotherapy regimens. This trial has four arms: (1) the standard arm: etoposide, carboplatin, cyclophosphamide, and vincristine, (2) doxorubicin, dactinomycin, cisplatin, and vincristine, (3) methotrexate, and (4) temozolomide and irinotecan.

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Proton Therapy for Skull Base Chordomas in the Pediatric and Adolescent Patient

20

Eugen B. Hug

Contents

Abstract

Radiation therapy for skull base tumors requires knowledge, skill, and experience by the radiation oncologist. Tumors often require high target dosages, which can conflict with the competing goals of normal organ dose limitation for risk reduction of long-term functional impairments and anatomic disfigurement in the surviving children and adolescents. Protons are well suited to meet those challenges, specifically by employing active scanning technology. Chordomas represent the most challenging histology. Postoperative or definitive proton therapy with target doses ranging between 72–76–80GyRBE for small to large tumor volumes, respectively, has resulted in local control rates similar to the adult patient cohort.

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Due to the rarity of the disease no prospective randomized data are available, but comparison with published data using alternative conformal and/or stereotactic photon modalities strongly indicates a more favorable outcome using protons. Considering the anatomically close proximity of tumors to critical normal structures in the skull base, high target dosages require also relatively high normal tissue dose constraints compared to general radiation oncology practices. Likely due to favorable dose–volume effects of protons, i.e., its sharp dose fall-off within defined organs, the rates of severe adverse events appear acceptable. This chapter reviews the principles and practice of proton therapy for skull base chordomas.

20.1 Introduction

Skull base tumors can arise either directly from bony, cartilaginous, or soft tissues composing the skull base or by direct extension from either extracranial or intracranial origins. Examples for the former are chordoma, chondrosarcoma, and osteogenic malignancies like osteosarcoma and Ewing's sarcoma of the skull base. The latter mainly comprises extracranial parameningeal rhabdomyosarcoma and intracranial meningiomas. Rhabdomyosarcomas constitute the most common histology and those children and adolescents are typically enrolled in national or international clinical protocols specifying radiotherapy parameters. This chapter focuses on the management of skull base chordomas that due to their radioresistant nature require tumoricidal radiation doses exceeding tolerance of surrounding normal tissues and organs. Target contouring and dose prescriptions based on knowledge about the natural history of chordomas, their propensity and likelihood of spread and involvement of specific anatomic compartments as well as definition of normal organ at risk tolerance dose levels are the key components to give this vulnerable group of patients the optimum chance of survival with the least risks of permanent, treatment-related impairments.

Chordomas are rare tumors, and the overall incidence across all age groups is approximately 0.1 per year per 1,000,000 population (Rombi et al. 2013). Only 5% of cases have been described in the pediatric age. A recent review of the Surveillance, Epidemiology, and End Result (SEER) database identified that in a period of 38 years (1973–2011) only 86 pediatric patients ≤19 years of age within a cohort of 1358 primary chordoma patients (Lau et al. 2016).

Chordomas arise from remnants in the notochord thus are midline structures occurring in the clivus superiorly down to the sacrococcygeal region inferiorly. Its distribution in the adult population along the axial skeleton is approximately 50% in skull base and cervical spine, i.e., occipito-cervical tumors, 30% in the sacrococcygeal region, and 20% throughout the T- and L-spine vertebral bodies.

An important treatment management question is, if chordomas in pediatric patients have a different pathophysiological profile, i.e., natural history, compared to their adult counterparts. Indeed, on occasion a child will present with a short clinical history of rapidly evolving symptoms accompanied by fast tumor growth. Indeed, the SEER database review confirmed that despite the majority of primary chordomas present with loco-regional involvement (90.4%), pediatric patients had

more distant disease (14.8 vs. 9.2%, $p < 0.05$) (Lau et al. 2016). Despite ongoing efforts to better characterize these tumors, no reliably reproducible prognostic factor has been identified (Hoch et al. 2006).

20.2 Presenting Symptoms

The majority of chordomas is relatively slowly growing thus can reach considerable size before creating symptoms. In general, symptoms are due to compression, displacement, or pressure of normal structures (Borba et al. 1996; Hug et al. 1999). Chordomas typically remain extraaxial and almost never invade brain parenchyma, spinal cord, or cranial nerves. Rather, symptoms are a function of compression of normal structures in the region of the tumor. Diplopia from CN-VI compression in the cavernous sinus is the predominant symptom from upper skull base tumors. Suprasellar tumor extension will frequently cause bitemporal hemianopsia via pressure on the optic chiasm. Trigeminal nerve dysfunction may result in involvement of Meckel's cave. Headaches may be associated with intracranial extension and displacement or compression of normal brain parenchyma. Since chordomas do not invade a brain parenchyma itself, seizures are rarely observed. Involvement of the lower clivus will cause symptoms depending on region of growth. Destruction of clivus and subsequent impairment of various neural foramina in the inferior skull base, impairment of the lower cranial nerves may be a first sign of inferior skull base tumors causing slurred speech due to XII nerve dysfunction with hemiatrophy of the tongue, or dysphagia or potential aspiration. Impairment of swallowing may result from either anterior chordoma growth into the retropharyngeal soft tissues or by involvement of the lower cranial nerve function. Posterior clival intracranial extension can result in brainstem compression and its accompanied symptoms. Further inferior extension involving the occipito-cervical junction with potential erosion of C1 and/or massa lateralis may cause severe headaches, mechanical instability of the occipito-cervical junction, and a foramen magnum syndrome with upper C-spine compression.

20.3 The Role of Surgery

The role of surgery in chordomas is undisputed. It is at least as important in children as in adult patients according to a recent review of 86 pediatric chordoma patient included in the SEER Database. For the pediatric patient cohort having surgery, only survival was significantly longer than for adults (22.5 vs. 14.3 years, $p < 0.001$) (Lau et al. 2016). Munzenrider et al. reported that gross total or near total resection—if achievable with acceptable risks—is associated with the highest chance of permanent local control in both adult and pediatric patients (Munzenrider and Liebsch 1999). In children, this requires often two-stage surgical procedures, each addressing a different portion of tumor resection. Postoperative radiotherapy should preferably be integral part of the initial treatment strategy. Thus, these children benefit significantly from an interdisciplinary management team as outlined previously in a case report by Dr. Habrand (Habrand et al. 2016). In general, with possibly few exceptions in the

infant age group, this should be followed by postoperative high-dose radiation. Proton radiotherapy has been shown to have advantages in dose delivery and normal tissue sparing in this situation. It is not clear, at this time, whether it is better to proceed with immediate postoperative high-dose radiation therapy after gross total resection or to delay radiation therapy in young children with chordoma. In case of radiographically confirmed near total or subtotal resection, however, there is little doubt that postoperative high-dose radiation treatment should be recommended unless specific extenuating circumstances exist. In cases of large tumors where gross total resection is not feasible, a strategic debulking procedure probably also has significant merits including decompression of critical normal structures that are dose-limiting (e.g., optic chiasm, optic nerves, brainstem, or cervical spine) for symptom control and optimal radiation planning. The total tumor dose required for gross residual disease generally exceeds the tolerance of adjacent organs at risk (OAR). When the tumor abuts and/or compresses these OARs, tumor dose in that area will be limited to respect the maximum permissible OAR dose. Hug and Munzenrider reported a relationship between an increased incidence of local failure in cases where the chordoma abuts or compresses OARs (Hug et al. 1999; Munzenrider and Liebsch 1999).

The advent of endoscopic minimally invasive surgery has revolutionized the surgery of skull base tumors. Children with small anterior or mid skull base tumors are now spared from large open craniotomies; however, in patients with large chordomas with bilateral extension towards the brainstem and/or massive extension into the lower skull base, upper cervical spine, or parapharyngeal/paravertebral soft tissues, major two-stage approaches with or without occipito-cervical fusion might still be required. We have presently no indication that subtotal resection with significant residual tumor and high-dose particle therapy is equivalent in outcome compared to a near total resection with high-dose particle therapy. This emphasizes the need to maximize surgery as long as it is feasible in the individual patient.

20.4 Target Delineation

Target delineation should consider the anatomic compartments at risk of harboring microscopic disease. Treating only radiographically visible disease seen on diagnostic MR or CT scans is insufficient and will likely result in poor local control probability. Studies of radiosurgery to the gross residual disease without a margin for microscopic disease report inferior local control rates. In contrast, treatment contouring for tumor delineation for patients with chordoma can be separated into three approaches: One for gross residual disease (gross tumor volume, GTV), one for high-risk macroscopic disease (GTV), and one for low- to intermediate-risk microscopic disease (clinical target volume, CTV). In clinical practice, an oncologic en bloc resection is not possible for skull base tumors, and tumors are resected in a piecemeal fashion.

In practice, it is best to define the GTV as a combination of demonstrated, unequivocal gross disease *as well as* areas of high-risk microscopic disease. A GTV should include the immediate surgical bony resection margins in the skull base, the area surrounding major blood vessels, or the entire cavernous sinus even if partially involved on MRI. Frequently, there can be discrepancy between the surgeon's report of a gross

total resection and postoperative imaging suggesting small area of residual disease or equivocal findings. In general, any area that has persistent abnormal imaging findings postoperatively should be considered as being at high risk for macroscopic disease.

The CTV is defined as volume/anatomic compartments considered to be of low to intermediate risk for microscopic disease. Examples would be the prepontine space if the resected tumor involved the prepontine space, or the surgical access route and tumor bed with anatomic margin. A uniform CTV margin is not recommended since the CTV is often highly irregular and may vary in different dimensions. For example, a 1–2 cm margin would be appropriate when extracranial tumor extension into the posterior pharyngeal soft tissues is noted but a 2–3 mm margin only is needed into the brain parenchyma. Chordomas in general do not invade the brain parenchyma. Therefore, even in cases of significant initial compression of the temporal lobes causing edema within the temporal lobes, the edematous portion of the temporal lobe does not require inclusion in the CTV. Rather, in case of re-expansion of the temporal lobe following surgery a small rim of 2–3 mm typically suffices.

An approximate 5% risk of seeding into the surgical axis route has been reported in the adult chordoma population (Munzenrider and Liebsch 1999). In children, in case of an anterior transnasal transsphenoidal approach, it is useful to extend the CTV indeed into the nasal cavity or paranasal sinuses as shown in Fig. 20.1. In case of a transcranial approach, however, a strategy to routinely include the entire surgical access would result in a majority of children in significant permanent side effects; thus, this approach has not been favored in transcranial approaches.

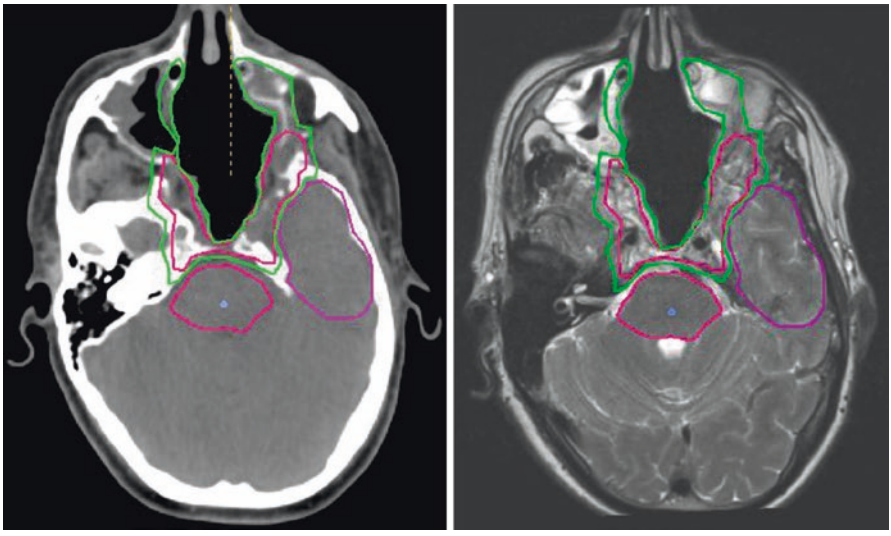

Fig. 20.1 Target contouring of a large skull base chordoma with extensive extracranial extension following subtotal, transnasal/transsphenoidal resection. Gross tumor volume (GTV) includes residual gross disease, equivocal areas as per imaging, and potential high-risk microscopic disease (*red*). Clinical target volume (CTV) includes GTV, potential microscopic areas but respecting anatomic barriers and considerations of infiltrative potential, as well as nasal surgical route. Note: brain parenchyma typically not included in the CTV except an outer "rim"

20.5 Tumor and Target Volume Prescription Doses

Most available data in clinical practice are based on 1.8–2.0 GyRBE dose fraction regimen, assuming a relative biologic effectiveness (RBE) factor of 1.1 of protons versus photons.

Although no formal dose escalation study has been conducted, there appears to be a radiation dose–response curve for chordomas. This conclusion is supported by the inferior results associated with photon therapy with doses of 66–68 Gy in contrast to the vast majority of proton data, where GTV prescription doses are in excess of 72 GyRBE. It appears that the minimum dose for very small GTV targets should be 72 GyRBE, for small to medium size tumors approximately 75–76 GyRBE and for large targets up to 78–80 GyRBE.

For the clinical target volume (CTV), doses analogous to general sarcoma principles for low-risk microscopic disease are used, i.e., doses between 50 and 54 GyRBE. Figures 20.2 and 20.3 depict typical isodose distributions that can be accomplished with spot scanning technology for locally advanced skull base chordomas.

Although chondrosarcomas are very rare in children compared to chordomas, it is worthwhile to briefly outline some differences, as they have been established in young adults and adults in general: No prospective trials have been undertaken between chordomas and chondrosarcomas, it appears that higher local control rates can be obtained in chondrosarcomas with total prescription dosage ranging between 70 and 76 GyRBE. Most published data indicate actuarial local control rates >80% and up to 95% at 5-years and even 10-year local control rates >80% for chondrosarcomas, which is even more remarkable considering the higher percentage of chondrosarcoma patients compared to chordoma patients with medium- to large-size disease since they are relatively unresectable compared to chordoma due the inherent calcified nature. There is presently no analysis available that indicates a dose differential between smaller size and larger size chondrosarcomas since local control rates appear equally high. In clinical practice, the GTV dose ranges between 70 GyRBE for small residual disease and 75 GyRBE for large-volume disease. If the patient is referred postoperatively for no residual disease, then presumably high-risk areas could be treated to approximately 66–68 GyRBE only.

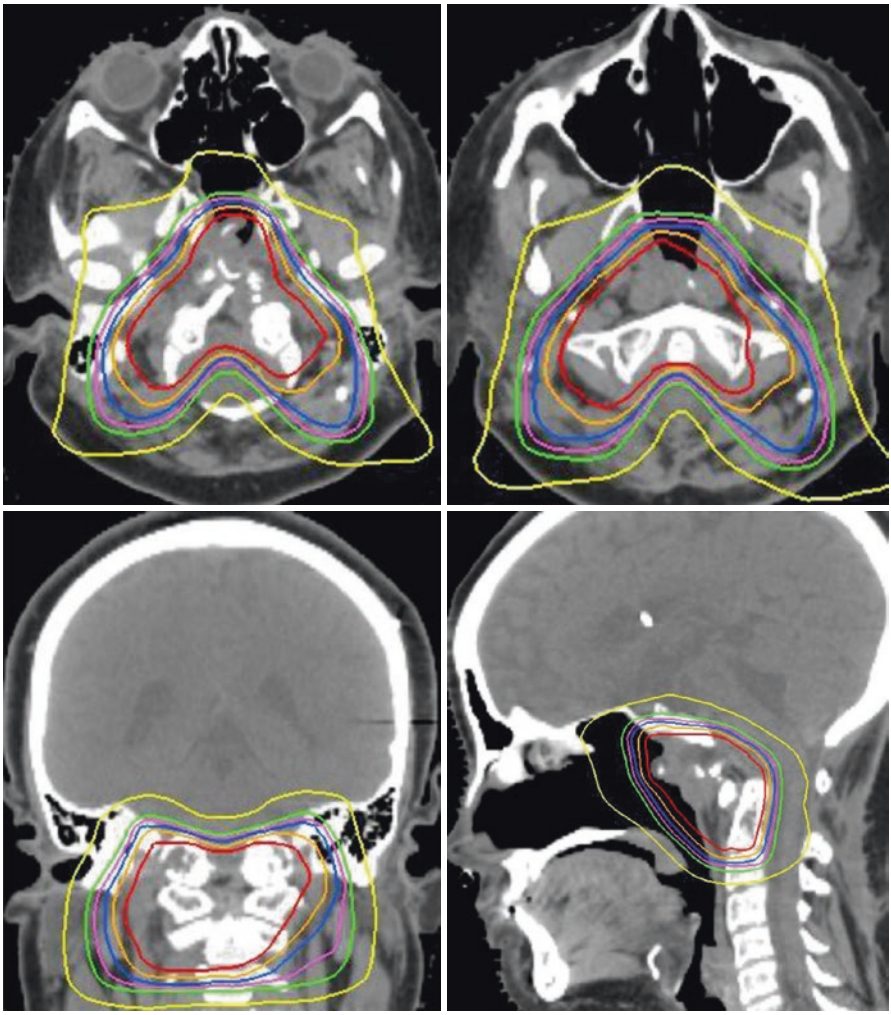

Fig. 20.2 A 13-year-old boy with extensive chordoma of the clivus with extracranial extension. Status post 2 subtotal resections. Proton therapy of GTV to 75.7 GyRBE and CTV to 54 GyRBE at 1.8 GyRBE dose per fraction

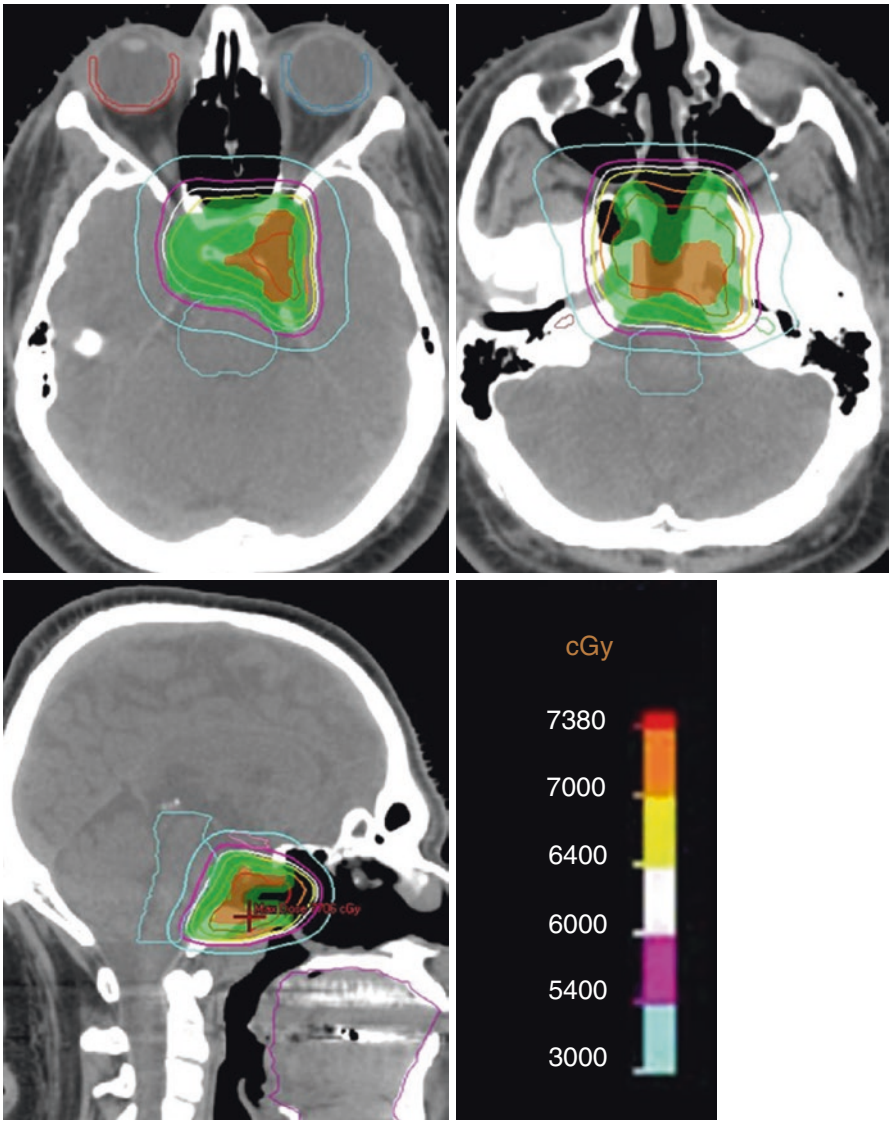

Fig. 20.3 Chordoma in a 19-year-old male. Status post-transnasal subtital resection. Contour display of PTV of CTV (*green shaded volume*) and GTV (*red volume*). Proton therapy prescription of CTV to 54 GyRBE (*green shaded volume* = PTV of CTV). GTV to 73.8 Gy (RBE) at 1.8 GyRBE dose per fraction

20.6 Organs at Risk, Special Dose Considerations

A matter of significant debate remains the critical OAR constraints since the maximum permissible dosages used in some proton centers exceed the typical dose constraints used in conventional photon therapy. The general low risk of high-grade

adverse events reported after proton therapy with high critical OAR constraints is likely supported by a dose–volume effect, i.e., the sharp dose fall-off within an OAR. This is mentioned in the QUANTEC report for OAR recommendations where it is explicitly stated that "for dosages at the level of 60 Gy no data are presently available on the dose volume effect" (Marks et al. 2010).

The ALARA (As Low As Reasonably Achievable) rule of dose exposure applies to each patient. If a tumor is not in immediate vicinity, abutting or compressing an OAR, then every effort should be made to keep this OAR at lower dose levels compared to situations with tumor abutment. The following OAR constraints are presently used by the author and reflect general guidelines only that need to be carefully adjusted to the individual patient and situation. The author allows a maximum dose to 0.01 cm^3 up to 60 GyRBE to either optic chiasm or one of the optic nerves. Dose levels up to 60 GyRBE to single optic structures have resulted in the majority of publications in severe adverse event rates, i.e., grade 3 or higher toxicity, of optic structures of less than 1% (Munzenrider and Liebsch 1999). One should consider that inherently the dose tolerance of optic structure is likely lower if the patient has preexisting visual impairment. In addition, OAR constraints to optic structures should be reduced if the patient has monocular vision. In the author's opinion, a significant risk of complete blindness is unacceptable and renders the patient unsuitable for proton therapy. Ethical considerations apply to the use of high-dose radiation analogous to surgical resection. If complete tumor resection would require resection of the optic chiasm, such tumor is deemed "unresectable" by the neurosurgeons. Radiation dose to the optic structures that are associated with a high risk of complete blindness should not be considered.

With regard to the brainstem, the author uses a surface dose constraint of 64 GyRBE and a brainstem center dose of 53 GyRBE, as they have been developed early on by the group at the Harvard Cyclotron Laboratory and Massachusetts General Hospital (MGH/HCL). The surface dose can be defined as meaningful volume (e.g., 0.5 cm^3) and as the isodose line that is repeatedly permitted to touch the brainstem surface. The low brainstem center dose ascertains a sharp dose fall-off inside the brainstem. Based on the publication in 1999 by Debus who reported the MGH/HCL experience (Debus et al. 1999), this approach has resulted in exceedingly low rate of brainstem toxicity in adults and children with skull base chordomas and chondrosarcomas. At most there are only anecdotal reports of severe brainstem injuries in other large series.

Grade 3 or higher brain parenchymal toxicities remain the highest single organ severe adverse event rate reported in high-dose skull base tumor treatments. Several publications have reported rates of approximately 4–6% for adult patients. Despite significant efforts of predictive analysis, at present no generally agreed upon OAR constraints have proven to reduce this rate significantly. A constraint of 72 GyRBE to <2 cm^3 of volume per individual lobe appears practical. The medial temporal lobes are at the highest risk when treating superior skull base tumors, which may be due to the competing adjacent OARs. In order to avoid the optic chiasm, optic nerves and brainstem require use of lateral fields that either range out in the contralateral medial temporal lobe with passive scattering technology or place repeated highly weighted spots in the medial temporal lobes with active spot scanning. These

issues illustrate the need of additional fields besides lateral beams for upper skull base lesions to minimize the risk of temporal lobe necrosis especially when the PTV extends into this area.

20.7 Normal Tissue Constraints Versus Target Coverage

GTV prescription doses for either residual chordoma or chondrosarcoma exceed the majority of normal tissue tolerances; hence, the specification of OAR constraints significantly impacts on the general ability to cover the GTV volume and defines the steepness of the shoulder region of the target dose–volume histograms. Figure 20.4

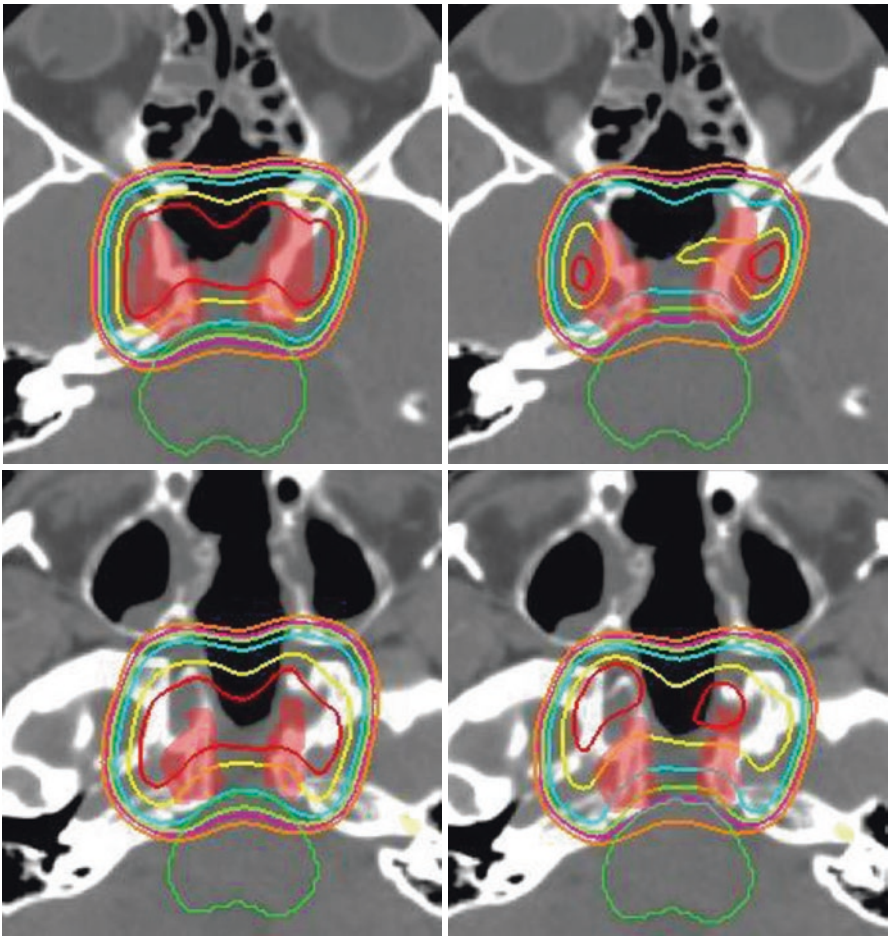

Fig. 20.4 Influence of decreasing OAR constraints on resulting target coverage. Prescription to GTV 74 Gy(RBE). OAR constraint for optic nerves and chiasm of 60 Gy(RBE) (Panel **a**) versus 54 Gy(RBE) (Panel **b**). OAR constraint for brainstem surface of 64 Gy(RBE) (Panel **c**) versus 58 Gy(RBE) (Panel **d**). Isodose display ranging from 54 (*orange*) to 64 (*blue*) to 74 Gy(RBE) (*dark red*)

illustrates a patient treated to a total target dose of 73.6 Gy (RBE) for relatively small residual disease chordoma of the upper clivus with no brainstem compression and no optic apparatus abutment—a rather favorable situation. Treatment plans were generated using identical contours and prescription dose with either the author's OAR constraints of 60 and 64 GyRBE or the more common limits of 55 and 55 GyRBE to the optic chiasm and brainstem surface, respectively. The resulting GTV DVHs are displayed in Fig. 20.5. The use of lower OAR constraints alone resulted in a significant reduction of therapeutic dose for this small and favorable GTV. Although the exact coverage reduction is dependent on institution specific equipment, it exemplifies qualitatively the importance for each treating physician to carefully consider their OAR constraints and integrate published proton center constraints into their plans. Using low OAR constraints might allow a lower risk of high-grade complications but might also considerably reduce the patient's chances of local control and potentially eradicate any gain in tumor control probability by protons over conventional photon therapy.

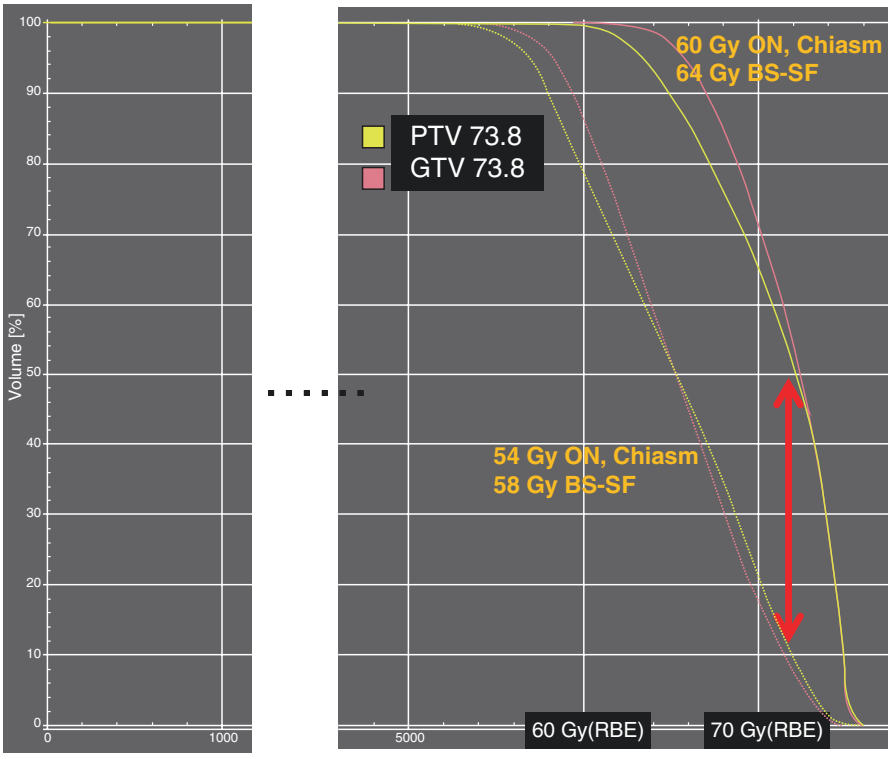

Fig. 20.5 Influence of OAR dose constraints on target coverage according to dose–volume histogram

20.8 Prognostic Factors

In general for skull base tumors, chordomas need to be distinguished from chondrosarcoma since they are two distinctly different histologies with different prognosis. Low-grade chondrosarcomas by and large have a better prognosis following high-dose proton therapy than chordomas. Since the majority of skull base chondrosarcomas can be controlled long term with proton therapy, little information is available on prognostic factors. There is no reliable information available if large size, unresectable skull base chondrosarcomas have a lesser prognosis compared to small residual disease following high-dose proton therapy.

In contrast, for low-grade chordomas various prognostic factors have been identified in the adult population that determines the likelihood of accomplishing local control and long-term survival. Although those have not been specifically validated for the pediatric population, this still serve as helpful guidelines.

(a) Size of residual disease plays an important role: Small-volume disease (defined as approximately 25–30 cm^3) appears to be correlated with an excellent long-term prognosis of >90% at 5 years. The chances drop significantly from small-volume to mid-size (approximately 50 cm^3) to larger volumes.
(b) Compression or tumor abutment of dose-limiting OARs at the time of proton therapy is correlated with reduced chances of obtaining permanent local control—likely due to the dose gradient between maximum permissible OAR dose and tumoricidal prescription dose.
(c) High-grade as compared to low-grade histology correlates as well with survival.

There is no consistent evidence in the published literature that patients with recurrent disease will fare worse compared to patients receiving proton therapy at the time of initial diagnosis. It remains a matter of discussion if postoperative proton therapy can be delayed in very young children after near total resection. A policy of watchful waiting with frequent MRI scans has to be carefully weighted against the possible disadvantages of recurrent disease requiring additional surgery at time of detection. No clear recommendations can be made and since the data support either side. The natural history of low versus fast tumor growth plays an important role in the decision process.

20.9 Proton Therapy Results

Historically, proton therapy results have been consistently superior to conventional proton therapy. In 1999, the MGH publication by Munzenrider established the excellent prognosis for chondrosarcomas following high-dose proton therapy and established the mixed prognosis for chordoma patients depending on the

previously stated prognostic factors (Munzenrider and Liebsch 1999). At the time, however, the chordoma data were clearly superior to any available photon data. At present, the best available data have shown 5-year-old local control rates even of long term for favorable chordomas of approximately 80% and 5 years and 80% even at 10 years considering that for small chordomas this may well be up in the 90% range even long time but less favorable for large-sized chordomas with compression of OARs. Conventional photon data have historically and consistently produced inferior results but most recent publication by the Canadian Group (Saghal 2015) has raised the possibility of excellent long-term data even by use from high-dose, conformal photon therapy. Undoubtedly, it would be very beneficial that prospective trials will establish best practice, also establish and confirm outcomes data according to prognostic factors before ultimately proceeding with a direct photon-to-proton comparison. In addition, we presently face with a dramatic transition of proton therapy from passive scattering technology to spot scanning technology and within the spot scanning technology from first-generation equipment to more advanced delivery technology (Lomax et al. 2004).

Few retrospective series have been published outside case reports. Rombi for the group at Paul Scherrer Institute, Switzerland, reported on pediatric patients treated with spot scanning-based proton therapy delivery technique (Rombi et al. 2013). Twenty-six pediatric patients ranging in age between 3.7 and 20.8 years (mean age 13.2 years) were treated at the PSI for chordoma or chondrosarcoma. Nineteen chordoma and 7 chondrosarcoma patients with tumors originated from the skullbase (17) and the axial skeleton (9). The mean prescribed dose was 74 GyRBE (range, 73.8–75.6) for chordoma and 66 GyRBE (range, 54–72) for chondrosarcoma, at 1.8–2.0 GyRBE dose per fraction. With a mean follow-up period of 46 months (range, 4.5–126.5), actuarial 5-year local control rates were 81% for chordoma and 80% for chondrosarcoma and actuarial 5-year overall survival rates were 89% for chordoma and 75% for chondrosarcoma, respectively. With relatively limited follow-up, the authors did not report any grade 3 or higher late toxicities. Benk et al. reported the MGH/HCL experience of 18 pediatric patients with chordomas located at either skull base (15) or C-spine (3) and treated with mixed photons and protons to a median dose of 69 GyRBE (Benk et al. 1995). At a median follow-up of 72 months (range, 19–120), the actuarial local control and overall survival at 5 years was 63% and 68%, respectively. Hug et al. for the group at Loma Linda University Medical Center (LLUMC) analyzed 13 skull base pediatric patients (10 chordoma and 3 chondrosarcoma), treated with protons (6 patients) or mixed protons and photons (7 patients) to a median prescribed dose of 73.7 and 70 GyRBE for chordoma and chondrosarcoma, respectively (Hug et al. 1999). After mean follow-up of 40 months (range, 13–92 months), 5-year local control and 5-year overall survival was 60%, and 100% chordoma and chondrosarcoma, respectively. Table 20.1 summarizes the results of the few larger retrospective studies reported thus far.

Table 20.1 Summary of studies using PT in pediatric chordomas and chondrosarcomas

Institution (first author)	#	Tumor site (#)	Histology	RT type (#)	Dose (GyRBE)	5y-LC	5y-OS	F/U months (range)
MGH (Benk 1995)	18	SB (15), C-spine (3)	All CH	P + X (18)	Med 69.0	63%	68%*	Med 72 (19–120)
LLUMC (Hug 2002)	13	SB	10 CH	P (6), P + X (4)	Med 73.7	60% (CH)[#]	60% (CH)	Mean 37 (13–86)
			3 CS	P + X (3)	Med 70.0	100% (CS)[#]	100% (CS)	
PSI (Rutz 2008)	10	SB (6), axial skeleton (4)	6 CH	P	Med 74.0	100%[#]	100%[#]	Med 36 (8–77)
			4 CS		Med 66.0			
CPO (Habrand 2008)	30	SB (16), C-spine (1), both (13)	27 CH	P + X (29)	Mean 69.1	77% (CH)	81% (CH)	Mean 26.5 (5–102)
			3 CS	P (1)	Mean 65.3	100% (CS)	100% (CS)	
PSI (Rombi 2013)	26	SB (17), axial skeleton (9)	19 CH	P	Mean 74.0	81% (CH)	89% (CH)	Mean 46 (5–126)
			7 CS		Mean 66.0	80% (CS)	75% (CS)	

number, *RT* radiotherapy, *LC* local control, *OS* overall survival, *F/U* follow-up, *SB* skull base, *CH* chordoma, *CS* chondrosarcoma, *P* proton therapy, *X* X-ray therapy

Notes: *patients with cervical spine chordoma had a significant worse survival than the other skull base patients ($p = 0.008$); [#]at last follow-up. **Overall survival of the males was significantly superior to female patients ($p = 0.002$)

20.10 Systemic Therapy

The effect of conventional chemotherapy agents has been limited in the management of chordoma. Some young children have been managed with upfront chemotherapy, due to extensive loco-regionally or distant presentation, but results have been of limited success except some delay in disease progression measured in months.

Newer approaches using small molecule-targeted agents, such as imatinib and sorafenib, have resulted in some disease stability (Stacchiotti and Casali 2011; Stacchiotti et al. 2012; Bompas et al. 2015; Di Maio et al. 2015; Hindi et al. 2015). Brachyury, a nuclear transcription factor, is a strong mediator of the epithelial to mesenchymal transition and is over-expressed in chordoma. A recombinant vaccine encoding brachyury that activates human T cells has been developed. It has yielded encouraging preliminary results in a phase 1 study for patients with progressive chordoma (Heery et al. 2015). These therapies, however, have been restricted to small adult clinical trials and require further evaluation for both adults and children.

20.11 Summary

Proton therapy offers excellent chances of permanent local control survival and for many children patients with skull base chordomas. The outcomes data for chondrosarcomas are already excellent for essentially all patient groups. They are good for pediatric chordoma patients with good prognostic factors, namely small residual disease. For unfavorable prognostic factors, further improvements are needed that should be best established by enrolling patients in prospective clinical trials. The role of systemic therapy needs further refinements. Late effects data to elucidate on the long-term effects of high-dose proton therapy are presently still missing, but high-grade toxicities within the first 3–5 years after therapy are within acceptable range.

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Pituitary Tumors: Pituitary Adenomas and Langerhans Cell Histiocytosis Associated Diabetes Insipidus

21

Ralph P. Ermoian

Contents

Abstract

Pituitary adenomas are rare in children, with corticotropinomas being the most common pituitary adenoma in pre-pubescent children and prolactinomas being the most common pituitary adenoma in adolescents. In children, the primary management of these tumors is surgical or medical, with radiation reserved for cases of uncontrolled functioning tumors or patients with unresectable residual

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disease. Diabetes insipidus (DI) is a common manifestation of Langerhans cell histiocytosis (LCH). There is limited data to support early radiation therapy in patients with LCH to the hypothalamic pituitary axis to increase the probability of resolution of DI.

21.1 Introduction

The differential diagnosis of sellar and suprasellar tumors includes craniopharyngiomas, central nervous system germ cell tumors, gliomas, xanthogranulomas, metastases, pituitary adenomas, and Langerhans cell histiocytosis (LCH) involving the pituitary gland. Craniopharyngiomas are the most common sellar tumor and are discussed in Chap. 16. Germ cell tumors are typically located in the suprasellar region and are discussed in Chaps. 14 and 15 and gliomas are discussed in Chap. 11. This chapter addresses PAs and LCH involving the pituitary gland.

21.2 Pituitary Adenomas

21.2.1 Epidemiology

Pituitary adenomas are rare tumors in children. They represent 1.6–2.7% of all pediatric suprasellar brain tumors (Kane et al. 1994). Most cases present in adulthood and pediatric pituitary adenomas represent 3–6% of surgically treated PAs (Webb and Prayson 2008). The most common pituitary adenoma in pediatric patients is prolactinoma, which is predominantly found in adolescent girls. The most common pituitary adenoma found in pre-pubescent pediatric patients is corticotropinomas, the ACTH-producing tumors of Cushing's disease. In patients older than 6, 75% of pediatric Cushing's syndrome is caused by Cushing's disease; in younger children, Cushing's disease is almost always the cause of Cushing syndrome (Stratakis 2012). ACTH-producing tumors, while overall rare, are more common in school-aged children and decrease in frequency in adolescent ages. Even less common PAs include somatotropinomas (5–15% of pediatric pituitary adenomas result in excess growth hormone production), and nonfunctioning adenomas (4–6% of pediatric adenomas). Thyrotropinomas and gonadotropinomas occur vanishingly rarely in children (Steele et al. 2010; Kunwar and Wilson 1999; Mindermann and Wilson 1995; Keil and Stratakis 2008).

21.2.2 Predisposing Factors

Most pituitary adenomas in children are sporadic. Nonetheless, prolactinomas, corticotropinomas, and somatotropinomas have been associated with multiple endocrine neoplasms type I (MEN-1) syndrome and somatotropinomas have also been associated with McCune Albright Syndrome, Carney Complex, and familial acromegaly (Lafferty and Chrousos 1999).

21.2.3 Presenting Symptoms

For functioning pituitary adenomas their presentation is typically associated with excess endocrine production. Patients with prolactinomas present with pubertal delay or failure, menstrual abnormalities, and/or galactorrhea. Patients with corticotropinomas present with signs and symptoms of excess cortisol production including weight gain and growth failure, hypertension, striae, premature adrenarche/hirsutism, diabetes, and other symptoms. Compared with adult patients with Cushing's syndrome, children with the syndrome are less likely to present with sleep disruption, muscular weakness, and problems with memory (Stratakis 2012). Patients with somatotropinomas present with symptoms of growth hormone excess including gigantism and acromegaly. Depending on the size of the tumor, functioning pituitary adenomas can also present with symptoms from the mass effects of the tumor. The symptoms associated with nonfunctioning PAs are due to the mass effects of the tumor, including pan-hypopituitarism and vision changes, classically bitemporal hemianopsia (Lafferty and Chrousos 1999). Children may be less likely to realize and bring to caregivers' attentions visual deficits until they become more profound.

21.2.4 Radiographic Findings

Magnetic resonance imaging (MRI) is the most important imaging modality for patients with suspected pituitary adenomas. Coronal and sagittal T1-weighted spin-echo MRI series of the sella and suprasellar regions before and after administration of gadolinium are the series of choice, and should be obtained with 3 mm or finer intervals. Pituitary adenomas often appear hypoenhancing compared to the normal pituitary gland. Dynamic contrast enhancing and spoiled gradient recalled acquisition (SPGR) MRI sequences have been described as helpful in visualizing corticotropinomas (Friedman et al. 2007; Patronas et al. 2003). Tumors smaller than 1 cm are classified as microadenomas and tumors larger than 1 cm are classified as macroadenomas. Corticotropinomas are usually microadenomas and up to a third are not visualized on MRI imaging (Kanter et al. 2005; Batista et al. 2005). Tumors greater than 4 cm are sometimes referred to as giant adenomas.

21.2.5 Workup

In addition to imaging and a complete history and physical examination, the workup of pituitary adenomas includes complete endocrinology evaluation and ophthalmologic assessment. Physical exam findings include visual deficits and stigmata of endocrinopathies such as striae and hirsutism, and gigantism. Because corticoadenomas are often too small to be seen on MRI imaging, bilateral inferior petrosal sinus sampling (BIPSS) with ovine corticotropin-releasing hormone (oCRH) administration is often part of the workup. Patients with ACTH-secreting pituitary adenomas have a central to peripheral ACTH concentration ratio greater than 2 (Stratakis 2012). Table 21.1 summarizes the physical signs and symptoms, laboratory findings, and principal treatment modalities for adenomas in children.

Table 21.1 Manifestations, laboratory evaluations, and preferred treatment modalities of pituitary adenomas in children

Tumor	Clinical manifestations	Laboratory evaluation	Preferred treatment modalities in children
Prolactinoma	Pubertal arrest, galactorrhea, menstrual abnormalities, pituitary deficiencies, visual symptoms, and headache	Elevated serum PRL+/− elevated serum GH	1. Dopamine antagonists such as bromocriptine, pergolide, and cabergoline
			2. Transsphenoidal surgery
Corticotropinoma	Weight gain, growth arrest, hypertension and striae, premature adrenarche/ hirsutism, menstrual irregularities, insulin resistance	Tests for Cushing Syndrome: 24 h UFC, low dose dexamethasone suppression test, BIPSS	Transsphenoidal surgery
Somatotropinoma	Gigantism before epiphyseal closure, acromegaly, glucose intolerance/diabetes, visual symptoms, headache, hyperprolactinemia symptoms	Random GH, IGF-1, oral glucose tolerated test, TRH test	Somatostatin analogs: octreotide long-acting agents (dopamine agonists)
Nonsecreting adenoma	Growth or pubertal failure, visual symptoms, headache, pituitary deficiencies		Transsphenoidal surgery

PRL prolactin, *BIPSS* bilateral inferior petrosal sinus sampling, *GH* growth hormone, *IGF* insulin growth factor, *UFC* urine free cortisol, *TRH* thyrotropin-releasing hormone

21.2.6 Treatment

In pediatric patients, the primary management of pituitary adenomas is medical or surgical, depending on the type of adenoma, and is shown in Table 21.1. The preferred surgical technique is transsphenoidal resection (TPR). TPR can be undertaken with very low rates of morbidity and mortality rate of approximately 0.5%. This is particularly true at large volume surgical centers with experienced surgeons. The most common complications of TPR include diabetes insipidus and fluid and electrolyte abnormalities. More serious complications like meningitis, vision loss, stroke, and cerebrospinal fluid leak occur in 1.5% of cases (Barker et al. 2003). In a series limited to pediatric patients, surgeons using microscopic endonasal TPR were able to achieve gross total resections (GTR) in 24 of 29 patients with tumors not involving the cavernous sinus, but only 2 of 7 patients with tumors involving the cavernous sinus. Normal pituitary function was restored in 19 patients without adjuvant treatment, the average hospital stay was 1.6 days, and serious surgical complications were limited to one case of sinusitis (Tarapore et al. 2011).

There is concern for the late effects and risks of radiation therapy. Therefore radiation therapy is reserved for cases of uncontrolled functioning tumors or patients with unresectable residual disease.

21.2.7 Radiation Therapy Techniques

When radiation is employed to treat pediatric patients with pituitary adenomas techniques are similar to those used in adults. For patients with tumors that are at least 3 mm from the optic chiasm and/or optic nerves, stereotactic radiosurgery is usually an option. For other tumors, conventionally fractionated radiation therapy is employed.

21.2.7.1 Conventionally Fractionated Radiation Therapy

When treating with conventionally fractionated radiation, the gross tumor volume (GTV) is defined by the MRI imaging and planning CT. Fine cut imaging, preferably less than 2 mm slices, is preferred for optimal tumor delineation. A clinical target volume (CTV) expansion may not be necessary for a tumor that is not infiltrative. A CTV expansion of 5 mm may be employed in areas where tumors are seen to be invasive, along the skull base, or in the cavernous sinus. Planning target volume (PTV) expansions of as small as 3 mm can be employed with daily image guidance, depending on the treating institution. Often the entire sella turcica is encompassed in the PTV. In addition to the target volumes, normal structures contoured should include the optic apparatuses (eyes, lacrimal glands, optic nerves, and optic chiasm), lens, hippocampus, and temporal lobes. The prescribed radiation dose is dependent on whether the tumor is a functioning or nonfunctioning PA. Nonfunctioning adenomas can be treated with 45–50.4 Gy in 1.8 Gy fractions. Functioning PAs should be treated with 50.4–54 Gy in 1.8 Gy fractions. In addition to photon radiation, conventionally fractionated proton radiation has been described (Wattson et al. 2014).

21.2.7.2 Stereotactic Radiosurgery

Stereotactic radiosurgery (SRS) provides the most conformal external beam radiation with the logistical advantage of a single fraction of radiation. This intervention can be delivered with either Gamma Knife (Elekta Instrument, Stockholm, Sweden) or linear accelerators. The GTV is pituitary adenoma and the prescribed dose is typically 15 Gy (12–20 Gy) to the tumor surface (50% isodose line with Gamma Knife) for nonfunctioning adenomas and 25 Gy (15–30 Gy) in functioning pituitary adenomas. The optic chiasm dose should be restricted to $\leq$9 Gy. An example is shown in Fig. 21.1.

21.2.8 Outcomes

Most reports are from series that are composed mostly or completely of adult patients. Outcomes are measured in terms of tumor volume, biochemical control, and sequelae of treatment. Tumor control greater than 85% is anticipated whether

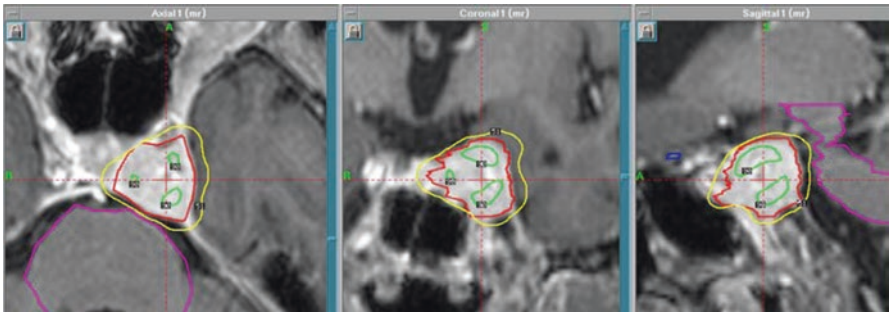

Fig. 21.1 Gamma knife planning for pituitary adenoma involving the left cavernous sinus. Axial, coronal, and sagittal views on T1-weighted MR scans. The 50% isodose line covers the lesion completely

patients are treated with fractionated radiation therapy or fractionated SRS. In most series of patients treated with SRS, the tumor was controlled in greater than 90% of cases. Biochemical or hormonal control is not as excellent as tumor control.

Corticotropinoma. In a review of 5 series involving 241 patients (including treated with SRS, conventionally fractionated photon radiation, and proton radiation) published between 2013 and 2014, the tumor control rates ranged from 83 to 100% and the biochemical remission rates were 22–76% (Tritos and Biller 2015). In a somewhat older review from 2002, 10 studies in which 255 patients were treated with fractionated radiation therapy had remission of Cushing's disease occurred in 55–100% of patients but at the expense of pituitary function in 14–56% of patients. The time to remission ranged from 4 to 26 months. Among 185 patients treated with SRS on 8 studies, the biochemical complete response rate was 63–100%, but occurred earlier than with conventionally fractionated radiation (Mahmoud-Ahmed and Suh 2002).

Somatotropinomas. In a review of 9 series of patients treated with conventionally fractionated radiation therapy, between 5 and 70% achieved remission, with the largest series (884 patients) achieving a 60% remission rate. Growth hormone reduction lagged tumor size regression, the former taking place over years. With stereotactic radiosurgery, biochemical remission rates range between 23 and 50% with side effect of hypopituitarism developing in up to 20% of patients (Castinetti et al. 2009).

Prolactinomas. Compared to other functioning PAs, prolactinomas are associated with the poorest metabolic control rates. In a recent review of SRS series published since 2000, the average endocrine remission rate was 34.7% using a median marginal dose of 24 Gy. The mean post-radiosurgery hypopituitarism rate was 14.8% (Ding et al. 2014).

Nonfunctioning PAs. In a review of 9 studies that included 1261 patients treated with conventional fractionation, the 10-year control rate was 74–97%. In 21 studies that included 648 patients, the local control with stereotactic radiosurgery was 88–100%. Up to a quarter of patients in these series developed pituitary dysfunction following radiation (Kanner et al. 2009).

21.3 Langerhans Cell Histiocytosis Involving the Pituitary Gland

21.3.1 Epidemiology and Predisposing Factors

LCH is caused by infiltrating CD1a+/CD207+ pathologic dendritic cells forming inflammatory lesions. It is typically characterized by skin and bone lesions, although other organ systems can be involved including the liver, spleen, bone marrow, lung, bone marrow, and central nervous system—including the pituitary gland. The incidence of LCH is between 2 and 10 children per million (Guyott-Goubin 2008). The median age at presentation is 1.8 years and the frequencies of presentations with single organ involvement and multi-organ involvement are approximately equal (Bhatia et al. 1997). LCH can infiltrate the hypothalamus and/or posterior pituitary gland and cause diabetes insipidus (DI). It is estimated that 5–50% of patients with LCH have DI and it is often associated with skull lesions that may precede the DI (Grois et al. 1995; Dunger et al. 1989). DI can present before or after the presentation of other LCH lesions (Prosch et al. 2004; Donadieu et al. 2004). There is conflicting data regarding whether systemic treatment of LCH presents subsequent development of DI (Donadieu et al. 2004; Grois et al. 2006; Chellapandian et al. 2015). Recurrent BRAF mutations have been found in 57% of LCH lesions (Badalian-Very et al. 2010). Patients are risk-stratified by organ system involvement; pituitary gland involvement without involvement of the liver, spleen, or bone marrow is considered low-risk.

21.3.2 Radiographic Findings and Workup

Patients often present with an erythematous, papular rash resembling a diaper rash. They may also have a focal painful bone lesion that appears as a well-circumscribed lytic lesion on plain films. Such patients should undergo a bone survey to look for additional lesions. The diagnosis is confirmed with positive immunohistochemical staining of S100 and CD1a and the presence of Birbeck granules on electron microscopy as seen in Fig. 21.2 (Badalian-Very et al. 2013). Patients with DI by history and laboratory evaluation, or patients with LCH lesions of the facial bones or anterior or middle cranial fossa, should also undergo an MRI of the brain with particular attention to the T1 sequences of the pituitary gland pre- and post-gadolinium. It is common to find absence of the bright spot or infundibular thickening on T1-weighted sequences, the latter demonstrated in Fig. 21.3.

21.3.3 Treatment

The use of radiation therapy in treating LCH is declining. Although LCH lesions are extremely sensitive to radiation, concerns about late effects have led to a decrease in its use except for rare circumstances. Therefore, 6–10 Gy of radiation is reserved for severely painful solitary lesions where resection, curettage, or steroid injection has

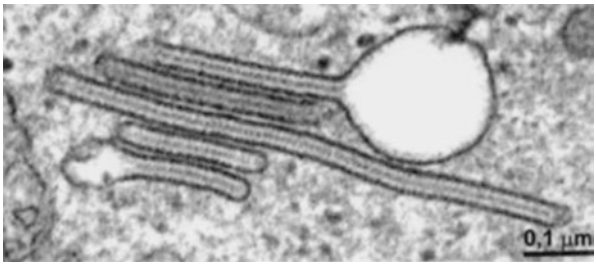

Fig. 21.2 Birbeck granules seen on electron microscopy

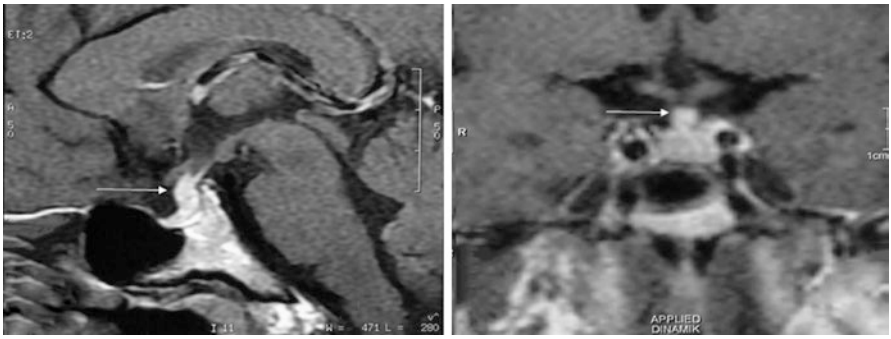

Fig. 21.3 Sagittal and coronal T1-weighted images demonstrate infundibular thickening. From Valladeau J, Dezutter-Dambuyant C, Saeland S. (2003) Langerin/CD207 Sheds Light on Formation of Birbeck Granules and Their Possible Function in Langerhans Cells. Immunologic Research. 28(2)93–1007

either been ineffective or would be too morbid. Patients with lesions in the facial bones, anterior cranial fossa, or middle cranial fossa receive 1 year of prednisone and vinblastine in an effort to decrease the risk of CNS involvement (Grois et al. 2006). The same regimen is effective for patients with CNS involvement.

The role of radiation therapy in treating LCH patients with DI is controversial. Patients with DI at presentation do not have improvement of DI with chemotherapy. Therefore, radiation therapy has been used in an effort to avert or ameliorate DI. In small retrospective studies, radiation therapy did not improve DI symptoms in long-term survivors (Kocheta et al. 2014; Grois et al. 2006; Smith et al. 1973). However, larger cohorts from the Mayo Clinic and the Massachusetts General Hospital have reported decreased desmopressin use associated with use of radiation. In the former case, 10 of 28 patients treated with radiation had improvement of DI, with a higher complete response rate in patients starting treatment within 14 days of diagnosis (5 of 19, compared to 1 of 9, respectively) (Minehan et al. 1992). In the latter series, 2 of 14 patients had complete response with both patients initiating radiation therapy

within 3 days of diagnosis, and in both cases the initial ADH deficiency was not complete (Rosenzweig et al. 1997). Thus, if there is a role for radiation therapy in LCH-induced DI, it is with early initiation, and has to be weighed against late side effects and risks.

21.3.4 Radiation Techniques

The case series describing radiation therapy are largely from the era of two-dimensional or three-dimensional planning. For example, the series from Massachusetts General Hospital describes 5 cm × 5 cm to 7 cm × 7 cm portals with parallel opposed fields (Rosenzweig et al. 1997). However, modern radiation therapy techniques should be employed to conformal isodose lines around the hypothalamus and sella, and reduce dose to normal tissues like the temporal lobes and hippocampi. Typical radiation doses range from 10 to 20 Gy in conventional fractionation.

21.3.5 Outcomes and Late Effects

Low-risk patients—such as those with pituitary gland involvement—have an approximate 99% overall survival rate; however, many of them will first have two to four relapses requiring subsequent treatments (Minkov et al. 2008).

The efficacy of radiation therapy in treating DI in LCH patients is described above. No prospective studies have compared radiation therapy versus no radiation therapy in management of LCH associated DI. In assessing late effects of treatment, it is important to note that growth hormone function can be disrupted in patients who do not undergo radiation therapy (Donadieu et al. 2004). However, the Mayo Clinic observed that patients who received radiation therapy were more likely (43% vs. 12%) to experience additional endocrine abnormalities than those patients who did not receive radiation (Minehan et al. 1992). Late effects on bone growth and neurocognitive function have not been reported in the case series cited.

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Pediatric Brain Metastases

22

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Abstract

Brain metastases (BM) are a frequent occurrence in adults malignancies, with an expected 20–40% of adult patients expected to develop BM during their disease course. In comparison, the brain is a rare site of metastasis in pediatric extracranial solid tumors with an estimated incidence in the order of 1–10%. Nevertheless, with continuing improvements in systemic therapies leading to prolonged survival, the incidence of pediatric BM may rise. While there is a broad body of literature on the incidence and management of adult BM, including large randomized clinical trials, there is a paucity of published data on pediatric BM, limited primarily to small series and cases reports. Pediatric BM may present synchronously or more commonly in the setting of prior extracranial metastases, particularly to the lungs. Treatment has typically included surgical resection for isolated or symptomatic lesions, radiation therapy, chemotherapy, and possibly immunotherapy. Although the outcome for pediatric patients with BM is in general very poor, there are some reports of long-term survivors, suggesting that aggressive multimodal therapy may be warranted in a subset of patients.

22.1 Introduction

The development of brain metastases (BM) is a frequent occurrence in adults with cancer, with an expected 20–40% of adult patients expected to develop BM during their disease course, particularly patients with lung and breast carcinomas, gastrointestinal cancers, and melanoma (Nayak et al. 2012). As a result, there is an extensive body of literature regarding the incidence and management of adult BM, including large randomized clinical trials. Moreover, the published data on the use of advanced radiation therapy treatment delivery techniques, such as stereotactic radiosurgery (SRS), has focused overwhelmingly on adults with BM. In comparison, the brain is a very rare site of metastasis in pediatric solid tumors and the incidence is not as well defined, being characterized primarily by retrospective case series and case reports. Complicating the interpretation of the paucity of available data is significant heterogeneity between studies, including which pediatric malignancies are included or excluded as well as the fundamental definition of BM. There are generally two types of metastatic spread to the brain described: extradural and parenchymal metastases. Malignancies such as rhabdomyosarcomas and osteosarcomas which arise from neighboring parameningeal structures can spread locally leading to extradural space metastases. Meanwhile, the more traditional definition of BM is that of hematologic spread resulting in circumscribed lesions in the brain parenchyma. While some of the literature includes both types of BM, other studies are limited to only parenchymal lesions arising from distant hematogenous spread. The aim of this chapter is to describe the epidemiology and etiology of BM in the pediatric oncology population as well as define the typical presenting symptoms and

radiographic findings. We will also discuss the work-up, management, and clinical outcomes of BM in pediatric oncology, elaborating on some of the more common pediatric tumors predisposing to BM.

22.2 Epidemiology

Based on a review of the contemporary literature, the overall incidence of BM in pediatric oncology patients is estimated to be between 1–10% in clinical studies and 6–13% in autopsy series (Bouffet et al. 1997; Vannucci and Baten 1974; Graus et al. 1983; Wiens and Hattab 2014; Stefanowicz et al. 2011; Suki et al. 2014; Kebudi et al. 2005). The incidence of brain metastasis in children was first estimated from autopsy data from 1950 to 1972, when Vannuci and Batten found the presence of BM in 13 of 217 (6%) of patient with pediatric malignancies; interestingly noting that all patients who had developed BM had also been found to have pulmonary metastases (Vannucci and Baten 1974). In a subsequent review of autopsy data from 1973 to 1982, parenchymal BM were noted in 18 of 139 patients (12.9%) (Graus et al. 1983). In a review of brain metastases in children with solid tumors treated at the Centre Léon Bérard between 1987 and 1995, 162 of 486 patients eventually developed distant metastases, including 12 brain metastases (2.4%) detected by imaging, with 10 patients having clinically detectable BM (Bouffet et al. 1997). The most common tumors causing brain metastases were Ewing's sarcoma (three patients), neuroblastoma (three patients), and osteogenic sarcoma (three patients). Several recent single institution registry series have also reported a similar incidence. For instance, Suki et al. reported the incidence of BM (parenchymal, epidural, and dural) from pediatric extracranial solid tumors treated at The University of Texas M.D. Anderson Cancer Center between 1990 and 2012 and noted an incidence of 1.4%, with 54 of 3950 patients diagnosed with BM (Suki et al. 2014). A Polish series determined 10 of 511 (2.0%) pediatric patients treated from 1992 to 2011 for extracranial solid tumors developed BM (Stefanowicz et al. 2011). Meanwhile, Wiens et al. reported 26 out of almost 4000 pediatric patients treated at Indiana University developed BM (not from direct extension), with an estimated incidence of about 2.2% (Wiens and Hattab 2014). While the spectrum of primary tumors may vary significantly between contemporary series, with for instance the Indiana series having >3000 germ cell tumors while the MD Anderson series having a relative predominance of sarcomas, the overall incidence of BM appears to be about 1–3% in recent studies.

BM in children are most likely to arise from soft tissue sarcoma, Ewing sarcoma, osteosarcoma, melanoma, retinoblastoma, neuroblastoma, kidney tumors including Wilms tumor, germ cell tumors, acute lymphoblastic leukemia, acute myelogenous leukemia, and non-Hodgkin lymphoma. The majority of those from solid extracranial tumors are supratentorial (89–100% in published series), and in most series, 60–90% of the metastasis are solitary (Wiens and Hattab 2014; Stefanowicz et al. 2011; Suki et al. 2014; Kebudi et al. 2005; Paulino et al. 2003; Goldman et al. 2007).

22.3 Pathophysiology

The development of BM in children as the sole site of metastatic disease appears to be quite rare and most commonly occurs in the presence of existing extracranial metastases. The site of initial metastatic disease has most frequently been found to be the lungs; however, the liver, bone, bone marrow, and abdomen are also noted sites of metastases prior to the development of brain lesions (Wiens and Hattab 2014; Stefanowicz et al. 2011; Suki et al. 2014; Kebudi et al. 2005; Goldman et al. 2007). Although BM may develop directly from a primary tumor, there are few reports of isolated CNS parenchymal metastases. The precise mechanism and sequence of events culminating in the development of BM has not been entirely elucidated; however, it is a multistep process which involves interplay between tumor cells phenotype and the brain microenvironment with ample evidence suggesting a "seed and soil" hypothesis. Parenchymal BM primarily arise from a hematogenous route of spread following a chain of complex steps typically referred to as the "metastatic cascade" including detachment of tumor cells, intravasation, transport or embolization, extravasation, colonization, and angiogenesis. The positive correlation with the presence of pulmonary metastases may plausibly be attributed to the access of escaped metastatic cells to the arterial circulation returning to the left atrium where tumor cells can subsequently enter the intracranial arterial system and seed the brain, with a predilection for the gray and white matter junction (Sul and Posner 2007). Meanwhile, for leukemias and lymphomas, CNS spread is thought to be through hematogenous spread via the venous and capillary system, petechial hemorrhages during thrombocytopenia, or via direct extension from the bone marrow. The choroid plexus and bridging veins between the bone marrow and superficial arachnoid are thought to be potential sites of infiltration into the central nervous system as well (Goldman et al. 2007; Sul and Posner 2007).

22.4 Clinical Presentation

Due to the rare incidence of BM in children, routine staging or surveillance imaging of the brain is not commonly performed. As such, most BM are detected after presenting with symptoms which prompt CNS-directed imaging revealing intracranial disease. As previously discussed, patients that develop intracranial disease are more likely to have disseminated metastases at presentation, particularly to the lung, or have recurrent or multiply recurrent disease that has already metastasized to extracranial sites. With improvements in survival for patients with aggressive disease as well as the improved detection with magnetic resonance imaging, the incidence of BM in children may thus rise (Goldman et al. 2007). The median age of incidence of BM is between age 11 and 13 in recent published clinical series and occurs between a median of 8 months to 16 months after diagnoses of the primary tumor (Stefanowicz et al. 2011; Suki et al. 2014).

Pediatric patients with BM from solid tumors often have symptoms of increased intracranial pressure with commonly reported symptoms including focal neurologic deficits such as motor weakness or sensory deficits, seizures, altered mental status, headache, nausea and vomiting, nystagmus, ptosis, head tilt, and visual field deficits (Wiens and Hattab 2014; Suki et al. 2014; Paulino et al. 2003; Goldman et al. 2007; Parasuraman et al. 1999). For leukemias and lymphomas, additional commonly reported symptoms may include nuchal rigidity, irritability, cranial nerve involvement manifesting as tinnitus, vertigo, facial numbness, and oculomotor palsies.

22.5 Imaging of Brain Metastases

As is the case in the adult setting, imaging plays a vital role in the diagnosis and management of BM, both in the setting of a known diagnosis of malignancy with new neurological signs or symptoms and in screening in patients with tumors with a relative elevated predilection for the development of BM. Moreover, pediatric BM have similar neuroimaging findings to those occurring in adults. BM are predominately located at the gray-white matter junction and at border zones between major arterial vascular territories and are most frequently found in the cerebral hemispheres, followed by the cerebellum and less frequently involving the basal ganglia.

Although magnetic resonance imaging (MRI) is more sensitive than computed tomography (CT) for the detection of BM, CT remains an important modality in the initial evaluation and emergent perioperative assessment. Non-enhanced CT is frequently the first imaging modality obtained upon presentation with neurological deficits due to its accessibility and tolerability as well as its efficiency in ruling out life-threatening emergencies which require prompt neurosurgical intervention such as hemorrhage or hydrocephalus. BM may appear hypodense, isodense, or hyperdense with hypodensity associated with vasogenic edema while acute hemorrhage presents with a hyperdense signal. Contrast-enhanced is often pursued if there is a contraindication or lack of prompt accessibility to MRI, with BM typically having a nodular solidly enhanced or ring-enhanced appearance. Contrast-enhanced MRI is, however, more sensitive in detecting small or multiple brain metastases and thus if an MRI is anticipated, there may be no additional benefit to obtaining a contrast-enhanced CT. Similarly, if there are diffuse BM noted on CT and there is no plan for surgical or stereotactic radiosurgery intervention, there is likely to be little added value to obtaining a contrast-enhanced MRI. On MRI, BM typically exhibit iso- or hypointense signal on T1-weighted images although hyperintensity may be noted in the case of intratumoral hemorrhage. T2-weighted and FLAIR images typically demonstrated hyperintensity extending beyond the lesion reflecting vasogenic edema. On contrast-enhanced MRI images, BM may appear as either a solid nodular hyperintensity or a ring-like hyperintensity with central hypointensity representing central necrosis (Stefanowicz et al. 2011; Porto et al. 2010; Nabavizadeh et al. 2014). There can be additional tumor histology-dependent characteristics such as

calcifications in osteosarcoma and hemorrhagic appearance in melanoma or neuroblastoma (Porto et al. 2010; Nabavizadeh et al. 2014). Advanced MRI imaging techniques such as magnetic resonance spectroscopy, magnetic resonance perfusion, and diffusion-weighted imaging may also be helpful in establishing a diagnosis of BM versus other possible pathologies. Figure 22.1 illustrates the MRI characteristics of a BM in a pediatric patient with metastatic high-grade sarcoma.

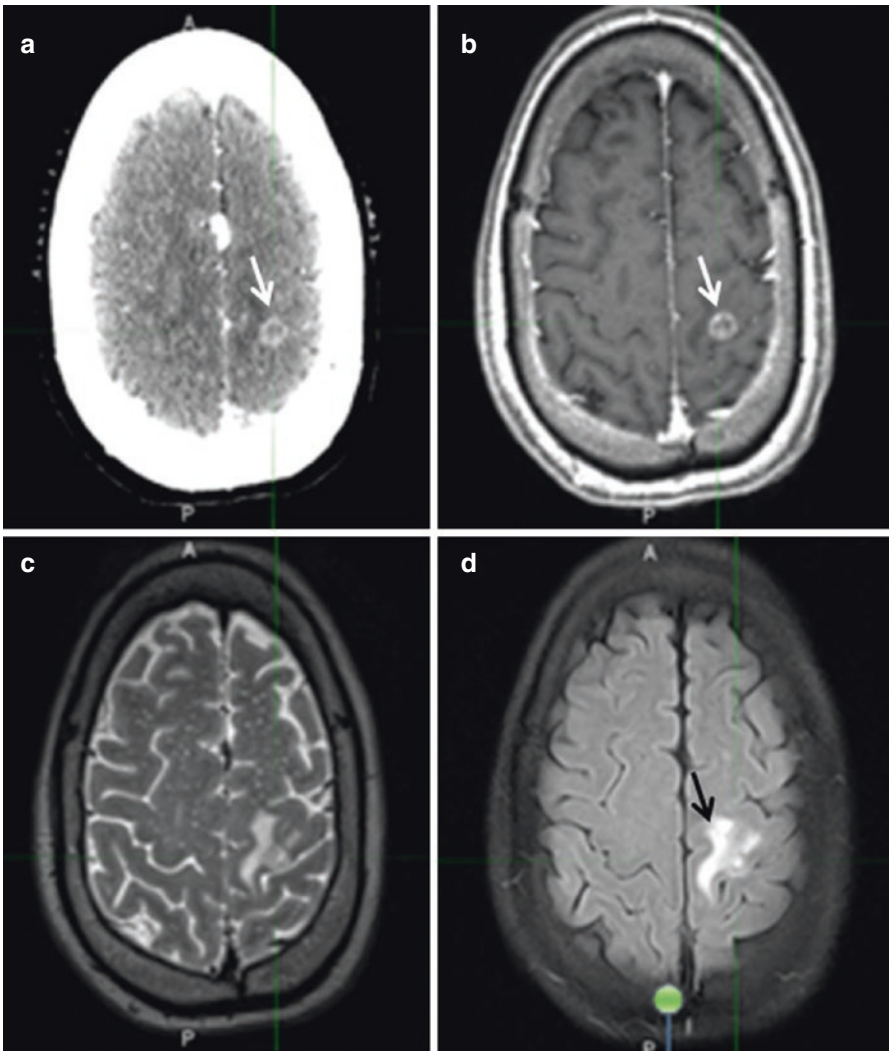

Fig. 22.1 (**a**) Contrast-enhanced CT scan with solitary ring-enhancing lesion (*white arrow*), (**b**) contrast-enhanced T1-weigted MRI with solitary ring-enhancing lesion with hypointense necrotic core (*white arrow*), (**c**) T2-weighted MRI and (**d**) FLAIR images demonstrating hyperintensity extending beyond the lesion reflecting vasogenic edema (*black arrow*)

22.5.1 Ewing Sarcoma

Ewing sarcoma is the second most common bone tumor in pediatric patients, resulting in 200–250 cases a year in the United States. Primary sites of involvement include the pelvis, femur, and ribs. Due to advances in surgery, chemotherapy, and radiation therapy, survival approaches 70–80% for localized disease (Goldman et al. 2007). Though the main sites of metastases are the lungs, bone, and bone marrow, Ewing sarcoma is one of the most common types of pediatric cancers to develop BM, with 3–16% of patients progressing to CNS metastases. Sixty to 100% of cases reported in the literature were found to have simultaneous lung lesions (Bouffet et al. 1997; Stefanowicz et al. 2011; Kebudi et al. 2005; Paulino et al. 2003; Parasuraman et al. 1999). Parasuram et al. who included both parenchymal and direct extension estimated that close to half of the metastases are hematogenous in origin while the other half are via direct extension (Parasuraman et al. 1999). In their analysis, Bouffett et al. only included patients with parenchymal metastases and excluded patients with disease arising from direct extension; estimating the rate of parenchymal disease from hematogenous spread as approximately 5.4% (Bouffet et al. 1997).

The management of BM arising from Ewing sarcoma has generally included consideration of surgical resection in the setting of symptomatic or solitary lesions as well as whole brain radiation therapy (WBRT) and chemotherapy. Paulino et al. reported six cases of Ewing sarcoma patients with BM. While BM was identified at autopsy in one case, the balance were treated with either chemotherapy alone, surgery followed by radiation, or a combination of radiation and chemotherapy. Two patients died of their metastatic CNS disease, and the remaining three died from systemic disease. The median survival after the diagnosis of BM was 1.5 months (Range: 1–9 months) (Paulino et al. 2003). Weins et al. reported three Ewing sarcoma patients in their series with BM were treated with a combination of surgery and radiation with a median survival of 4 months from the diagnosis of CNS spread (Wiens and Hattab 2014). While most patients were treated with WBRT in published series, there are isolated case reports utilizing stereotactic radiation in the setting of adjuvant treatment (van Dams et al. 2016). Nonetheless, the outcomes have been poor with most patients dying within 1 year of the development of BM though there are some reports of long-term survivors (Paulino et al. 2003; Parasuraman et al. 1999; van Dams et al. 2016).

22.5.2 Rhabdomyosarcoma

Rhabdomyosarcomas are the most common pediatric soft tissue sarcomas with approximately 250 cases a year in the United States, comprising approximately 10% of childhood solid tumors. Up to 20% of patients will eventually progress to metastases, most frequently in the lungs, lymph nodes, and bone marrow (Goldman et al. 2007). The incidence of BM in the literature has ranged from 2 to 10%. In a study of 104 patients with rhabdomyosarcoma, 6.7% of patients developed BM,

with all seven patients having prior or synchronous distant metastatic disease (Paulino et al. 2003). BM develops at a median of 12 months after initial diagnosis via hematogenous spread or through direct extension (Paulino et al. 2003; Parasuraman et al. 1999).

Risk factors include parameningeal disease and distant disease at extracranial sites. Parameningeal rhabdomyosarcoma with cranial nerve palsies, intracranial tumor extension, and skull base erosion are at a particularly increased risk of metastatic spread to the brain. The treatment approach of BM has similarly included possible surgical resection of solitary and symptomatic lesions as well as radiotherapy and chemotherapy, with parenchymal BM carrying a poor overall prognosis with most patients dying within 1 year (Kebudi et al. 2005; Paulino et al. 2003; Parasuraman et al. 1999). Chemotherapy has typically consisted of multiple agents, at times including intrathecal methotrexate. Reported radiation doses and fields have not been standardized but have in general consisted of WBRT with doses ranging from 30 Gy in 20 fractions to 50 Gy in 25 fractions (Stefanowicz et al. 2011; Paulino et al. 2003). A recent case series reported the outcomes of two rhabdomyosarcoma patients with infratentorial metastases. Both patients were treated with aggressive trimodality treatment. One patient aged 1 year and 11 months underwent a gross total resection followed by 23.4 Gy to the tumor cavity and ifosfamide/carboplatin/etoposide (ICE) chemotherapy and remains alive without disease at 8 months. The second patient developed metastatic disease involving the pons and cerebellum 16 months after initial diagnosis and was treated with subtotal resection, craniospinal irradiation (CSI) to 30.6 Gy followed by an additional 14.4 Gy boost, ICE chemotherapy, and allogenic stem cell transplant. He remains alive without disease at 10 months (Osawa et al. 2011).

22.5.3 Osteosarcoma

Osteosarcoma is the most common pediatric primary bone tumor, typically arising from the femur, proximal tibia, or pelvis. Although the lungs are the most common site of distant metastases, approximately 1.8–16% of pediatric osteosarcoma patients will develop CNS metastases, making it one of the most common primary solid tumors to develop BM (Graus et al. 1983; Wiens and Hattab 2014; Suki et al. 2014; Paulino et al. 2003; Marina et al. 1993). In some series, the incidence of BM has increased in the setting of modern chemotherapy, from 4.5% before 1982 to 15.5% from 1982 onward (Marina et al. 1993). Patients develop CNS lesions at a median of 22–24 months from initial diagnosis (Graus et al. 1983; Paulino et al. 2003). Although metastatic disease can arise from extracranial extension from lesions in the calvarium, the primary method of spread is thought to be most frequently hematogenous. In a retrospective study of 254 patients treated at St. Jude Children's Hospital, 13 patients developed parenchymal metastatic disease compared to 3 with spread from adjacent sites (Marina et al. 1993). Moreover, most osteosarcoma patients with BM have extracranial metastatic disease, with 70–100%

patients presenting with prior or simultaneous pulmonary metastases (Wiens and Hattab 2014; Paulino et al. 2003; Marina et al. 1993). Nevertheless, there are rare reports of patients presenting with a parenchymal BM as their first site of relapse (Niazi et al. 2009).

Similar to the management strategies employed in other sarcomas, such as rhabdomyosarcoma and Ewing sarcoma, the treatment of BM in osteosarcoma involves surgical resection for solitary or symptomatic lesions as well as radiation therapy and possibly further chemotherapy. The prognosis after the diagnosis of BM is typically bleak, with most patients succumbing within 6 months, although there are some exceptional reported cases of long-term survivors after 5 years treated with multimodal therapies (Wiens and Hattab 2014; Marina et al. 1993; Wexler et al. 1993).

22.5.4 Neuroblastoma

Neuroblastoma comprises 8–10% of all childhood cancers, making it the most common extracranial solid tumor in children. The treatment approach is multimodal and may include chemotherapy, surgery, radiation therapy, high-dose chemotherapy with stem cell rescue, and immunotherapy. Although infants less than 1 year old tend to have very favorable outcomes despite the presence of metastatic disease, older children may present with extensive metastatic disease at the time of diagnosis with a very poor prognosis. Metastases typically develop by means of lymphatic and hematogenous spread, most commonly to bone marrow, bone, liver, skin, and uncommonly lungs (Goldman et al. 2007). BM are a rather rare occurrence in neuroblastoma although they have been reported in a number of series with increasing incidence over time. In fact, the incidence of BM in newly diagnosed neuroblastoma has been reported to have increased from 1.7% in the early 1980s to 11.7% in the 1990s, likely due to more effective systemic therapies (Kramer et al. 2001). Contemporary series estimate the incidence of BM between 1 and 10.4% (Suki et al. 2014; Paulino et al. 2003; Matthay et al. 2003; Zhu et al. 2015). Patients typically present in conjunction with extracranial disease or as isolated metastases, and disease may involve both the parenchyma and the leptomeninges, with the former being more common in infants older than 1 year of age and the later more common in infants less than 1 year old (Matthay et al. 2003; DuBois et al. 1999). As metaiodobenzylguanidine (MIBG) imaging has been reported to have a low sensitivity for smaller brain metastases, MRI imaging remains the favored imaging modality when BM are suspected (Nabavizadeh et al. 2014; Matthay et al. 2003).

Management of neuroblastoma BM may consist of surgical resection of isolated or symptomatic lesions, WBRT or focal irradiation, and salvage chemotherapy with stem cell rescue. Even with aggressive multimodal treatment, the prognosis remains very poor and most patients with BM succumb to their disease (Paulino et al. 2003; Croog et al. 2010). Nevertheless, rare long-term survivors have been reported

(Stefanowicz et al. 2011; Zhu et al. 2015; Croog et al. 2010). A study from St. Jude's Children's Research Hospital of high risk neuroblastoma patients treated for BM between 1979 and 1989 reported two long-term survivors who were treated with CSI and were alive at 50 and 62 months after diagnosis of relapse (Kellie et al. 1991). More recently, Croog et al. reported the results of 26 patients with parenchymal BM treated at Memorial Sloan Kettering Cancer Center from 1989 to 2007. The study included two cohorts: 16 patients who received CSI and 13 patients who received WBRT or focal irradiation in conjunction with their salvage treatment. The patients in the CSI cohort received between 12.6 and 21.6 Gy to the neuroaxis with or without a boost to the tumor cavity from 25.2 to 36.6 Gy in conjunction with intra-Ommaya radio-immunotherapy with ^{131}I-8H9 and ^{131}I-3F8. While 2 patients died of their disease (did not receive intra-Ommaya radio-immunotherapy) and 1 patient died of other causes, 13 patients remain alive at a median follow-up of 28 months. Three patients experienced a CNS recurrence which was treated with additional craniospinal or focal radiation therapy. Patients who were treated with WBRT or focal irradiation had a median survival of 8.8 months after CNS diagnosis, and 62% of patients experienced a CNS recurrence. Of note, the patients not receiving CSI also did not receive intra-Ommaya radioimmunotherapy at diagnosis of CNS disease (Croog et al. 2010). Zhu et al. reported their series of eight patients with high-risk neuroblastoma with brain metastases; of three long-term survivors (>2 years), two received craniospinal irradiation. None of these patients received intra-Ommaya radio-immunotherapy (Zhu et al. 2015). While the optimal regimen has not been determined, given that most long-term survivors reported in the literature received CSI, incorporating the neuroaxis in the radiotherapy treatment field and consideration of radio-immunotherapy appears to be the most effective treatment approach reported to date.

22.6 Hepatoblastoma

Hepatoblastoma is associated with multiple genetic syndromes (Beckwith-Wiedemann syndrome, Familial Adenomatous Polyposis syndrome, Li-Fraumeni syndrome, and Trisomy 18). It presents with right upper quadrant mass, anemia, thrombocytosis, abdominal pain, and increase in alpha-fetoprotein (AFP). Neoadjuvant chemotherapy followed by resection has improved survival to over 80% for patients who underwent a total resection (Goldman et al. 2007). As with many of the discussed tumors, the most common site of metastases is the lung. The incidence is between 3 and 5% (Wiens and Hattab 2014). A recent review of brain metastases arising from hepatoblastoma reports 39 cases of BM in published literature. Of these patients, 24% patients were diagnosed at age older than 4, and 63% had synchronous or prior pulmonary metastases. Treatment is similar to other brain metastases: surgery for solitary lesions, radiation, and/or chemotherapy (Rai and Feusner 2016). The cases of prolonged survival beyond 1 year were achieved with a combination of surgical resection, focal radiation therapy, and systemic chemotherapy (Rai and Feusner 2016; Robertson et al. 1997).

22.7 Germ Cell Tumors

Extracranial germ cell tumors account for approximately 3–5% of all pediatric cancers, typically arising from the ovaries, testes, coccyx, and mediastinum (Goldman et al. 2007). As intracranial germ cell tumors are discussed elsewhere in this book, the discussion below focuses specifically on BM from extracranial primaries.

The reported incidence of brain metastases from germ cell tumors varies significantly, ranging between 0.005 and 20% (Wiens and Hattab 2014; Suki et al. 2014; Spunt et al. 2004; Gobel et al. 2010). A study of 206 patients with extracranial germ cell tumors treated at St. Jude Children's Research Hospital over a period of 40 years found 16 patients with CNS metastases. Two were diagnosed with metastases at presentation; 21 developed CNS disease during the disease course; and 2 patients were found incidentally to have CNS disease at autopsy evaluation (Spunt et al. 2004). Recent series from Indiana University reported an incidence of 0.5% with follow-up of over 3000 patients treated for germ cell tumors, while Suki et al. reported an incidence of 43%, with an elevated incidence particularly among patients with the choriocarcinoma histologic subtype (Wiens and Hattab 2014; Suki et al. 2014). Moreover, Stefanowicz et al. reported a case of patient with a mixed germ cell tumor who developed BM with pathologic evaluation demonstrating predominantly features of the choriocarcinoma component (Stefanowicz et al. 2011). As such, patients with choriocarcinoma may be at relative increased risk of BM in comparison to other histologic subtypes of germ cell tumors. Patients develop BM at a median of 7 months after initial diagnosis, with the majority of patients having pulmonary metastases prior to or at the time of BM (Spunt et al. 2004). In addition to histologic subtype and pulmonary metastases, primary mediastinal disease is also associated with increased risk for BM (Gobel et al. 2010).

Similar to other pediatric BM, patients with extracranial germ cell tumors with BM are treated with a combination of surgical resection, radiation, and chemotherapy. Most patients treated with radiation received between 20 and 35 Gy to the partial brain or 30–35 Gy to the whole brain with a boost of 3.5–14.8 Gy (Spunt et al. 2004). Though outcomes are generally poor, aggressive multimodal therapy may lead to rare long-term survivors (Wiens and Hattab 2014; Spunt et al. 2004).

22.8 Melanoma

Melanoma accounts for 1–3% of all pediatric cancers. Prognosis is dependent on stage, similar to that of adults. The incidence of BM in patients with melanoma has been reported between 8 and 18% and at a median of 20 months following diagnosis (Goldman et al. 2007; Rodriguez-Galindo et al. 1997). In a review of 44 pediatric melanoma patients treated at St. Jude's Children's Research Hospital, Rodriguez-Galindo et al. reported the outcomes of 8 patients who developed CNS disease. Of the six patients with available demographic information, five had extracranial metastatic disease, four with pulmonary metastases. On imaging, most of the lesions

were supratentorial, though two patients had cerebellar lesions; three patients had solitary metastases; and most of the lesions demonstrated intralesional hemorrhage. The patients were treated with a combination of symptomatic management, WBRT to 45 Gy, chemotherapy, surgery, and interferon-alpha. Despite aggressive therapy, only three of eight patients were alive at a median of 5 months, with most dying of their CNS disease. The one long-term survivor in this series (alive without disease at 34 months) was treated with surgical resection, radiation therapy, multi-agent chemotherapy, and interferon-alpha (Rodriguez-Galindo et al. 1997). Similarly, in another reported case of a long-term survival of 13 years, the patient was treated with a similar multimodal approach, including surgical resection, radiotherapy, chemotherapy, and immunotherapy (Suki et al. 2014).

Melanoma has long been thought to exhibit a relative radio-resistance, with hypofractionated radiotherapy using larger doses per fraction resulting in improved local control rates (Stinauer et al. 2011). Similarly, the approach for BM in adults has transitioned to primarily more focal stereotactic radiosurgical techniques, either alone or with immunotherapy (Selek et al. 2004; Ahmed et al. 2016; Kiess et al. 2015). Incorporating similar strategies in the pediatric population may yield similar benefits.

22.9 Wilms Tumor

Wilms tumor accounts for 6–7% of pediatric malignancies with an incidence of 500 cases per year in the United States. Recurrence and prognosis is influenced by tumor size, patient age, histology, staging, loss of heterozygosity of chromosome 16q and 1p, level of telomerase expression, and tumor ploidy. Treatment is multimodal and includes surgery, chemotherapy with adjuvant radiation depending on stage and anaplastic histology. The most common metastatic sites are the lungs, regional lymph nodes, liver, and rarely to the bone. As in other tumors, multiple series have demonstrated an association with pulmonary metastases and the development of BM (Wiens and Hattab 2014; Paulino et al. 2003; Goldman et al. 2007). Advances in chemotherapeutic agents have decreased the rate of intracranial metastases from 13% in pre-1975 autopsy studies to 0–5% in modern studies (Vannucci and Baten 1974; Graus et al. 1983; Wiens and Hattab 2014; Suki et al. 2014; Kebudi et al. 2005; Paulino et al. 2003; Lowis et al. 1998). The time to development of CNS metastases ranges from 2 to 112 months after initial diagnosis (Wiens and Hattab 2014; Lowis et al. 1998).

Treatment approaches have typically included a combination of surgical resection, radiation, and chemotherapy with ifosfamide, carboplatin, and etoposide (ICE). Radiation therapy has usually consisted of WBRT with the use of CSI also having been reported (Bouffet et al. 1997; Wiens and Hattab 2014; Paulino et al. 2003; Lowis et al. 1998). There have been multiple reports of long-term survivors who were alive from 5 to 18 years after treatment completion; most of whom were treated with a multimodality approach including both radiation therapy and chemotherapy (Lowis et al. 1998).

22.10 Clear Cell Sarcoma of the Kidney

Clear cell sarcoma of the kidney (CCSK) constitutes 3–6% of primary childhood renal tumors. It typically has a more aggressive clinical behavior than Wilms tumor, and it is managed with surgical resection, chemotherapy, and radiation therapy. In contrast to the other solid tumors, bone tends to be the first site of metastases, with other sites including liver, lung, lymph nodes, and brain. Advances in chemotherapeutic agents have improved survival, with BM thought to be due to progression of micrometastatic disease that was initially present at the time of diagnosis (Goldman et al. 2007). The incidence of BM is reported to be from 20 to 30% in modern retrospective series (Wiens and Hattab 2014; Suki et al. 2014), with the median time from diagnosis to BM ranging from 22 to 24 months (Wiens and Hattab 2014; Radulescu et al. 2008). Radulescu et al. reported the results of eight patients who developed BM after initial diagnosis. Patients were treated with a combination of surgical resection, ICE chemotherapy, and radiation, with six patients alive without evidence of disease at a median follow-up of 30 months (Range: 24–71 months). All six patients had received radiation therapy and four patients received autologous stem cell transplant (Radulescu et al. 2008).

22.11 Rhabdoid Tumor of the Kidney

Malignant rhabdoid tumor of the kidney (RTK) occurs more frequently in infants and accounts for 1.5% of pediatric kidney cancers. It is an aggressive disease, with more than 80% of patients dying within a year of diagnosis. Treatment is multimodal and consists of surgery, chemotherapy, and radiation therapy. Studies have reported an incidence of BM of 10–21%, with CNS involvement present either at the time of diagnosis or during the disease course (Wiens and Hattab 2014; Kebudi et al. 2005). In the NWTS 1–5 studies, 30 of 142 patients with RTK developed CNS metastases. Of these, ten patients had pathologic analysis of their CNS disease. While metastases were confirmed in four patients, the balance of patients had a secondary CNS tumor (primitive neuroectodermal tumor, anaplastic astrocytoma, and atypical teratoid/rhabdoid tumor) (Tomlinson et al. 2005). Despite aggressive multimodal treatment, most patients with BM die of their disease.

22.12 Radiation Techniques

The most commonly used radiation therapy technique used in cases of pediatric BM is standard WBRT using a variety of dose-fractionation regimens with total dose ranging from 10 to 50 Gy. However, any discussion of radiotherapy for BM would be incomplete without examining important advanced conventional radiation techniques such as stereotactic radiosurgery (SRS).

Although WBRT for BM remains commonplace, adult BM are increasingly treated today with SRS with or without WBRT in an effort to improve outcomes

and/or patient quality of life (Aoyama et al. 2006; Sahgal et al. 2015). Decreasing the volume of irradiated brain is associated with improved neurocognitive outcomes, with a Phase III trial comparing SRS versus SRS and WBRT demonstrating a lower risk of significant decline in learning and memory function by 4 months in the group that received SRS alone (Chang et al. 2009). A recent meta-analysis suggests there is little survival benefit garnered from WBRT compared to SRS (Soon et al. 2014). Moreover, in select patients of fewer than four brain metastases, a recent meta-analysis suggested that SRS alone may confer a survival benefit in patients younger than 50 year of age (Sahgal et al. 2015). The higher dose per fraction may improve treatment efficiency in the case of histologies which exhibit relative radio-resistance such as sarcomas, melanomas, and renal cancers (Selek et al. 2004; Brown et al. 2008; Sheehan et al. 2003). Numerous retrospective studies have also investigated the combination of systemic therapies and immunotherapy with SRS (Ahmed et al. 2016; Kiess et al. 2015). Current guidelines for the management of adult BM prominently features SRS in the treatment paradigm (Linskey et al. 2010).

While the larger doses per fraction and tight margins are thought to be of benefit in adults, the potential risk of necrosis and possibility of marginal misses outside the treatment field have led to reticence in the use of SRS in children with BM. In addition, the duration of treatment delivery and the need for careful immobilization can also be challenging in pediatric population, with the possible need for anesthesia. There are no significant series in the literature on SRS for pediatric BM thus the thrust to employ SRS for BM in child is primarily founded on extrapolation of the adult literature. That being said, there are a number of published series demonstrating the feasibility of stereotactic radiosurgery in the pediatric population, particularly regarding arteriovenous malformations (AVM) but also for other primary or recurrent CNS tumors (Saran et al. 2002; Kano et al. 2010; Keshavarzi et al. 2009). For instance, Keshavarzi et al. reported a series of nine patients with primary CNS tumors, two of which were aged 12- and 14-years-old and treated with frameless optically guided cone-based stereotactic radiosurgery for juvenile pilocytic astrocytomas. Both patients were treated with 20 Gy in a single fraction and tolerated the treatment well with local control at 6 and 10 months, without adverse events reported. An additional patient in the series was treated with 5 Gy in five fractions for a pineocytoma with local control at 12 months and without adverse sequelae (Keshavarzi et al. 2009). A large series from the University of Pittsburgh also evaluated the feasibility of SRS in pediatric patients with recurrent ependymoma who had previously been treated with radiation therapy. The median age in this population was 6.9 years (Range 2.9–17.2) and the radiation dose was between 9 and 22 Gy in a single fraction. SRS was well tolerated with adverse effects occurring in only 2 of the 32 patients included in the study (Kano et al. 2010). Figure 22.2 illustrates a case of multiple pediatric brain metastases treated with WBRT (a) and a case of a solitary pediatric brain metastasis treated with SRS (b).

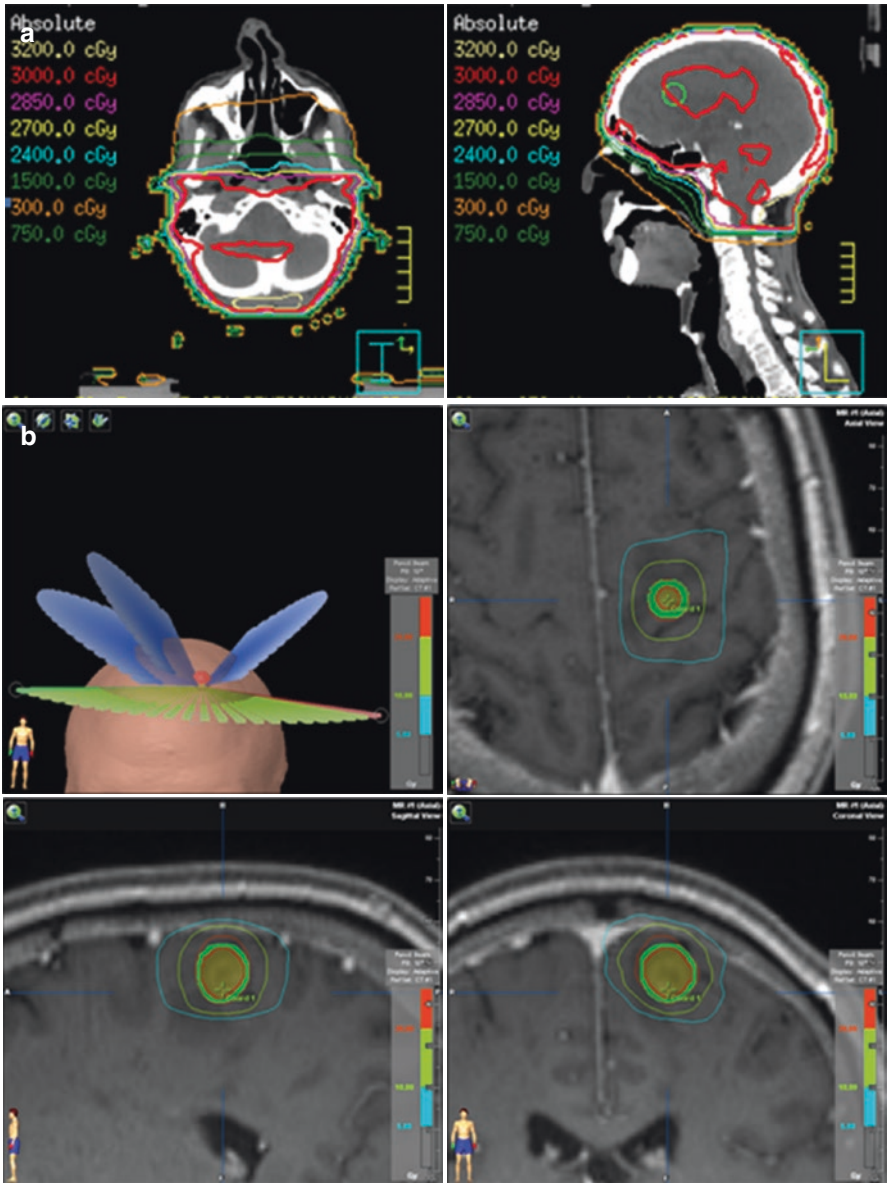

Fig. 22.2 (**a**) An 18-year-old boy with metastatic Ewing sarcoma with diffuse BM treated with WBRT to a total dose of 30 Gy in 3 Gy daily fractions, (**b**) a 15-year-old girl with high-grade sarcoma treated with frameless optically guided cone-based stereotactic radiosurgery to a solitary brain metastasis using a single isocenter and four dynamic arcs. A total dose of 20 Gy was prescribed to the 80% isodose, which covered 100% of the target

Conclusion

While the development of BM is a common occurrence in adult cancers, they are relatively rare in the setting of extracranial pediatric malignancies. Nevertheless, with continuing improvements in systemic therapies leading to prolonged survival, the incidence of pediatric BM may rise. They may present synchronously or more commonly in the setting of prior extracranial metastases, particularly to the lungs. There is limited published data on the management of pediatric BM and the optimal treatment approach has not been established. Treatment has typically included surgical resection for isolated or symptomatic lesions, radiation therapy, chemotherapy, and possibly immunotherapy. Although the outcome for pediatric patients with BM is typically dismal in the literature, with most succumbing to their disease, there are nonetheless rare reports of long-term survivors, suggesting there may be a subset of patients who may benefit from aggressive multimodality therapy. A multidisciplinary approach to the management of these patients and in prospective research is paramount in optimizing current treatments and developing new strategies which may improve outcomes.

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Part VI

Radiotherapy Practice

Anesthesia for Immobilization

23

Pascal Owusu-Agyemang

Contents

Abstract

Several methods of sedation have been described to enable successful treatment of children undergoing cranial irradiation. Careful planning and vigilance during the periprocedural period are essential to ensure the best outcomes. Standard monitoring and total intravenous anesthesia with or without a secure airway are common methods of anesthetic delivery. Observation in an adequately staffed and equipped recovery room should be considered for patients requiring a prolonged recovery from anesthesia.

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23.1 Introduction

The safe and successful delivery of radiotherapy requires patients to remain immobile for a given period of time. This may be difficult in children, particularly in those younger than 4 years old. Age appropriate anxiety and the inability to lay still and cooperate during treatment are some of the challenges faced when delivering care to younger children. Although it involves a significant amount of resources, treatment under anesthesia may be safest option for some younger children.

23.2 Manuscript

23.2.1 Personnel

Due to the complex medical history of children with intracranial pathology, it is recommended that an anesthesiologist or other physician trained and experienced in pediatric perioperative care be involved in providing sedation. Pediatric advanced life support certification is also recommended for anesthesia and nursing staff involved in the care of pediatric patients.

23.2.2 Treatment Room Set Up

Radiotherapy suites should ideally possess the oxygen delivery and suction outlets. Backup oxygen supply cylinders are recommended, and extra connection tubing may be needed to reach oxygen supply and suction outlets. Gas evacuation outlets will enhance the ability to use an anesthesia machine if needed. In any case, an anesthesia ventilator should be readily available.

23.3 Supplies

Most radiotherapy suites are located at a considerable distance from the main operating rooms. As a result, anesthesia equipment, supplies, and medication may not be readily available. It is, therefore, essential that carefully stocked supply carts and medication trays are available. These conditions may necessitate customizing existing supply kits to ensure availability of the most commonly used items.

23.3.1 Airway Supplies

In addition to appropriately sized endotracheal tubes and laryngoscopes, extra supplies of nasal cannulas, facemasks, and laryngeal mask airways (LMA) are required since these are most frequently used in this setting. Appropriate positive pressure ventilation systems for infants and children, and various sizes of oropharyngeal and nasopharyngeal airways should also be available.

23.3.2 Vascular Access Devices

Most children undergoing cranial irradiation will have some form of central venous access. Port-a-Cath access is usually performed at the beginning of the week, and de-accessed over the weekend if appropriate. As such, local anesthetic creams, access needles, and special sterile access kits should be readily available. Central line dressing kits and heparin flushes should also be available.

23.3.3 Medication

A complete set of anesthesia and emergency drugs with a written pediatric dose schedule should be immediately available. In addition, an institutional emergency cart complete with pediatric defibrillator paddles, and vasoactive drugs should be immediately available in the treatment area. The latter will enable familiarity with the location of equipment and supplies in the event that help is required from other services at the hospital. Propofol is a commonly used anesthetic in this setting. Extra supplies of this medication with the appropriate delivery equipment should be stocked.

23.4 Monitoring

Standard monitoring including pulse oximetry, electrocardiography, noninvasive blood pressure, and capnography should be maintained throughout treatment and during the recovery process (Cote and Wilson 2008). Portable monitors are most practical in this environment. Supplemental oxygen may delay the diagnosis of respiratory depression; therefore, the use of capnography in addition to observing the child's face and chest wall motion with the help of cameras installed in the treatment room may allow for rapid detection of airway obstruction (American Society of Anesthesiologists Committee 1996). A separate camera directed towards the anesthesia monitor may be beneficial.

23.5 Anesthetic Management

23.5.1 Pre-procedural Assessment

A complete preanesthetic assessment including the child's medical history and physical examination should be performed before the start of the course of radiotherapy. The anesthetic plan, fasting guidelines, and venous access procedures are also discussed with the parents and/or care givers during this visit. Prescriptions for local anesthetic creams and instructions for application prior to vascular access are also provided. A complete set of vital signs should be obtained prior to the start of every treatment session. These measures may alert the physician to any changes in the physical status of the child.

23.5.2 Fasting Guidelines

The current practice recommendations of the American Society of Anesthesiologists regarding fasting are as follows: 2 h for clear liquids, 4 h for breast milk, 6 h for infant formula, 6 h for non-human milk, 6 h for a light meal, and 8 h for a full meal; however, both the amount and type of foods ingested need to be taken into account when determining an appropriate fasting period. For example, even a light meal consisting of fried or fatty foods and meat may prolong gastric emptying time, and additional fasting time may be appropriate. Also, non-human milk has been shown to be similar to solids in gastric emptying time. The amount ingested must therefore be considered when determining an appropriate fasting time (American Society of Anesthesiologists Committee 2011). If possible, younger children should be scheduled earlier in the day due to a limited tolerance of prolonged fasting times.

23.5.3 Delivery of Anesthesia

The choice of anesthetic technique should be tailored to the specific procedure and the ability to safely deliver care. It is essential that there is cooperation between the anesthesia team and radiotherapists during radiotherapy simulation, and molding of the thermoplastic immobilization masks. It is the responsibility of the anesthesiologist to ensure that airway patency is not compromised due to the design of the mask. Excessive head flexion should be avoided, and decisions about the most favorable way to maintain airway patency should be made at this time. Slight neck extension or the use of an oral airway may be considered before the decision to intubate. Total intravenous anesthesia with propofol and oxygen delivery with nasal cannula or a face mask has been shown to be safe in children undergoing procedural sedation (Anghelescu et al. 2008). However, several factors need to be taken into consideration before the decision to use propofol and an unprotected airway. First, the duration of the procedure may significantly impact the amount of propofol administered, which may in turn increase the risk of complications associated with the use of the drug. In a large retrospective review of 3833 procedures performed under propofol sedation, there were significant differences in the incidence of complications between anesthesia sessions of more than an hour and those of 31–60 min ($p = 0.0001$). There were also significant differences in complications between anesthesia sessions longer than 60 min and those of less than 30 min in duration ($p < 0.0001$). While the odds of complications during procedures longer than 60 min were 4.25 times that for procedures of 30–60 min, the odds for procedures over 60 min were 9.85 times that for those of less than 30 min (Anghelescu et al. 2008). Therefore, securing the airway for longer procedures should be considered. Second, airway pathology, pulmonary status, and patient positioning should be considered before the decision to use an unprotected airway. Patients with obstructing airway lesions or those with chronic lung disease may benefit from a secure airway. Also, patients with tight-fitting immobilization masks may be easier to ventilate with a secure airway in place. Options for securing the airway may include the use of an

LMA, or endotracheal intubation. And third, the use of stereotactic frames during procedures such as gamma knife treatment may preclude easy access to the airway in the event of an emergency and necessitate a secured airway. In addition, equipment and devices to unlock the stereotactic frames should be at hand for frame-based radiation procedures.

On rare occasions, excessive movement or "twitching" may be observed in children despite high doses of propofol administration. In these instances, the addition of low dose opiates may facilitate a reduction in propofol dosage. It must however be noted that the risk of airway compromise may be increased with the concomitant use of opioids and propofol. In recent years, the alpha-2 adrenergic receptor agonist, dexmedetomidine, has gained increased use during pediatric sedation. However, the increased risk of bradycardia, and the prolonged recovery times should be taken into account when this drug is chosen (Mason et al. 2008; Koroglu et al. 2006).

Alternate methods of immobilization, such as securing the anesthetized child to the treatment table with the aid of straps may aid in preventing physical injuries such as falls. Personal blankets may be used to keep patients warm. However, a forced air warmer may be considered for patients with treatment sessions lasting more than 30 min.

23.5.4 Patient Recovery and Discharge

Patients requiring a recovery time of a few minutes may be monitored and discharged by the anesthesia team from the treatment room. However for prolonged recovery, it is preferable that patients be monitored in a separate recovery room by certified recovery room nurses, or by nurses with advanced adult and/or pediatric life support training. The recovery room should have oxygen and suction outlets, and the availability of emergency resuscitation drugs.

The following criteria should be met before discharge from the treatment area.

1. Patients should be awake and be able to maintain their airway without assistance or special positioning
2. Hemodynamically stable
3. And be in the company of a responsible adult.

Patients not fulfilling the above criteria or those requiring an extended period of recovery should be observed and monitored in an appropriately staffed and equipped recovery area.

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Image Guidance in Pediatric Brain Radiotherapy

24

Sara Alcorn and Stephanie Terezakis

Contents

Abstract

Image guided radiotherapy (IGRT) in pediatrics provides a means for reduction of treatment volumes by permitting for the use of highly conformal plans with smaller treatment margins. IGRT may additionally allow for dose escalation and adaptive radiotherapy strategies. Current practice patterns and clinical protocols support the use of weekly or daily IGRT as standard practice in pediatric brain-directed IGRT. However, the benefits of IGRT must be weighed against its costs including potentially significant additional radiation dose, supporting the need to

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study lower dose IGRT protocols in this population. This chapter reviews common modalities of IGRT and the literature regarding its use specific to pediatric brain radiotherapy.

Image guided radiotherapy (IGRT) has become routine practice in the treatment of pediatric brain tumors (Alcorn et al. 2014a). Image guidance is generally defined as the use of imaging performed prior to or during radiation treatment delivery with the goal of improving localization of regions of interest including the target volume and adjacent organs at risk (Dawson and Jaffray 2007; Verellen et al. 2008; Gupta and Narayan 2012). IGRT has gained increasing popularity as the by-product of advances in conformal radiotherapy, which requires precise and accurate target localization (Verellen et al. 2008). Although data supporting its application in pediatrics is limited, extrapolation of findings from the adult population suggests that IGRT may permit for the use of smaller setup margins, reduction of dose to normal structures, escalation of dose to target volumes, and implementation of adaptive radiotherapy strategies (Michalski et al. 2001; Jaffray et al. 2007; Castadot et al. 2010; Ahunbay et al. 2010; Dong 2012). Common modalities for pre-treatment imaging to be discussed include planar radiographs, computed tomography (CT), magnetic resonance imaging (MRI), ultrasound, and a variety of tracking systems (AAPM 2009; Gupta and Narayan 2012; Goyal and Kataria 2014).

24.1 Indications

There is limited data directing the clinical use of image guidance for pediatric brain radiotherapy. In general, the frequency and modality for image guidance rests on the balance of a number of patient- and treatment-specific variables. Potential patient-specific factors suggesting the need for frequent brain-directed IGRT include patient age, performance status, tumor location, and baseline steroids requirement (Alcorn et al. 2014b). Treatment delivery factors favoring frequent IGRT include increased conformality of the plan, closer proximity to critical structures, smaller CTV-to-PTV margins used, and reirradiation. These factors are weighed against the costs associated with IGRT, which are detailed in Sect. 24.3 of this chapter.

One particularly compelling role for IGRT appears to be in the management of treatment targets in the central nervous (CNS) system. Results of a survey from an international pediatric research consortium demonstrated that daily or weekly IGRT is used in nearly 100% of cases of CNS-directed radiotherapy (Alcorn et al. 2014a). Moreover, all recent CNS protocols within Children's Oncology Group (COG) have included stipulations for IGRT, such as allowance for smaller CTV-to-PTV margins when daily IGRT is employed. This suggests that the majority of providers and protocol developers see frequent IGRT as an acceptable standard of care for pediatric brain radiotherapy.

24.2 IGRT Approaches

24.2.1 Planar-Based IGRT

Target localization by planar modalities includes portal imaging and diagnostic quality X-ray techniques. Portal imaging is created using X-rays generated by the linear accelerator. Traditionally, portal imaging was performed using film cassettes. However, the film-based approach has now been largely replaced by electronic portal imaging devices (EPID), which use optical, ionization chamber, or active-matrix flat-panel detectors to create digital images (Antonuk 2002). Although generally in the megavoltage range (MV), kilovoltage (kV) portal imaging may be possible on some systems (Goyal and Kataria 2014); a typical MV portal image of a brain treatment field is shown in Fig. 24.1a. Diagnostic quality kV radiographs can also be utilized for verification of target position (Antonuk 2002); such imaging is obtained using on-board X-ray devices attached to the linear accelerator or via off-board X-ray equipment located elsewhere in the treatment room. Current regimens for brain-directed IGRT with proton therapy generally use diagnostic quality kV-planar images for target localization.

In most cases, the target structure itself cannot be localized on planar imaging due to lack of adequate contrast for soft tissue delineation by this modality. Thus, localization for planar-based brain IGRT is generally directed toward bony or metal surrogates (Alcorn et al. 2014a); particularly for proton-based brain radiotherapy, fiducials may be inserted into the outer table of the skull to improve localization (Chen et al. 2007). As treatment is generally targeted as at a surrogate with planar imaging, changes in target conformation or location over time may not be readily detected. Moreover, the two-dimensional nature of planar imaging does not allow for assessment of rotational error (Goyal and Kataria 2014).

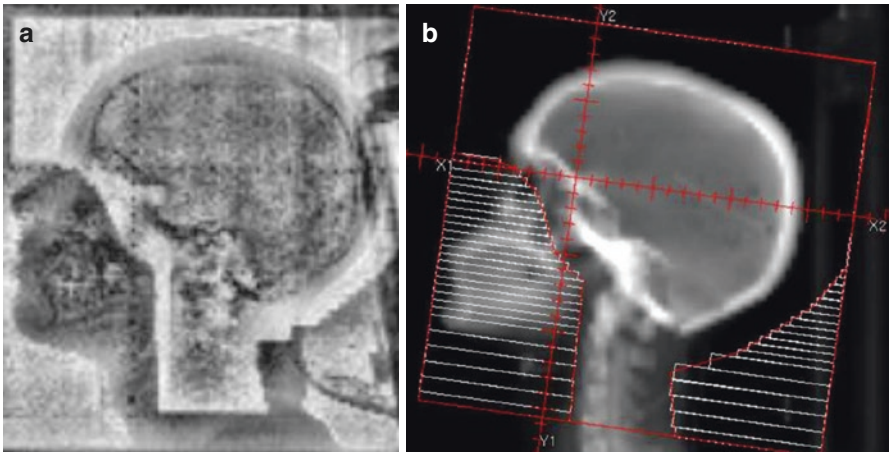

Fig. 24.1 (**a**) Electronic portal imaging device (EPID)-based imaging (**b**) compared to the digitally reconstructed radiograph (DRR) from the planning image set for whole brain treatment fields for a 15-year-old patient managed with craniospinal irradiation

24.2.2 CT-Based IGRT

The most common modality used for pediatric brain IGRT is CT imaging (Alcorn et al. 2014a). Images may be generated by devices located on the linear accelerator such as with cone-beam CT (CBCT) or by off-board equipment such as with CT-on-Rails units. With CBCT, an attached X-ray imaging system acquires multiple kV- or MV-planar radiographs as the gantry rotates, and an algorithm then reconstructs these radiographs into volumetric images (Jaffray et al. 2002). With CT-on-Rails, the treatment table is physically moved between a kV-CT scanner for imaging and a gantry for treatment (de Crevoisier et al. 2006; Goyal and Kataria 2014). For Tomotherapy units, the treatment beam itself is used to create MV-CT images for IGRT (Ruchala et al. 1999; Goyal and Kataria 2014). CBCT technology for proton therapy is also being developed (Engelsman et al. 2013).

Although better than planar-based IGRT, there is generally still insufficient soft tissue contrast to visualize the target volume on CT-based IGRT for brain treatment. As such, bony anatomy or metallic clips or markers are generally used as surrogates for alignment purposes. Moreover, CT-based IGRT cannot be performed concurrently with radiation treatment delivery, as the photons from the treating beam would interfere with image acquisition. As such, intrafractional error cannot be corrected in real-time when the treatment beam is on.

24.2.3 MRI-Based IGRT

Although uncommonly used in clinical practice to date, MRI-based IGRT may be particularly useful in the treatment of pediatric brain tumors. First, the improved soft tissue distinction afforded by MRI may allow for better target localization for brain targets. Additionally, MRI does not utilize ionizing radiation, thus reducing the total radiation dose delivered as compared to planar- or CT-based IGRT. Moreover, available systems can perform real-time image guidance during radiation delivery, allowing for intrafractional adjustments. Of note, MRI-based IGRT is particularly susceptible to artifacts from motion and metal densities (Goyal and Kataria 2014) and may require anesthesia for the treatment of pediatrics.

24.2.4 Other IGRT Modalities

Additional means for IGRT include ultrasound and PET imaging as well as optical, infrared, and electromagnetic tracking systems (Goyal and Kataria 2014). Ultrasound is an attractive modality for pediatric IGRT because it lacks ionizing radiation and could potentially be used for real-time target localization. However, inadequate penetration of ultrasound through intact bone limits its use in the treatment of brain tumors after fusion of the fontanelles has occurred. Similarly, although PET systems mounted to the treatment unit have been described (Nishio et al. 2010), they may be of limited utility for brain tumors, where background PET-avidity of

the brain parenchyma reduces the ability to delineate the target volume. Use of infrared and optical tracking is not reported for pediatric brain IGRT. Electromagnetic tracking would require surgical insertion of transponders into the brain, reducing its appeal for the treatment of brain targets.

24.2.5 Image Guidance Procedure

The general procedure for patient positioning with 3D-imaging based IGRT is outlined in Fig. 24.2. The patient is positioned on the treatment table, usually by means of an immobilization device with or without alignment to surface markers. The image guidance scan (such as a CBCT) is obtained, and the treatment site is identified either by direct visualization of the target or by means of a surrogate (e.g., nearby bony structure, fiducial marker). The image guidance scan is compared to images derived from the treatment planning scan such as digitally reconstructed radiographs (DRR). Physical shifts in patient positioning on the treatment table are then performed such that the treatment area visualized on the image guidance scan aligns with its location on the corresponding images from the treatment planning. As such, the isocenter for treatment delivery is shifted. Additional image guidance scans may be undertaken to verify patient position before, during, or after treatment. Images obtained comparing kV-CBCT to DRR are shown in Fig. 24.3.

Stereotactic brain radiotherapy with both photons and protons requires additional setup steps to ensure adequate target delineation given relatively large fractional doses, rapid dose fall-off, and the use of small or no treatment margins. For units utilizing a gamma source, a rigid head frame is generally affixed to the patient, and treatment is delivered on the same day as the planning image set is obtained. Localization is achieved via two coordinates associated with the rigid head frame (Chen et al. 2007). For linear accelerator-based treatment, a thermoplastic mask is standardly used, with imaging for treatment planning performed in

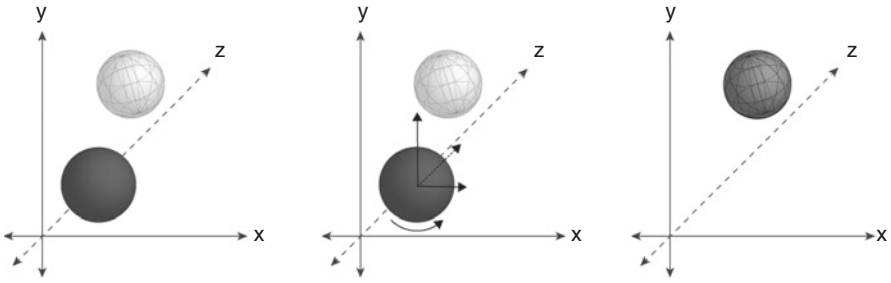

Fig. 24.2 (**a**) The target volume is identified on image guidance scan (*dark sphere*) and is compared to images from the treatment planning image set (*white sphere*). (**b**) The treatment table and/or patient are physically shifted in the *x*, *y*, and *z* translational directions and rotated such that the positions of these volumes are aligned (**c**). *Figure courtesy of Jacob S.J. Joseph*

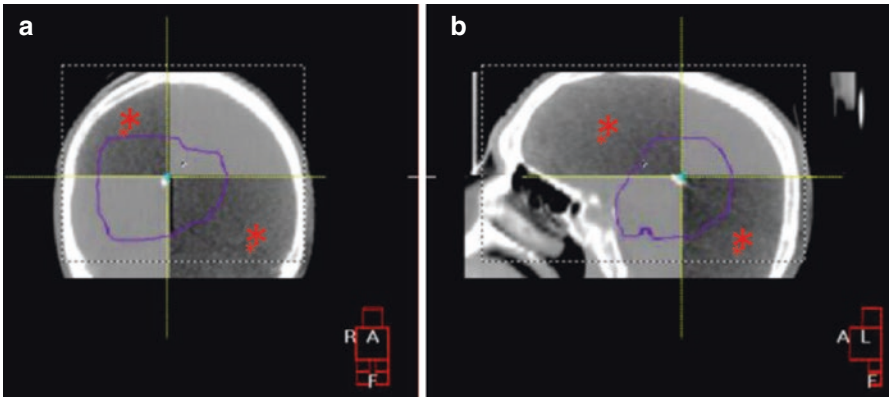

Fig. 24.3 (**a**) AP and (**b**) lateral kilovoltage cone-beam CT (kV-CBCT) performed for a supratentorial tumor boost using IMRT for the same patient as in Fig. 24.1. The PTV is outlined in *purple*. The kV-CBCT image is overlaying the planning CT in a checkerboard pattern after the alignment procedure in Fig. 24.2 was performed. The kV-CBCT images are marked with *red asterisks*. Increased scatter in kV-CBCT image set augments noise and decreases image quality as compared to the planning CT. Nonetheless, note that the bony anatomy is well visualized on both the kV-CBCT and planning CT images

advance of the treatment delivery. IGRT for stereotactic radiotherapy using standard linear accelerators typically involves either planar or CBCT alignment as per Fig. 24.3. For robotic linear accelerators, brain-directed IGRT is generally achieved with multiple planar images directed at the skull anatomy. A 2D–3D image registration algorithm is used to align the planar images to the planning image set, and shifts are made in the plan delivery to correct for setup discrepancies and patient movement. 2D images are repeated periodically during the course of treatment to account for intrafractional changes (Fu and Kuduvalli 2008). In proton-based stereotactic radiotherapy, IGRT is generally comprised of kV-planar images targeting either bony anatomy or fiducials within the skull bone (Chen et al. 2007).

24.3 Potential Advantages/Disadvantages

24.3.1 Advantages of IGRT

By improving localization of the target volume, IGRT maximizes precision and accuracy of radiotherapy delivery. This not only improves coverage of the target volume but potentially minimizes the dose to adjacent normal tissue that may have been inadvertently treated without adequate localization. Such precision is of particular importance for brain-directed IGRT, where excess dose to critical and sensitive structures such as the optic apparatus and brainstem can have especially morbid or fatal effects. For example, Beltran et al. (2012) showed that relatively small

rotational errors (≥4°) in the CNS could result in significant changes in dose to the PTV as well as adjacent serial organs.

Moreover, IGRT allows for the use of smaller treatment margins. Per the ICRU definition, the CTV-to-PTV margin accounts for both internal organ motion and patient setup error (Stroom and Heijmen 2002). Improved target delineation through IGRT allows for positional adjustments to be made to account for internal movement of the target over the course of treatment. Further, increased setup accuracy with IGRT reduces setup variations. By addressing both features of the CTV-to-PTV margin definition, IGRT thus allows for reduction in the margin required to account for these uncertainties (Goyal and Kataria 2014).

In turn, by reducing the margins required, the treatment volume can be reduced. In combination with increasingly conformal radiotherapy techniques, this also allow for dose escalation strategies that target the intended treatment volume while sparing nearly normal tissue (Michalski et al. 2001; Jaffray et al. 2007). This may be particularly relevant for radioresistant tumor types, where such dose escalation has been associated with improved local control (Pollack et al. 2002; Chauvet et al. 2003). Additionally, the premium for increased conformality and smaller volumes may be especially high when treating pediatrics given concern for late toxicity related to both cumulative dose and distribution of dose received.

Equally exciting is the potential for the employment of adaptive radiotherapy protocols with the use of IGRT. Data suggests significant change in both the volume of the target and of adjacent normal structures over the course of radiotherapy in select disease entities. Such variation results in the potential for subsequent error in the actual dose delivered versus the dose estimated at the time of initial planning (Bucci et al. 2007; Frank et al. 2008). Adaptive radiotherapy seeks to address this problem through alteration in the treatment plan over the course of radiotherapy. Such alterations could help to account for tumor growth or shrinkage and changes to organ motion or patient weight that develop over the course of treatment. These types of changes are of particular importance since deformation of the target volume or other structures of interest may not be correctable with simple rigid couch shifts performed during routine IGRT (Dong 2012). Additionally, by further addressing internal motion and setup errors, adaptive radiotherapy may allow for further reduction in CTV-to-PTV margins.

Techniques for optimal delivery of adaptive radiotherapy remain investigational; one promising approach relies on using deformable image registration techniques to fuse CBCT images to planning CT image. The cumulative dose to the target and other organs is then recalculated, and altered treatment volumes are applied (Dong 2012). An additional means for adaptive planning utilizes functional imaging such as PET and MRI to direct treatment to specific physiologic changes observed within the target over the course of radiotherapy (Cao 2011). Particularly relevant to the pediatric population is an adaptive radiotherapy protocol for craniopharyngioma reported by Beltran et al. in which weekly MR imaging and replanning were used to account for changes in target volume caused by fluctuations in cyst size during radiotherapy (Beltran et al. 2009). Otherwise, applications of these techniques to the pediatrics population have not been extensively published to date.

An additional benefit of IGRT is that it provides a means for estimation of the margins necessary to account for treatment uncertainties. Comparison of alignment between serial scans approximates inter-fraction error. Comparison of pre- and post-treatment imaging indicates the degree of intrafractional error. Inter- and intrafractional errors combine to estimate total random error. Inter-patient and group mean error estimate systematic error. These two values form the basis of popular recipes used to define adequate treatment margins across a population (Van Herk 2004, 2011).

24.3.2 Disadvantages of IGRT

Despite these benefits, there are a number of important disadvantages to IGRT that must be considered. A primary concern in the use of pediatric brain IGRT is the lack of prospective evidence supporting the efficacy of IGRT in this patient population, particularly when combined with increasingly conformal plans and reduced margins. Because recurrence in brain sites may be especially morbid, the cost of in-field and marginal misses may be especially high. Moreover, implementation of IGRT strategies requires specialized training for radiation therapists, physicist, and physicians, creating the risk for inappropriate application and delivery of this technology.

Even optimally performed IGRT cannot account for a number of residual uncertainties that plaque radiotherapy delivery. The consistency and accuracy of GTV and CTV delineation by the planning physician may limit treatment efficacy. Moreover, the surrogates used for IGRT may not be sufficient to account for internal motion and deformation of the target (van Herk 2011). In brain IGRT, the target volume is poorly identified on planar- and CT-based imaging, requiring reliance on bony or metallic surrogates. However, the target may grow, or swelling may cause a shift in position relative to the volume on treatment planning imaging. Setup to bone with IGRT would not likely be affected, and the internal motion may go undetected.

Of primary concern to many physicians is the total dose contributed by frequent IGRT. The contribution from daily portal-based IGRT may be significant, contributing an additional 2–3% of the prescribed dose to the target and nearby structures (Hitchen et al. 2012). Dose to bone over the course of multi-fraction CBCT may approach 8.4 Gy (Ding and Coffey 2009), and such regimens may also increase the relative risk of secondary malignancy (Kim et al. 2010). Please see Sect. 24.4 for a detailed discussion of these studies. Indeed, the ICRP suggests that even at low doses below 100 mSv, “it is scientifically plausible to assume that the incidence of cancer or heritable effects will rise in direct proportion to an increase in the equivalent dose in the relevant organs and tissues” (Grégoire and Mackie 2011).

Additional disadvantages include increased cost and time associated with these scans, both for the patient and providers. Each scan can take upward of 2–3 min, which may be significant in the treatment of a restless child or on a treatment machine with a full patient schedule. In most practices, IGRT images must be approved by the treating physician prior to administration of the next radiation

treatment, which is time intensive and potentially disruptive to workflow. Monetary costs to the patient and health care system may also be substantial.

24.4 Trials/Clinical Data

There is a paucity of studies in the literature examining the use of image guidance in pediatric brain radiotherapy, with very few prospective studies specific to this patient population in print. As such, we review available data below, most of which focuses on delivered dose and toxicities asscoiated with image guidance in the pediatrics population.

24.4.1 Radiation Doses and Toxicities Associated with IGRT

Regarding dose contribution from portal imaging, Hitchen et al. (2012) performed a retrospective review of 20 pediatric patients treated for brain tumors with IMRT. Each patient received portal imaging of treatment fields and orthogonal setup fields in the craniofacial region, and dose–volume histograms were estimated from this imaging. Patients received a mean of 58.5 portal images, with a mean of 173.3 monitor units from portal imaging per patient. The maximum, minimum, and mean percentages of prescribed dose to the PTV from portal imaging was 2.9% (±0.7%), 2.2% (±1.0%), and 2.5% (±0.7%). Percentage of prescribed dose from portal imaging was 2.8% for brainstem, 2.6% for the optic apparatus and cochlea, and 2.4% for the hypothalamus and pituitary areas. The authors concluded that this extra dose may result in exceeding the dose tolerance of nearby critical structures and suggested the use of lower dose portal imaging when possible.

To estimate the dose to normal tissues delivered by kV-CBCT, Ding et al. (2009) reviewed imaging for eight patients including three children. The same CBCT technique was used for both adult and pediatric patients (125 kVp, 80 mA, 25 ms). The Vanderbilt-Monte-Carlo-Beam-Calibration was used to calculate dose to organs. Dose from kV-CBCT was found to be highly dependent on patient size, with higher doses delivered to normal structures in the pediatric versus adult patients. Tissues with higher atomic number were found to receive higher dose, likely due to increased probability of the photoelectric effect at the kV range for these materials. As such, dose to bone was found to be 2–4 times higher than that to soft tissues, with an estimated 4.5–8.4 Gy to bone over a 25–35 fraction course from kV-CBCT for pediatrics. This has implications for normal tissue toxicity, particularly in pediatric patients with open growth plates susceptible to deformity and growth retardation from radiation. Similarly, Zhang et al. (2012) estimated the doses contributed by kV-CBCT by reviewing 42 pediatric patients treated to head and neck and pelvic regions. Monte Carlo code was used to calculate 3D dose distributions of kV-CBCT scans, and correlations between mean organ dose, age, weight, and head and hip circumferences were analyzed. For the head and neck sites, the whole head structure

received the highest dose at approximately 5.5–7.5 cGy per scan, again likely because of increased probability of the photoelectric effect given the high atomic number of the skull material. The mean dose to the eyes and optic apparatus was approximately 2.5–3.5 cGy per scan. Moreover, these data suggested that weight and head circumference were appropriate indices for dose estimation with kV-CBCT. Age was found to be an inferior index given large variability in patient size across ages. In combination, these data support use of lower dose kV-CBCT protocols in pediatrics.

24.4.2 Use of Lower Dose Pediatric IGRT Protocols

Given the desire to reduce the dose associated with kV-CBCT used for image guidance, an international pediatric consortium sought to prospectively employ and evaluate a low-dose protocol for CBCT in pediatric patients treated to CNS sites (Alcorn et al. 2014b). A lower dose CBCT protocol with skin dose of 0.1 cGy per scan was employed for pediatric CNS IGRT; for reference, the adult protocol used has a surface dose of approximately 0.17 cGy per scan. As a proxy for setup accuracy, the physical table shifts were measured between setup with laser alignment versus with CBCT in the transverse (x), superior-inferior (y), and anterior-posterior (z) translational directions and calculated the vector magnitude ($\mathrm{VM} = \sqrt{(x^2 + y^2 + z^2)}$) of these shifts. A total of 2179 CBCT images from 96 pediatrics patients were analyzed. Median age was 9 years (range 1–20 years), with median Karnofsky performance status of 80 (range 40–100), 44% supratentorial tumor location, 48% baseline steroid requirement, and 32% anesthesia requirement. Patients were treated over a median of 30 fractions (range 12–33). In analysis pending publication, setup parameters were 3.13 mm, 3.02 mm, 1.64 mm, and 1.48 mm for VM group mean, inter-patient, inter-institution, and random error, respectively. Image quality with the low-dose protocol was rated as excellent or adequate in 99% of evaluated scans. On multivariable analysis, there were no significant differences in mean VM by age, gender, performance status, target location, extent of resection, concurrent chemotherapy, or steroid or anesthesia use. These data suggest successful employment of a lower dose protocol for CT-based IGRT across a variety of patients in pediatrics, with mean VM approximating the CTV-PTV margin of 3 mm commonly used in brain-directed IGRT. Moreover, review of one institution's data for adults treated with the standard-dose CBCT and pediatrics treated with the lower dose CBCT protocol for brain-directed IGRT showed that there was no significant difference in calculated VM between these two populations (Huynh-Le et al. 2014). This further validates the adequacy of the lower dose protocol in pediatrics and suggests that its use should be considered in the adult population as well.

Although not specific for brain-directed IGRT, additional support for the use of lower dose IGRT protocols in pediatrics is garnered from the work of Kim et al. (2010), investigating absorbed and effective dose from two different kV-CBCT regimens. The study performed abdominal CBCT imaging on an anthropomorphic

phantom of a 5-year-old using either standard-dose CBCT (125 kVp, 80 mA, 25 ms) or a lower dose CBCT (125 kVp, 40 mA, 10 ms) protocols. Again, image quality with the lower dose protocol was felt to be adequate for localization to bone. The absorbed dose per scan to regional organs at risk was found to be significantly higher for the standard- versus lower dose CBCT protocol, ranging from 5.1 to 7.2 cGy per scan versus 1.1–1.6 cGy, respectively. Subsequent estimations of relative risk of cancer incidence for various organs were also substantially higher for the standard- versus lower dose scans; this value was highest for stomach malignancies at 1.053 versus 1.012, respectively. Although Kim's study contains simulated data for abdomen-directed IGRT, its conclusions support the use of reduced-dose IGRT protocols across treatment sites.

Future research warranted includes comparison of disease and toxicity outcomes with and without the use of IGRT, prospective review of low-dose versus standard-dose image guidance protocols, and early investigation into the application of adaptive radiotherapy in the pediatrics population.

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Conformal Radiation Therapy for Pediatric CNS Tumors

25

Thomas B. Daniels and Nadia N. Laack

Contents

Abstract

3D conformal radiation therapy (3DCRT) and intensity-modulated radiation therapy (IMRT) are both commonly utilized for pediatric brain tumors. 3DCRT has been available for a longer period. There is protracted follow-up on patients treated with 3DCRT. IMRT is a newer technology that developed in parallel with advances in other radiation delivery such as image guidance. Similar tumor coverage can be either 3DCRT or IMRT. They differ in the ability to achieve conformity around irregularly volumes. IMRT can achieve highly conformal plans although intense modulation can impact dose homogeneity. VMAT is a form of IMRT rotational. The addition of static or rotational beams can expose nontarget tissue to lose dose radiation. The balance of tumor coverage and dose

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homogeneity against the impact of collateral radiation to nontarget tissues impacting neurocognitive functioning for cranial radiation or anticipated renal and cardiopulmonary function in craniospinal radiation is the main factor in deciding what the optimal photon radiation treatment is for pediatric CNS tumors.

25.1 Introduction

3D conformal radiation therapy (3DCRT) and intensity-modulated radiation therapy (IMRT) are both commonly utilized for pediatric brain tumors. 3DCRT has been available for a longer period. There is protracted follow-up on patients treated with 3DCRT. IMRT is a newer technology that developed in parallel with advances in other radiation delivery such as image guidance. Similar tumor coverage can be either 3DCRT or IMRT. They differ in the ability to achieve conformity around irregularly volumes. IMRT can achieve highly conformal plans although intense modulation can impact dose homogeneity. VMAT is a form of IMRT rotational. The addition of static or rotational beams can expose nontarget tissue to lose dose radiation. The balance of tumor coverage and dose homogeneity against the impact of collateral radiation to nontarget tissues impacting neurocognitive functioning for cranial radiation or anticipated renal and cardiopulmonary function in craniospinal radiation is the main factor in deciding what the optimal photon radiation treatment is for pediatric CNS tumors.

25.2 Conformal Radiation Therapy for Pediatric CNS Tumors

3D conformal radiation (3DCRT) utilizes manual optimization of beam parameters to conform around a tumor volume. 3DCRT is "forward planned." Multiple beam angles are manually generated, weighted, and modified create a dose distribution that confirms around a tumor volume delineated on a CT scan. The development of multileaf collimators mounted in the machine head enabled beam shaping without the need to create a custom-made cerrobend aperture for each individual beam. The MLC along with advances in computational power paved the way for intensity-modulated radiation therapy (IMRT).

IMRT is "inverse-planned" and utilizes inverse optimization and computer-based generation of beam parameters and intensities as defined by a set of desired dose constraints put in at the beginning of the planning process (Bakiu et al. 2013). The desired tumor coverage and normal tissues are prioritized by the radiation oncologist and put in by the planner. Prioritization of dose–volume metrics for tumor coverage versus dose to organs at risk is individualized based on tumor and patient-specific factors and is a critical component of radiation planning. A computer algorithm produces multiple iterations that attempt to meet the planning constraints until it produces the "best fit" radiation plan that meets as many planning parameters as possible. Clinical judgment to modify prioritization of optimization

parameters may be needed for iterations of constraints that are not acceptable either due to risk of toxicity or inadequate tumor coverage.

IMRT can be delivered with fixed beams or with a rotating intensity fan-beam, a technique called tomotherapy. In axial tomotherapy, the patient remains static during treatment. Serial tomotherapy is the use of multiple axial tomotherapy slices, but the patient is static during delivery then the couch is translated prior to the next delivery (Mackie 2006). Whereas in helical tomotherapy, the patient is translated through the bore of the machine while the gantry rotates similar to a diagnostic spiral CT scan (Fenwick et al. 2006). All forms of tomotherapy are volumetrically modulated arc therapy (VMAT), which is a form of IMRT. VMAT is a form of IMRT. Like fixed beam IMRT, dose rate and MLC leaf speed vary during delivery. But unlike fixed beam IMRT, the gantry rotates during VMAT delivery.

Although the number of operational protons centers in the United States is growing, in 2014 the majority pediatric patients receiving radiation are being treated with photons in the United States (Chang et al. 2014); thus, knowledge of optimal treatment options with conformal photon techniques remains important. The vast majority of RT centers in the United States are capable of both 3D and IMRT techniques. When deciding on the more optimal photon modality for treating a pediatric CNS tumor, one must consider tumor coverage, conformity and heterogeneity of the plan, and the doses to critical normal structure.

The conformity index (CI) can be defined as the ratio of the volume covered by the prescription dose to the target volume. Ideally, the CI equals 1, with no tissue outside the tumor exceeding prescription dose. IMRT and VMAT can generally achieve more superior conformity indices than 3DCRT, particularly if the target volume contour is concave or convex. IMRT plans can now generate homogeneous dose distributions in a tumor volume although a heavily modulated plan with a steep dose gradient next to critical structures can lead to increased dose heterogeneity. The heterogeneity index can be expressed as the ratio between the maximum point dose and the prescription dose. Adequate tumor volume coverage can be achieved with either 3DCRT or IMRT so the nontarget dose is often the deciding factor.

If a critical normal structure is embedded within a PTV, dose heterogeneity within the PTV could lead to "hotspots" in the normal structure as well. Dose heterogeneity is of particular concern for suprasellar tumors where the prescription dose can approach the maximum tolerable dose to the optic chiasm. The improvements in conformity with IMRT and VMAT over 3DCRT must be weighed against the potential long-term effects of integral dose (ID) to the patient. ID is equal to the volume integral dose deposited in a patient equal to the mean dose times the volume irradiated (Aoyama et al. 2006). ID is the area under the curve of a differential absolute-dose absolute-volume histogram (D'Souza and Rosen 2003). ID is tumor volume, patient volume, dose, and plan parameter dependent (Pirzkall et al. 2002). Although some publications report higher ID with IMRT (Hall and Wuu 2003), ID from IMRT (Hermanto et al. 2007) has been reported as lower than 3DCRT for radiation of gliomas (Koshy et al. 2004; Hermanto et al. 2007).

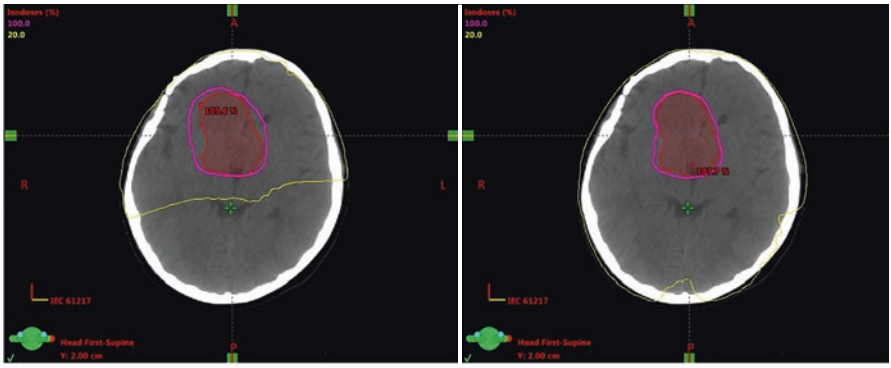
The long-term side effects of radiation to a developing brain can be profound depending on the radiation dose and volume of brain irradiated. Different parts of

the brain have varying sensitivities to radiation with differing long-term effects. Neurogenesis is very sensitive to radiation, and limiting the radiation dose to the hippocampus and the subventricular zone may preserve neurocognitive function base on accumulating evidence (Eriksson et al. 1998; Monje et al. 2007). Mammalian models have shown that there is a differential in recovery between the two regions after ionizing radiation (Hellstrom et al. 2009). Sparing of the neurogenic niches is possible without compromising coverage of the tumor volumes (Blomstrand et al. 2012). In the field of pediatric neuro-oncology, in particular, there is a growing understanding of the relationship between dose–volume metrics and quantifiable long-term neuro-endocrine toxicities. The conformity of the prescription around the target volume can increase with more complex treatment delivery; however, as one increases the number of beam angles, as in VMAT, the low dose bath of normal tissues may increase and is an important consideration for pediatric CNS tumors (Fogliata et al. 2009).

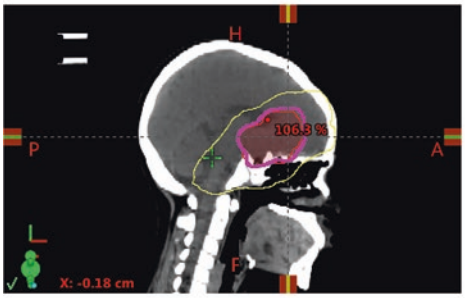
IMRT and VMAT offer the ability to treat a tumor more conformity while potentially exposing more of the nontarget tissues lower dose (see Fig. 25.1). More monitor units are required for intensity-modulated plans and leakage through MLCs contributes to increased low dose scatter dose in and outside of the field versus 3DCRT. The risk of the secondary malignant neoplasm (SMN) in the radiation field that would not be treated with 3DCRT must be considered against the benefits of sparing adjacent organs at risk that an intensity-modulated plan can afford. Although the quantification of increased secondary malignancy risk IMRT is difficult, it is believed to be higher than 3DCRT (Hall and Wuu 2003) with younger patients being more likely to develop an SMN (Lee et al. 2016). In a study measuring doses in distant of field nontarget tissue in a pediatric anthropomorphic phantom for various brain tumors, peripheral doses to the ovaries, testes, and breast were higher utilizing fixed beam IMRT than in 3DCRT although there was not a linear correlation to the number of monitor units (Mansur et al. 2007).

The understanding of SMN risk after is limited as many reports have small numbers from single institutions or have limited follow-up of modern techniques. Various mathematical models exist for estimating SMN and a large part of our understanding stems from estimated total body doses to survivors of the atomic bomb and other organ-specific models have been proposed. The calculated risk of SMN of fixed beam IMRT vs. VMAT in the medium to high-dose region exceeding 2.5 Gy is approximately equal (Moteabbed et al. 2014). There is no threshold radiation dose for SMN development. In other words, any tissue receiving any radiation could in theory develop an SMN.

Comparable tumor coverage can be achieved with both 3D and IMRT techniques. Reports comparing the two techniques bear this out although the long-term follow up is generally longer in 3DCRT making such comparisons more challenging. The proliferation of IMRT delivery has also accompanied technological advancements in 6D treatment couches, image-guidance, and thermoplastic immobilization devices, all of which has made more conformal treatment with minimal intra-fractional variability possible (Lightstone et al. 2012). Although dosimetric



3D image to go below left image



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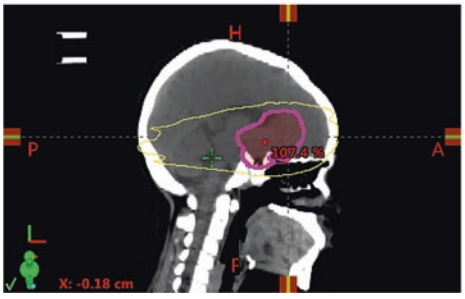

Fig. 25.1 A non-coplanar 3DCRT plan on *left* shows a less conformal prescription dose distribution around the concave PTV in *red*. An IMRT plan is more conformal around the PTV with more brain receiving a low dose

comparisons between 3D and various IMRT techniques have long been possible, there are fewer publications detailing long-term clinical outcomes of pediatric CNS malignancies treated with IMRT. Low grade glioma (LGG) represents a heterogeneous subset of pediatric CNS tumors in terms of pathology and prior therapies before radiation. Patterns of recurrence using IMRT techniques including simultaneous integrated boost do not differ from 3DCRT. Most recurrences occur in the

primary tumor volume (Paulino et al. 2013). Hippocampal sparing VMAT dosimetry has been described (Kazda et al. 2015). Regardless of radiation technique a primary determinant of neurocognitive effects, as well as recurrence, is age at the time of treatment (Merchant et al. 2009; Oh et al. 2011; Paulino et al. 2013). Similarly for ependymoma and craniopharyngioma the utilization of 3DCRT versus IMRT does not impact recurrence (Merchant et al. 2006, 2013; Schroeder et al. 2008; Greenfield et al. 2015).

Estimates of different long-term toxicities based on dosimetric data are speculative but possible. CNS germinoma has an excellent prognosis. For whole ventricular RT (WVRT), IMRT spares normal brain better than 3DCRT for which the fields are opposed laterals (Chen et al. 2010). Estimates of the 5-year effect of either 3DCRT or VMAT on IQ of patients with CNS germinoma receiving WVRT 23.4 Gy followed by a boost to 21.6 Gy have been calculated. The VMAT plan had better a CI with only a slightly higher HI. Due to improved conformity and less to the temporal lobes, the projected IQ of the VMAT patients was higher than 3DCRT (Qi et al. 2012).

The superior conformity of IMRT over 3DCRT after craniospinal axis irradiation (CSI) is evident when comparing boost plans covering the posterior fossa (PF) for medulloblastoma. 3DCRT covering the PF with opposed fields covering 90% of the cochlea with the prescription dose while covering 50% of the pituitary gland with 80% of the prescription dose. IMRT can reduce the 90% coverage of the cochlea to 33.4% while reducing the 50% coverage of the pituitary to 20% of the PF prescription dose (St Clair et al. 2004). For treatment of the resection cavity plus margin for medulloblastoma, the CI of IMRT is superior to 3DCRT without an increase in recurrence. 3D conformal radiation and IMRT allowed for a limited volume of the posterior fossa to be covered, making radiation to the resection cavity plus margin an option. Both approaches offering sparing of critical structures compared to 2D radiation of opposed laterals using bony anatomy to define the posterior fossa. A three-dimensional beam arrangement utilizing oblique coplanar wedged pair can offer similar coverage to the posterior fossa while sparing the cochlea and pituitary gland at the cost of a higher dose to the thyroid than opposed laterals (Tarbell et al. 2000).

The group from Memorial Sloan Kettering has published their experience using fixed beam IMRT to treat IFRT for the boost after CSI. In this series, there were no isolated posterior fossa recurrences outside of the boost volume. Treating the resection cavity plus a margin was effective with no recurrences in 10 patients with a median follow-up of 42 months in a report from Memorial Sloan Kettering (Merchant et al. 1999). The authors describe six combinations of gantry and couch positions for a midline tumor. Patients did receive cisplatin-based chemotherapy but the short-term ototoxicity compared favorably to other reports (Polkinghorn et al. 2011). The group from Baylor utilized IMRT for IFRT boost and compared the dosimetry and toxicity to a cohort treated with 3DCRT. All patients were in the pediatric age group and received chemotherapy. Despite receiving more cisplatinum, the patients treated with IMRT had a lower rate of hearing loss: 13% Grade 3 or 4 versus 64% in the conventional RT group ($p < 0.014$). Forty-seven percent of the IMRT group had no hearing loss (Huang et al. 2002).

A variety of techniques have been utilized for craniospinal radiation. Prone treatment allows for easily visualization of the SSD skin marking but adds to the difficulty

with the changing geometry of couch rotations for the spinal fields and collimator rotation for the cranial field, particularly in patients who are undergoing anesthesia. Common practice today is supine treatment for craniospinal axis radiation. Photon CSI is now done with 3D planning a minimum. IMRT can be done for the entire volume or in conjunction with 3DCRT. A standard 3D approach includes choosing spine isocenters at fixed distances from the brain field isocenter, then shifting the asymmetric jaws to "feather the gap" at matched fields (Parker and Freeman 2006). IMRT can be used in an otherwise 3D plan to match the fields over several centimeters, allowing for one CSI plan as opposed to generating multiple 3D plans at different match lines. Helical tomotherapy has the advantage that the entire craniospinal volume in a single uninterrupted field (Fenwick et al. 2006). Intensity-modulated radiation can improve the conformity of a craniospinal radiation plan but has a higher integral dose than a 3D plan (Mascarin et al. 2011; Harron and Lewis 2012).

VMAT for the spinal portion of CSI offers several dosimetric advantages of a standard 3DCRT plan with a single poster field on the spine including more conformity with less heterogeneity in the target volume. VMAT can give a lower mean cardiac dose, while giving a higher mean lung dose with a smaller percentage of the lung receiving higher doses above 20 Gy for a prescription dose of 23.4 Gy (Lee et al. 2012). Despite the entire lungs receiving some "low dose bath" from VMAT CSI with concurrent chemotherapy, acute radiation pneumonitis is rare (Penagaricano et al. 2009). An alternative to straight posterior beam to cover the spine is a 3-field approach. A 3D-CRT 3-field plan using a straight posterior two posterior oblique fields compares favorable to VMAT when comparing heart dose, while giving slightly more dose to the kidneys, and distributing more high dose but less low dose to the lungs (Bandurska-Luque et al. 2015).

Photon radiation is commonly utilized for the treatment of pediatric brain tumors and has the most long-term published data on tumor control and side effects. The decision to utilize IMRT or 3DCRT depends on many factors. Dose conformity is superior to IMRT at the cost of slightly higher heterogeneity and increased integral dose. When deciding between 3DCRT and IMRT, the treating radiation oncology must consider the benefits of conformity versus the potential long-term effects of low doses to organs at risk. Our understanding of the long-term toxicities of radiation for pediatric CNS malignancies continues to evolve as the relationship between radiation dose and critical normal structures including the hippocampus continues to expand.

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Proton Therapy for Pediatric Brain Tumors

26

Anita Mahajan

Contents

Abstract

Proton therapy is a form of charged particle radiation therapy that has potential benefits to reduce toxicities in children with brain tumors. Despite the theoretical benefits of PRT, full acceptance of this treatment modality in this patient population has not occurred. This chapter will review the history, potential benefits, current status, evidence, and future opportunities of proton therapy for children with brain tumors. It will discuss the role of PRT, the type of patients that are being treated, and where this modality may be most beneficial.

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26.1 Introduction

One of the major roles of a radiation oncologist is to develop a patient-specific radiation plan that allows effective delivery of radiation dose to the target volumes and to minimize dose to uninvolved tissues. In order to accomplish this ideal, practitioners need to evaluate patient and disease specific factors and apply available radiation treatment delivery modalities strategically. Radiotherapy options that allow improved target delineation, dose conformality, treatment delivery accuracy and precision are possible because of technological advances in the last several decades. Particle therapy has leveraged the unique dose deposition characteristics associated with charged particles to further improve the therapeutic index. In this chapter, the potential benefits, clinical applications, available data, and future directions associated with proton therapy (PRT) will be summarized.

26.2 History

Ernest Rutherford discovered the proton in 1919 with the word proton referring to the Greek word "first." Interestingly, William Henry Bragg had already described the Bragg peak phenomenon of the dose deposition of fast charged particles in matter in 1903. This unique energy deposition profile is characterized by a sharp drop-off of dose deposition at a specific depth based on particle energy with virtually no dose delivered distal to that depth. In addition, when compared to X-ray radiation, the entry dose also was attenuated. In 1946, Robert Wilson suggested the strategic use of fast protons for the treatment of cancer with the hypothesis that patients would have fewer side effects and possibly better tumor control. The first patient was treated at the Lawrence Berkeley Lab in 1954 (Wilson 1946) and since then PRT is 53 centers worldwide and over 118,000 patients have received this treatment.

26.3 Proton Therapy Delivery Systems

All particle therapy facilities require an accelerator to generate high energy particle beams. For PRT, the typical therapeutic proton energies that are clinically used are as low as 60 MeV for superficial targets such as the eye, to 250 MeV to treat an adult pelvis. For the brain, energies between 120 and 160 MeV are adequate. One common clinical accelerator is a cyclotron in which particles are accelerated by a rapidly varying electric field, and they held to a spiral trajectory by a static magnetic field. Other systems use a synchrotron accelerator which accelerates particles to various energies with a time-dependent magnetic field. In both systems, particle beams are directed into treatment rooms by a series of magnets. Gantries are now available that allow isocentric techniques similar to X-ray delivery systems. Heavier particles such as carbon ions require larger accelerators and gantry systems to create and bend a high energy beam.

In the past, large buildings were needed to house the accelerator and treatment delivery systems in multiple rooms; however, newer technologies allow small footprint accelerators with single room PRT now commercially available.

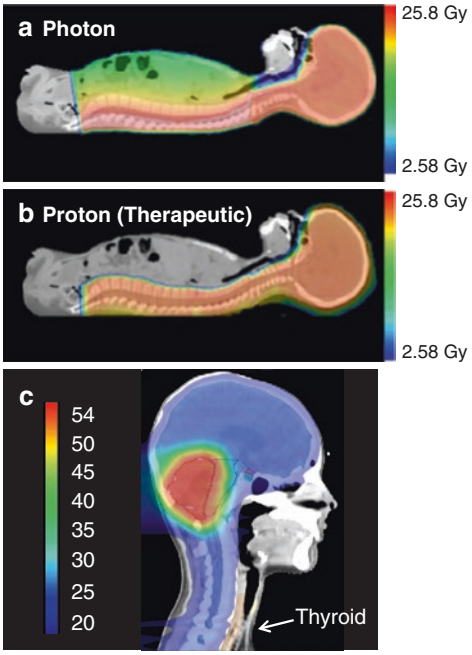
Traditionally, PRT has been delivered by passive scatter techniques which can shape the beam with field-specific devices known as compensators and apertures. Pencil beam PRT, a more recent technology that is available at new facilities, does not require patient-specific beam shaping devices that require additional time and resources to manufacture. This advance in PRT technology can deliver highly conformal radiation dose to complex target volumes through multiple layers of dose given to the target by varying the energy of the proton pencil beam. This development has allowed the use of intensity modulate proton therapy (IMPT) (Blattmann et al. 1990).

26.4 Preliminary Dosimetric Studies in Children

The use of PRT in pediatric patients was evaluated later than adults due to the complexity of treating children in nonhospital-based environments. Soon after hospital-based facilities became available, PRT was advocated for use in children due to the lower integral dose to the body (Miralbell et al. 2002; St Clair et al. 2004; Yuh et al. 2004; Lee et al. 2005). In these early studies, PRT was considered for common childhood tumors including medulloblastoma, retinoblastoma, and rhabdomyosarcoma which are quite different than the skull base tumors and choroidal melanoma that had been treated in adults. These dosimetric studies confirmed technical feasibility with consistently lower normal tissue doses that could potentially lower the risk of late effects, in particular secondary malignancies.

Craniospinal irradiation (CSI) requires large fields that exit through the body when using standard X-ray techniques. PRT has been explored for this indication since the reduction in exit dose through the patient's body would limit dose to uninvolved organs within the neck, chest, abdomen, and pelvis to lower the risk of organ dysfunction. St. Clair et al. and Lee et al. described the potential dosimetric benefits of proton CSI (p-CSI) in patients with medulloblastoma (Lee et al. 2005; St Clair et al. 2004). St. Clair performed a dose volume histogram (DVH) analysis of p-CSI to x-CSI and intensity-modulated X-ray CSI (IMXT-CSI) plans in a 43-month-old boy. The p-CSI plan used a standard beam arrangement with two opposed cranial fields and a single posterior spine field that encompassed the entire vertebral body. The authors describe a significant dose reduction to the cochlea, transverse colon, stomach, kidney, stomach, heart, and lung with p-CSI. Interestingly, IMXT-CSI DVHs revealed a reduction in high dose delivered to nontarget structures, but increased low dose volumes were noted in comparison to standard x-CSI (St Clair et al. 2004).

Howell et al. evaluated dosimetric data on 18 patients between the age of 2 and 18 years planned with p-CSI and x-CSI. Weight and height varied between 11.9–138.2 kg and 85–191 cm, respectively. There was normal tissue sparing in all cases for all avoidance structures with more homogeneous target coverage (Howell et al.



d Organ	Mean Dose (Gy)	Maximum Dose (Gy)
Testis	0	0
Kidney	1.3	19.3
Pancreas	1.6	17.9
Liver	0.4	19.3
Heart	0.9	16.7
Lung	1.6	23.0
Esophagus	7.7	19.1
Thyroid	2.3	8.8
Parotid Glands	4.5	18.3
Cochlea	26.2	32.7
Hypothalamus	24.9	27.2
Pituitary	24.0	24.8
Lacrimal Glands	8.5	14.9
Lens	4.8	2.6
Cribriform Plate	23.4	25.1

Fig. 26.1 (**a**, **b**) Isodose comparison of proton and photon craniospinal irradiation (CSI) with elimination of exit dose through the patient's neck, chest, abdomen and pelvis. (**c**) Isodose distribution of typical medulloblastoma with CSI and boost. No additional dose is delivered to the neuroendocrine structures, brain and thyroid gland. (**d**) Numerical mean and maximum doses to normal structures with proton CSI

2012). Yoon et al. described the dosimetric benefit of p-CSI in comparison to x-CSI and tomotherapy-CSI in 10 patients with varying diagnoses. Interestingly, tomotherapy-CSI, similar to IMXT-CSI, showed an intermediate normal tissue dose in comparison to p-CSI and x-CSI, but increased total body low dose compared to the other techniques. Tomotherapy had a more favorable DVH comparison for the parotid glands, lens, and thyroid gland in comparison to p-CSI and x-CSI (Yoon et al. 2011). Figure 26.1 illustrates the difference in exit dose between PRT-CSI and XRT-CSI. A substantial reduction in radiation dose to the thyroid gland was seen which could result in a lower rate of primary hypothyroidism and secondary tumors.

As expected, the cranial doses are not different between PRT and XRT for CSI; however, PRT provides an advantage during the boost portion of treatment. For example, as shown in Fig. 26.1, the PRT boost plan for a typical patient with medulloblastoma would allow a reduction in dose to the neuroendocrine structures, optic apparatus, and supratentorial brain structures such as the hippocampi. The above studies also noted a reduction of the total dose delivered to nontarget intracranial structures, including the hypothalamus, pituitary gland, eyes, optic chiasm, and cochlea with PRT (Lee et al. 2005; St Clair et al. 2004).

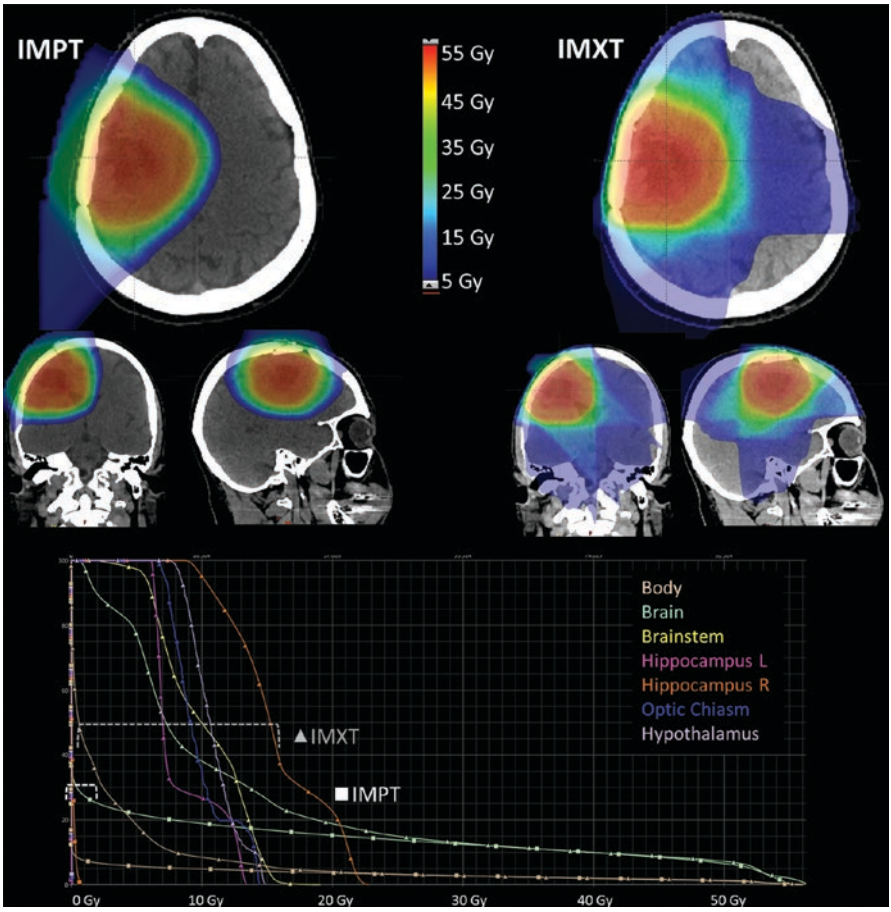


Fig. 26.2 Isodoses and dose volume histogram comparison of proton IMPT and X-ray IMRT radiation plans for a right frontal low grade astrocytoma treated after resection. Overall dose to all adjacent normal structures is lower with the proton plan

There has also been interest in using PRT for non-CSI brain irradiation needed in the management of other common pediatric brain tumors such as ependymoma, low-grade glioma, craniopharyngioma, and spinal tumors. Dosimetric studies have also suggested the ability to reduce the integral dose to the intracranial structures outside of the target volume as demonstrated in several early studies (Archambeau et al. 1992; Merchant et al. 2008; Amsbaugh et al. 2012b; Boehling et al. 2012; Eaton and Yock 2014). The models employed in these studies suggest decreased effect on neurocognition. An example of the dosimetric difference between PRT and IMXT for low grade glioma is demonstrated in Fig. 26.2. There is a significant dose reduction to several critical normal tissues as shown by the isodoses and dose volume histograms of the final plan for a typical low grade right frontal astrocytoma. The advantages of CSI with respect to sparing of organs within the torso would apply for patients with spinal canal tumors.

26.5 Current Status

PRT has gained acceptance within the pediatric oncology as a treatment option for children with curable brain tumors. PRT is usually not recommended in situations where there is a poor prognosis and limited chance of long-term survival. Efforts have been made to collect annual data on how and why PRT is being used in children. In the United States, the Pediatric Proton Foundation (PPF) collected data indicating an increasing number of children treated with PRT from 465 in 2010 to 989 in 2014. This increase reflects a greater acceptance, awareness, and access to proton centers within the United States. Central nervous system tumors make up approximately 70% of the indications for PRT in the United States with the top three diagnoses being: ependymoma, medulloblastoma, and low-grade glioma. The majority of patients referred to proton centers are younger than 10 years and more than half are under 5 years of age.

In 2015, the Particle Therapy Co-Operative Oncology Group (PTCOG) collected specific data on pediatric patients being treated worldwide in particle therapy centers for the previous year. A total of 1349 children were treated in 29 centers worldwide with PRT (Courtesy of Martin Jermann PTCOG.ch). Further details of the types of tumors will be collected in future surveys.

26.6 Clinical Outcomes

One of the earliest clinical reports on PRT for pediatric brain tumors was by McAllister et al. who reviewed the outcomes of 28 patients. At a median of 25 months, treatment-related toxicity was low. It was also noted that those histologies with poor outcome continued to be a challenge and further follow-up was warranted to evaluate late effects (McAllister et al. 1997). Since then studies have been published evaluating the efficacy of PRT and early toxicities on various tumor histologies including craniopharyngioma, ependymoma, atypical teratoid rhabdoid tumor, and low-grade glioma (Suneja et al. 2013; Neelima et al. 2012; Mizumoto et al. 2015; McGovern et al. 2014; Luu et al. 2006; Lucas et al. 2015; Hug et al. 2002; Fossati et al. 2009; Eaton and Yock 2014; Bian et al. 2013; Amsbaugh et al. 2012a). All studies have reported similar tumor control rates as X-ray therapy with comparable or better toxicity profiles. Long-term outcomes with robust longitudinal evaluations are now emerging.

Yuh et al. first described the outcomes of three 3-year-old girls who were treated with p-CSI from 2001 to 2003. Expected acute toxicities including odynophagia, hoarseness, dysphagia, leukopenia, nausea, and vomiting were absent, but grade 2 dermatitis was noted. Interestingly, in these young patients, the plan did not encompass the whole vertebral circumference in an interest to spare the bone marrow. The authors reported no vertebral growth asymmetry at a time of the report but they cautioned that only a short follow-up was available at that time (Yuh et al. 2004). Acute toxicities in 48 pediatric patients receiving PRT for brain tumors were reported by Suneja et al. In this report 12 patients received p-CSI and compared to the non-CSI group, they were noted to have a higher frequency of grade 2 and 3

anorexia and nausea, but not vomiting, alopecia, or dermatitis (Suneja et al. 2013). In our experience, 40% of our patients experience nausea requiring antiemetic for nausea prophylaxis. Most patients experience some degree of alopecia and dry skin depending on the final dose. Bone marrow suppression and recovery is being actively evaluated (unpublished data). Owusu-Agyemang reviewed the anesthesia experience at our institution of 340 patients treated between 2006 and 2013. One hundred and thirty (40%) patients were treated with p-CSI and anesthesia for all of part of the course of treatment. The treatments were tolerated well with a very low incidence of unexpected events (Owusu-Agyemang et al. 2014).

Ray et al. have reported clinical efficacy on 22 patients with leptomeningeal spinal metastasis who were treated with p-CSI. The authors concluded of these patients, who were treated with definitive intent, 68% had a durable response at 1 year. Treatment toxicities included grade 1 erythema during treatment (Ray et al. 2013). Bian et al. reported favorable outcomes with good tumor control in five of six patients at 24 months post p-CSI for disseminated pilocytic astrocytoma (Bian et al. 2013). Jimenez et al. reported excellent tolerance of p-CSI in 11 young patients (median age 41 months, range 28–62 months) after maximal surgical debulking and pre-radiotherapy chemotherapy. Only 1 of 15 patients had local tumor failure at a median of 39 months post-RT (Jimenez et al. 2013). Yock et al. reported outcomes on 59 pediatric patients with medulloblastoma who were enrolled on a phase II single arm study. Acceptable rates of rates of ototoxicity, cognitive loss, and endocrinopathies compared to historical controls were reported. Progression-free survival was 83% at 3 years and 80% at 5 years. The authors conclude that PRT is an acceptable treatment option for children with medulloblastoma when considering efficacy with a possible reduction in side effects (Yock et al. 2016).

Additional reports have been published describing the various aspects of p-CSI. Moeller et al. reported favorable 1-year auditory outcomes in patients who received p-CSI for medulloblastoma. The authors describe a reduced rate of high degree of hearing loss in patients who had been followed at least a year in comparison to previously published X-ray based CSI treatments (Moeller et al. 2011). Jimenez also described patient toxicity outcomes in a cohort of young patients treated with chemotherapy followed by PRT. Six of the nine patients who had measurable hearing loss had measurable pre-RT loss. All nine had received cisplatinum pre-RT. Three patients had grade 2 endocrinopathies requiring hormone replacement. Early neurocognitive evaluation has not revealed any significant decline in this cohort (Jimenez et al. 2013). Kulthau et al. reported health-related quality of life (HR-QoL) outcomes of 142 patients of whom 61 received p-CSI. Those patients who received p-CSI versus those who received partial brain PRT were noted to have worse score HR-QoL but similar tumor related HR-QoL. In this study, both CSI and chemotherapy were associated with inferior HR-QoL scores (Kuhlthau et al. 2012). Comparison to patients treated with XRT was not available for this cohort.

For other non-CSI indications, results are emerging suggesting a possible therapeutic benefit of PRT with respect to toxicity profiles and tumor control, but prolonged follow-up is still lacking. In particular, neurocognitive, quality of life, auditory, radiographic evaluation and brain stem injury is of great interest (Eaton and

Yock 2014; Gunther et al. 2015; Indelicato et al. 2014; Kahalley et al. 2016; Lassen-Ramshad et al. 2015; Pulsifer et al. 2015). One of the most devastating complications of radiotherapy is brain stem necrosis. Indelicato et al. have quantitatively reviewed their experience of brain stem necrosis in 563 pediatric patients treated with PRT between 2007 and 2013 at their institution. The authors reported a 3.8% cumulative risk at 2 years with a 2.1% risk of a grade three or high brain stem injury. Risk factors include younger age, posterior fossa tumor location, and 17% of the brain stem dose receiving 55 Gy or higher. Overall, the authors suggest similar guidelines as what is established for non-PRT modalities; however, further evaluation is ongoing.

Jones et al. raised concerns regarding the possibility of differential relative biologic effectiveness (RBE) between tumor cells and normal tissue. In current practice, an RBE of 1.1 is used for planning purposes but the authors suggest that it may actually vary between 0.8 and 1.2 depending on the type of tissue that is being irradiated (Jones et al. 2012) Additional concerns regarding a varying RBE within the Bragg peak have also been raised (Mohan et al. 2013). Sethi et al. reported the failure patterns in 109 patients with medulloblastoma treated with PRT. There has been no relationship noted between radiotherapy techniques, proton end of range, linear energy transfer (LET), and RBE in the 16 patients who exhibited a relapse during the median follow-up of 38.8 months (Sethi et al. 2014). Further study is required to determine whether differential RBE or LET planning approaches should be considered (Mohan et al. 2013).

Pencil beam PRT has been used for pediatric indications including medulloblastoma, germ cell tumors, and skull base chordoma (Rutz et al. 2008; Park et al. 2015; Lin et al. 2014; Hill-Kayser and Kirk 2015). Preliminary results are promising and as more experience is gained, additional advances in PRT with scanning beam will allow further gains in the management of pediatric brain tumors.

26.7 Non-proton Charged Particles

Other non-proton charged particles such as carbon ion or helium ions may have a role in this group of patients; however, due to the lack of experience with these particles and their effect on normal tissue in children, experience is limited. In the PTCOG survey for 2016, fewer than 50 children were treated with carbon ion worldwide. Additional study is warranted for radioresistant tumors where dose escalation or hypofractionation is of interest.

26.8 Cost-Effectiveness

Since particle therapy systems require a large infrastructure, expensive equipment, and specialized personnel, cost associated with PRT has been under scrutiny. Several authors have evaluated the cost-effectiveness of PRT at a patient and society level. These studies suggest that PRT is a cost-savings approach for treatment for medulloblastoma in children by the reduction of toxicities in comparison to XRT-based

techniques. Contributing factors to cost-effectiveness included IQ loss, hearing loss, osteoporosis, cardiac disease, and SMNs (Hirano et al. 2014; Mailhot Vega et al. 2013; Lundkvist et al. 2005). Hirano et al. reported that there was a 99% probability that p-CSI would be cost-effective at a societal willingness to pay value with respect to hearing loss and cochlear dose (Hirano et al. 2014). Mailhot et al. evaluated the impact of the reduced need for growth hormone in patients where the neuroendocrine structures were spared with PRT. They concluded that PRT was cost-effective with regard to growth hormone replacement needs if the hypothalamus and pituitary gland could be spared in comparison to XRT techniques (Mailhot Vega et al. 2015). Verma et al. reviewed the literature to identify where PRT may be the most cost-effective, and they concluded that PRT was most valuable in several pediatric brain tumors (Verma et al. 2016).

26.9 Ethics

Concern has been raised regarding the ethical considerations of the increased expense and possible lack of access for children to proton therapy centers. Wolden argues that at this time long-term outcomes are lacking to uniformly support PRT for all patients requiring CSI despite the theoretical advantages and early results (Wolden 2013). Johnstone et al. argue that the PRT centers are obliged to treat all patients who are referred to them because of the theoretical advantages and existing clinical data and also stated that parents should be given counseling regarding the option for PRT so they can make an informed decision on their child's behalf (Johnstone et al. 2013).

Conclusions

PRT for pediatric brain tumors has been studied and increasingly used over the past 15 years. From the (1) preliminary theoretical considerations, (2) multiple dosimetric evaluations, (3) predictive model applications, and (4) clinical outcomes, there is mounting evidence that PRT provides equal tumor control and will be associated with fewer RT-related toxicities. PRT in children can be time-consuming and technically challenging and the utmost attention should be paid to every aspect of the treatment. Future refinements including the use of pencil beam PRT may allow further reduction in normal tissue doses and neutron contamination. Additional thought to RBE or LET weighted planning is also warranted to refine the treatment planning and improve the therapeutic ratio.

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Craniospinal Irradiation

27

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Contents

Abstract

Please check the hierarchy of the section headings and confirm if correct.

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27.1 Introduction

Craniospinal irradiation (CSI) is a critical component of the definitive management for pediatric central nervous system tumors that have a propensity to disseminate throughout the neuroaxis. CSI is most commonly employed in the multi-modality treatment of medulloblastoma, the second most common pediatric brain tumor (Ward et al. 2014). Bloom et al. published the seminal report in 1969 demonstrating the cure of medulloblastoma with CSI alone (Bloom et al. 1990). Since that time, clinical outcomes have improved with the addition of chemotherapy, and the CSI dose required for standard-risk patients has been reduced while still maintaining excellent outcomes (Packer et al. 1999). CSI is additionally utilized in the definitive treatment of supratentorial primitive neuroectodermal tumors (SPNET) (Jakacki et al. 1995; Chintagumpala et al. 2009) and intracranial germ cell tumors (Ogawa et al. 2004; Maity et al. 2004; Bamberg et al. 1999), as well as in the setting of relapsed or disseminated ependymoma, atypical teratoid rhabdoid tumors (ATRT), gliomas, or leukemia. This chapter will review CSI dose prescription, target volume definition, treatment techniques, and clinically relevant issues related to treatment delivery and acute and late toxicity monitoring and management.

27.2 CSI Dose

CSI dose prescription is dependent upon tumor histology and disease stage. Standard doses for the treatment of medulloblastoma with the use of chemotherapy include 23.4 Gy for standard-risk disease (Packer et al. 1999, 2006) and 36–39.6 Gy (Zeltzer et al. 1999; Gajjar et al. 2006) for high-risk disease in 1.8 Gy daily fractions. Lower doses for standard-risk patients are also under investigation. A pilot study using 18 Gy CSI for 10 children younger than 5 years of age at diagnosis demonstrated disease control in 7 out of 10 children and resulted in minimal neurocognitive deficits (Goldwein et al. 1996). Based on these preliminary results, the recently completed Children's Oncology Group (COG) phase III trial ACNS 0331 randomized patients 3–7 years old with standard-risk medulloblastoma to 18 vs. 23.4 Gy CSI. Five-year results, published in abstract form, demonstrated inferior disease control and overall surivival in the reduced dose CSI arm and thus, 23.4 Gy remains the recommneded dose for standard risk patients (Michalski et al. 2016). So far, publi sh ed analysis of this trial has not reported outcomes according to molecular grouping of medulloblastoma. An ongoing study at St. Jude Children's Research Hospital opened in 2013 is further testing an even lower CSI dose of 15 Gy for the favorable risk group of patients with WNT pathway medulloblastoma (NCT01878617), though this remains investigational.

Hyperfractionated dosing schemes have been evaluated in comparison with standard daily fractionation for medulloblastoma. The HIT-SIOP PNET 4 trial employed 36 Gy CSI in 1.0 Gy BID, with a total cumulative dose of 68 Gy to the tumor bed and demonstrated equivalent tumor control with no apparent reductions in long-term toxicity (Lannering et al. 2012). Additional studies have evaluated the role of hyperfractionation (Gandola et al. 2009), and while disease control appears comparable, no discernible benefit to hyperfractionation has been reported and thus daily fractionation remains the standard of care.

Traditionally, the treatment for SPNET has been similar to high-risk medulloblastoma and has included 35.2–36 Gy CSI in 1.6–1.8 Gy/day for children 3 years and older (Jakacki et al. 1995; Timmermann et al. 2002). However, recent data from St. Jude supports favorable outcomes with the use of risk-adapted reduced dose CSI to 23.4 Gy for SPNET with no metastatic disease and no or minimal residual primary tumor following surgery (Chintagumpala et al. 2009). In the setting of disseminated ependymoma, ATRT, or glioma, CSI doses of 36–39.6 Gy are also typically recommended for older patients.

For non-germinoma germ cell tumors, the immediate past COG protocol ACNS0122 utilized 36 Gy CSI followed by 54 Gy involved field boost after induction chemotherapy. However, based on excellent results in patients with complete or partial response to chemo (Balmaceda et al. 1996) and encouraging results from patients with mixed non-germinoma GCTs treated with whole ventricle and boost irradiation only (Matsutani et al. 1998; Matsutani 2001), the ongoing trial ACNS1123 initially evaluated the use of whole ventricular radiation in patients with a complete or partial response to chemotherapy, though the trial has now been amended to recommend the use of CSI in all patients. For disseminated pure germinoma, CSI doses of 21 Gy with the use of chemotherapy or 24 Gy with radiation therapy alone, each followed by a local tumor boost, are used. The use of CSI has been abandoned in patients with localized pure germinoma disease due to excelled outcomes with whole ventricular irradiation (Shikama et al. 2005; Rogers et al. 2005; Calaminus et al. 2013).

CNS involvement of leukemia is responsive to lower doses of spinal irradiation. Spinal doses of 15–18 Gy have been used in combination with cranial doses of 24 Gy (Kumar et al. 1995; Hiniker et al. 2014). Doses of 20–24 Gy are often required for chloromas related to acute nonlymphocytic leukemia or myelodysplastic syndrome (Bakst et al. 2012).

CSI is often avoided for patients <3 years old out of concerns for significant neurocognitive toxicity with its use in younger patients (Walter et al. 1999; Chapman et al. 1995). Postoperative multi-agent induction chemotherapy followed by high-dose chemotherapy consolidation and stem cell rescue form the mainstay of therapy for this age group, with radiation therapy often reserved for patients with residual or progressive disease following chemotherapy (Geyer et al. 2005; Dhall et al. 2008; Rutkowski et al. 2005). Involved field radiation rather than CSI is preferred for children less than 3 without metastatic disease (Ashley et al. 2012). For young children with metastatic disease who still remain a high risk for disseminated tumor progression, the current COG protocol for medulloblastoma and SPNET ACNS 0334 recommends a reduced dose of 18 Gy CSI when used, followed by a tumor bed boost to a total of 45–54 Gy depending on age and response to chemotherapy.

27.3 CSI Target Volume

The goal of CSI is to deliver homogeneous therapeutic dose to the entire intracranial volume and subarachnoid space throughout the spine. A CT simulation should be performed and field borders should be adjusted based on three-dimensional anatomy to ensure adequate coverage of the entire cranium and thecal sac. Important regions to consider when defining the cranial volume and fields include adequate

coverage of the cribriform plate and the middle cranial fossa. Radiation therapy (RT) quality control studies have demonstrates an increase risk of supratentorial failures when inadequate margin on the temporal fossa is used in the whole brain fields (Miralbell et al. 1997a; Carrie et al. 1999). Outlining the cribriform plate may be helpful to ensure appropriate margin is maintained at the close interface with the eyes. In addition, sufficient margin at the calvarium should be allowed to maintain adequate coverage of the subfrontal region. Customized blocking can aid in minimizing dose to the eye and lens.

The spinal treatment volume should be defined in order to ensure coverage of the inferior thecal sac, and the lateral sacral nerve roots may also be included. It is recommended that sagittal T2-weighted MRI images be used to identify the lower border of the thecal sac for each patient. The inferior border of the spinal field should be 2 cm below the termination of the thecal sac, typically falling between the S2–S3 interspace and S4. The lateral margin of the spine field should cover the recess of the entire vertebral bodies with approximately 1 cm margin (which may vary depending on patient body size) on each side to ensure adequate coverage of the subdural space extending along the nerve roots. Dose should be prescribed to cover the whole vertebral bodies for children who are not skeletally mature in effort to prevent asymmetric growth and spinal deformity. When a posterior-anterior photon field is used, treatment prescribed to the anterior spinal canal will most often encompass the vertebral bodies. With the use of IMRT or proton therapy, the vertebral bodies should be included within the target volume to ensure coverage.

The following organs at risk should be contoured for dose recording and appropriately constrained during the boost portion of the treatment: cochlea, lens, optic nerves and chiasm, hypothalamus and pituitary, brainstem, spinal cord, and the whole brain. Contouring subregions of the brain such as the supratentorial and infratentorial brain, right and left temporal lobes, and hippocampi may also be of use given the recognized associations between dose-volume statistics for these regions and cognitive outcomes.

27.4 CSI Technique

27.4.1 Three-Dimensional Conformal Photon Therapy

The standard and most commonly utilized treatment technique for the delivery of CSI is three-dimensional conformal photon radiotherapy (3DCRT) involving the use of two parallel opposed cranial combined with one or more posterior-anterior (PA) spine fields, depending on the patient length. Either the prone or supine positioning can be utilized (Hawkins 2001). A retrospective analysis comparing supine versus prone CSI treatment demonstrated no difference in clinical outcomes according to treatment technique, and patients treated in the supine position have significantly lower rejection rate of cranial port films (8% vs. 35%) (Verma et al. 2015). The supine position also facilitates easier airway access for patients requiring anesthesia (Thomadsen et al. 2003) and is generally preferred by anesthesiologists as prone positioning may require intubation to secure the airway.

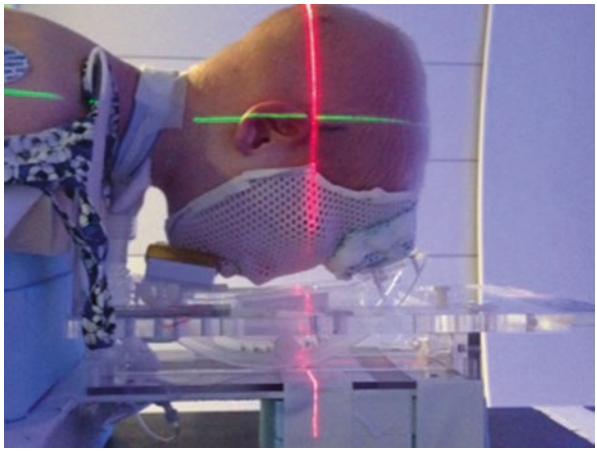

Fig. 27.1 Picture of cranial immobilization in the prone position using an aquaplast mask face cradle

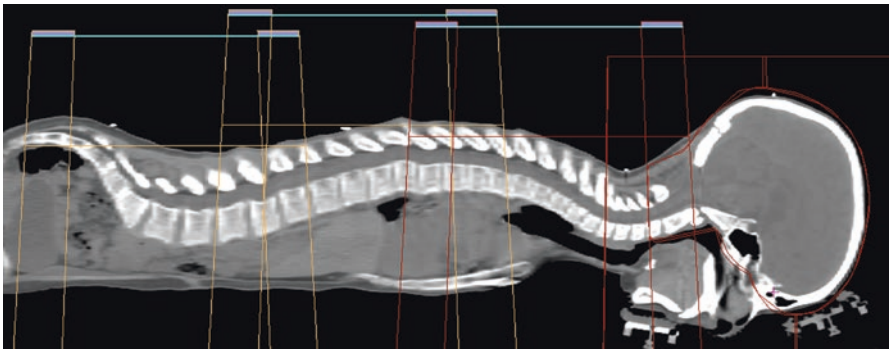

Fig. 27.2 Picture of craniospinal field matching where the divergence from the upper and lower spine fields is matched at the anterior spinal canal

At the time of simulation, a thermoplastic mask can be used along with a custom head cushion or neck cradle for immobilization of the cranium in either the prone or supine position (Fig. 27.1). With either position, it is important to allow for maximum extension of the chin in order to minimize exit dose of the posterior spine field though the mandible and oral cavity. An alpha cradle system or vacuum bag can additionally be used to enhance immobilization of the spine.

An SSD or SAD setup can be used. SSD setup can facilitate the use of extended source to surface distance to increase field size. The SAD setup places isocenter at appropriate depth within the patient, and though field size is limited, this method can facilitate ease of setup and shifting between fields, as straight longitudinal shifts from the cranial field isocenter to the spine field isocenters can be used.

For the matching of multiple spine fields, the divergence from the upper and lower spine fields is matched at the anterior spinal canal (Fig. 27.2). When matching multiple spine fields in this way, the gap length between the two fields at the skin

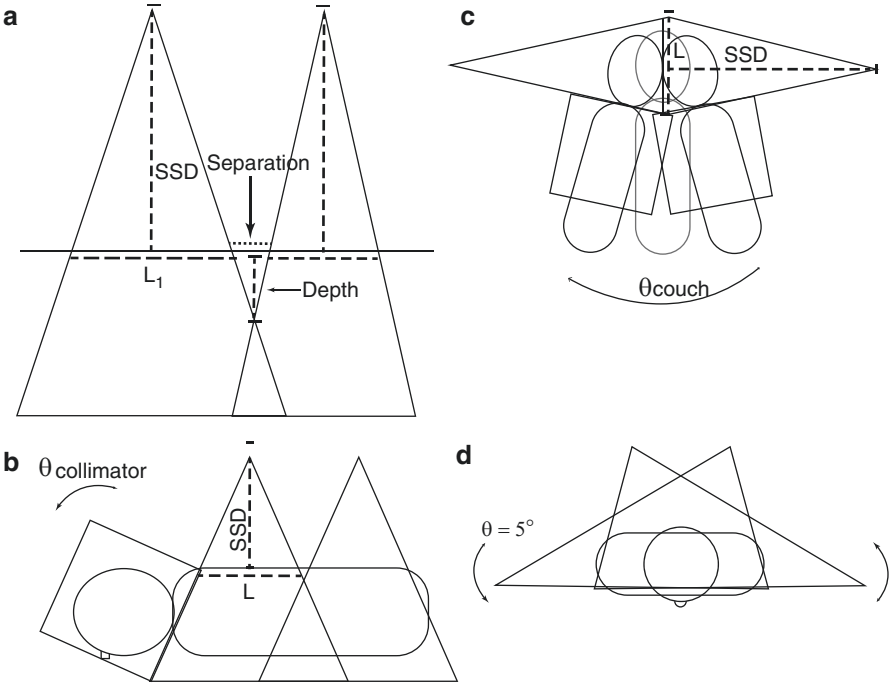

Fig. 27.3 Illustration of craniospinal field setup, including the gap calculation to allow for field matching (**a**), collimator rotation to match the cranial field with the superior divergence of the spine field (**b**), couch kick to avoid divergence from the whole brain field into the spine field (**c**), and a gantry rotation to create a light posterior oblique field in order to spare the contralateral lens (**d**)

surface (often between 10 and 20 mm) is given by the following equation, where S = separation, L = the length of the PA spine field, Depth = depth at which the two fields superimpose (or the anterior spinal canal), and SSD = the source to surface distance of the PA spine field (Fig. 27.3a):

$$Gap = S_{(\text{field1})} + S_{(\text{field2})} = \frac{1}{2}\left(\frac{L_1 \times \text{Depth}_1}{SSD_1}\right) + \frac{1}{2}\left(\frac{L_2 \times \text{Depth}_2}{SSD_2}\right)$$

The lower border of the cranial field should be placed in the lower cervical spine superior to the shoulders so as to avoid interference and should be collimated to match the divergence of the upper spine field. The angle of collimation can be found by the following equation (Fig. 27.3b):

$$^{\theta}\text{collimator} = \tan^{-1}\left(\frac{1}{2} \times \frac{L}{SSD}\right)$$

The lower cranial field and the superior spine field should nearly abut with a 0–5 mm gap. A modified table angle can additionally be used to account for caudal divergence of the craniocervical fields. This is done by rotating the couch towards

the gantry by the following angle, where SAD = source to axis distance of the lateral cranial fields (Fig. 27.3c):

$$^{\theta}\text{couch} = \tan^{-1}\left(\frac{1}{2}\times\frac{L}{SAD}\right)$$

Additionally, the gantry angle of the cranial fields can be rotated in an anterior-posterior fashion by approximately 5° to create a light posterior oblique field in order to spare the contralateral lens in younger patients (Fig. 27.3d). The junctions between matching spine fields and the matching superior spine and cranial field should be feathered by 5–10 mm, approximately every 9 Gy or five fractions. Accordingly, the lower border of the cranial field and the size of each spine field must be able to accommodate repeated decrease or increase in field length as the borders are moved with feathering. The largest field size at a standard SSD should be 40 cm or less to allow for feathering.

27.4.2 Advanced Photon Techniques

The use of 3DCRT with treatment field overlaps or gaps described above can provide significant dose heterogeneity throughout the target volume as well as considerable dose delivered to organs anterior to the vertebral body. The use of more advanced photon treatment modalities, such as IMRT (Cao et al. 2012; Parker et al. 2007; Pai Panandiker et al. 2007), volumetric modulated arc therapy (VMAT) (Bedford et al. 2012; Lee et al. 2012), and helical tomotherapy (TOMO) (Sharma et al. 2009; Bauman et al. 2005), has also been described. These techniques can be incorporated into CSI treatment planning in multiple ways. IMRT can be used with the standard matched PA spine fields, to modulate the dose delivered to the planning target volume according to the varying depth and target shape, thereby improving conformality and reducing dose delivered anterior to the spinal canal (Parker et al. 2007). Further, these techniques can facilitate the use of treatment planning optimization to create a uniform dose distribution over an overlap region between two fields, and eliminate the need for field matching and feathering (Cao et al. 2012). The use of these techniques has been shown to improve dose conformality, reduce heterogeneity, and reduce the dose delivered to anterior structures such as the heart and liver as well as the total integral dose (Parker et al. 2007; Pai Panandiker et al. 2007; Bauman et al. 2005).

27.4.3 Electron Therapy

The use of electrons has also been proposed in effort to reduce acute effects of CSI by reducing the anterior depth of the treatment volume. In 1985, Maor et al. described the use of 15–17 MeV electrons prescribed such that the 90% isodose line covered at least 3 mm anterior to the estimated location of the spinal cord after

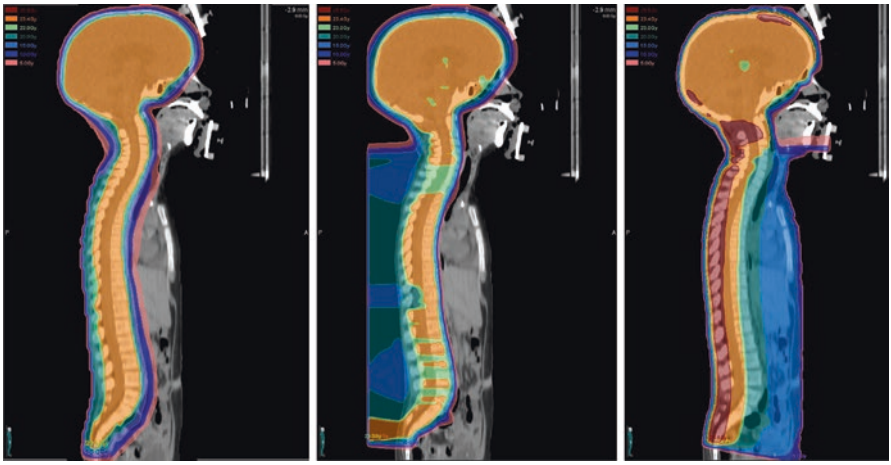

Fig. 27.4 A comparison of the dose distribution with pencil beam scanning proton therapy (*left*), passive scattered proton therapy (*middle*), and three-dimensional conformal photon therapy (*right*) in the sagittal plan. Note the significant sparing of structures anterior to the vertebral bodies with the two proton therapy plans as compared to photon therapy and the improved dose homogeneity and skin sparing provided by the pencil beam scanning CSI plan

correction for bone heterogeneity (Maor et al. 1985). A later comparison between patients treated with this technique and photon therapy at MD Anderson Cancer Center demonstrated that radiation dermatitis and weight loss were similar between electron and photon treated patients, while patients treated with electrons experienced higher rates of leukopenia and thrombocytopenia (Chang et al. 2002).

27.4.4 Proton Therapy

Proton radiation therapy (PRT) is an alternative to the photon therapy techniques described above. Due to the unique dosimetric properties of PRT, characterized by reduced entrance dose and minimal to no exit dose, PRT has been demonstrated to deliver equivalent target volume coverage while significantly reducing the dose delivered to all structures anterior to the vertebral bodies as well as the dose received to critical intracranial structures following boost treatment (Miralbell et al. 1997b; St Clair et al. 2004; Kirsch and Tarbell 2004) (Fig. 27.4). This reduced radiation dose delivered to normal tissues is expected to reduce multiple treatment related sequelae of craniospinal irradiation (St Clair et al. 2004; Chung et al. 2013; Merchant et al. 2008; Brodin et al. 2011; Fossati et al. 2009). Based on this dosimetric data and the promising clinical data (Yock et al. 2016; Sethi et al. 2014), the number of pediatric medulloblastoma patients treated with proton therapy is steadily increasing in the United States (Andrew 2014).

Treatment setup and delivery of passively scattered three-dimensional conformal PRT are similar to that described above for 3DCRT, though subtle differences do exist. The angle of divergence for PRT beams is less than that for photon therapy, and thus the equations listed above for photon therapy do not apply. Spine fields are likewise matched at the anterior thecal sac, and this is setup visually using the simulation CT. Skin gaps, if using the prone technique, can then be directly measured from the CT to be used for daily treatment setup. The aperture of the cranial field is designed to match the minimal divergence from the superior spine field, and no collimator rotation is used. A table kick is also not required to match divergence between the cranial and spine fields. Additionally because of the absence of exit dose, a posterior-anterior oblique on the cranial fields is typically used to avoid the contralateral lens (Cochran et al. 2008). Also, the extension of the chin is of lesser concern as there is no risk for exit dose from the spine fields through the mouth and therefore chin is positioned to maximize airway safety and minimize skin folds at the back of the neck.

Intensity modulated proton therapy with pencil beam scanning (PBS) further improves the dose distribution with the use of protons by eliminating the need for field matching and improving dose homogeneity and conformality (Fig. 27.4) (Timmermann et al. 2002; Lin et al. 2014). Similar to the IMRT capabilities described above, PBS allows for treatment planning using gradient dose optimization to create a uniform dose distribution in overlap regions without requiring field matching or feathering (Lin et al. 2014; Yom et al. 2007). With the use of PBS, the cranium can be treated with two lateral or oblique fields, or with a single PA field. In addition to improving dose homogeneity and easy of treatment setting, the use of PBS as opposed to passive scattering protons may have additional benefits such as reduced skin dose, as well as reduced hardware costs and reduced neutron scatter dose (Lomax et al. 2004).

27.4.5 Treatment Setup Verification

X-ray imaging, kV or MV, is imaging which is typically used to ensure accurate alignment of bony anatomy of the cranial field prior to treatment. The spine can then be set up based on the cranial field with the use of additional kV imaging when treating in the supine position or with the use of direct visualization of light fields on the patient's skin in the prone position. Daily imaging of the spine can also be used to ensure adequate daily setup. Using daily MV cone beam CT, Gupta et al. have analyzed the three-dimensional setup errors with the use of IMPT for CSI delivery and have demonstrated a distinct trend towards increasing inaccuracy from the brain towards the lumbar spine, with 3D vector displacement of 2.28, 1.45, and 3.15 mm for the brain, upper spine, and lower spine, respectively (Gupta et al. 2015). This study and other similar analyses highlight the need for accurate immobilization techniques, PTV margin expansions, and the use of image guidance with the delivery of CSI (Stoiber et al. 2011; Al-Wassia et al. 2013).

27.4.6 Treatment Delivery and Toxicity Monitoring

Current COG protocols for medulloblastoma and SPNET recommend the initiation of CSI within 31 days of surgery. Analysis of the HIT-SIOP PNET 4 trial demonstrated worse prognosis among patients for whom RT was delayed more than 7 week from surgery (Lannering et al. 2012), while multiple single institution retrospective reviews have failed to identify a direct relationship between clinical outcomes and time between surgery and RT initiation (del Charco et al. 1998; Paulino et al. 2003). However, effort should also be made to minimize treatment interruptions for completion of therapy within 45 days, as the prolongation of radiation treatment has been correlated with worse disease control (del Charco et al. 1998; Paulino et al. 2003). Patients receiving craniospinal irradiation with or without concurrent chemotherapy are at risk for acute hematologic and non-hematologic toxicity. Those treated with concurrent non-vincristine chemotherapy such as daily carboplatin or who have been treated with chemotherapy prior to radiation are at increased risk of leukopenias. Complete blood counts with differential should be monitored weekly during treatment. If ANC is ≤500/μL, the use of growth factors or switching to the involved field boost part of treatment should be considered. However, a break in the radiation therapy simply for uncomplicated low blood counts should be avoided to minimize the overall duration of radiation therapy (del Charco et al. 1998; Paulino et al. 2003). CSI should be resumed when the ANC has risen to >750 μL or increased by 10% on 2 consecutive days. Platelets should be transfused when <30,000/μL and clinically indicated, and CSI should be restarted when >50,000/μL or when platelet counts have increased >10% on two consecutive tests. Red blood cell transfusions may be recommended when the hemoglobin falls below 9 mg/dL. In effort to minimize treatment delays, if CSI must be held, RT can be continued by switching to the boost field.

Gastrointestinal toxicity is a common non-hematologic acute effect. Patients may be treated with ondansetron for nausea. Additional second-line medications including dexamethsone, lorazepam, antihistamines, or marinol can be used in combination with ondansetron for severe nausea. Patients who have significant postoperative residual nausea and vomiting often have significant trouble with the CSI. Severe cases have responded well to aprepitant. Nutrition should be closely monitored and patients should be weighed weekly and received nutritional counseling as appropriate. Appetite stimulants such as cyroheptadine or marinol may be of value. Enteral or parenteral support should be considered for a >10% weight loss. When delivered with chemotherapy, pneumocystis prophylaxis with trimethoprim/sulfamethoxazole given 2 consecutive days per week is often recommended for patients during and 2 months following completion of radiation therapy.

Patients who received craniospinal irradiation are at risk for multiple late treatment related sequelae, the risk of which may be dependent upon the dose received to particular tissues as well as the patient age and the receipt of additional therapies. Long-term follow-up should focus on late effect monitoring and management. COG recommendations for late effect monitoring are listed in Table 27.1.

Table 27.1 COG long-term follow-up guidelines for patients who received craniospinal irradiation

Late effect	Recommendations
Secondary malignancy	• Yearly inspection and palpation of skin and soft tissues in irradiated field • History to ask about changing nevi, bone pain, neurologic symptoms • Brian MRI as clinically indicated • Thyroid exam yearly • Colonoscopy every 5 years beginning at 10 years after RT or age 35, whichever is last (if >30 Gy to bowel) • Healthy behavior such as not smoking, drinking, maintaining healthy weight and diet
Skin changes	• Dermatologic exam yearly
Neurocognitive defect	• Assess for educational and/or vocational progress yearly • Baseline neurocognitive assessment and then periodically in follow-up as clinically indicated or if evidence of impaired progress
Clinical leukoencephalopathy	• Neurological exam yearly
Craniofacial abnormalities	• Physical exam and psychosocial assessment yearly
Endocrine dysfunction	• Annual screening, including height, weight, BMI, blood pressure, and physical exam with tanner stage assessment • Growth and nutritional status assessment every 6 months until sexually and skeletally mature • X-ray for bone age in poorly growing children • Endocrine consult if doses >30 Gy or if decline in growth velocity or growth/weight below the third percentile • Counsel on healthy lifestyle • Thyroid exam yearly
Cataracts/other ocular toxicity	• History for visual change • Eye exam yearly including visual acuity and fundoscopic exam • Ophthalmologist exam as clinically indicated or yearly if RT dose >30 Gy to cranium, or orbit
Hearing deficits	• History for hearing difficulties • Otoscopic exam yearly • Audiology exam yearly for 5 years or until age 10, then every 5 years
Xerostomia/dental abnormalities	• Oral exam yearly • Dental exam every 6 months
Cardiac (any dose to heart)	• Pulmonary and CV exam yearly • Baseline EKG at entry into follow-up then as clinically indicated • Echocardiogram every 2 years if <5 years old and any RT dose to heart, or every 5 years if >5 years old and any RT dose to heart • Fasting blood glucose or HbA1c and lipid profile every 2 years
Musculoskeletal growth problems	• Height, weight, and sitting height yearly • Spine exam for scoliosis and kyphosis • Spine films if clinically apparent curve, orthopedic consult as indicated • Counsel on risk of fracture (if doses >40 Gy)
Gastrointestinal Issues/esophageal stricture (>30 Gy)	• History for chronic enterocolitis • History of dysphagia with GI or surgery consult for symptomatic patients
Carotid artery disease (>40 Gy)	• Yearly carotid exam, neurologic exam and history yearly • Doppler US as clinically indicated

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28 Special Radiation Techniques for Pediatric Brain Tumors: Hypofractionation, Radiosurgery, and Brachytherapy

Susan M. Hiniker and Iris C. Gibbs

Contents

Abstract

Radiation is an important component in the treatment of pediatric brain tumors. Because of the concern for late radiation complications, innovative strategies to improve radiation effectiveness and reduce toxicity have been investigated. Here, we describe hypofractionation, stereotactic radiosurgery, and brachytherapy as advanced radiotherapeutic technologies and strategies currently in use in the treatment of pediatric brain tumors.

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28.1 Introduction

Radiation therapy is an important component of the overall treatment paradigm in many tumors of the pediatric central nervous system (CNS). However, the use of cranial radiotherapy in children is associated with concern for long-term morbidity including neurocognitive and growth effects, and risk of secondary malignancy (Merchant et al. 2005, 2009; Shih et al. 2009; Vern-Gross et al. 2014; Lawrence et al. 2010). As such, efforts have been made to reduce or omit the use of cranial radiotherapy in children where possible. Yet, the omission of radiation in the treatment of certain pediatric CNS malignancies has been associated with higher relapse rates in a number of trials (Balmaceda et al. 1996; Kellie et al. 2004), thereby leading to its continued incorporation despite the risk of side effects. Importantly, many of the studies that reported deleterious side effects associated with radiation included patients treated with older radiation techniques, thereby potentially overestimating the magnitude of the deficits associated with current techniques. Recent advances in technology allow for more precise localization with image guidance and smaller margins, thereby reducing the volume of brain receiving radiation and decreasing the dose received by adjacent areas, while allowing the safe delivery of a larger dose per fraction. We discuss here advanced radiotherapeutic technologies and strategies currently in use in the treatment of pediatric brain tumors, and outcomes in specific disease sites.

28.2 Treatment Types

Hypofractionated radiotherapy refers to the shortening of a course of external beam radiation therapy (EBRT) into fewer fractions with higher dose per fraction, while generally maintaining equal or greater biologically effective dose (BED). Interest in hypofractionation first developed in the 1950s and continued through the 1970s, largely due to increased demand for adjuvant radiation in breast cancer and limited resources to provide this care. However, a high rate of side effects associated with early hypofractionation strategies, including skin fibrosis and brachial plexopathy, limited the adoption of this strategy (Ko et al. 2011; Friberg and Ruden 2009). While hypofractionation has obvious practical benefits such as shortening treatment courses and improving the convenience to patients and families, it also has important radiobiological effects (Slotman et al. 1996). The basis of the radiobiological effect of hypofractionation continues to be a source of debate, with some arguing that effects can be predicted by the linear-quadratic (LQ) model, and others arguing that the effect of hypofractionation is greater than that predicted by the LQ model. This greater radiobiological effect sometimes reported with hypofractionation may be related to multiple factors, including differential radiosensitivities of the heterogeneous population of tumor cells and the potential role for immunologic effects in modulating radiation-induced damage (Ko et al. 2011; Yu et al. 2015). Furthermore, shortening of treatment time may reduce tumor cell repopulation during treatment, particularly important in aggressive CNS tumors with rapid doubling times (Iuchi et al. 2014). In employing a higher dose per fraction, the use of hypofractionation

may also allow for the effective treatment of tumors previously considered radioresistant. However, these putative benefits must be weighed against the potential short-term and long-term side effects of hypofractionated therapy, which are less well understood than conventional treatment protocols (Iuchi et al. 2014).

Stereotactic radiosurgery (SRS) was developed in the early 1950s as a method of treating an intracranial lesion with an ablative dose of radiation, made possible by the ability to precisely localize the target, often utilizing real-time tracking (Leksell 1951). This precise localization allows for treatment with little to no margin around the tumor and with extremely steep dose falloff. Multiple types of SRS exist, including Gamma Knife radiosurgery (GKS), which uses multiple cobalt-60 sources and directs these sources to a central target at the isocenter, with an accuracy of 0.3 mm. GKS requires an invasive head frame for immobilization and depending on the contour of the volume to be treated may require multiple isocenters. In contrast, linear accelerator-based (linac-based) SRS utilizes a single X-ray source that moves around the patient, with the collimator having the capability of using cones or multileaf collimators, enabling treatment with static fields or moving arcs. The couch is also mobile, allowing correction for translational and rotational errors. Additionally, since linac-based SRS can be performed with a noninvasive mask instead of frame-based immobilization, treatment fractionation is more feasible.

Brachytherapy is a specialized form of internal radiation therapy which, in the setting of CNS disease, is delivered in an interstitial manner and generally involves implantation of iodine-125 seeds. This treatment will deliver dose directly to the area of implantation, but with a rapid dose falloff thus minimizing dose to the adjacent normal brain. The procedure is typically performed immediately after biopsy, often using a target software program (Ruge et al. 2011a). In contrast to externally delivered radiotherapy, brachytherapy provides prolonged low-dose activity, potentially minimizing toxicity while providing consistent and ongoing treatment of the lesion in question (Peraud et al. 2007).

28.3 Considerations in Pediatric Patients

Special considerations must be given to pediatric patients, in terms of practical aspects of the logistics of therapy, as well as in attention to long-term effects. The typical radiosurgical and radiotherapeutic considerations require modification for the treatment of children, particularly in the area of immobilization. Frame-based techniques typically require skull fixation with pinning for the precise localization of the target volume, in order to ensure safe and accurate delivery of a higher dose of radiation. The thinner and relatively flexible skulls of young children require extra consideration in pinning to avoid damage to normal tissues. In addition, the thin skull of a child is more deformable than that of an adult, potentially complicating accuracy of treatment. Attempts have been made at noninvasive immobilization for frame-based SRS, with trials of various head immobilization techniques, including helmet techniques attached to the upper teeth (Greitz et al. 1980; Kingsley et al. 1980). However, these may make airway access for anesthesia difficult or

impossible. Other immobilization devices without skull fixation have been studied, but may produce errors up to 3–4 mm, precluding the safe and accurate delivery of high-dose radiation in a single fraction (Kooy et al. 1994). Robotically controlled radiosurgical systems such as CyberKnife use a frameless delivery system that relies on an advanced fusion algorithm to provide similar accuracy to frame-based systems (Giller et al. 2007). This produces comparable accuracy as frame-based systems using a noninvasive approach and a simple custom face mask, which can be modified to provide access for anesthesia (Murphy and Cox 1996).

Another important consideration in the treatment of children is the frequent need for anesthesia which can be particularly challenging when combined with certain immobilization techniques. Even older children undergoing GKS or frame-based radiotherapy in which immobilization is paramount may require general anesthesia, increasing the risks associated with therapy. In a study of 68 pediatric cases of anesthesia and stereotactic radiosurgery, there were four serious events associated with procedures (Stokes et al. 1995). Because of the risks and challenges associated with daily general anesthesia, the fact that SRS is completed in one to five fractions is particularly appealing in the pediatric patient population.

Despite the practical benefits of hypofractionating therapy in children with CNS disease, there remains the hypothetical concern for increased side effects, such as brain necrosis. Image-guided hypofractionated or SRS approaches treating smaller fields and with less volume of the adjacent brain receiving radiation may help limit such toxicity and are also beneficial in considering the known radiation dose–volume effects in the brain in children (Lawrence et al. 2010). Another major concern in treating children with CNS-directed radiation is the risk of secondary malignancies later in life. However, models have estimated a relatively low risk of secondary malignancy after SRS, which is less than the risk of death from general anesthesia (Rowe et al. 2007). Finally, the optimal dosing of hypofractionated or SRS in pediatric patients remains to be determined. Concerns for late effects have prompted some attempts to decrease doses by approximately 25% in pediatric patients (Giller et al. 2007). However, such dose reductions have been reported to result in inferior local control as compared to standard adult doses (Smyth et al. 2002). The rate of serious adverse events such as radiation necrosis remain relatively low at this time and has prompted some to increase radiation doses to the adult level (Tanaka et al. 1996).

28.4 Individual Applications of Hypofractionation and Stereotactic Radiosurgery

28.4.1 Malignant Disease

28.4.1.1 Brainstem Glioma

Diffuse Intrinsic Pontine Glioma

Perhaps the best-known use of hypofractionation in pediatric CNS tumors is in the setting of diffuse intrinsic pontine glioma (DIPG). Despite many trials of systemic therapy and various radiotherapeutic alterations including hyperfractionation,

conventionally fractionated radiation therapy has remained the standard of care (Vallero et al. 2014). The standard course of radiation typically involves 6 weeks of daily radiation, but outcomes remain poor with most children surviving less than a year after diagnosis. A small retrospective case series found that hypofractionation (45 Gy in 15 fractions) had no major effect on survival and was reasonably well tolerated. However, several patients required steroids and/or reduction of the daily fraction size from 3 to 2 Gy (Negretti et al. 2011). Similarly, another study of hypofractionated therapy (13–16 fractions) with a matched-cohort analysis comparing conventionally fractionated radiation showed comparable overall survival (9.0 vs. 9.4 months in the hypofractionated and conventional therapy groups, respectively) (Janssens et al. 2013). Toxicity was comparable between the two groups. In the largest study to date of hypofractionated therapy for DIPG, Zaglhoul et al. conducted a trial of 71 patients randomized to either 39 Gy in 13 fractions or 54 Gy in 30 fractions. Although the study failed to demonstrate statistical non-inferiority of hypofractionation, the two groups had comparable results. Hypofractionation had a worse median overall survival (7.8 vs. 9.5 months) but better 1-year survival (36.4% vs. 26.2%) (Zaghloul et al. 2014). As in other studies, there was no significant difference in toxicity between the two groups. In summary, hypofractionation appears to yield similar outcomes and toxicity to conventional therapy, while significantly reducing the duration of treatment. Therefore, hypofractionation appears to be a reasonable and safe approach, particularly in patients who may have difficulty attending treatment, or who wish to minimize the burden of treatment in this disease with a relatively short overall survival.

Focal Brainstem Glioma

Focal brainstem gliomas are a distinct subset of brainstem gliomas with a more indolent course and better prognosis, yet resection is technically challenging or impossible, and the tumor location commonly poses issues due to local progression. The use of SRS has been explored as both an adjunct and an alternative to surgery. A retrospective review of 20 patients treated with GKS from 1990 to 2001 suggests that SRS may be an effective treatment for focal brainstem glioma. A prescribed dose of 10–18 Gy was delivered, with tumor shrinkage in 12 patients and complete remission in 4 patients. As in other studies of SRS, intratumoral changes in magnetic resonance enhancement were frequently seen but did not correlate with response (Karger et al. 1997; Kihlstrom et al. 1994). Side effects were generally well tolerated, though there was one patient who despite responding radiographically, developed fluctuating impairment of consciousness (from somnolence to coma) lasting for 6 months (Yen et al. 2007). These results were similar to another retrospective report of 12 patients with focal brainstem glioma treated with GKS, with mean peripheral dose of 12 Gy, where responses and stable disease were seen in 6 and 5 patients, respectively (Fuchs et al. 2002).

The radiosurgical experience in young children with focal brainstem glioma is limited. There is concern for increased toxicity in these children given ongoing neurologic development. Encouraging results have been reported in a case report of two children, ages 2.5 and 5.5 years. In each case, the tumor was located in an area not amenable to microsurgical resection. These patients were successfully treated

with GKS with a mean tumor dose of 14–16 Gy and peripheral doses of 11–12 Gy. Both children showed remarkable tumor shrinkage and no adverse neurologic outcomes, at follow-up of 4 and 8 years (Liao et al. 2012).

Thus far, the limited evidence in pediatric focal brainstem gliomas has found stereotactic radiosurgery is both a safe and effective alternative to surgery in select cases. In cases where treatment-related toxicity occurs, they appear to be most commonly transient neurological deficits that resolve over time (Sharma et al. 2008).

28.4.1.2 Ependymoma

The standard treatment for ependymoma involves surgery followed by postoperative radiation therapy. Given favorable outcomes, effort has been made toward reducing radiation fields in the setting of nondisseminated disease. The primary pattern of failure in pediatric ependymoma patients is local, with extent of surgery reported by multiple groups to be the most important prognostic factor in survival (Robertson et al. 1998). Radiation dose also appears to be important in outcome particularly in those patients who have undergone subtotal resection (Lo et al. 2006). Two trials of SRS boost in the primary management of unfavorable ependymoma have been reported with favorable results. In a study of patients with residual tumor measuring 3 cm or less in diameter following initial surgery and chemotherapy or following conventional radiation, SRS boost was prescribed to the 80% isodose line with maximum dose ranging from 11.25 to 18.75 Gy. Of a total of five patients, four patients who received SRS within 30 days of primary radiation remained alive without progression of disease at a median of 24 months post-treatment (Aggarwal et al. 1997). No acute neurotoxicity was noted in any patient though one patient developed an apparent subacute reactive process which required treatment with short-term steroids with subsequent resolution of symptoms (Aggarwal et al. 1997). A single patient was treated with SRS boost 6 months after initial external beam radiation therapy, and this was the only patient who developed progressive disease. A report of the Washington University experience in treating nine children with unfavorable ependymoma found similar benefit to incorporating SRS in primary therapy. In four patients treated with SRS as part of primary therapy, none had experienced relapse at 3 years. Dose was 14–18 Gy prescribed to the 50% isodose line for patients treated with GKS, and 14–20 Gy to the 80–90% isodose line for patients treated with linac-based SRS, with only two severe side effects noted, including one patient with post-treatment seizure disorder and one patient with facial nerve palsy (Mansur et al. 2004). A phase II trial which planned to incorporate SRS boost after conventional EBRT if there was residual enhancement of the tumor following EBRT would have helped assess the benefit of SRS in unfavorable ependymoma, but unfortunately the study was closed due to poor accrual (Lo et al. 2006).

The use of hypofractionation and SRS has been more widely reported in the setting of recurrent ependymoma. Liu et al. reported the outcomes of six children with locally recurrent ependymoma treated with maximally safe resection, followed by hypofractionated irradiation on a linear accelerator to 24–30 Gy in three fractions. With a follow-up of 28 months, all six children are alive without evidence of

disease, with three children having evidence of radiation necrosis clinically or on imaging, but none requiring intervention (Liu et al. 2009). At the Mayo Clinic, 26 patients with recurrent ependymomas had SRS, 8 of whom were under the age of 18 years. The investigators report 3-year local control rate of 72%, and 2 patients (8%) with symptomatic radiation necrosis after SRS, both of whom had undergone previous EBRT (Stauder et al. 2012). Another study of recurrent ependymomas treated with SRS was reported by the Pittsburgh group. Among 39 patients with a median age of 22.8 years, 32.1% of patients remained alive at 5 years after SRS, with a progression-free survival of 45.8%. It appeared that smaller volume and homogenous contrast enhancement were significant predictors of response to SRS, and other groups have reported this as well. Though children are generally thought to have poorer outcomes than adults with more aggressive anaplastic ependymoma, there was no significant difference seen by age in this study (Kano et al. 2010). Others have found less encouraging results in the setting of recurrent ependymoma. In one study which included 25 patients with recurrent ependymoma, only 12% remained disease-free on follow-up (Hodgson et al. 2001), while another study of 7 patients treated with SRS for recurrence found none remained in remission on follow-up (Grabb et al. 1996).

Disseminated recurrence can also occur in the setting of ependymoma, with leptomeningeal involvement more common in high-grade ependymoma and a median survival after diagnosis of disseminated disease of 7 months (Calvo et al. 1983). The use of SRS in the setting of disseminated recurrence has not been well studied though a case report of two pediatric patients suggests that SRS may be an effect treatment in this challenging setting. Two children with nodular recurrent disease after initial therapy were treated with SRS to these lesions and remained alive without progression of disease at over 21 months after treatment (Endo et al. 2004).

28.4.1.3 Low-Grade Glioma

Low-grade gliomas demonstrate varying aggressiveness in the pediatric population.

Given that the extent of resection and presence of residual disease after surgery correlates with outcome, there has been interest in using SRS to ablate residual disease (Kortmann et al. 2003), both in the adult (Heppner et al. 2005) and pediatric population (Wang et al. 2006). There is a fairly extensive body of literature regarding the use of stereotactic radiosurgery in patients with pilocytic astrocytoma. In this setting, SRS has been shown to be associated with better progression-free survival (PFS) and complete tumor response as compared with chemotherapy or standard fractionated external beam radiation therapy (Boethius et al. 2002). In a report of 49 patients treated with SRS for pilocytic astrocytomas, tumor control was achieved in 33 of 49 patients (67%), and in 85% of patients with solid, circumscribed tumors. Two patients had temporary acute side effects attributed to radiation, but no permanent complications occurred (Hadjipanayis et al. 2002). Other studies have shown similar promising results (Hallemeier et al. 2012).

In the pediatric setting, Kano et al. report their experience with stereotactic radiosurgery for pilocytic astrocytomas in 50 children, with median age of 10.5

years (Kano et al. 2009). Median margin dose was 14.5 Gy. Progression-free survival after SRS including tumor growth and cyst enlargement was 70.8% at 5 years, and best response was seen in patients with small volume residual solid tumors (Kano et al. 2009). Similar results were found in long-term follow-up of patients treated with GKS for low-grade astrocytoma, including a report of 51 patients, 12 with grade I astrocytomas and grade II astrocytomas. The patients with grade I astrocytoma were primarily pediatric, with mean age of 9.8 years and had a control rate of 91.7%. Radiation-induced edema occurred in 18 patients (16 of whom had grade II disease), cyst formation/enlargement in 5 patients, and transient tumor enlargement in 3 patients, all of whom had grade II disease (Kida et al. 2000). Somaza et al. found similar results in early outcomes after SRS for growing pilocytic astrocytomas in childhood (Somaza et al. 1996).

Among studies including a wider variety of low-grade gliomas, Weintraub et al. reported the use of GKS in the treatment of 24 pediatric patients with low-grade glioma, all of whom had tumors that were unresectable or showed residual disease or recurrence after surgery. At a median imaging follow-up of 74 months and median clinical follow-up of 144 months, 75% of patients had a decrease in tumor size of at least 50%, and complete tumor resolution occurred in 21%. Eighty-three percent of patients had progression-free survival extending to the date of last follow-up. Pretreatment tumor size was the only significant predictor of tumor progression-free survival. The authors conclude that GKS can provide good control of residual or recurrent gliomas in pediatric patients (Weintraub et al. 2012). In the setting of retreatment, outcomes after SRS for glial neoplasms of childhood in a series of 25 children were reported, 13 with pilocytic and low-grade astrocytomas, and 11 had received previous fractionated external beam radiation therapy. At median follow-up of 21 months, 11 of these 13 children had tumor control and all were alive (Grabb et al. 1996).

A prospective trial at Dana Farber examined the use of stereotactic radiotherapy and marginal failures in a study enrolling 81 pediatric patients with low-grade gliomas, including 50 with low-grade astrocytoma, 23 with residual or recurrent craniopharyngioma, 4 with posterior fossa ependymoma, and 4 with other types. They received fractionated stereotactic radiotherapy to a mean total dose of 52.2 Gy in 1.8 Gy daily fractions. Progression-free survival was 82.5% at 5 years and 65% at 8 years. Marginal failures were not seen, supporting the use of minimal margins using stereotactic techniques. Six patients had local progression, all of which were within the tumor bed and had received full prescription dose (Marcus et al. 2005).

28.4.1.4 Medulloblastoma

Incorporation of a stereotactic radiosurgical boost into the treatment of medulloblastoma has been reported as a strategy to improve local control in patients with incomplete response to initial therapy or with well-defined recurrent disease. In a study by Patrice et al., 12 patients were treated with subtotal resection and 2 with gross total resection. SRS was delivered to the site of residual disease in 3 patients and to a well-defined site of recurrence in 11 patients. Of note, the three patients treated with a boost as part of initial treatment strategy did not experience local

failure at a median follow-up of 27 months, while 6 of 11 patients treated for recurrent medulloblastoma died of progressive disease (Patrice et al. 1995). Similarly promising results in the incorporation of a boost into the initial treatment strategy were reported by Woo et al., with SRS boost to the tumor bed delivered in patients with high-risk medulloblastoma thought to be at elevated risk of local recurrence, with prescription doses of 4.5–10 Gy prescribed to the 80–100% isodose lines. All four patients treated in this manner remain alive without evidence of disease at 12–48 months after treatment (Woo et al. 1997). The only late effect was panhypopituitarism in one patient, which was attributed to the previous whole brain radiation. No patients experienced necrosis in this study.

Stereotactic radiosurgery has also been effectively used in the treatment of small volume metastatic relapsed medulloblastoma, as noted above in the Patrice report, in which 5/11 patients with recurrent disease experienced freedom from second progression after SRS. King et al. reported a series of three pediatric patients treated with Gamma Knife to recurrent medulloblastoma nodules, with single fraction treatment and doses ranging from 15 to 25 Gy. At a mean follow-up of 39 months, two patients were in complete remission, and one had stable disease. No adverse effects related to SRS were noted (King et al. 2014).

28.4.1.5 Primitive Neuroectodermal Tumor

The data for the use of SRS in the management of pediatric primitive neuroectodermal tumor (PNET) is small and primarily involves treatment of local failure or distant intracranial recurrence after multimodality therapy (Hodgson et al. 2001). In the University of Pittsburgh experience using GKS for recurrent pediatric PNETs, seven patients underwent a total of 15 GKS procedures for locally recurrent disease or distant intracranial recurrence. All patients died of disease, with median survival of 37 months from initial diagnosis, and 15 months from GKS. Two patients had early progressive disease (median survival 5 months from GKS), and five had delayed progression (median survival after progression 30 months). GKS appeared to be well tolerated in these patients, all of whom were previously treated with craniospinal irradiation and chemotherapy. However, six of seven children ultimately died of systemic disease (Flannery et al. 2009). Given the overall poor outcomes of these patients pointing to the likelihood of the presence of disseminated disease at time of relapse, others have questioned the value and appropriateness of SRS in this setting (Boop 2009).

28.4.1.6 Germ Cell Tumor

The use of SRS has also been investigated as a boost strategy in patients with intracranial germ cell tumors. Zissaidis et al. reported the results of stereotactic radiotherapy for the treatment of intracranial germ cell tumors without spinal involvement in 18 patients, with tumors measuring less than 50 mm in maximum diameter. Median dose to the tumor was 48 Gy in 1.8–2 Gy daily fractions. Five patients with multiple midline tumors received CSI followed by stereotactic boost to the tumor sites. Eight patients with germinoma in a single site received whole brain radiation followed by a stereotactic boost. Of five patients with mixed histology, two received CSI plus boost,

and three received tumor only treatment. Fourteen patients are alive and free of disease at a median follow-up of 38 months. One patient developed hypothyroidism after treatment that was not present prior to radiation (Zissiadis et al. 2001). As the appropriate radiation fields in the first-line treatment setting of germinomas are currently being studied with a goal to reduce volume and dose where possible, treatment using a stereotactic approach could prove to be an important tool in this setting.

28.4.2 Benign Disease

28.4.2.1 Arteriovenous Malformation

The most common cause of intracranial hemorrhage in children is arteriovenous malformation (AVMs). Management options include observation, embolization, resection, or stereotactic radiosurgery. There is a relatively large experience reported in the use of SRS in the treatment of pediatric AVMs. In a report of the United Kingdom, experience in treating children with AVMs, 363 patients with a mean age of 12 (range 1–16 years) were treated with a total of 410 treatments, with an obliteration rate of 71.3% in patients treated once, and 62.5% in patients who were retreated, with overall obliteration rate of 82.7%. No correlation was detected between outcome and radiosurgical dose when dose was between 20 and 25 Gy, suggesting that 20 Gy may be sufficient (Dinca et al. 2012).

In the University of Virginia, experience with 200 pediatric patients treated with SRS for AVMs, 49.5% achieved total angiographic obliteration with initial GKS, and obliteration rate increased to 58.6% after second or multiple GKS, and 4.8% achieved subtotal obliteration. The hemorrhage rate was 5.4% within 2 years after GKS, and 0.8% between 2 and 5 years. Of note, six patients developed neurological deficits accompanying the radiation-induced changes, and two patients developed asymptomatic meningiomas 10 and 12 years after GKS (Yen et al. 2010). Promising results were also reported by the University of Pittsburgh group in their experience treating 135 pediatric patients with SRS for AVMs, with median margin dose of 20 Gy. Angiographic obliteration was 67% at 5 years and 72% at 10 years. Hemorrhage occurred in 6% of patients during the latency period. Permanent neurologic deficits related to radiation occurred in two patients following SRS, with cyst formation in one patient (Kano et al. 2012).

28.4.2.2 Craniopharyngioma

Craniopharyngiomas are benign tumors of epithelial origin arising from the remnants of Rathke's pouch, and though benign, are potentially dangerous due to local growth and invasion of visual structures, hypothalamus, and pituitary. These tumors can occur in children and adults, and most reports of outcomes after SRS for craniopharyngioma include both adult and pediatric patients. Kobayashi et al. report the long-term outcomes of GKS for residual or recurrent craniopharyngiomas after microsurgical resection, with attempts at dose de-escalation with a mean tumor margin dose of 11.5 Gy, and a tumor control rate of 79.6%. Thirty-eight of 98 patients were children (Kobayashi et al. 2005). Other studies have shown similar

findings, with radiosurgery for craniopharyngiomas appearing to be safe and fairly effective, with 5-year tumor control rates of 67–69% (Niranjan et al. 2010; Minniti et al. 2009; Xu et al. 2011).

28.4.2.3 Pituitary Adenoma

Pituitary adenomas are more common in adults than in children, and the initial treatment is often surgical. In cases of residual disease or when surgery is not employed, SRS is a treatment option, and dose needed depends on the secretory status of the tumor (Jagannathan et al. 2009). In one of the largest studies of secretory pituitary adenomas treated by GKS, Sheehan et al. reported tumor growth control rates of 90% and endocrine remission rates of 20–54% (Sheehan et al. 2011). Endocrine remission was more commonly seen with growth hormone and adrenocorticotropic hormone-secreting tumors (53% and 54%, respectively) and less commonly with prolactinoma and Nelson's syndrome (26% and 20%, respectively). Furthermore, this study showed that marginal radiation dose not only directly correlated with endocrine control but also inversely correlated with time to achieve endocrine control. In the Kobayashi et al., study of adults and children treated with GKS for Cushing disease, a complete response rate of 30%, overall response rate of 85%, and tumor control rate of 100% were reported. Higher control rate was found with microadenomas and small adenomas. Post-treatment endocrine remission was achieved in 35% and decreased hormone levels in 85% of patients (Kobayashi et al. 2002).

28.4.2.4 Vestibular Schwannoma

Vestibular schwannomas are relatively rare in children, and when present are often in association with neurofibromatosis type 2 (NF-2). In a report of 55 young patients with vestibular schwannomas under the age of 40, including pediatric patients, the 5-year rate of freedom from additional management was 96% at a median follow-up of 5.3 years. Hearing preservation rate was 87% at 10 years, while preservation of facial and trigeminal nerve function was 98.2% and 96.4%, respectively. No patient developed a secondary radiation-induced tumor (Lobato-Polo et al. 2009). Longer follow-up is needed to show the rate of long-term tumor control and risk of radiation-induced tumorigenesis. Regis et al. have previously reported that young age is a positive prognostic factor for functional preservation and functional hearing preservation, confirmed by data from Pittsburgh (Regis et al. 2004). However, many younger patients with vestibular schwannomas also have NF-2, and there is a theoretical concern for a higher rate of malignant transformation after radiation in this population, though this has not yet been borne out clinically. It has been reported that patients with NF-2 have worse local control and more complications than other patients, but also have worse outcomes with surgery (Mathieu et al. 2007). Further study is needed to determine the optimal treatment approach in such patients.

28.4.2.5 Meningioma

SRS has been shown to have a high local control rate in the treatment of grade I meningiomas, with local control rates comparable to complete resection, and with

low morbidity (Pollock et al. 2003). Im et al. performed a retrospective analysis of childhood meningiomas. Surgery was performed in all 11 cases first, and radiotherapy was used in patients with residual disease and recurrence. Two patients received GKS 2.5 and 5 years after initial surgery due to disease recurrence, and without local recurrence. One additional patient received GKS after subtotal resection of a cavernous sinus meningioma and has had stable disease with no evidence of progression 2.5 years later (Im et al. 2001). SRS has also been reported to be effective in the treatment of radiation-induced meningiomas (Galloway et al. 2011).

28.5 Special Cases

28.5.1 Infants

Infants with brain tumors are a special patient population with often somewhat distinct disease courses and response to treatment. For example, congenital glioblastoma multiforme shows genetic distinctions from adult GBM with variable cure rate, with a percentage of patients becoming long-term survivors of disease (Macy et al. 2012; Song et al. 2010). Given the known deleterious neurocognitive effects associated with cranial irradiation in early childhood, most protocols attempt to delay radiation with the use of intensive chemotherapy until at least the age of 3 years. While some subgroups of patients have done well with this strategy, including those with nondisseminated, completely resected desmoplastic medulloblastoma, other groups are likely to benefit from the incorporation of radiation at an earlier time point. Radiosurgery is an attractive option in minimizing dose to adjacent normal tissue in these patients, with reports not showing the associated cognitive decline seen in with larger-field external beam radiation therapy (Kondziolka et al. 1990). Issues include immobilization, with skull fixation difficult in infants due to thinner skulls. Giller et al. report on the feasibility of image-guided robotic radiosurgery in five infants with malignant brain tumors using CyberKnife and report successful completion of treatment in all five patients. At a mean follow-up of 11 months, three patients remain alive without progression of disease. No radionecrosis or neurologic toxicity was observed in these patients (Giller et al. 2004). Special immobilization techniques for infants were employed in this study, including stabilization of the entire infant body with a Vac-Lok bag, and head immobilization with Accuform mold and Aquaplast mask, cut out to allow access for general anesthesia equipment.

28.6 Brachytherapy

The use of brachytherapy for pediatric CNS tumors has been primarily reported in the setting of inoperable low-grade gliomas. While overall survival for these tumors is over 90% at 5 years, late relapses lead to a progression-free survival of closer to 70% (Ruge et al. 2011b). Treatment often consists of a multimodality approach, and

if the tumor is located in a deep or eloquent area such that it is not completely resectable, radiation may be used to increase local control. However, dose to adjacent normal brain parenchyma including the margin needed for setup in external beam radiation carries the risk of adverse neurocognitive sequelae. Brachytherapy is an attractive option because of lack of required margin for planning treatment volume and steep dose gradient. One of the earliest reports of this technique by Voges et al. describes the German experience with 19 children with a deeply located cerebral glioma, including 13 with low-grade glioma and 6 with high-grade glioma. Patients with low-grade gliomas received a mean dose of 74 Gy to the tumor surface with mean dose rate of 85.3 Gy, with all patients responding to treatment and a mean tumor volume reduction of 77% at 6 months after treatment (Voges et al. 1990). A separate pilot study using interstitial iodine-125 alone or in combination with microsurgery for pediatric patients with eloquently located low-grade glioma showed a complete or partial response in all 11 patients treated, with no perioperative or radiogenic complications during follow-up (Peraud et al. 2007). Notably, treatment success was not impacted by tumor location, and even deep-seated tumors were successfully treated. Functional outcome scores were improved or stabilized in all patients. Herrera et al. report their experience with 12 pediatric patients treated for pilocytic astrocytomas with interstitial iodine-125 with low-dose rate and calculated reference dose of 60 and 100 Gy to the outer rung of the tumor. Patients treated were as young as 8 months old. They report that 11 of 12 tumors shrank in response to treatment. Two patients experienced transient symptoms after treatment including edema and leg paresis, and both of these patients' symptoms resolved. No neurocognitive effects were noted in these patients at longest follow-up for 13.4 years (Herrera et al. 2007).

Ruge et al. report an analysis of 142 children with unresectable low-grade gliomas treated with stereotactic brachytherapy with implantation of iodine-125 seeds. They report survival at 5 and 10 years of 93% and 82%, with no difference between WHO grade I and II tumors, and relapse occurring in 14.8% of patients at a median follow-up of 67.1 ± 57.7 months. Importantly, neurologic status improved (57.8%) or remained stable in 23.0% of patients. They report a procedure-related mortality rate of zero and treatment-induced permanent morbidity of 3%, with no reported radiation-induced necrosis requiring surgery or vascular issues such as moyamoya disease, concluding that this is a safe and effective local treatment strategy. (Ruge et al. 2011a). A study reported by Korinthenberg et al. in 94 pediatric patients with low-grade glioma reported similar survival outcomes at 5 and 10 years after treatment (97% and 92%, respectively) though noted progressive disease requiring adjuvant treatment in 31.9% of patients (Korinthenberg et al. 2011). One might expect decreased neurocognitive impact due to smaller volume of brain receiving radiation though prospective neurocognitive testing was not performed in the Ruge study. Brachytherapy is more likely practitioner dependent, but in the hands of expert practitioners, can be an effective treatment option for patients with small unresectable low-grade gliomas. Of note, there is a size limit of 5 cm diameter in order to reduce risk to surrounding brain tissue. Given the steep dose gradient, this technique can be utilized adjacent to critical and functionally important structures. I-125 has

been the primary isotope utilized in low-grade glioma due to the long potential doubling time of tumor cells, with decay occurring over approximately 9 months (Ruge et al. 2011b). In the past, high-activity implants with shorter implantation times of 3–6 days and dose rates of 0.007–0.013 Gy/min have been used, but without superior efficacy and inducing radiation necrosis requiring surgery in an unacceptably high proportion of patients (Ruge et al. 2011b).

28.7 Toxicity

While SRS and hypofractionated radiation therapy are generally well tolerated in the short term, it is important to consider potential long-term effects, particularly in pediatric patients. Radiation-associated brainstem injury is an important potential toxicity with SRS. In a study primarily focusing on adult patients, Davidson et al. examined delayed toxicity from GKS to lesions in and adjacent to the brainstem. After treatment of 114 lesions in and adjacent to the brainstem, 13 patients demonstrated clinical evidence of delayed toxicity with a median latency of 6 months to development of toxicity. Toxicity included new cranial neuropathy and brainstem edema and/or hydrocephalus. After treatment, of 13 patients with toxicity, 8 had complete recovery of clinical symptoms, 3 had partial recovery, and 2 had no improvement. No patient with toxicity had tumor growth (Davidson et al. 2009). Other studies have also examined the integral brainstem dose associated with toxicity after hypofractionated SRS (Mayo et al. 2010; Clark et al. 1998).

Radiation-induced tumorigenesis is also an important consideration in pediatric patients. Galloway et al. reported favorable outcomes in patients who developed meningiomas after previous radiation treatment to the central nervous system in childhood (Galloway et al. 2011). There does not appear to be a significant risk of malignancy associated with stereotactic radiosurgery, based on multiple studies (Rowe et al. 2007) (Kondziolka et al. 2008; Santacroce et al. 2012), but longer follow-up will be needed to clearly establish the risk.

28.8 Follow-Up

It is widely understood that interpretation of imaging response after radiation and in particular SRS can be difficulty due to post-treatment effects, including transient tumor edema mimicking disease progression (King et al. 2014). In a study of observed post-treatment imaging changes in children treated with stereotactic radiosurgery for intracranial tumors, MRI changes related to treatment were frequent, and generally resolved within 6–15 months (Nath et al. 2011). The recommendation is therefore for a period of careful observation should early imaging show possible progression of treated disease after radiosurgery. It is important to interpret imaging findings in the context of timing of treatment and expected post-radiation changes.

Conclusions

In summary, advanced radiotherapeutic techniques including hypofractionation, SRS, and brachytherapy offer the possibility of safely treating pediatric patients with CNS tumors with a steeper dose gradient and sparing normal brain tissue more effectively than can be achieved with standard external beam radiation therapy. While data for patients treated in this manner continue to accumulate, results thus far are promising, and this approach should be considered in the context of recurrent disease or as a boost in primary treatment of unfavorable tumors. The promising results in the retreatment setting as well as in the setting of planned boost as part of primary therapy in unfavorable tumors argue for further exploration of this technique in the pediatric population. Further study will allow a better understanding of the efficacy and risks involved, which appear favorable at this time.

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Reirradiation

29

Patricia E. Daly and Normand J. Laperriere

Contents

Abstract

Historically, once a previously radiated pediatric brain tumor recurred, options generally included repeat surgery and possible systemic agents, but inevitably this approach has rarely been associated with significant survival beyond 1–2 years. As a result of significant technological improvements in the delivery of radiotherapy over the last 15 years which has allowed better tumor coverage with sparing of adjacent normal tissues both at initial treatment and at recurrence, and in

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the absence of useful systemic therapy at recurrence for most pediatric brain tumors, reirradiation has become a commonly recommended treatment at recurrence in several pediatric brain tumors. Several institutional reports have appeared over the last decade, which have demonstrated relative safety and some evidence of benefit in terms of prolonged survival much beyond what was previously reported without reirradiation at recurrence following prior radiation. Reirradiation of recurrent malignant gliomas and diffuse intrinsic pontine gliomas has demonstrated some prolongation of life in the order of 3–9 months with good short-term resolution of neurologic symptoms in most children, and currently represents a useful palliative approach. Reirradiation in recurrent intracranial ependymoma and medulloblastoma have also demonstrated a significant prolongation of life with a minority of patients surviving on the order of 5–10 years following their second course of radiotherapy, suggesting possible long-term tumor control where previously that was not possible. This chapter will summarize the outcomes of reirradiation in these recurrent pediatric brain tumors.

29.1 Background

The diagnosis of a recurrent CNS tumor confers a dismal prognosis in most cases. As technology and therapies improve, clinicians are faced with increasingly complex management decisions with little evidence to guide the decision-making process. In both adult and pediatric oncology, the line between curative and palliative cases is becoming progressively blurred with progression-free survival and quality of life outcomes representing increasingly important clinical endpoints. In addition, the developing pediatric brain is a unique environment where the potential for salvage must be weighed carefully against the acute and late effects of therapy. For previously irradiated patients, those risks are not easily quantifiable and the potential benefits are not well documented. In recent years, a number of institutions have retrospectively reported their experience in reirradiating childhood recurrent CNS tumors. Ethically, it would be difficult to obtain a higher level of evidence in the form of a randomized trial in this setting and so, for now at least, decisions must be guided on retrospectively reported clinical experience. However, the number of publications is small and papers reporting outcomes from reirradiation are heterogeneous in almost all aspects including tumor type, use of surgery, type and utilization of chemotherapy and radiotherapy technique, and modality.

In order to interpret the literature, we should have an understanding of some basic concepts. Whenever we irradiate the brain we are limited by potential toxicity and the tolerance of critical structures, most importantly the optic chiasm, optic nerves, the brainstem, the spinal cord, and the brain itself. The response of normal tissue to radiation is not only dependent on overall dose but also on fraction size and the interval between courses of radiotherapy. Tolerance is increased with lower doses per

fraction. This is the rationale behind prescribing longer courses of radiation with conventional (1.8–2 Gy) fractions in radical treatments and using shorter courses with larger fraction sizes in the palliative setting. Most models that predict toxicity are based on conventional fractionation schedules. Ablative stereotactic regimes use very large fraction sizes and work via different radiobiological principles and so cannot be compared directly to fractionated regimes. Other factors which contribute to normal tissue responses include the use of chemotherapy, the type of radiotherapy used (e.g., particle therapy vs. photons), and also the overall volume treated. Host factors are also important such as intrinsic radiosensitivity and comorbidities.

29.1.1 Biologically Effective Dose (BED)

When comparing one fractionation scheme with another, it is typical to refer to the BED which is a measure of the true biological dose delivered by a combination of dose per fraction and total dose to a particular tissue. The BED is defined as the total dose that would be required in very small dose fractions to produce a particular effect as indicated by the linear quadratic equation (Joiner and Kogel 2009). In order to calculate the BED, the tissue must be given a numerical value which quantifies the fractionation sensitivity called α/β which is typically 2 or 3 for late responding tissue such as brain and spinal cord.

29.1.2 Normal Tissue Tolerance

In 2010, a series of papers attempted to provide detailed dose constraints for normal tissue in the modern era. These are known as the Quantitative Analyses of Normal Tissue Effects in the Clinic (QUANTEC) guidelines and have been adopted worldwide. The QUANTEC guidelines for the critical CNS structures are as follows. These are for conventional fractionation unless stated otherwise.

1. Brainstem: The entire brainstem may be treated to 54 Gy and smaller volumes of the brainstem (1–10 cc) may be irradiated to maximum doses of 59 Gy for dose fractions ≤2 Gy. Risk of toxicity appears to increase markedly at doses >64 Gy. For single-fraction stereotactic radiosurgery, maximum brainstem dose of 12.5 Gy is associated with low (<5%) risk (Mayo et al. 2010b).
2. Optic chiasm and optic nerves: The incidence of radiation-induced optic neuropathy (RION) is low for a point maximum (Dmax) <55 Gy. The risk increases (3–7%) in the region of 55–60 Gy and becomes more substantial (>7–20%) for doses >60 Gy. For single-fraction SRS, the studies have indicated the incidence of RION is rare for a Dmax <8 Gy and becomes >10% in the range of 12–15 Gy (Mayo et al. 2010a).
3. Spinal cord: The estimated risk of myelopathy is <1% at 54 Gy and <10% at 61 Gy. Reports of myelopathy from stereotactic radiosurgery to spinal lesions appear rare (<1%) when the maximum spinal cord dose is limited to the equiva-

lent of 13 Gy in a single fraction or 20 Gy in three fractions (Kirkpatrick et al. 2010).

4. Brain: There is an estimated 5% and 10% risk of symptomatic radiation necrosis at a BED of 120 Gy (range, 100–140) and 150 Gy (range, 140–170), respectively (corresponding to 72 Gy and 90 Gy in 2 Gy fractions with α/β ratio of 3). The brain is especially sensitive to fraction sizes >2 Gy and twice-daily RT. In radiosurgery, the risk of complications increases with the size of the target volume. Toxicity increases rapidly once the volume of the brain exposed to >12 Gy is >5–10 cm^3 (Lawrence et al. 2010).

Applying these dose constraints is relatively straightforward when irradiating for the first time but much more difficult when embarking on subsequent courses of radiotherapy and targeting tissue which has already received maximum dose. Normal tissue has an ability to repair and "forget" some of the dose received but the degree of repair is uncertain. Repair is subject to effects from total dose, dose per fraction, dose rate, and elapsed time from the course of radiotherapy. The use of chemotherapy can also sensitize normal tissue to radiotherapy. The most robust data on reirradiation comes from animal models in the spinal cord. These models suggest partial repair of radiation-induced subclinical damage becoming evident about 6 months post-RT and increasing over the next 2 years. Reirradiation tolerance depends on the initial dose as well as on the time elapsed since initial radiation (van der Kogel 1993). Recovery of the brain is thought to have a similar mechanism. In a review of toxicity data in reirradiated adult gliomas, radiation-induced normal brain tissue necrosis was found to occur at cumulative total doses of greater than 100 Gy in 2 Gy fractions (BED 200 Gy with α/β ratio of 2) but time since previous irradiation was not found to be a significant factor (Mayer and Sminia 2008). This review suggests that the brain may be more tolerant to reirradiation than previously hypothesized. But does the same apply to the developing pediatric brain? The concept of reirradiation to treat relapsed pediatric CNS tumors is not new. As far back as 1979 Cumberlin described "essentially complete relief of symptoms" in relapsed medulloblastoma patients who were reirradiated to both the posterior fossa alone and to the craniospinal axis. In this small series toxicity was noted, with one death from radionecrosis in the presence of controlled disease (Cumberlin et al. 1979). What is new however is the use of modern technology to irradiate homogeneously and precisely using high doses and also modern imaging techniques which enable us to identify areas of radiation-induced damage. Modern pediatric reirradiation studies are discussed below.

29.2 Studies by Tumor Type

29.2.1 Ependymoma

Salvage options in previously irradiated recurrent ependymoma are limited with 2-year overall survival rates historically being as low as 29% (Goldwein et al. 1990).

Table 29.1 Reported outcomes in reirradiated ependymomas

Author technique year	Median PFS post RT2	Median OS post RT2	Median PFS No RT2	Median OS No RT2
Merchant FFRT 2008	NA	67% at 5 years	NA	NA
Merchant CSI 2008	53% at 4 years	NA	NA	NA
Merchant SRS 2008	NA	20% at 5 years	NA	NA
Bouffet 2012	3.3 years	4.5 years	6 months	11 months
Zacharoulis 2010	18 months	51 months	8 months	22 months
Stafford SRS 2000	18 months	40.8 months	NA	NA
Kano SRS 2010	41.6% at 3 years	23% at 3 years	NA	NA
Hoffman SRS 2014	40.8 months	71% at 2 years	NA	NA
Mohindra PDR 2013	35.7% at 4 years	60% at 4 years	NA	NA

PFS Progression-Free Survival, *OS* Overall Survival, *RT2* reirradiation, *FFRT* Focal Fractionated Radiation Therapy, *CSI* Craniospinal Irradiation, *SRS* Stereotactic Radiosurgery, *PDR* Pulsed Dose Radiotherapy, *NA* Not Available

Surgery is rarely curative in this disease and chemotherapy has a limited role. Despite historical reluctance to reirradiate children, the lack of alternatives in this group of patients has led to some developments in this area. There are many issues to consider when deciding to reirradiate such as the aim of therapy, the age of the patient, the sites of relapse, and the target volume. For example, should the whole craniospinal axis be irradiated if the recurrence is localized? Doing so confers extra morbidity but not doing so may leave the patient at an unacceptable risk of distant CSF relapse. In addition, ependymomas typically occur in the posterior fossa in close proximity to the brainstem that has dose limitations as described above. Table 29.1 describes the reported outcomes from the reirradiation papers as detailed below.

There have been several recent publications on this issue (Table 29.1). In one of the largest papers on reirradiation for recurrent ependymoma, Merchant and colleagues retrospectively reviewed the outcome of 38 children with relapsed ependymoma, who underwent a second course of radiotherapy either in the form of stereotactic radiotherapy (SRS), craniospinal irradiation (CSI), or focal fractionated reirradiation (FFRT) (Merchant et al. 2008). There was no uniform policy as to who underwent reirradiation or other alternative salvage therapies over the time of this review. All children in this series were managed for localized disease at initial presentation. Thirty-six patients received a median dose of 50.4 Gy (range, 37.8–60.4 Gy) with conventional fractionation for their initial course of radiotherapy (RT1). Two patients had hyper-fractionation schedules initially. Only one had CSI at diagnosis. Thirteen patients with local failure were treated by using FFRT to a median dose of 52.2 Gy (range, 50.4–54 Gy). Median combined total dose was 111.6 Gy (range, 98.4–120 Gy) and the median time from initiation of RT1 to RT2 was 23 months (range, 10–82 months). With a median follow-up of 30 months (range, 2–136 months) after RT2, 10 of the 13 were alive and disease free. Three patients died from metastatic disease within 20 months of RT2. Nineteen patients

with a mix of local and metastatic disease had CSI and focal boost after attempted resection of all disease. Three patients with local failure only received CSI for salvage therapy, one of whom experienced relapse with metastatic disease after 6 months despite CSI dose of 39.6 Gy. Nine of 12 patients with metastatic disease were disease free at a median follow-up of 22 months (range, 3–69 months). Despite three recurrences, none of the 12 patients with metastatic disease had died in the follow-up period. Of the four patients who had both local and metastatic recurrence, only one survived and was still alive 20 years after reirradiation. Symptomatic cerebellar necrosis was noted in one patient in an area that received a total of 99 Gy. This patient had the shortest interval between RT1 and RT2 of 4 months. Another patient developed myelopathy and changes on imaging in the cervical spine in an area that had had surgery and 54 Gy and another patient developed a second high grade glial neoplasm in an area that received 59.4 Gy. Six patients were treated with radiosurgery using a median dose of 18 Gy (range, 15–20 Gy) with five patients receiving treatment within the prior high dose region and four patients had surgical resection prior to SRS. The median time from initiation of RT1 to RT2 was 21.9 months (range, 7.5–67.7 months). Four patients relapsed within 18 months and died of disease. Two progressed with local failure only and two had combined local and distant failure and all four patients had neuroimaging or pathologic evidence of necrosis. Another patient died of radiation necrosis at 40 months, and the last patient required surgery and hyperbaric oxygen for necrosis but was disease free 10 years post treatment. This paper gives reasonable evidence to support reirradiation in ependymoma but toxicity, especially for SRS, remains an issue. In addition, despite toxicity, local control was not optimal in the SRS group.

Bouffet and colleagues reported their experience with reirradiation in recurrent ependymomas in 2012 (Bouffet et al. 2012). This paper is unique as it reports not only survival and toxicity data but also quality of life and molecular markers. Eighteen patients were reirradiated, 2 with SRS, 12 with FFRT, and 4 with CSI due to disseminated recurrence. The median time from RT1 to RT2 was 2.2 years. Of those who received FFRT, the retreatment median dose was 54 Gy (range, 45–59.4 Gy) with total cumulative doses between 108 and 113.4 Gy. Reirradiation was well tolerated overall but toxicity was noted in one patient who received SRS to the primary lesion. This patient had both clinical and imaging evidence of radiation necrosis associated with significant neurological decline. Similar to Merchant's findings, all four patients who underwent CSI due to metastatic disease were alive at a median follow-up of 1.9 years (range, 0.6–4.7 years). A notable finding which was also suggested in some other studies (Merchant et al. 2008; Lawrence et al. 2010; Hoffman et al. 2014) was that the time to progression after reirradiation was significantly longer than the time to initial recurrence/progression (3-year PFS was 61% after reirradiation vs. 25% after first course or radiation). In order to investigate this further, the authors examined the role of γH2AX as a marker of radiation-induced DNA damage. Positive γH2AX expression at the time of resection before reirradiation predicted longer time to progression in reirradiated patients (p 0.002). All tumors that were negative for γH2AX recurred within the first 2 years suggesting radioresistance. Such markers may become increasingly important when

selecting appropriate patients for reirradiation in the future. Three-year overall survival was 7% ± 6% in 29 patients that were treated with surgery and/or chemotherapy at recurrence and 81% ± 12% for 18 patients who were treated with reirradiation in addition to surgery and/or chemotherapy at recurrence. It is important to note that the cohort of 18 patients who were reirradiated represented a consecutive series of recurrent patients after it was decided to reirradiate all patients with recurrent ependymomas that likely minimizes possible selection bias.

In 2009, Liu published a small series of six patients who were reirradiated with 24–30 Gy in 8–10 Gy fractions via external beam RT and all were alive at a median follow-up at 28 months (Liu et al. 2009). However three patients developed radionecrosis, two of which were symptomatic. That same year outcome data from the UK reported reirradiation in 14 children of whom 9 had focal fractionated radiotherapy, three had stereotactic single-fraction or hypo-fractionated RT and two had craniospinal RT (Messahel et al. 2009). The authors noted that older children who received craniospinal radiotherapy (n = 10, including those who were radiation naïve) at relapse had a better outcome than those who received either focal radiotherapy or none at all.

SRS is attractive in the reirradiation setting as it minimizes the amount of normal tissue treated, hence potentially reducing late effects such as IQ changes and also means less time spent having treatment versus a repeat 5 or 6 week course of radiotherapy. However, the studies described above indicate that the risk of radionecrosis may be unacceptably high. A number of studies have specifically looked at outcomes following SRS for relapsed ependymoma. Stafford published the outcomes of 11 patients previously treated to a median of 54 Gy followed by gamma knife SRS to 18 Gy (Stafford et al. 2000). There were two cases of radionecrosis, one in a patient who had received 24 Gy and another in a patient who had two SRS in abutting locations treated to 18 and 12 Gy. Local control was achieved in 82% of sites and the estimated 3-year rate of local control was 68%. Distant failure occurred in two patients. Kano reported a median survival of 27.6 months after SRS median dose of 15 Gy in 21 patients, 36.7 months after 52.2 Gy EBRT. Necrosis was identified on imaging in two patients, one of whom was symptomatic. The interval between EBRT and SRS in these two patients was 22 and 37 months. Distant intracranial or spinal relapse after RT and SRS occurred in ten patients. On univariate analysis factors associated with distant tumor relapse included patients with spinal metastases before RT (p = 0.037), a tumor located in the fourth ventricle (p = 0.002), and an interval <18 months between RT and SRS (p = 0.015) (Kano et al. 2010). In a review of 12 patients who were treated with SRS (24–30 Gy) over 3–5 fractions after 55.8 Gy of EBRT, Hoffman reported a 3-year local control rate of 89% (Hoffman et al. 2014). The median time from RT1 to RT2 was 25 months. Six patients showed radiological changes consistent with radiation necrosis at a median of 5 months including one patient who received SRS outside the RT1 radiation field. Five patients were symptomatic and three received treatment with bevacizumab. It seems that the benefit of the high doses per fraction comes with a price in the reirradiation setting. Mohindra et al. took a different approach in an older group of ependymoma patients who were median age 25 at reirradiation and median age 10 at RT1 (Mohindra et al. 2013).

They utilized pulsed dose radiotherapy (PDR) which uses a low dose rate of 6 cGy/min, in comparison to 400–600 cGy/min for conventional delivered radiotherapy, which should allow for enhanced normal tissue repair. The median interval between two radiation courses was 58 months (range, 32–212 months) with a median of 48.4 Gy delivered conventionally in RT1 and a median cumulative radiation dose per site of 105.2 Gy (range, 90–162.4 Gy). Half of the lesions were controlled at last follow-up. None of the patients developed necrosis on serial magnetic resonance imaging scans, but one patient had progressive radiculopathy which was treated with hyperbaric oxygen. This study had only five patients with low RT1 doses and very long intervals between RT courses in an older population. Additionally, lowering the dose rate means prolonging the individual fraction time that may not be acceptable for younger patients. It is difficult to draw conclusions from this study but it does provide some food for thought on an alternative treatment regime.

All papers mentioned the benefit of maximally safe resection in this disease and most included metastasectomy where possible. The studies consistently report a survival benefit with reirradiation and fractionation seems to be the less toxic approach in terms of radionecrosis. The appropriate retreatment volume is debatable as distant relapses occur even with local control and so the option of reirradiating with CSI and boost should be considered on an individual basis. There is some evidence that those treated with CSI at relapse do well.

29.2.2 Medulloblastoma

Historically, relapsed medulloblastoma (MB) has a median survival of approximately 12 months (Packer and Finlay 1996). Several recent publications discuss their experience on reirradiation in recurrent medulloblastoma (Table 29.2). More recently, Wetmore published results on 38 relapsed medulloblastoma patients, 14 of whom were reirradiated and concluded that the use of reirradiation as a component of salvage therapy may prolong survival (Wetmore et al. 2014). Until 2003, the initial radiation dose for standard risk (SR) patients was CSI (23.4 Gy), posterior fossa RT (36 Gy), and primary-site RT (55.8 Gy) using a 2-cm clinical target volume (CTV) margin. After 2003, SR patients received CSI (23.4 Gy) and

Table 29.2 Reported outcomes in reirradiated medulloblastoma

Author (number of cases)	Median PFS	Median OS
Wetmore (14)		5 years 55%, 10 years 33% from original diagnosis with re-RT at relapse
		5 years 46%, 10 years 0% from original diagnosis with no re-RT at relapse
Baskt (13)	5 years: 48%	5 years 65%
Chojnacka (8)	6.5 months	17.5 months
Saran (12)	12 months	29 months

PFS Progression-Free Survival from relapse unless otherwise stated, *OS* Overall Survival from relapse unless otherwise stated, *re-RT* reirradiation

primary-site RT (55.8 Gy) using a 1-cm CTV. High-risk (HR) patients received CSI (36–39.6 Gy) followed by primary-site RT (55.8 Gy) using a 2-cm (pre-2003) or 1-cm (post-2003) CTV margin. There was a 39-month median interval between RT1 and RT2. Those who were reirradiated included 11 originally SR patients and three originally HR patients. Eight of these 11 patients received CSI and "boost" to the primary site of recurrence, two patients received only spinal re-RT (site of disease recurrence), and one patient received a second course of focal RT to the site of recurrence in the posterior fossa. None of the HR patients were reirradiated with CSI. Overall the median retreatment dose was 36 Gy (18–54 Gy) with a total cumulative dose of 91.9 Gy (73.8–109.8 Gy). Six SR patients had tumor progression after receiving re-RT (CSI and boost) and five of these had tumor recurrence within the volume of CSI but outside the boost area. One patient had disease recurrence both inside and outside the retreated volume. This paper reported a statistically significantly higher rate of radionecrosis in those who were reirradiated in comparison to those who were not (64% vs. 29%). The cumulative doses received in those with necrosis were not detailed. However, the necrosis was asymptomatic and did not require intervention. There was also a higher rate of hypopituitarism and hypothyroidism noted in the reirradiated group but this did not reach statistical significance. In addition, one patient had treatment stopped early due to cerebral edema. Bakst reported outcomes on 13 patients who were reirradiated for medulloblastoma, 11 of whom completed the therapy with a median follow-up of 30 months (range, 0–176 months) post RT2 (Bakst et al. 2011). Median time from RT1 to RT2 was 57 months (range, 25–112 months) and reirradiation always followed chemotherapy and surgery. The median initial CSI dose was 36 Gy (18–36 Gy) with boost to tumor of 54 Gy (50–59.5 Gy). The median reirradiation dose was 30 Gy (range, 19.8–45 Gy), with a median fraction size of 1.5 Gy (range, 1.0–1.8 Gy). Median cumulative maximum dose to the brain or spine was 84 Gy (range, 65–98.4 Gy). Only one patient received CSI for RT2 to a max cumulative dose of 66 Gy. There were six failures at a median of 17 months (range, 2–59 months), of which five were in patients with gross disease at time of reirradiation. Failures occurred both in and out of the RT field. Two patients underwent further surgery followed by a second course of reirradiation to 30 Gy to the posterior fossa with a cumulative combined dose of 115.8 Gy and 110 Gy. Reirradiation was well tolerated with one case of asymptomatic in field radiation necrosis at 39 months. Other toxicity included significant hearing loss in 38% but this may have been multifactorial and also 15% of patients developed hypopituitarism. Neurocognitive impairment was noted in one patient.

Chojnacka reported cumulative doses received to the critical structures in addition to outcomes in eight children with recurrent brain tumors who underwent reirradiation (Chojnacka et al. 2011). Six of the eight patients had medulloblastoma, one had a germ cell tumor and another has a non-germ cell tumor. The interval between radiation courses was between 5 and 51 months and the median follow-up was 16 months (range, 6–27 months). The initial dose was 55.11 Gy via 1.67 Gy fractions (range, 40–55.11 Gy). The retreatment dose was 40 Gy in 2 Gy fractions with a total cumulative dose of 75 Gy (range, 65–95 Gy) and a median cumulative BED of 144 Gy (range, 126–181 Gy). Among six children who progressed during

the first year after reirradiation, two progressed in the treatment area. In the other cases, there was spread in the brain (2), spine (1) or throughout the CNS (1) without progression in the irradiated field. No grade 3–5 acute toxicity was detected. Four children had grade 1 radiotherapy toxicity, not requiring medication, and the other four had grade 2 headache and vomiting that required steroids in low doses and/or antiemetic treatment. The highest brainstem retreatment point dose was 37.93 Gy in one patient with a mean of 8.87 Gy and the highest mean brainstem dose was 18.40 Gy with a point maximum of 21.63 Gy. The maximum reirradiation average dose to the optic pathway was 20.42 Gy. Point maximum doses were not described for this structure, nor were the cumulative maximum doses for these critical structures. In addition, the smaller initial doses per fraction used could have allowed for greater normal tissue repair between RT courses. In five patients reirradiated for medulloblastoma, Padiovani reported local control for all patients (Padovani et al. 2011). Four patients had CSF progression with a median follow-up of 28 months (range, 14–36 months). These patients had initial CSI median 36 Gy (23.4–36 Gy) with tumor median dose of 54 Gy (54–55.8 Gy) with a focal retreatment median of 29.3 Gy (20–36 Gy) with a median cumulative BED2 of 168 Gy. Neurological toxicity was not noted in this group. All patients had received standard salvage chemotherapy when first diagnosed with relapse and either progressed or did not respond.

Massimino explored salvage options in relapsed medulloblastoma, mostly focusing on high dose chemotherapy but also including ten patients who had reirradiation (Massimino et al. 2009). All patients had CSI and tumor boost to at least 54 Gy as part of their initial RT. The CSI dose varied from 19.5 Gy in 1.5 Gy fractions to 39 Gy in two daily fractions of 1.3 Gy. Seven patients had retreatment with CSI to a total dose of 20.2 Gy via twice-daily fractions of 1.3 Gy and three had focal only treatment exceeding 50 Gy. Survival for the series as a whole (including non-reirradiated) was a median of 41 months (range, 11–93 months). Radiation-induced neurological toxicity was not commented on.

The use of radiosurgery and fractionated stereotactic radiotherapy (FSRT) has also been explored in medulloblastoma. Saran et al. described toxicity in 3 of 14 patients treated with FSRT to 30–40 Gy in 5 Gy fractions having had prior CSI and 50–55 Gy to the primary (Saran et al. 2008). The patients developed symptoms of raised intracranial pressure during treatment, requiring high-dose corticosteroids. One required debulking surgery for refractory symptoms 10 weeks after completion of FSRT. One patient developed radiation necrosis during the first year in addition to the presence of residual/recurrent disease. No other late toxicity after SCRT was noted. The median survival was 29 months. Nine recurrences were observed with a median time to progression of 12 months (range, 5–19). Four patients relapsed within the FSRT site. Five patients recurred outside the SCRT region in the posterior fossa and three patients recurred in the supratentorial brain. Leptomeningeal tumor spread was reported in five patients and the spinal axis was the sole site of relapse in two patients. One patient developed osseous metastases. Milker-Zabel reported a local control rate of 89.7% in 20 patients with 29 lesions treated with FSRT ($n = 21$) or radiosurgery ($n = 8$) (Milker-Zabel et al. 2002). All patients had prior CSI and tumor boost to 54 Gy. Eighteen of the twenty-nine

lesions were within the original boost volume. Mean total dose for reirradiation was 24 Gy via 4 Gy fractions for FSRT and 15 Gy for radiosurgery. Mean follow-up was 88.5 months. Local tumor progression was seen at a mean of 5 months in three cases. A multifocal intracranial progression was seen in nine patients and five patients developed additional spinal metastases. Thirteen patients died with disseminated craniospinal progression at a median of 72.6 months. The authors report that no acute or chronic side effects greater than grade 2 occurred and there was no increased intracranial pressure seen after SRS. No patient developed symptomatic brain radionecrosis.

As almost all patients with medulloblastoma have had CSI at the time of initial RT and therefore focal treatment is the most common approach at relapse. Again those with gross residual disease at time of reirradiation seem to fair worse. Local control of these recurrences seems to be feasible but distant relapse remains a problem. Alternative strategies need to be employed to deal with this risk and perhaps in the evolving era of targeted agents we may see improvements in distant relapse.

29.2.3 Gliomas

In a study on palliative reirradiation in pontine gliomas, Fontanilla (Fontanilla et al. 2012) reirradiated the brainstem to 18–20 Gy with concomitant chemotherapy in six children who had previously received 54–55.8 Gy. Minimum time between courses was 8 months. The treatment was well tolerated and four children showed clinical improvement in symptoms and radiological decrease in size of the lesion. The median clinical progression-free survival time was 5 months post RT2. In non-pontine, high grade glioma patients, Muller (Muller et al. 2014) reported the outcomes of eight patients who underwent reirradiation having received an initial median dose of 59.4 Gy (range, 54–60 Gy). Five had FSRT to a median of 30.6 Gy (range, 30.6–55.8 Gy) with a median time between RT courses of 9 months. Three had hypo-fractionated treatment with 24.2–30 Gy in 5–10 fractions (one via fractionated SRS). Three patients had temporary but significant improvement of the neurological status and regression of the lesions on imaging. No major toxicities (including radionecrosis) occurred and no treatment-related deaths were reported but overall survival in this group was only 4.6 months. The short survival of these patients means that it may be reasonable to accept an increased risk of radionecrosis, which is considered a late effect and the benefit in terms of quality of remaining life may outweigh this risk.

29.3 Particular Radiation Planning Issues

A summary of reported complications is contained in Table 29.3. The location of the recurrence is what determines the difficulty and potentially the dose of reirradiation. For example, reirradiating a local recurrence in the fourth ventricle located immediately adjacent to an already maximally treated brainstem is more

Table 29.3 Summary of cumulative dose, local control, and neurotoxicity with fractionated radiation

Author	Time between RT1 and RT2 (months)	RT2 dose	Cumulative doses	Local control	Neurotoxicity
Merchant	23 months (10–82 months)	52.2 Gy (50.4–54 Gy)	111.6 Gy (98.4–120 Gy)	50%	In CSI group: Symptomatic necrosis—99 GY short inter RT interval of 4 months
					Myelopathy in cervical spine—surgery and 54 Gy
					Second high grade neoplasm—59 GY
Bouffet	26.4 months	54 Gy (45–59.4 Gy)	108–113.4 Gy	NA	No necrosis
Mohindra PDRT	58 months (range: 32–212 months)		105.2 Gy (range, 90–162.4 Gy)	50%	No necrosis
					Radiculopathy treated with HBOT
Wetmore	39 months	36 Gy (18–54 Gy)	91.9 Gy (73.8–109.8 Gy)	NA	64% asymptomatic necrosis
Bakst	57 months (25–112 months)	30 Gy (19.8–45 Gy), with 1.5 Gy fractions	84 Gy (65–98.4 Gy)	NA	1 case asymptomatic necrosis
Chojnacka	5–51 months	40 Gy	75 Gy (65–95 Gy)	67%	
Padiovani		29.3 Gy (20–36 Gy)	BED2 168 GY (approx. 84 Gy)	100%	No necrosis
Fontanilla	8 months	18–20 Gy	72–75.8 Gy	0%	No Grade 3/4 toxicity
Muller	9 months	30.6 Gy (30.6–55.8 Gy)		0%	No Grade 3/4 toxicity

RT1 first course of radiation, *RT2* second course of radiation, *FFRT* focal fractionated reirradiation, *CSI* craniospinal radiation, *NA* not available

challenging and potentially more toxic than an intracranial recurrence distant from critical structures. This supports the need to individualize delivered dose in each case.

Most studies do not describe the Clinical Target Volume (CTV) or Planning target volume (PTV) margins used most likely because it was variable even within the individual papers due to physician discretion. It would seem sensible to reduce the margins where possible in the retreatment scenario. Merchant use a 5-mm CTV, Bouffet a 0–10-mm CTV, and Liu used a 3-mm CTV, whereas Chojnacka defined the PTV as a 4-mm expansion around the GTV without a CTV. Radiation planning should be carefully considered with particular attention paid to initial and retreatment hot spots

in order to minimize the risk of radionecrosis. Particle therapy such as protons may offer a benefit in avoiding previously treated normal structures (McDonald et al. 2013) but evolving data from proton radiotherapy centers has shown radionecrosis to be a concern even after one course of radiotherapy (Indelicato et al. 2014), possibly related to variations of the biologic effective dose in the region of the Bragg peak, and so protons may not be appropriate in this setting.

Conclusion

The above papers support the approach of reirradiation in selected cases of relapsed childhood brain tumors with most studies demonstrating a survival benefit with some evidence of long-term survivors. There appears to be an excellent rationale in recurrent ependymomas in the absence of alternative effective therapies other than surgery and there appears to be a sizeable minority that experience prolonged survival. Patients with recurrent malignant gliomas and DIPG seem to derive some additional survival with some improvement of neurologic symptoms, such that this seems reasonable in selected cases. The toxicity data remains crude and so it is very difficult to draw conclusions on optimum dose and tolerances of critical structures (Table 29.3). The risk of radionecrosis seems to be greater with SRS in comparison to conventionally fractionated approaches. It is our opinion that going with conventionally fractionated radiotherapy approaches would seem to be the most prudent course in this situation. This may come at some cost in the immature pediatric brain as it may result in further neurocognitive problems. Bouffet et al. (Bouffet et al. 2012) were the only group to look in detail at the neurocognitive outcomes after reirradiation and they described a decline in IQ in all seven patients who were reassessed post RT2. Baskt (Bakst et al. 2011) noted that one patient required extra educational assistance during college and Milker-Zabel (Milker-Zabel et al. 2002) commented on a patient who presented with intellectual deficits requiring adapted schooling. Children having reirradiation should also be monitored for endocrine abnormalities (Wetmore et al. 2014; Bakst et al. 2011). The patients described in the above papers had differing systemic agents that may contribute to radiosensitivity in an unquantifiable manner. Concomitant chemotherapeutic agents may sensitize both the target and the normal tissues and need to be considered when pushing radiation dose tolerances. Symptomatic neurological improvement is also described and so reirradiation may also play a role in palliation where concerns about toxicity are not so pertinent.

Future papers should detail doses to critical structures and report toxicity in relation to doses received in order to build a body of evidence to help us determine reirradiation tolerances. At this point, it seems that the evidence supports reirradiation for both symptom management and for a survival benefit in selected cases.

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Part VII

Radiotherapy Toxicity and Management

Neuropsychological Late Effects of Radiotherapy for Pediatric Brain Tumors

30

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Contents

Abstract

Advances in the treatment of pediatric brain tumors have led to an overall increase in survival rates, which in turn has led to increased identification of physical, cognitive, academic/vocational, and socioemotional sequelae among survivors. Research to date has shown radiotherapy to account for a significant

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amount of variance in neurocognitive outcomes. However, other predisposing factors have also been identified, and research into the relative role of the direct and indirect effects of medical, child-specific, and broader contextual/environmental factors on outcomes in this population is needed. This chapter describes our current knowledge of neuropsychological and associated functional outcomes among survivors of pediatric brain tumor as well as the current literature on associated predisposing factors, pathophysiology, and evidence-based interventions for remediation and prevention. Methodological issues are also discussed in order to provide context for understanding limitations of current findings and to identify important future directions.

As overall survival rates among children with brain tumors have improved in conjunction with modern advances in detection and treatment, issues faced by survivors over the long term have become an area of increased research and clinical focus (Howlader et al. 2015). Neuropsychological "late-effects," the delayed emergence of such cognitive, academic, and socioemotional/behavioral sequelae in the first few years following treatment, are among the various morbidities experienced by pediatric brain tumor (PBT) survivors. There is a substantial and growing literature documenting the nature of such late effects as well as their associated risk factors and neuropathology. Even more recently, research examining the evidence for possible therapeutic or preventative interventions has emerged.

30.1 Predisposing Factors

There are many factors that may contribute to the neuropsychological functioning of PBT survivors, but most of these variables are not fully understood or addressed in each study, making it difficult to understand the specific relationship between radiation therapy (RT) and neuropsychological functioning as well as to establish broader predictive models of neuropsychological outcomes in PBT survivors. Within this context, treatment-related variables have been the most studied predisposing factor in neuropsychological outcomes following PBT. Overall, RT has been associated with the greatest neurocognitive risks though much variance in outcomes remains unaccounted for in the existing literature (de Ruiter et al. 2013; Silber et al. 1992). Long-term neuropsychological effects related to RT may be mitigated by RT intensity or type (Reddick et al. 2014). Whole brain and craniospinal RT carry the greatest risk, while modern approaches to focal RT (e.g., 3D conformal and intensity-modulated RT) reduce radiation exposure to healthy brain tissue (Moore 2005; Mulhern et al. 2004b; Olsson et al. 2014). Higher RT doses may yield greater deficits. In medulloblastoma (MB) patients, for example, reduced-dose craniospinal RT has been associated with less intellectual decline than traditional craniospinal RT doses (Moxon-Emre et al. 2014; Ris et al. 2001).

Surgical intervention and chemotherapy are also risk factors (Beebe et al. 2005; Ris et al. 2008; de Blank et al. 2016), but the evidence has been mixed. With respect to surgery, the contribution of postsurgical cerebellar mutism to neuropsychological outcomes has likely been underappreciated, particularly given that as many of 24% of MB patients may experience this phenomena (Robertson et al. 2006). Cerebellar mutism often co-occurs with other neurological symptoms of emotional lability, ataxia, and hypotonia that together are described as posterior fossa syndrome. While speech typically returns, other symptoms of posterior fossa syndrome may persist or resolve slowly over months or years. Further, patients who exhibit posterior fossa syndrome remain at risk for long-term cognitive, academic, and psychosocial dysfunction (Palmer et al. 2010; Schreiber et al. 2014; Wolfe-Christensen et al. 2007). Chemotherapy contributions to PBT outcomes are difficult to study due to variations in agents across tumor presentations as well as the fact that chemotherapy is often given in combination with RT, leading to confounded findings (de Ruiter et al. 2013). Although chemotherapy is generally thought to be less toxic than RT, the *addition* of chemotherapy with RT may confer declines in cognition (e.g., learning and memory) beyond those associated with RT alone (Di Pinto et al. 2012). Many treatment regimens utilize chemotherapy in very young children to avoid or delay RT in an attempt to decrease the long-term cognitive impact.

The well-documented effects of PBT treatment, particularly RT, on neuropsychological outcomes are moderated by age at diagnosis/treatment and time since diagnosis/treatment. Specifically, younger age at diagnosis and treatment has been related to poorer processing speed, working memory, broad attention scores, and intellectual functioning in MB patients treated with surgery, RT, and chemotherapy (Palmer et al. 2013; Schreiber et al. 2014), lower nonverbal intellectual functioning in children with MB treated with reduced-dose RT plus adjuvant chemotherapy (Ris et al. 2001), and lower IQ and math skills in patients with pure germinomas and non-germinomatous germ cell tumors who received chemotherapy and/or RT (Sands et al. 2001). With respect to time since diagnosis/treatment, neurocognitive deficits often worsen or become more evident over time (de Ruiter et al. 2013; Palmer et al. 2001), with some studies providing evidence of a steep decline shortly after treatment followed by a decreased rate of decline from year to year thereafter (Palmer et al. 2003; Spiegler et al. 2004).

Beyond treatment-related variables, there are also a variety of tumor-related variables that may impact neurocognitive functioning. However, it is challenging to isolate the influence of tumor location and pathology since these variables are confounded with other medical and treatment factors. For example, MBs, which are associated with notable neurocognitive risk, are infratentorial, often diagnosed at young ages and treated with multimodality therapy including an effort for complete surgical resection, craniospinal radiation therapy, and chemotherapy. Within this context, the research regarding tumor location has been mixed. While an early study documented that children with supratentorial, hemispheric tumors had more general cognitive impairment (Ellenberg et al. 1987), a more recent study reported that infratentorial tumor location was associated with worse outcomes than supratentorial tumor location after accounting for age at diagnosis and RT dose (Patel et al.

2011). The role of tumor location may vary depending on what specific domains of cognition are being assessed. For example, after accounting for RT and chemotherapy, PBT patients with third ventricle region tumors exhibited worse verbal learning performance than patients with cerebellar tumors. In contrast, patients with cerebellar tumors experienced weaker working memory (King et al. 2004). The relationship between specific aspects of cognition and areas of daily functioning may also vary by tumor location. For example, auditory attention span has been found to significantly predict communication skills for a group of patients with cerebellar tumors. This is in contrast with verbal memory being a significant predictor of socialization skills in a group of patients with third ventricle region tumors (Papazoglou et al. 2008). Tumor size and risk status are also associated with different outcomes. Tumor size, for example, has been associated with lower IQs (Olsson et al. 2014). Higher risk pathology has been linked to lower processing speed, working memory, broad attention scores, and intellectual functioning in MB patients (Palmer et al. 2013; Schreiber et al. 2014) though, as stated above, higher risk pathology is confounded with other medical and treatment factors.

Certain demographic variables, such as patient sex, socioeconomic status, race, and premorbid cognitive status, may impact performance. Regarding sex, there is some evidence that cognitive declines and neurological changes may be more severe in females compared with males (Palmer et al. 2003; Reddick et al. 2014; Ris et al. 2001). However, recent research has found greater long-term (mean 4.6 years post-diagnosis) risk with male gender, but, overall, factors other than sex (e.g., tumor size) may be better predictors of long-term deficits (Olsson et al. 2014). Few studies have focused on socioeconomic factors such as family income or parent education although parent education and marital status have been found to be associated with baseline cognitive functioning (Palmer et al. 2013). In addition, lower socioeconomic status 1–2 years post-PBT diagnosis has been associated with behavior problems 3–4 years post-diagnosis (Kullgren et al. 2003). Similarly to socioeconomic factors, there is a paucity of studies examining ethnicity/race as a primary predictor of long-term neurocognitive outcomes although race was found not to be associated with baseline scores or changes in working memory, processing speed, or attention at 5 years post-diagnosis in survivors of MB who had undergone both RT and chemotherapy (Palmer et al. 2013).

Stronger cognitive abilities at baseline have been associated with greater declines in functioning over time in PBT survivors. For example, in MB patients, higher processing speed, working memory, and attention scores at baseline have been associated with greater declines in these domains across a 5-year period (Palmer et al. 2013). Furthermore, higher baseline functioning has been associated with greater declines in IQ scores over a 4-year follow-up period in children with MBs who received reduced-dose RT plus adjuvant chemotherapy (Ris et al. 2001).

30.2 Pathophysiology

Cranial RT has documented effects on the microglial and microvasculature environments, neurogenesis, neuro-inflammatory responses, and apoptosis. These constitute potential underlying mechanisms in the pathophysiology of RT-induced,

neuropsychological sequelae. Of the various postulated pathophysiological changes underlying neurocognitive sequelae of RT in PBT survivors, cortical and subcortical white matter changes have received the most attention. Numerous studies support an association between cranial RT and reductions in normal appearing white matter (Fouladi et al. 2004; Mulhern et al. 2004c) though some of these studies are not specific to PBT and instead report on samples of patients with mixed pediatric cancer diagnoses who received RT with or without chemotherapy. Imaging research indicates that increased treatment intensity is associated with reduced white matter volumes (Reddick et al. 2014). Direct correlations between normal appearing white matter and neurocognitive outcomes, including IQ, math, and verbal working memory, have also been reported (Fouladi et al. 2004; Jacola et al. 2014; Mabbott et al. 2006). Mulhern et al. (2001) found that normal appearing white matter largely explained the association between age at CRT and IQ in MB survivors after controlling for time since CRT. More recently, diffusion tensor imaging (DTI) studies have confirmed changes in white matter integrity resulting from RT exposure and are moving researchers toward a better understanding of those white matter tracts that may be most vulnerable. In particular, one study of long-term survivors of MB treated with RT found indications of worse white matter integrity in the frontal lobes compared to the parietal lobes even though both regions received the same RT dose (Qiu et al. 2007). Another DTI study in patients with posterior fossa tumors identified worse white matter integrity within the cerebellar region of the cerebello-thalamo-cerebral tract among patients treated with surgery and RT compared to surgery only (Law et al. 2011). Further, this study found that worse white matter integrity within this tract was associated with worse working memory functioning. This finding is consistent with other DTI studies that have shown correlations between IQ and white matter integrity in both PBT and mixed acute lymphoblastic leukemia (ALL) and PBT samples (Khong et al. 2006; Mabbott et al. 2006).

Beyond white matter changes, radiation-induced hippocampal damage is another pathophysiological change that has been documented following cranial RT, and research spans animal models as well as both adult and pediatric brain tumor studies. In studies of mice who received whole brain RT, reduced neurogenesis has been associated with a chronic inflammatory response (Monje et al. 2003), and changes in neurogenesis have been associated with hippocampal-dependent spatial memory deficits 3 months after RT (Rola et al. 2004). Studies of adult and pediatric brain tumor patients have also documented abnormalities in the hippocampus and other structures important for memory following RT, with some studies documenting associated deficits in memory or auditory attention upon neurocognitive assessment (Farjam et al. 2015; Jayakar et al. 2015; Riggs et al. 2014).

30.3 Clinical Presentation and Consequences

The following section provides an overview of the neuropsychological sequelae of PBT. Because the literature in some aspects of neuropsychological functioning is extensive and because of potentially limited applicability of older findings to modern treatment protocols, we primarily focus herein on studies that were published in

Table 30.1 Common neuropsychological measures cited in the pediatric brain tumor literature by domain assessed

	Neurocognitive domain						
	Intellectual/ global cognitive functioning	Academic achievement	Visuospatial and motor	Attention and working memory	Memory	Processing speed	Executive functioning
Measurement instrument	WISC Full Scale IQ	WJ-Achievement	WISC Perceptual Reasoning Index	WISC Working Memory Index	CVLT	WISC Processing Speed Index	DKEFS subtests
	WAIS Full Scale IQ	WIAT	Beery VMI	Conners CPT	CMS	WJ-Cognitive Processing Speed/ Cognitive Efficiency	Trail Making Test B
	WJ-Cognitive General Intellectual Ability	WRAT	Pegboard Tests (various)	Digit span tasks (various)	WMS	Trails Making Test A	Verbal fluency tasks (various)

Beery VMI Beery Developmental Test of Visual-Motor Integration, various editions, *CMS* Children's Memory Scale, Conners *CPT* Conners Continuous Performance Test, various editions, *CVLT* California Verbal Learning Test, various editions, *DKEFS* Delis Kaplan Executive Function System (e.g., Trail Making Test, Verbal Fluency, Tower Test), *TOL-Dx* Tower of London-Dx, *WAIS* Wechsler Adult Intelligence Scale, various editions, *WISC* Wechsler Intelligence Scale for Children, various editions, *WIAT* Wechsler Individual Achievement Test, various editions, *WJ Achievement* Woodcock Johnson Tests of Achievement, various editions, *WJ Cognitive* Woodcock Johnson Tests of Cognitive Abilities, various editions, *WMS* Wechsler Memory Scale, various editions, *WRAML* Wide Range Assessment of Memory and Learning, various editions, *WRAT* Wide Range Achievement Test, various editions

the last decade, as well as meta-analyses. Table 30.1 can be used as a guide to some of the common neuropsychological measures cited in the present review.

30.3.1 Neurocognitive Functioning

With regard to neurocognitive changes associated with PBT treated with RT, changes in overall intellectual functioning have been well documented. A recent meta-analysis by de Ruiter et al. (2013) examined intellectual functioning in PBT patients relative to normative samples and showed moderate to large effect sizes for estimates of global, verbal, and visuo-perceptual intellectual abilities on the WISC-III. Research estimates a 2–4 point decline in IQ per year in the first 4 years post-treatment, with steeper declines shortly following treatment and some plateauing thereafter (Spiegler et al. 2004). Older children (mean age at diagnosis = 11 years) have been shown to evidence a delay before declines in IQ performance are apparent, whereas younger children (mean age at diagnosis = ~6 years) have been shown to evidence early declines followed by later stabilization (Palmer et al. 2003); however, longer follow-up is needed to fully understand this pattern. Neurocognitive

declines in IQ as well as other specific cognitive domains typically reflect a slowed rate of skill acquisition relative to healthy peers rather than loss of existing abilities.

With respect to specific neurocognitive skills beyond IQ, much of the brain tumor literature has focused on measures of attention, processing speed, and executive functions in the assessment of short- and long-term neurocognitive deficits. In fact, following their review of the literature on neurocognitive functioning in individuals with pediatric MB patients, Palmer (2008) created a model that proposes that impairments in attention, processing speed, and working memory underlie the deficits in more distal areas of functioning, including intellectual abilities and academic achievement. This is consistent with literature documenting such associations in typically developing children and in survivors of ALL (Fry and Hale 1996; Schatz et al. 2000).

Studies examining attention have utilized both standardized rating scales and performance-based tests to document deficits in this patient population. Although ratings often remain below clinically significant levels, parents and teachers report greater attention problems on standardized rating scales than are reported in normative populations (Moyer et al. 2012; Willard et al. 2014). Adolescents also self-report greater attention problems than normative populations although these scores also fall within normal ranges, i.e., within one standard deviation of the mean (Beek et al. 2015). Parent-rated attention problems have been associated with worse social functioning in survivors of PBTs and ALL (Moyer et al. 2012), demonstrating a clear functional impact of attention changes post-treatment.

Meta-analytic research has indicated large effect sizes for deficits in standardized, performance-based measures of attention, including Trail Making Test A and Conners Continuous Performance Test (CPT) in comparison to normative samples (Robinson et al. 2010). An additional meta-analysis documented a large effect size for greater CPT omission errors (sustained attention) in comparison to normative samples but nonsignificant differences in CPT commission errors (disinhibition; de Ruiter et al. 2013), suggesting that treatment may result in more inattention, but not impulsivity, in survivors. However, in a study examining performance across a combination of measures tapping attention and working memory in MB survivors who had received RT and chemotherapy, scores fell in the average range at baseline and were estimated to remain in the low-average to average range 5 years post-diagnosis (Palmer et al. 2013). Thus, differences across measures exist, likely related in part to various measures assessing different aspects of attentional functioning and at varying degrees of measurement refinement. PBT research to date has generally not utilized more experimental tasks to investigate specific components of attention that map onto established models of attention (e.g., Petersen and Posner 2012). However, one study that did so documented significantly worse performance on a computerized measure of the orientating attention network in a group of 19 patients treated with surgery only for cerebellar astrocytomas relative to 48 healthy controls (Quintero-Gallego et al. 2011).

Given findings of attention problems, the question has been raised as to whether PBT survivors with such difficulties are captured within the diagnostic criteria of

Attention-Deficit/Hyperactivity Disorder (ADHD). Kahalley et al. (2011) found that 9% of their sample of 100 pediatric brain tumor survivors met strict criteria for ADHD, a prevalence rate that is not significantly different than the upper limits of the estimated rate of ADHD in the United States. However, many children with significant attention difficulties and impairment were not accounted for using strict DSM-IV diagnostic criteria, suggesting that the attention difficulties seen in this patient population may differ from those experienced by children with developmentally based impairments in attention. The conceptual framework of Sluggish Cognitive Tempo (SCT) has been utilized in the literature to describe a subset of children with ADHD who demonstrate signs of lethargy, day dreaming and staring, and poor organization. Research by Willard et al. (2013) documented greater parent-rated SCT symptoms in PBT survivors (mixed diagnoses and treatments) compared with ALL survivors and healthy controls. SCT symptoms were significantly and negatively correlated with overall IQ and working memory scores, but not processing speed scores. Multiple medical variables, including tumor location, radiation field, age at radiation, age at diagnosis, time off-treatment, were not significantly related to SCT scores.

In addition to deficits in attention, PBT survivors as a group show slower processing speed. For example, lower WISC Processing Speed Index scores (in comparison to the normative group) have been recently documented in a group of survivors with multiple tumor types (Kahalley et al. 2013).Furthermore, on the WJ-III Cognitive, MB patients who were treated with surgery, risk-adapted RT, and high-dose chemotherapy with stem-cell support evidenced slower processing speed than general population norms (Palmer et al. 2013). In addition, a recent study of a diagnostically mixed sample of PBT survivors treated with RT also documented deficits in reaction times on the ImPACT test, a brief computerized assessment typically used to screen concussion, relative to sibling controls and a solid tumor control group (Conklin et al. 2013).

Executive functions refer to the cognitive abilities responsible for maintaining internal goals to perform task-relevant behaviors (Miller and Cohen 2001) and may include working memory, inhibitory control, planning, problem solving as well as other higher order cognitive functions utilized for goal-direct behaviors (e.g., sequencing, switching, monitoring). Of these, working memory is the best studied in PBT. For example, research suggests that PBT survivors score worse on a variety of standardized verbal and spatial working memory measures in comparison to both patients with other solid tumors and sibling controls (Conklin et al. 2012, 2013). Additional research suggests that children with posterior fossa tumors who received RT and/or chemotherapy perform more poorly on measures of working memory than do either children with posterior fossa tumors who underwent surgery only or healthy controls (Law et al. 2011). While deficits in working memory have been observed across multiple PBT groups, deficits in this domain are not entirely consistent across studies. For example, Mabbott et al. (2008) did not find differences in working memory between survivors who had undergone surgery and RT for posterior fossa tumors, survivors who had undergone surgery only for posterior fossa tumors, and survivors of non-CNS tumors. With respect to broader executive

functioning beyond working memory, Winter et al. (2014) found that most survivors of PBTs exhibited executive functioning abilities that were broadly within normal limits for age (although at the lower end of that range); however, a sizeable subset of survivors exhibited clinically significant executive functioning deficits, which appeared to be consistent with broadly impaired abilities, affecting both higher- and lower order executive functions (i.e., processing speed and working memory).

Although attention, working memory, and processing speed have been the most frequently studied domains of neurocognition to date in pediatric brain tumor populations, there is evidence that these individuals may also show deficits in other areas, including language, visuospatial skills, memory,and fine motor control. Overall mean effect sizes across studies examining deficits on measures of language and visuospatial functioning in comparison to normative samples fall in the large range (Robinson et al. 2010). Despite earlier research documenting mixed findings that may have been related to tumor location (King et al. 2004; Spiegler et al. 2004), more recent research has also documented memory deficits in survivors of PBT on both neuropsychological tests (Jayakar et al. 2015; Özyurt et al. 2014; Riggs et al. 2014) and on the ImPACT test (Conklin et al. 2013). With regard to fine motor control, overall mean effect sizes across studies examining measures of psychomotor speed fall in the large range (Robinson et al. 2010) for PBT patients in comparison to normative samples.

30.3.2 Academic Functioning

The neurocognitive deficits often present in PBT survivors can be accompanied by academic skill difficulties though studies are mixed with regard to the extent of academic impairment in PBT survivors. For example, Mabbott et al. (2005) examined standardized reading, spelling, and math performance, as well as parent and teacher ratings of school performance, in 53 patients with posterior fossa tumors who had all undergone RT. All academic measures fell approximately one standard deviation (12–15 points) below normative means. Extent of resection, use of chemotherapy, and RT dose were not associated with academic scores or ratings. In addition, Conklin et al. (2008) found significant declines over time in standardized reading, but not spelling or math reasoning scores, in survivors of ependymomas treated with RT. Supratentorial tumor location and multiple surgeries were associated with worse reading performance at baseline, and male sex, longer symptomatic intervals, pre-RT chemotherapy, hydrocephalus, and younger age at RT (<5 years) predicted significant decline in reading scores over time. Research by Holland et al. (2014) suggests that it is academic fluency deficits (e.g., rate and accuracy of academic skill performance), rather than skill deficits per se, that are most affected in PBT survivors, likely attributable to the deficits in attention, processing speed, and working memory discussed earlier in this review. In addition to the cognitive deficits that likely contribute to the academic difficulties that many patients experience, it is important to note that other factors, such as school absence, may also contribute to difficulties across subjects.

A recent study of ependymoma survivors identified higher rates of clinically significant school competence problems (e.g., parent ratings of academic performance, participation in special education, and history of grade retention) that were identifiable relatively early following RT (6 months) and persistent throughout the 5-year study period (Willard et al. 2014). Reduced school competence has implications for long-term educational and vocational outcomes. Several studies of adult outcomes among PBT survivors have identified increased risk for "proximal" educational performance difficulties, (e.g., grade retention, special education placement, and worse proficiency test performance), as well more "distal" educational and vocational outcomes (e.g., worse graduation test performance, lower high school and college graduation rates, and increased unemployment; Barrera et al. 2005; de Boer et al. 2006; Kirchhoff et al. 2010; Lorenzi et al. 2009; Mitby et al. 2003; Pang et al. 2008).

30.3.3 Adaptive, Emotional/Behavioral, and Psychosocial Functioning

Aspects of adaptive, emotional/behavioral, and psychosocial functioning are also among the areas that can be affected in PBT survivors. With regard to adaptive functions (activities of daily living), research has documented mild weaknesses in some domains compared with normative populations, but scores remain within one standard deviation of the mean (e.g., Robinson et al. 2015). Ashford et al. (2014) found greater adaptive skill deficits in PBT survivors who had received RT compared to both sibling controls and solid tumor controls. However, there are other variables besides RT that may impact adaptive functioning. For example, Robinson et al. (2015) did not find a relationship between RT dose and parent ratings of adaptive functioning but did find an association between tumor size and overall adaptive functioning scores as well as conceptual, practical, and social skills. Furthermore, in a group of patients with ependymoma, lower baseline adaptive scores were associated with pre-RT chemotherapy, shunt placement, number and extent of surgical resections, and younger age at treatment (Netson et al. 2012). In a study of craniopharyngiomas survivors, females evidenced greater decline than males in parent-rated functional communication skills over a 5-year period (Netson et al. 2013).

Results from studies examining emotional functioning in brain tumor survivors are mixed. Mabbott et al. (2005) found that parent and teacher ratings of internalizing and externalizing symptoms on standardized behavioral rating scales fell broadly within normal limits, but clinically significant internalizing symptoms were identified in another study (Poggi et al. 2005). Post-traumatic stress symptoms that are subclinical for a diagnosable PTSD have been reported in family members of survivors and, less consistently, survivors themselves (Kazak et al. 2001, 2004a). Results from a study by Brinkman et al. (2012) suggest that parent-reported depression/withdrawal symptoms may be higher for female survivors than males. Importantly, findings from a large study by Brinkman et al. (2013a, b, c) suggest that medical professionals working with PBT survivors during childhood and into

adulthood should be vigilant about assessing for mental health difficulties, as over 11% of their sample of survivors ranging from 10 to 35 years of age reported that they had experienced suicidal ideation. This is much higher than the prevalence of suicidal ideation (SI) in the general US adult population (3.7%; Crosby et al. 2011). Those who had undergone surgery were 3.5 times more likely to experience suicidal ideation than those treated with other modalities, including RT.

Multiple studies have examined social difficulties experienced by PBT survivors. Studies examining parent ratings on standardized rating scales have generally not identified clinically significant social difficulties in PBT survivors. For example, a recent study of patients treated for ependymomas found stable parent ratings of social competence from baseline to 5 years following RT (Willard et al. 2015). Still, social functioning has been shown to fall significantly below population norms in some PBT samples (Brinkman et al. 2012; Willard et al. 2014), and one study identified that a subset of survivors are at greater risk for clinically significant internalizing problems, social problems, and withdrawal, with the latter two difficulties associated with longer time since diagnosis (Poggi et al. 2005). Patients themselves may be more likely to underestimate the social difficulties they are experiencing (Radcliffe et al. 1996). In a study including PBT survivors, survivors were more likely to overestimate their leadership popularity and underestimate isolation and victimization when compared with ratings completed by their peers (Salley et al. 2014). Difficulties in social functioning may be associated with different aspects of neurocognition, including overall intellectual abilities (Brinkman et al. 2012; Holmquist and Scott 2002), attention difficulties (Moyer et al. 2012), and/or executive dysfunction (Wolfe et al. 2013a, b).

30.4 Methodological Considerations

It is necessary to view the existing literature pertaining to the neuropsychological sequelae of PBT and their associated risk factors within the context of a number of critical methodological considerations. A review of such considerations serves to highlight the unique challenges inherent in conducting neurocognitive research with the PBT population and also serves to identify important future directions in the field.

Small sample sizes are a hurdle to conducting outcome studies in PBT due to low population base rates and attrition related to survival rates. Typically, larger samples are achieved by sacrificing specificity (i.e., samples of mixed diagnostic, treatment, and/or age groups), accruing patients over longer periods of time, and/or accruing patients through collaborative organizations, such as the Children's Oncology Group (COG). Due to variation in available resources (e.g., trained professionals, testing instruments) across member institutions within organizations like COG, the latter strategy often results in studies characterized by missing data or limitations in the cognitive domains that are assessed. While these are general limitations in the research, specialty programs have published on relatively large samples that are less mixed with respect to tumor type, and such studies are an important development in the literature.

The PBT literature comprises numerous studies that lack control groups, more typically comparing samples of PBT survivors to published test norms, "a strategy which does not effectively control potentially important factors, such as demographics or issues related to chronic illness. Furthermore, neurocognitive outcome models likely involve direct and indirect effects of a combination of medical, child-specific, and broader contextual predisposing factors (e.g., family functioning), but there is a relative lack of attention to many of these nonmedical factors. Finally, advances in PBT treatment protocols/technology typically outpace the collection of neuropsychological outcome data, resulting in research that is less applicable to the current state of the field. This is particularly true for studies that accrue large sample sizes by recruiting over extended periods of time, or for longitudinal studies that require a number of years to study neuropsychological outcomes over time in the same cohort. In fact, longitudinal studies are far outnumbered by cross-sectional designs, making it difficult to examine or account for maturational changes.

30.5 Therapeutic Interventions

Research examining the efficacy of various interventions for neuropsychological late effects in PBT survivors has begun to receive increased attention in the last 10–15 years. This is reflected in the COG Long-Term Follow-Up Guidelines (COG-LTFU Guidelines; Children's Oncology Group 2013), which recommend neuropsychological assessment and yearly history-taking/psychosocial assessment to triage survivors to school-liaison services, community-based disability services, pharmacological interventions, direct psychological services, and cognitive rehabilitation. Occupational, physical, and speech therapies address overlapping areas of functioning with neuropsychology and are typically considered and coordinated in the neuropsychological care of PBT survivors. While some of these recommendations rely heavily upon clinical experience and established patterns of practice in the field, others have varying degrees of evidence supporting their implementation in survivors of PBT.

30.5.1 Pharmacologic Interventions

There are limited pharmacologic studies focused solely on PBT survivors, but methylphenidate (MPH) is the most extensively studied pharmacologic intervention in mixed samples of pediatric cancer patients who have received CNS-directed therapies, including RT and/or intrathecal methotrexate and cytarabine. The published studies have primarily been generated from two independent, randomized, double-blind, placebo-controlled trials and document positive, short-term outcomes on direct measures of attention and parent/teacher ratings of behavior at intervals up to 3 weeks following medication initiation (Conklin et al. 2007, 2010a; Mulhern et al. 2004a; Thompson et al. 2001). The most recent of these studies

(Conklin et al. 2010a) documented that positive medication response was predicted by higher parent and teacher ratings of attention problems prior to the medication trial, and it also documented a lower overall medication response rate in the pediatric cancer sample (45%) than has been reported in the developmental ADHD literature (~75%). Possible explanations for this finding proposed by the authors included this study's more stringent criteria for positive response through the use of reliable change indices, a higher incidence of poor prognostic factors in their sample relative to developmental ADHD samples (i.e., lower hyperactivity and more comorbid learning and neurologic issues), and a potentially different etiologies of attention problems (e.g., genetic polymorphism in pediatric ALL v. dopamine transport/reuptake in developmental ADHD). In one of two studies examining side effects of MPH in pediatric cancer survivors, Conklin et al. (2009) reported that MPH was well tolerated overall in their randomized trial, with increased side effects associated with moderate dose (0.6 mg/kg) (versus either placebo or low dose (0.3 mg/kg)), female gender, and lower IQ. Consistent with findings in the developmental ADHD literature, side effects ratings during all 3 weeks of the trial were actually lower than baseline ratings prior to MPH initiation, which has been posited to be due to "side effects" on rating scales reflecting attention problems that are *responsive* to MPH as opposed to adverse medication effects which are *the result* of MPH.

One limitation of these randomized trials has been their short follow-up periods. However, two non-randomized studies have reported on longer term outcomes examined in the final phase of Conklin and colleagues' trial (see Conklin et al. 2007, 2010a; Mulhern et al. 2004a). Collectively, these studies demonstrate that the improvements documented at 3 weeks following initiation of medication are maintained at 12 months, as measured by direct measures of attention, parent ratings of social skills and behavioral problems, and parent, teacher, and self-report (adolescent subsample) ratings of attention (Conklin et al. 2010b; Netson et al. 2011); however, examination of the pattern of change across the 12-month period identified mild rebound in cognitive problems and inattention between months 6 and 12 of the medication trial. As part of this same 12-month trial, Jasper et al. (2009) documented significant deceleration of BMI and weight, but not height, in the MPH treatment group during the 12-month trial, but no growth deceleration was found in a case-matched, unmedicated, comparison group. Given that the rate of growth deceleration for the MPH group was modest relative to Center for Disease Control normative data, the authors contended that MPH was reasonably well tolerated with respect to short-term growth, particularly given the propensity toward obesity that is present among pediatric cancer survivors; however, longer trials remain needed to elucidate any growth effects that may emerge after 12 months of MPH treatment.

Beyond MPH, numerous studies have documented increased use of antidepressants and other psychoactive medications among pediatric cancer survivors relative to siblings, peers, and the general population (Brinkman et al. 2013b; Deyell et al. 2013; Lund et al. 2015; Portteus et al. 2006), but efficacy studies of these psychoactive medications are not available in the literature. However, Brinkman et al. (2013c)

published a report from the Childhood Cancer Survivor Study (CCSS) demonstrating an association between psychoactive medications (i.e., antidepressants, anticonvulsants, CNS stimulants, and neuroleptic medications) and impaired functioning across multiple domains of neurocognition (i.e., task efficiency, organization, memory, and emotional regulation), and the effect of psychoactive medications on neurocognition was above and beyond that of established predictors of neurocognitive impairment, including RT, neurologic history, and acute psychological distress. The associational nature of this finding does not elucidate whether the relationship between psychoactive medications and neurocognition is causal or simply reflective of the underlying neurological impairment for which the medications initially were prescribed.

Donepezil, an acetylcholinesterase inhibitor, has been the focus of two studies in adult brain tumor survivors and one study in PBT survivors. Both a prospective, open-label phase-II study (n = 24; Shaw et al. 2006) and a randomized, placebo-controlled phase III trial (n = 198; Rapp et al. 2015) of adults irradiated for brain tumors documented multiple areas of cognitive improvement at the end of 24-week trials relative to baseline, and the former study also demonstrated positive changes in health-related quality of life and mood. However, the randomized, placebo-controlled trial also found that observed cognitive improvements were only significantly different between the Donepezil and placebo groups at the end of the 24-week trial for patients with more significant cognitive impairment at baseline. In the only study published in the PBT literature to date, Castellino et al. (2012) demonstrated that Donezepil was well tolerated in a sample of 11 PBT survivors who received >23.4 Gy RT and were at least 1-year status post-cancer treatment at the time of the open-label trial. Preliminary findings in support of cognitive benefits on executive functioning, visual memory, and aspects of attention and auditory/verbal working memory were documented and suggest that future trials examining the potential benefit of Donepezil in PBT survivors are warranted.

30.5.2 Cognitive Remediation

In recent years, various cognitive remediation techniques have received increasing attention as potential interventions for the neurocognitive deficits experienced by PBT survivors. This line of empirical research essentially began with the work of Butler and colleagues (Butler 1998; Butler and Copeland 2002; Butler et al. 2008), who investigated the efficacy of the Cognitive Remediation Program (CRP). This program involves a tripartite model of rehabilitation techniques (hierarchically graded, massed practice to strengthen attentional control and information processing speed), educational interventions (15 metacognitive strategies to address preparedness, task approach, on-task behavior, and generalization), and clinical psychology techniques (cognitive-behavioral interventions to improve resistance to distraction and the ability to self-coach). While preliminary studies provided early empirical support for the CRP, the results of a follow-up, multicenter, randomized controlled trial of pediatric cancer survivors with CNS-involved disease or

treatments were mixed. There was significant improvement (generally small to medium effect sizes) on measures of academic achievement, self-reported metacognitive strategies use, and parent (not teacher) ratings of attention, but there was no improvement on direct measures of neurocognitive functioning. In a pilot study of a different cognitive remediation program involving a 15-session, clinic-based program to teach compensatory learning and problem-solving skills in survivors of pediatric cancers involving CNS disease or treatments ($n = 12$) and associated cognitive deficits, there was only qualified evidence of efficacy in two areas (social skills and writing) though parent and child satisfaction were high (Patel et al. 2009).

In contrast to the time- and resource-heavy interventions described above, online, computerized cognitive training programs have been the focus of more recent investigations, targeting working memory or broader executive functioning in particular. Conklin et al. (2015) identified a number of advantages of such programs compared to the pharmacological interventions and in-clinic cognitive remediation programs previously employed with samples of PBT survivors, including broader geographic reach due to remote administration capability, reduced time burden with scheduling flexibility, engaging interfaces for child participants, ease of progress monitoring, and reduced medical contraindications. Kesler et al. (2011) conducted a 1-arm, open trial investigating the efficacy of an online cognitive rehabilitation program developed by Lumos Labs to train cognitive flexibility, working memory, and attention in a small sample of ALL or PBT survivors who were ≥6 months status post-CNS-directed treatment. Utilizing a pre-post design, significant improvements were reported in processing speed and cognitive flexibility as well as visual and verbal declarative memory, and the program was associated with changes in fMRI activation patterns in the dorsolateral prefrontal cortex; however, associations between the cognitive and fMRI changes were not investigated. Further, only immediate post-intervention outcomes were reported, so the lasting impact of the intervention is unknown.

Following initial demonstration of feasibility and acceptability of the working memory intervention Cogmed (www.cogmed.com) in samples of ALL and infratentorial PBT survivors with a history of CNS-directed therapies (Cox et al. 2015; Hardy et al. 2013), another research group reported on the findings of a randomized, single-blind, waitlist-controlled trial to investigate the efficacy and neural correlates of change associated with Cogmed in survivors of PBT and ALL who received CNS-directed therapy (Conklin et al. 2015). After completing the 5- to 9-week Cogmed program, the intervention group demonstrated greater benefit than controls on direct measures of working memory, attention, and processing speed as well as caregiver ratings of inattention and executive dysfunction. However, improvements in processing speed did not generalize to measures of academic fluency, and thus a functional benefit associated with these preliminary findings has not been clearly evidenced. While fMRI was not completed for the waitlist controls, the intervention group evidenced training-related neuroplasticity in the left lateral prefrontal, left cingulate, and bilateral medical frontal areas; however, these activation changes were not associated with change in working memory scores. Taken together, the current body of research highlights potential promise of these techniques for the

remediation of some neuropsychological late effects experienced by pediatric cancer patients with CNS disease or treatment histories, but studies investigating the maintenance and generalization of these deficits beyond very specific cognitive tasks are an essential next step before utilization of such programs should be broadly recommended for this population.

30.5.3 Educational Interventions

The COG-LTFU Guidelines recommend baseline neuropsychological evaluation upon entry into long-term follow-up (2 years post-treatment) and periodically as clinically indicated thereafter (Children's Oncology Group 2013). More recent guidelines published as part of a collaborative effort of experts in the field (see Wiener et al. 2015) also conclude that there is support in the literature for the importance of neuropsychological evaluation but provide less clear guidance regarding the time of evaluation (Annett et al. 2015). Ultimately, the authors recommended neuropsychological evaluation upon completion of treatment and at regular 2–3-year intervals thereafter, unless otherwise clinically indicated. Empirical studies documenting the efficacy of neuropsychological evaluation for PBT survivors or even mixed pediatric cancer samples are limited. Quillen et al. (2011) reported that less than half of the recommendations in neuropsychological reports were implemented by parents in a mixed sample of pediatric cancer survivors. In another study, despite approximately 75% of a small sample of parents and teachers of PBT survivors reporting a sound understanding of the neuropsychological report, less than half of the recommendations were implemented (Cheung et al. 2014). In a sample of children treated with chemotherapy and 18 Gy cranial RT for ALL, however, Anderson et al. (2000) reported improved reading and spelling skills between initial neuropsychological evaluation at 2 years post-treatment and a follow-up evaluation 3 years later when the initial evaluation was accompanied by verbal feedback to parents and provision of written information to both parents and school. While a comprehensive neuropsychological report has the potential to be an effective intervention for PBT survivors by way of prescribing the specific school services and accommodations that should be most beneficial for a given child in the academic setting, it is an ongoing challenge to be sure that these reports are provided to the school and that the recommendations are implemented appropriately.

A formal plan for continuation of school during treatment, for school reentry, and for implementation of appropriate educational interventions is important following diagnosis and during survivorship (Mitby et al. 2003). Many specialized pediatric cancer centers utilize school liaison professionals to support such planning and to communicate information between the medical and educational teams. However, while formal educational interventions (i.e., school personnel workshops, peer education programs, comprehensive programs involving multiple educational interventions) were the subject of several empirical investigations over a decade ago, no such studies have been generated in recent years. Furthermore, none of the

available studies exclusively included children with primary CNS disease or CNS-directed treatment who are at highest risk for poor school adjustment and performance, and many studies have methodological limitations that hamper their contribution to the literature. Within this context, the available studies that did not specifically exclude children with brain tumors document preliminary but qualified evidence of increased participant knowledge about the child's medical condition, increased participant interest in interacting with a peer with cancer, and decreased personal worrying about cancer (Benner and Marlow 1991; Prevatt et al. 2000; Rynard et al. 1998; Treiber et al. 1986).

While no specific academic interventions have been investigated in survivors of PBT, one study investigated a math intervention based in Multiple Representations Theory in a sample of ALL survivors who received chemotherapy only (Moore et al. 2012). The intervention was associated with increases in calculation and applied math skills immediately following completion, but such improvements were not evident in reading and spelling, demonstrating specificity of the intervention. Improvements in applied math remained evident approximately 1-year following completion of the intervention and, overall, were larger than those following the CRP intervention studied by Butler and colleagues (Butler 1998; Butler and Copeland 2002; Butler et al. 2008), highlighting the question of whether specific academic interventions may be a more effective use of resources than broad cognitive remediation techniques when attempting to remediate specific academic skill deficits. Future interventions will be needed to directly address this question.

30.5.4 Socioemotional Interventions

Existing socioemotional intervention studies within the field of pediatric cancer have been primarily conducted in mixed diagnostic groups and, thus, may have more limited applicability to PBT survivors, for whom socioemotional risk is elevated (Zeltzer et al. 2009). The most developed programs have targeted three areas: maternal problem-solving, post-traumatic stress in the child and family members, and child social functioning. The maternal problem-solving intervention has thus far been studied with respect to its benefits for mothers of newly diagnosed pediatric cancer patients, and evidence of efficacy has been documented in three randomized controlled trials (Sahler et al. 2002, 2005). To our knowledge, no studies to date have investigated the indirect effects of this intervention on the psychosocial adjustment of survivors themselves.

In a sample of 150 adolescent cancer survivors, their parents, and their adolescent siblings, Kazak et al. (2004b) conducted a randomized wait-list control trial of a family intervention that integrates cognitive-behavioral and family systems approaches to target post-traumatic stress symptoms related to the cancer experience. The study evidenced significant post-treatment reductions in symptoms of post-traumatic stress, specifically intrusive thoughts among fathers and arousal among survivors. There were no effects demonstrated for the mothers in the sample.

Investigations of two different manualized social skills interventions studied in newly diagnosed childhood cancer patients or PBT survivors ≥6 months off-treatment have documented preliminary evidence of their benefit on outcomes including parent and child ratings of behavior problems, parent ratings of school and social competence, patient ratings of social competence, and patient perceptions of peer and teacher social support (Barakat et al. 2003; Varni et al. 1993). Guided by the Social Competence Model (Yeates et al. 2007), which postulates that social-affective and cognitive-executive processes are linked to social problem solving and collectively contribute to social performance and ultimately social adjustment, Schulte et al. (2014) examined an 8-week, social skills group intervention in a small sample of PBT patients (mean = 3.9 years post-cancer treatment) and identified improvements in social performance behaviors such as maintaining eye contact with peers, social conversations with peers, and cooperative play. No improvements were found for social problem solving. Nevertheless, the areas of demonstrated benefit are important for PBT survivors, and future controlled trials that further investigate each hypothesized level of social competence may help guide social interventions in the future.

30.6 Prevention

Attempts to prevent or minimize neuropsychological sequelae of radiation in pediatric patients have largely focused on reducing the dose and volume of radiation or on delaying RT to avoid the increased neurocognitive risk that has been associated with younger age at treatment. Reduced craniospinal RT doses have been shown to be associated with attenuated, albeit still significant, cognitive and academic decline, with some of these associations moderated by factors such as age or higher baseline IQ (Mulhern et al. 2005, Ris et al. 2013). Other RT techniques (hyperfractionation) and chemotherapy regimens (chemoprotectants) have been utilized to effectively increase the radiation dose delivered to the tumor without increasing the associated toxicity, and there is some support for attenuated IQ decline in PBT patients who received hyperfractionated RT (Carrie et al. 2009).

Conformal RT techniques (e.g., 3D conformal, intensity-modulated radiation therapy, intensity-modulated arc therapy, volumetric-modulated arc therapy) are guided by advanced imaging methods and enhanced computing to provide more precise radiation delivery to target areas while reducing irradiation of healthy tissue (Kun and Beltran 2009). Despite these advanced techniques, healthy tissue surrounding the target is exposed to entrance and exit radiation dose, and significant neuropsychological sequelae continue to be documented following these treatments though the effects have been shown to be reduced in some PBT studies (Jain et al. 2008; Kirsch and Tarbell 2004; Merchant et al. 2004). Given evidence supporting the role of crucial areas of neurogenesis, such as the hippocampus, in the pathophysiology of RT-related neurocognitive late effects in PBT patients, there is an opportunity to study whether use of advanced conformal techniques to avoid or minimize radiation exposure to these critical brain regions results in prevention of

some neurocognitive sequelae, particularly adverse memory outcomes. While no such studies have been published to date for PBT, adult brain tumor research has documented that hippocampal sparing techniques are associated with preservation of memory, quality of life, aspects of executive functioning, and processing speed, with one study showing verbal memory to be impaired by local irradiation in a dose–response relationship (increased dose to the left hippocampus, in particular) (Gondi et al. 2014; Tsai et al. 2015). These studies are limited by their short follow-up intervals (4 months), yet they do provide preliminary support for prior findings of a relationship between hippocampal RT dose and memory performance in adult brain tumor patients and suggest that such conformal techniques should remain an area of study with respect to prevention of neurocognitive late effects (Gondi et al. 2012).

While conventional radiation therapy (XRT) utilizes photons to penetrate tissue and deliver radiation to the target, proton beam radiation therapy (PBRT) may have superior physical properties for medical radiation. That is, PBRT deposits maximum dose at the maximum tissue penetration depth, which can be precisely conformed to the clinical target (Yock and Tarbell 2004). This results in less entrance dose and no exit dose, thereby minimizing irradiation of healthy tissue surrounding the target. By preserving more healthy brain tissue, PBRT may protect cognitive abilities in PBT patients better than RT; however, research investigating the neurocognitive outcomes associated with PBRT is only beginning to emerge in the available literature.

Three studies examining patients with MB/PNET (Jimenez et al. 2013), ependymoma (Macdonald et al. 2013), or low grade gliomas (Greenberger et al. 2014) documented no declines in mean IQ at follow-up evaluations conducted at 1–3 years, 1–5 years, and 1–8 years post-baseline, respectively. However, these studies were limited by very small sample sizes ($n = 5$ to $n = 14$) and lack of comparison groups. In a prospective study of a cohort of 43 children with MB at a median of 5.2 years status post-treatment with whole brain PBRT (median dose 23.4 Gy) and an additional boost dose to the posterior fossa or involved field (median dose 54 Gy), Yock et al. (2016) reported that FSIQ declined significantly by 1.5 points per year on average relative to baseline, explained, in particular, by declines in processing speed and verbal comprehension. FSIQ outcomes were moderated by age, reflecting declines in patients younger than 8 years but not those ≥8 years of age. Patients who received an RT boost to the whole posterior fossa (versus the involved field only) showed greater IQ decline although this finding was minimized by authors due to confounding with age at RT. Another report from this group examined IQ change in a sample of 60 patients with varied brain tumor histologies treated with PBRT (Pulsifer et al. 2015). While no change was identified in Full Scale IQ, a significant decline of 5.2 points on average was identified in processing speed scores, with greatest decline identified in younger patients and those with higher baseline scores. While these studies provided the first descriptions of neurocognitive outcomes in PBT patients treated with PBRT, neither study included a comparison group and, thus, did not directly address the question of whether PBRT is associated with neurocognitive sparing relative to XRT.

Kahalley et al. (2016) retrospectively examined IQ over time in a sample of PBT survivors (mixed tumor histologies) treated with XRT (n = 60) or PBRT (n = 90). This study supported the existing neurocognitive literature in documenting significant IQ decline following XRT, but significant IQ decline was not identified in patients treated with PBRT. Even so, no significant difference in the change in IQ over time was identified between the PBRT and XRT groups. As such, this study did not provide clear evidence that PBRT results in clinically meaningful sparing of global IQ beyond that of contemporary XRT protocols. While these findings may reflect a true lack of difference in IQ change over time between the two groups, alternative explanations include insufficient power, insufficient sensitivity of global IQ to neurocognitive change in patients treated with contemporary RT methods (e.g., compared to skills such as processing speed and executive functioning), and insufficient time between baseline and follow-up in the PBRT group to detect differences. Additional research is needed to fully investigate the degree to which PBRT results in neurocognitive sparing relative to modern XRT protocols used in the treatment of PBT.

Beyond advances in RT technology, studies of the genetic basis of individual sensitivity to radiation are an important step for developing effective, individualized treatments in children who are genetically susceptible to neurocognitive sequelae. However, while genetic mediators of neurocognitive outcome have been an area of focus in pediatric leukemia (Cole et al. 2015; Kamdar et al. 2011; Krull et al. 2008, 2013) as well as adult brain tumors (Correa et al. 2014), such research has not yet emerged in the PBT literature. In addition, pharmacologic prevention techniques, particularly those aimed at reversing RT effects on the microglial and microvasculature environments, neurogenesis, chronic inflammation, and apoptosis, may also hold promise. While these have not yet been studied in humans, animal models have identified several agents (i.e., nonsteroidal anti-inflammatory agents, lithium, peroxisomal proliferator-activated receptor agonists, shikonin) that impact these RT-induced pathophysiologic processes (Gan et al. 2015; Monje et al. 2003; Ramanan et al. 2009; Yang et al. 2009; Yazlovitskaya et al. 2006). In studies of mice, lithium delivered concomitantly with RT improved neurocognitive performance compared with RT alone, as did shikonin administered prior to RT. In contrast, dietary GW0742, a peroxisomal proliferator-activated receptor agonist, prevented RT-related increases in inflammatory markers and hippocampal microglial activation, but it did not restore hippocampal neurogenesis or prevent early delayed hippocampal-dependent cognitive impairment (Schnegg et al. 2013).

Lastly, engagement in physical exercise has well-documented physical and emotional benefits that are important for PBT survivors, who are at increased risk for cardiac and pulmonary late effects as well as socioemotional difficulties. Exercise has been shown to increase growth hormone (Blackmore et al. 2009) and reduce inflammation (Handschin and Spiegelman 2008), two potential mechanisms through which it could counteract the pathophysiological effects of RT. In rodent models, initial studies suggest that exercise is capable of ameliorating RT-induced deficits in both neurogenesis and cognition (Naylor et al. 2008; Wong-Goodrich et al. 2010). Given preliminary findings of a relationship between cardiorespiratory fitness and

executive functioning, particularly working memory, in PBT survivors, exercise may prove promising in attenuating cognitive late effects in humans, as well (Wolfe et al. 2013a, b).

30.7 Summary

The neuropsychological late effects experienced by PBT survivors have been an area of much research, but further investigation is needed to better understand the nature and predictors of neuropsychological late effects. As RT techniques become more advanced, earlier research may not accurately depict the risks associated with modern treatment protocols. Research into not only "proximal" effects on neurocognition and socioemotional functioning but also into "distal" or "real-life" outcomes is also needed to better understand the relationship between the identified neuropsychological late effects and functional abilities of survivors throughout childhood and into adulthood. As the pathophysiology of RT effects and its relationship to neurocognitive outcomes becomes better understood, promising avenues of medically based prevention are being introduced. However, the literature on various remediation and prevention techniques is in its infancy relative to the literature on neuropsychological late effects themselves, and expansion of the evidence base for prevention and remediation techniques represents an important future direction in the field.

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Endocrine Sequelae of Central Nervous System Irradiation

31

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Contents

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Abstract

Children with central nervous system (CNS) tumors who are treated with irradiation are uniquely at risk for the development of endocrinopathies due to acquired anterior pituitary and thyroid dysfunction, which can in turn negatively affect linear growth, pubertal development, metabolism, skeletal health, and quality of life. The risk for anterior pituitary dysfunction increases with the dose of radiation delivered to the hypothalamic-pituitary axis (HPA) and with the duration of follow-up. Concomitant spinal irradiation also increases the risk of primary hypothyroidism and thyroid neoplasia. Endocrine sequelae may take years to manifest, and their clinical symptoms may be indolent and nonspecific. Early recognition and treatment should lead to better long-term health outcomes and improvements in the quality of life of childhood brain tumor survivors. The radiation oncologist can help reduce the impact of long-term endocrine sequelae by understanding the HPA and thyroid dose tolerance and facilitating the early referral and timely diagnosis of at-risk patients.

31.1 Introduction

The endocrine system is frequently impacted by the treatment of pediatric malignancies, and up to 50% or more of childhood cancer survivors suffer from an endocrine sequela (Brignardello et al. 2013; Diller et al. 2009; Chemaitilly and Sklar 2010; Tonorezos et al. 2015; Gurney et al. 2003a; Miyoshi et al. 2008). Children treated with central nervous system (CNS) irradiation are uniquely at risk for the development of endocrinopathies due to acquired anterior pituitary dysfunction, which can in turn negatively affect linear growth, pubertal development, metabolism, skeletal health, and quality of life. The risk for anterior pituitary dysfunction increases with the dose of radiation delivered to the hypothalamic-pituitary axis (HPA) and with the duration of follow-up. All anterior pituitary hormones can be affected: growth hormone (GH), the gonadotropins (luteinizing hormone [LH] and follicle-stimulating hormone [FSH]), thyroid-stimulating hormone (TSH), adrenocorticotropic hormone (ACTH), and prolactin (PRL). Endocrine sequelae may take years to manifest, and their clinical symptoms may be indolent and nonspecific. Although the scope of this chapter will primarily include the neuroendocrine effects of cranial radiotherapy that involves the HPA, no less important are the other endocrine sequelae (see Sect. 31.4.6) that can arise from craniospinal radiotherapy, which is frequently employed in the definitive treatment of malignant CNS tumors in children.

31.2 Predisposing Factors

CNS tumors, the most frequent solid neoplasms diagnosed during childhood, are commonly treated with multimodality therapy (surgery, radiation therapy, and chemotherapy). Tumors can directly impact endocrine function by infiltrating the HPA,

Table 31.1 Dose tolerance, endocrine sequelae, and screening/evaluation recommendations for children with CNS tumors treated with radiation that involves the HPA

Hormone	Dose at which risk of dysfunction is increased	Endocrine consequence	Recommendations for screening and evaluation as clinically indicated
GH	≥18 Gy	• Growth hormone deficiency	• Growth velocity
		• Poor linear growth (may be masked by concomitant CPP)	• Tanner staging
		• Shorter adult height	• Bone age
			• IGF-1
			• GH provocative testing
LH/FSH	≥18 Gy	• CPP (girls <age 5 most susceptible); rapid linear growth (may be masked by concomitant GH deficiency)	• Growth velocity
		• Premature menarche	• Tanner staging
		• Shorter adult height	• Pelvic ultrasound (girls)
			• Bone age
			• LH/FSH and testosterone/estradiol
			• Leuprolide stimulation test
LH/FSH	≥30	• Hypogonadotropic hypogonadism	• Growth velocity
		• Delayed/incomplete puberty	• Tanner staging
		• Shorter adult height	• Bone age
			• LH/FSH, PRL, and testosterone/estradiol
TSH	≥30	• Central hypothyroidism	• Free T4 and TSH
		• Shorter adult height	
ACTH	≥30	• Central adrenal insufficiency	• 8 AM cortisol
		• Adrenal crisis	• Cosyntropin stimulation test
PRL	≥50	• Galactorrhea	• Prolactin
		• Hypogonadotropic hypogonadism	

HPA hypothalamic-pituitary axis, *GH* growth hormone, *LH* luteinizing hormone, *FSH* follicle-stimulating hormone, *TSH* thyroid-stimulating hormone, *ACTH* adrenocorticotropic hormone, *PRL* prolactin, *CPP* central precocious puberty

in which case the endocrinopathy may be present at cancer diagnosis. Alternatively, neuroendocrine dysfunction can arise immediately after surgery for a tumor proximate to the HPA or in a delayed fashion secondary to exposure of the HPA to deleterious doses of radiation (Table 31.1). In terms of radiation therapy, predisposing factors to consider include the age of the child at treatment, the radiation dose to the HPA, gender, and the time elapsed since irradiation.

Data suggest that age has a differential effect on susceptibility of the HPA to damage from irradiation (Darzy 2009). The risk of developing GH deficiency, in particular, has been associated with younger age at treatment by most but not all

authors (Diller et al. 2009; Chemaitilly and Sklar 2010; Darzy 2009; Chemaitilly et al. 2015a; Mulder et al. 2009; Brauner et al. 1986; Schmiegelow et al. 2000a).

Another important predisposing factor for injury to the HPA is the dose of irradiation. As would be predicted, the higher the radiation dose, the more likely the child is to develop endocrine sequelae (Chemaitilly and Sklar 2010; Tonorezos et al. 2015; Darzy 2009; Chemaitilly et al. 2015a; Mulder et al. 2009; Rutter and Rose 2007; Laughton et al. 2008; Merchant et al. 2011). Cranial radiotherapy doses ≥18 Gy impart a significant risk for GH deficiency, which can be an isolated event; doses ≥30 Gy increase the risk of LH/FSH, ACTH, and TSH deficiencies; and radiation doses exceeding 50 Gy are more likely to be associated with multiple anterior pituitary hormone deficiencies and hyperprolactinemia. Conversely, there is no exact threshold dose below which there is no risk of HPA injury, as GH deficiency can even be observed in children who receive low-dose (8–11 Gy) irradiation (Mulder et al. 2009). Although the use of proton therapy is better suited to spare the HPA when it is distal to the desired radiation target, well-designed studies comparing protons versus photons are lacking, although a recent cohort-simulation model would suggest that proton therapy may be more cost-effective for scenarios in which radiation dose to the hypothalamus can be spared (Mailhot Vega et al. 2015).

Third, the gender of the patient is another variable that may play a role in the risk of radiation-induced neuroendocrine dysfunction. Males appear to be at increased risk for any endocrine complication in general (Brignardello et al. 2013), and men may be at higher risk for LH/FSH deficiencies (Chemaitilly et al. 2015a). As also seen in the non-tumor population, girls are more likely to get central precocious puberty (CPP) (Darzy 2009; Chemaitilly et al. 2015b). Hyperprolactinemia also occurs more commonly in women (Darzy 2009; Constine et al. 1993).

Finally, the time elapsed since radiation treatment is an important determinant of the likelihood of having an endocrine disorder. Studies have documented that the cumulative incidence of a chronic endocrine condition continues to rise even decades after diagnosis (Brignardello et al. 2013; Diller et al. 2009). The same is true for HPA dysfunction, which may take years to evolve, especially with lower radiation doses (Chemaitilly and Sklar 2010; Tonorezos et al. 2015; Darzy 2009; Chemaitilly et al. 2015a; Merchant et al. 2011; Gleeson and Shalet 2004). Notably, the onset of pituitary dysfunction after irradiation can also occur within just a few years (Laughton et al. 2008), especially with higher radiation doses (Merchant et al. 2011).

31.3 Pathophysiology

The pathophysiology of radiation-induced injury to the HPA remains poorly understood, but it is believed that neuroendocrine dysfunction most likely arises from direct neuronal injury, although there may also be a contribution from vascular damage and reduced blood flow (Chieng et al. 1991). The hypothalamus is believed to be the site of the HPA most impacted by irradiation (Gleeson and Shalet 2004). This is based on the observation of a preserved GH response to exogenous GH-releasing

hormone in GH deficient patients exposed to cranial radiation and because of the known occurrence of hyperprolactinemia following high-dose radiotherapy to the CNS (Constine et al. 1993; Schriock et al. 1984; Lam et al. 1986; Schmiegelow et al. 2000b). There are, nevertheless, data supporting a certain degree of vulnerability of the pituitary gland to radiation, especially with higher radiation doses (Darzy 2009; Gleeson and Shalet 2004). It is therefore safe to assume that HPA dysfunction after irradiation most likely results from a combination of events at both the hypothalamic and pituitary levels.

In general, there is a hierarchy of anterior pituitary hormone loss after radiation therapy. GH is the most frequently impacted followed by LH/FSH, TSH, ACTH, and usually after much higher radiation doses, PRL (Brignardello et al. 2013; Gurney et al. 2003a; Darzy 2009; Chemaitilly et al. 2015a; Langsenlehner et al. 2007; Littley et al. 1989; Gan et al. 2015) (Table 31.1). As a rule, the posterior pituitary (the distal axons of hypothalamic neurons that synthesize arginine vasopressin and oxytocin) is not injured by radiation therapy, and hence, central diabetes insipidus is not a frequent or expected late effect of CNS irradiation but is more likely to result from direct tumor involvement or surgery (Brignardello et al. 2013; Miyoshi et al. 2008; Darzy 2009; Gleeson and Shalet 2004; Lam et al. 1986; Langsenlehner et al. 2007).

31.4 Clinical Presentation and Consequences

As discussed above, radiation-induced HPA dysfunction may occur years after the completion of therapy, and it is an evolutionary process that rarely encompasses all HPA hormones simultaneously from the outset. Because the onset of radiation-induced hypopituitarism is usually insidious, it may be difficult to diagnose. The symptoms may be mild and overlooked, especially in survivors who are coping with multiple treatment-induced morbidities. In addition, the presentation of multiple endocrinopathies, such as the coexistence of GH deficiency and CPP (Figs. 31.1 and 31.2), may make the clinical diagnosis challenging. The consequences of neuroendocrine dysfunction can have a profound long-term impact on the cancer survivor, including shorter adult height (that may be disproportional [Fig. 31.2]), obesity, low bone mass, a higher burden of chronic disease, increased frailty, and lower quality of life (Diller et al. 2009; Chemaitilly et al. 2015a).

31.4.1 GH Deficiency

GH deficiency (GHD) is the most common, and often the only, anterior pituitary hormone deficit following radiotherapy that includes the HPA in the radiation field. In a recent study of 748 long-term adult survivors of childhood cancer treated with cranial radiotherapy (including survivors of acute lymphoblastic leukemia and CNS tumors), the prevalence estimate of GHD was 46.5% (95%CI, 42.9–50.2%) (Chemaitilly et al. 2015a). The risk of GHD is even higher in cohorts of brain tumor

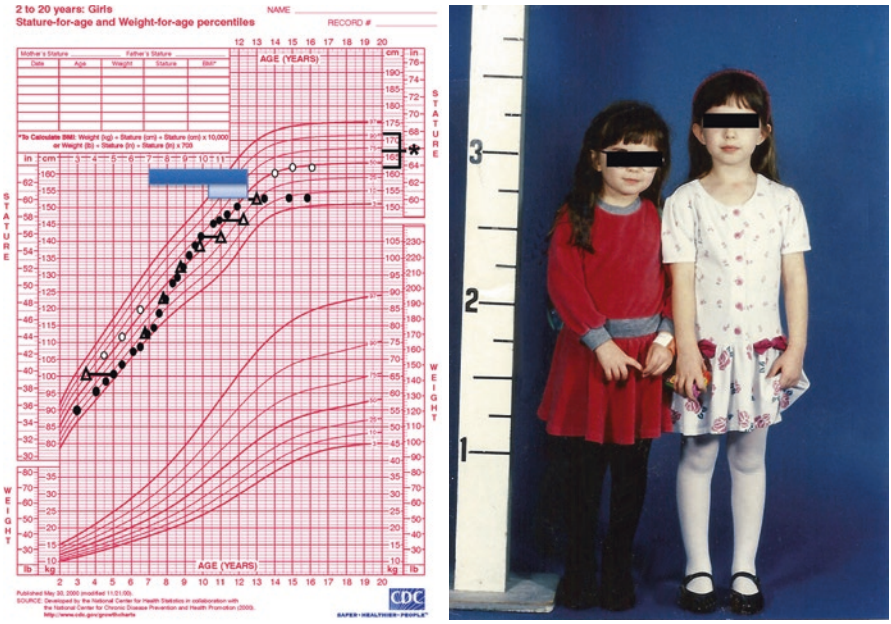

Fig. 31.1 Growth chart of a girl (*solid circles*) with a history of locally advanced retinoblastoma status post right eye enucleation, chemotherapy, and radiotherapy (39.6 Gy in 35 fractions) to the orbit, completed at the age of 17 months. Bone ages are represented by *open triangles*. She was diagnosed with growth hormone (GH) deficiency and then central precocious puberty and treated with recombinant human GH (*dark blue box*) and depot leuprolide (*light blue box*), respectively. The patient had menarche at age 8 and achieved a final height of 60 in., well below mid-parental height (*asterisk*). At age 23 years, she was diagnosed with hypogonadotropic hypogonadism. The patient's identical twin sister (*open circles*) was already significantly taller by the age of 5 years. She had menarche at age 12 and achieved a final adult height of 63.75 in. (Figure reproduced with permission from (Stephen et al. 2011))

survivors (Laughton et al. 2008). Based on the results of one study in 192 pediatric patients with localized brain tumors, a cumulative radiation dose of 16.1 Gy to the hypothalamus was determined to be the mean dose required to achieve a 50% risk of GHD at 5 years (Merchant et al. 2011).

Despite being common, however, GHD is not the only contributor to poor linear growth during childhood, especially during active cancer therapy when confounding factors such as poor nutrition and the use of glucocorticoids may also be present. Years after radiation therapy, concomitant endocrinopathies such as hypothyroidism and pubertal disorders may also affect height and growth velocity. Furthermore, final adult height in children with GHD may be negatively impacted by having received concomitant spine radiotherapy, which can directly damage the vertebral epiphyses and lead to disproportionate growth (upper/lower segment ratio < 0.9; arm span more than 5 cm > height; sitting height standard deviation < standing height standard deviation) (Fig. 31.2) (Diller et al. 2009; Shalet et al. 1987; Clayton and Shalet 1991; Edgar et al. 2009; Meacham 2003).

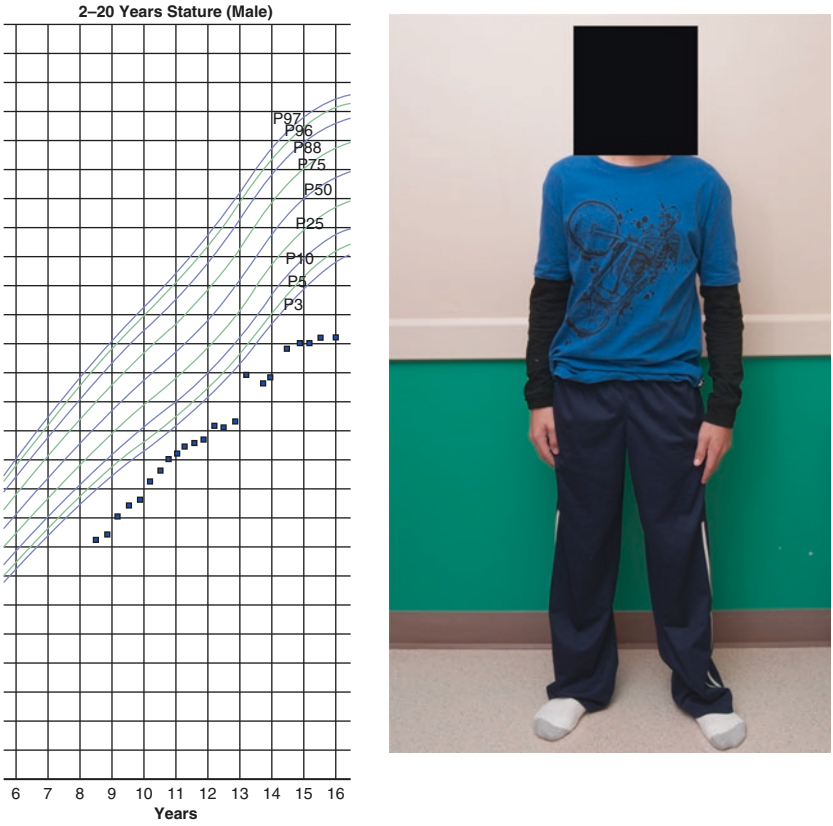

Fig. 31.2 A 15-year-old boy with a history of medulloblastoma diagnosed at age 14 months who ultimately received craniospinal irradiation (30 Gy with an additional 25.2 Gy boost to the posterior fossa) at the age of 5 due to recurrent disease. He was diagnosed with and initiated therapy for GH deficiency at the age of 8 and, at age 10 years, he started depot leuprolide due to early pubertal development. Despite these interventions, he had an extremely short final adult height and disproportionate stature (trunk disproportionately short compared with limbs)

The clinical presentation and diagnosis of GHD is reviewed in more detail elsewhere and is primarily based on auxological criteria (Growth Hormone Research Society 2000; Stanley 2012). In general, GHD classically manifests as a subnormal growth velocity (normal is >5 cm/year in prepubertal children) associated with a crossing of height percentiles. The bone age X-ray (plain radiograph of the left arm and wrist that assesses skeletal maturity via a comparison of the epiphyses with age-matched standards) is typically delayed for the child's chronologic age, and the insulin-like growth factor 1 (IGF-1) and IGF-binding protein 3 (IGF-BP3) are characteristically low for age and pubertal status. GH provocative testing is frequently utilized to confirm a diagnosis of GHD, and in fact is often required by third-party payors despite issues with reliability and reproducibility.

There are some notable exceptions regarding the presentation of GHD in the child who has received irradiation. First is that plasma IGF-1 and IGF-BP3 levels are not always reliable screening tests for GHD in children exposed to CNS radiation as they may be normal in individuals with a diagnosis proven by provocative testing (Weinzimer et al. 1999). Second, GHD may occur concomitantly with premature sexual maturation in a large number of pediatric cancer survivors (Figs. 31.1 and 31.2) (Sklar and Constine 1995), and therefore the bone age may not be delayed or may even be advanced; obesity and previous chemotherapy exposure (e.g., treatment with retinoic acid) may also influence the bone age in this fashion (Hobbie et al. 2011; Russell et al. 2001). Third, growth velocity may be normal in the child with profound GHD and concomitant CPP or obesity (Edgar et al. 2009). Finally, GHD may be partial and may be manifested only by a diminished pubertal growth spurt (Meacham 2003).

The treatment of GHD in childhood generally involves the use of daily subcutaneous injections of recombinant human GH, which in turn can improve final height outcome (Diller et al. 2009; Gleeson et al. 2003; Ciaccio et al. 2010), although children treated with radiotherapy may never fully achieve their genetic height potential (Beckers et al. 2010). Given the proliferative and pro-mitogenic properties of GH and IGF-1, the safety of GH therapy in individuals with a history of cancer has been an area of concern. Recent studies have not identified a clear risk from GH therapy, specifically as relates to the development of second CNS neoplasms (Patterson et al. 2014), and current understanding is that it is safe to prescribe GH to the pediatric cancer survivor as early as 1 year after cancer therapy is complete (Raman et al. 2015).

31.4.2 Central Precocious Puberty and LH/FSH Deficiencies

Puberty is characterized by the development of sex-specific secondary sexual characteristics, accelerated growth, and ultimately fusion of the growth plates and cessation of linear growth. In girls, breast development is the first sign of puberty whereas in boys, it is testicular enlargement with the possible and notable exception of those concurrently exposed to gonadotoxic therapies. CPP, commonly defined as pubertal onset before age 8 in girls and 9 in boys, arises from the premature activation of the hypothalamic-pituitary-gonadal axis and, if untreated, may cause a final adult height significant shorter than is genetically predetermined. LH and FSH deficiencies become apparent when the child has delayed entrance into puberty (>age 13 in girls or >age 14 in boys), delayed menarche (>age 16 in girls), or develops hypogonadotropic hypogonadism (amenorrhea in girls, low testosterone levels in boys with inappropriately low or normal LH/FSH levels) after puberty has begun. The diagnosis and treatment of pubertal disorders is more comprehensively reviewed elsewhere (Chen and Eugster 2015; Palmert and Dunkel 2012).

Cranial radiation is a significant risk factor for dysfunctional gonadotropin secretion (Diller et al. 2009; Laughton et al. 2008; Gleeson and Shalet 2004; Gan et al. 2015; Edgar et al. 2009; Meacham 2003; Stephen et al. 2011; Oberfield et al. 1996;

Armstrong et al. 2009a). CPP may occur following treatment with a wide range of cranial radiotherapy doses, especially >20–25 Gy (Gleeson and Shalet 2004; Muller 2002; Ogilvy-Stuart et al. 1994), with younger age at radiotherapy conferring the highest risk of CPP (Oberfield et al. 1996; Ogilvy-Stuart et al. 1994; Lannering et al. 1997). Patients who develop CPP following radiation doses exceeding 30 Gy have a significant risk of ultimately developing LH/FSH deficiencies (Constine et al. 1993; Toogood 2004; Brauner et al. 1984) (Fig. 31.1). The timing of menarche can also be impacted by irradiation, especially when treatment is received at ages younger than age 5, and both early and late menarche can occur (Armstrong et al. 2009b; Chow et al. 2008).

In pediatric cancer survivors, the clinical presentation of CPP can pose distinct challenges. As mentioned above, CPP can mask co-occurring GHD by inducing seemingly normal growth rates at the expense of rapid bone age advancement, leading to reduced adult height (Figs. 31.1 and 31.2). Importantly, increasing testicular volume, which is the hallmark of pubertal entrance in boys, may not be reliable in the identification of pubertal onset in male childhood cancer survivors who received cytotoxic chemotherapy or direct testicular radiation; thus a high index of suspicion and measurement of LH/FSH and testosterone levels supplement the physical exam (Armstrong et al. 2009a; Quigley et al. 1989). Plasma estradiol and gonadotropin levels and/or uterine length measurements using pelvic ultrasound may likewise be helpful in determining the pubertal status of a subset of girls.

31.4.3 TSH Deficiency

Deficiency of TSH secretion results in insufficient stimulation of thyroid follicular cells and resultant low circulating thyroxine levels, which can cause typical signs and symptoms of hypothyroidism in children, including decreased growth velocity, delayed skeletal maturation, constipation, skin dryness, and constitutional symptoms such fatigue and cold intolerance. The main risk factor associated with TSH deficiency is HPA exposure to radiation doses ≥30 Gy (Chemaitilly et al. 2015a; Laughton et al. 2008; Rose et al. 1999). As there is no widely available provocative testing, the diagnosis of central hypothyroidism is made by documenting a serum-free thyroxine level below the lab-specific normal range in the presence of a low, inappropriately normal, or minimally elevated serum TSH level. The evolution of TSH deficiency can be prolonged and the diagnosis difficult to make; often, the downward trend in thyroxine levels can help to alert the clinician to the diagnosis (Darzy 2009).

31.4.4 ACTH Deficiency

The hypothalamic-pituitary-adrenal axis, although more resilient, can also be damaged by the effects of irradiation. ACTH deficiency causes low serum cortisol levels through gradual atrophy of the adrenal cortex, and central adrenal

insufficiency can present with symptoms of anorexia/nausea, weakness, fatigue, and unintentional weight loss. Aldosterone production is not under the direct control of ACTH and so hyperkalemia and salt wasting are not components of ACTH deficiency although symptomatic hypotension can occur during episodes of acute physiological stress when the compensatory secretion of cortisol fails to occur. The main risk factor for central adrenal insufficiency is HPA exposure to radiation doses exceeding 30–40 Gy (Chemaitilly et al. 2015a; Laughton et al. 2008; Rose et al. 2005; Patterson et al. 2009). The diagnosis of ACTH deficiency is usually made after cosyntropin stimulation (Chrousos et al. 2009), as random morning plasma ACTH and cortisol levels may be unreliable (Patterson et al. 2009). ACTH deficiency can also be partial, and some patients may require only stress steroid coverage instead of commencing daily glucocorticoid replacement (Darzy 2009). Although one of the least common endocrine sequelae of CNS irradiation, central adrenal insufficiency is nonetheless an important entity to recognize given the potential life-threatening consequences of untreated cortisol deficiency, especially during acute illness.

31.4.5 Hyperprolactinemia

Hyperprolactinemia occurs after irradiation due to the loss of dopaminergic inhibition of prolactin secretion from the anterior pituitary, and this appears to be more common in adults (Constine et al. 1993). Elevated prolactin levels can cause galactorrhea and, through inhibition of gonadotropin secretion, hypogonadotropic hypogonadism. In childhood brain tumor survivors, it tends to be asymptomatic and rarely warrants intervention given the high rates of coexistent LH/FSH deficiencies and primary hypogonadism. Hyperprolactinemia is most common following radiation doses >50 Gy (Constine et al. 1993; Meacham 2003).

31.4.6 Other Endocrine Consequences of Irradiation Given for CNS Tumors

In addition to endocrine dysfunction directly related to irradiation involving the HPA, there are long-term metabolic consequences that are indirectly related to having been treated for a CNS tumor during childhood. Low bone mineral density occurs at a significantly higher rate (Gurney et al. 2003a), which likely reflects a combination of hypopituitarism, vitamin D deficiency, and a higher likelihood to have a sedentary lifestyle, especially in children with long-term neurologic sequelae. Survivors of CNS tumors treated with radiation also have an increased risk of obesity, especially with higher radiation doses and tumors such as craniopharyngioma that directly involve the hypothalamus (Diller et al. 2009; Gan et al. 2015; Meacham 2003; Gurney et al. 2003b; Lustig et al. 2003). As might be expected, the risk for hypertension, hyperlipidemia, and diabetes also appear to be

increased but may not always correlate with body mass index (Meacham et al. 2009; Gurney et al. 2006).

Craniospinal irradiation is frequently used in the treatment of malignant CNS childhood tumors, and the potential endocrinopathies that may result from spine irradiation should not be minimized. Most common is the development of primary hypothyroidism (often subclinical in nature), which occurs following exposure of the thyroid gland to scatter radiation; in one study in children treated for embryonal brain tumors, primary hypothyroidism was the second most common endocrinopathy, occurring in 65% of survivors at 4 years (Laughton et al. 2008). Thyroid carcinoma, chiefly papillary thyroid cancer (Sigurdson et al. 2005), is a common second primary tumor in childhood cancer survivors. In one study of medulloblastoma patients, it was the second most common secondary malignancy, diagnosed in 21% of survivors after a prolonged latency period (mean time to diagnosis 25 years after medulloblastoma diagnosis) (Ning et al. 2015). The risk of thyroid cancer increases with radiation doses up to 20–29 Gy, after which there is a fall in the dose–response relationship (Sigurdson et al. 2005). The testes and ovaries, although most impacted by cytotoxic chemotherapy (primarily alkylating agents), can also receive scatter radiation, which may contribute to the risk of developing primary gonadal dysfunction, particularly in females (Gleeson and Shalet 2004; Livesey et al. 1990).

31.5 Therapeutic Interventions and Prevention

For the clinician, there are several review articles and guidelines, such as those of the Children's Oncology Group (www.survivorshipguidelines.org), that offer guidance for the identification and screening of vulnerable patients (Tonorezos et al. 2015; Darzy 2009; Edgar et al. 2009; Meacham 2003; Gan and Spoudeas 2014; Children's Oncology Group 2013). In general, any child with a brain tumor who receives therapeutic irradiation is at increased risk for the development of an endocrine disorder. In children whose HPA is in the radiation field, especially if it receives ≥18 Gy, a physical examination including auxological assessment and pubertal (Tanner) staging should be performed at least every 6 months, and referral to a pediatric endocrinologist familiar with this population should be considered. Early signs of pituitary dysfunction include a change in growth velocity (i.e., crossing height percentiles) and the premature development of secondary sexual characteristics. The physical examination can be augmented by a laboratory evaluation and assessment of skeletal maturity as indicated (Table 31.1). Furthermore, for children also treated with spinal irradiation, annual measurement of thyroid function studies and examination of the thyroid and cervical lymph nodes, to identify primary hypothyroidism and thyroid cancer, respectively, is essential. The specific treatment of an endocrine disorder is tailored to the patient and the nature of the problem encountered, and in all survivors, a healthy lifestyle to minimize the development of low bone mass, obesity, and metabolic syndrome should be encouraged at each visit.

31.6 Summary

Endocrine complications are common in survivors of childhood CNS tumors treated with cranial or craniospinal irradiation, and they pose specific challenges in their clinical presentation. The radiation oncologist can help reduce the impact of long-term endocrine sequelae by understanding the HPA and thyroid dose tolerance and facilitating the early referral and timely diagnosis of at-risk patients.

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Ophthalmic Outcomes for Children Treated with CNS Radiation

32

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Contents

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Abstract

Central nervous system radiation may expose different parts of ophthalmic system to radiation, leading to transient or permanent injury. This chapter discusses the potential consequence of radiation to ocular, orbital, and periorbital structures, as well as the anterior and posterior optic pathways and cranial nerves. In addition, therapeutic interventions for acute and chronic side effects are provided.

32.1 Introduction

Vision is important for many important factors of life, including learning/education and activities of daily living. The World Health Organization defines moderate visual impairment as visual acuity between 20/60 and 20/200 (Steinkuller 2010). Even a moderate visual impairment will reduce a child's quality of living. Normal vision is dependent upon clarity of the ocular media (cornea and lens), normal retina and optic nerve, and normal remaining anterior and posterior visual pathways. Depth perception is dependent upon normal vision, and normal ocular alignment and movement.

32.2 Predisposing Factors

The treatment of pediatric neoplasms that involve the structures surrounding the eye (ocular adnexa), the globe, or the visual pathways may involve surgery, chemotherapy, and/or radiation therapy. Therefore, it may be difficult to determine which treatment modality most adversely impacted the ocular or visual system.

Genetic mutations that inhibit tumor suppression have clearly been shown to increase the risk of second malignancies in the field of radiation. Examples included radiation-induced sarcoma in patients with retinoblastoma (germ line mutation) and gliomas and peripheral nerve sheath tumors in patients with neurofibromatosis type 1 and 2.

Some chemotherapeutic agents are well known to cause ocular, oculomotor, or visual system side effects. These include conjunctivitis, corneal disease, and less commonly, ptosis and cranial neuropathy (Hazin et al. 2009; Singh and Singh 2012).

Neurosurgery for brain tumor biopsy or resection may lead to injury of the optic pathways, resulting in possible loss of visual acuity, loss of peripheral vision, or cranial nerve 3, 4, 5, or 6 injury.

32.3 Pathophysiology

The ocular structures that are at risk to be injured by direct or indirect radiation include the ocular adnexa (eyelids, lacrimal gland, and orbit), the globe (conjunctiva, cornea, crystalline lens, and retina). The visual pathways are also at risk for

injury (optic nerve/s, chiasm, optic tracts, and the visual cortex). Extraocular muscle innervation is provided by cranial nerves III, IV, and VI, and injury to one of these cranial nerves will result in strabismus. Cranial nerve V injury may lead to an anesthetic cornea with possible resultant corneal compromise.

Though the precise mechanism of radiation is not understood, it is believed to be due to free radical formation leading to destruction the DNA of the rapidly dividing cancer cells (Barabino et al. 2005). Most information about radiation dose relationship to visual toxicity comes from studies or reports on adult patients, as little has been studied regarding radiation tolerance in children specifically; however, children who are treated with higher doses at a younger age may be more susceptible to long-term effects (Larson et al. 1990).

32.4 Clinical Presentation

Indications for radiation have evolved over time. As an example, in the past external beam radiation therapy (EBRT) was routinely utilized for the treatment of retinoblastoma (Rb) until it was noted that many irradiated patients with germ line mutations of the Rb gene had a very high risk of secondary malignancies, especially in the field of radiation. This finding leads to a reduction in the usage of EBRT for retinoblastoma and now standard therapy for retinoblastoma includes systemic chemotherapy for chemoreduction, laser photocoagulation, intra-arterial and intra-vitreal chemotherapy, and plaque radiotherapy. EBRT may still be indicated in patients where globe preservation is desired, and other therapeutic interventions have been unsuccessful.

Orbital radiation in the pediatric population is primarily used for the following neoplasms that can involve the orbital structures: rhabdomyosarcoma, acute myelogenous leukemia, neuroblastoma, primary orbital bone tumors such as Ewing sarcoma, and rarely infantile hemangioma and Langerhans cell histiocytosis.

Indications for visual pathway irradiation include optic pathway gliomas, which may involve the optic nerve, chiasm/hypothalamus, and optic tracts.

Total body radiation (TBI), typically used in preparation for bone marrow transplantation, exposes the entire eye to radiation. TBI is used in patients with acute lymphoblastic leukemia and occasionally acute myelogenous leukemia.

Craniospinal irradiation (CSI) also exposes the eye to radiation and may be indicated in the treatment of common pediatric malignant brain tumors including medulloblastoma, ependymoma, and germ cell tumors.

32.5 Consequences

32.5.1 Lids, Lacrimal Gland and Drainage, Conjunctiva

The upper and lower eyelids are composed of skin, muscle, and are lined by conjunctiva. The lids contain various glands that are necessary for the creation of the three layers of tear film (Krachmer et al. 2011). Meibomian glands are oil glands

that contribute lipid to the tear film, preventing evaporation of tears (Servodidio and Abramson 1993). Meibomian glands are vertically arranged in the upper and lower lid, whose orifices line the eyelid margins, adjacent to the eyelashes. The aqueous portion of the tear film is created by the lacrimal gland and conjunctival glands of Wolfring and Krause. The final layer of the tear film, the mucinous layer, is supplied by the goblet cells of the conjunctiva. Blinking causes the tear film to travel across the surface of the eye and exit through the upper and lower puncta located on the medial aspect of the eyelids (Servodidio and Abramson 1993). The blink reflex, which is controlled by the trigeminal and facial nerves, helps spread the tear film over the anterior surface of the globe for lubrication (Krachmer et al. 2011).

Eyelids may exhibit transient erythema within hours to days of radiation doses as low as 2.5 Gy (Barabino et al. 2005; Gordon et al. 1995; Servodidio and Abramson 1993). Chronic changes may occur, including permanent loss of the lashes, telangiectasia, hyperpigmentation, and ectropion (Barabino et al. 2005; Gordon et al. 1995). These late effects occur with increasing frequency after fractionated radiation doses of 30–60 Gy (Servodidio and Abramson 1993). Nasolacrimal duct obstruction may occur after irradiation, secondary to stenosis of the punctae and canaliculi, leading to chronic epiphora (Barabino et al. 2005). Radiation to the lacrimal glands may cause atrophy leading to lack of reflex tearing (Gordon et al. 1995). Lacrimal glands also contribute to basal tearing, and lacrimal gland damage has been reported with a single dose of 20 Gy and after conventionally fractionated 50–60 Gy (Kennerdell et al. 1999).

The conjunctiva may develop inflammation (noninfectious conjunctivitis) or edema (chemosis) several weeks after therapy which lasts for several days after fractionated doses of 27–30 Gy (Barabino et al. 2005). With higher doses of 30–60 Gy, the conjunctiva may undergo more severe damage: keratinization, symblephara (adherence of the lid conjunctiva to the conjunctiva of the globe), and permanent loss of goblet cells (Barabino et al. 2005; Servodidio and Abramson 1993). If the goblet cell loss is substantial, the normal tear film composition may be disrupted, resulting in dry eye disease (DED) (Gordon et al. 1995).

32.5.2 Cornea

The cornea is a transparent, convex, avascular anterior structure of the eye which serves as a major source of refractive power (Krachmer et al. 2011). The anterior surface is covered by the tear film which provides the cornea with lubrication. Because the cornea is avascular, oxygenation of the corneal tissue from is direct absorption from the atmosphere. A healthy tear film is vital for corneal clarity and overall corneal health. The most superficial layer is the epithelium, composed of a single layer of non-keratinizing stratified squamous cells. The epithelium is able to regenerate, so minor epithelial defects often heal without scarring that would impair vision (Servodidio and Abramson 1993). Bowman's layer, composed of collagen fibrils, lies underneath the epithelium and does not heal

without scarring (Gordon et al. 1995). The stroma of the cornea is the thickest layer and comprises 90% of the total thickness. Descemet's membrane and the corneal endothelium are the final and inner most corneal layers, whose function is to maintain the cornea in a slightly dehydrated state, which is necessary for corneal clarity.

The cornea is particularly susceptible to radiation effects (Barabino et al. 2005). At radiation doses of 10–20 Gy, acute changes range from corneal epithelial irregularity, epithelial defects (corneal abrasion), keratitis (corneal stromal inflammation, infectious, and noninfectious), and decreased corneal sensation due to injury to the branches of cranial nerve 5, which innervates the cornea (Servodidio and Abramson 1993).

Late onset disease may occur when the cornea is exposed to radiation doses >40 Gy and include complete epithelial desquamation, stromal edema, and neovascularization. Chronic epithelial defects of the cornea may allow microbes to penetrate the exposed corneal stroma and lead to an infected corneal ulcer (microbial keratitis) (Barabino et al. 2005; Servodidio and Abramson 1993). At radiation doses 50 Gy or higher, keratinization and stromal scarring may occur, typically occurring several years after initial treatment (Barabino et al. 2005).

Corneal sensation is also vital to corneal health. The sensory nerves innervating the cornea are mostly derived from the trigeminal nerve (cranial nerve V). The cornea is highly innervated and the density of nerve endings is 300–400 times more than skin, so that most corneal diseases lead to intense pain, epiphora, and light sensitivity. Radiation injury to the trigeminal nerve may lead to neurotrophic keratopathy and induces a dry eye-type condition characterized by an abnormal tear film, corneal epithelial irregularity, and susceptibility to corneal ulcers, with possible corneal melting and/or permanent corneal scarring (Krachmer et al. 2011). Because of the diminished corneal innervation, these patients do not experience much pain.

32.5.3 Iris and Anterior Segment

The iris can also be affected by radiation. Acutely, with doses of 20 Gy, an iritis, or anterior uveitis, may occur due to leakage from the iris blood vessels (Servodidio and Abramson 1993). Patients may complain of photophobia, pain, epiphora, and occasionally decreased vision (Hazin et al. 2009). Anterior chamber inflammation is the hallmark of iritis and is found on biomicropscopy (slit lamp examination). Treatment of the iritis includes steroid and cycloplegic eye drops to dilate the pupil. Elevated intraocular pressure may transiently occur and may be treated with topical pressure lowering medications. The late effects of radiation on the iris are rubeosis iridis (iris neovascularization), posterior synechiae (scarring of the iris to the lens), or iris atrophy (Servodidio and Abramson 1993). Neovascular glaucoma may develop due to the rubeosis iridis. Patients may present with symptoms of acute glaucoma: pain, conjunctival injection, and corneal edema (Gordon et al. 1995).

32.5.4 Lens

The crystalline lens is a biconvex, clear structure in the eye and is a second major source of refractive power (Steinert et al. 2004). The normal lens is transparent, and any opacity of the lens, regardless of the size or density, is termed a cataract. Whether the opacity is visually significant depends on the location, size, and morphology of the cataract (Nelson and Olitsky 2005). The lens nucleus is central, surrounded by cortex, and the outermost layer is the lens capsule. Cataracts can develop in any of the lens components.

The lens in children is particularly susceptible to radiation due to the continuous mitotic activity (Servodidio and Abramson 1993). Acute lens changes may occur, such as lens edema, inducing myopia and secondary blurred vision (Servodidio and Abramson 1993). Cataract formation is a well-known late effect of radiation and was reported as early as 1908 (Barabino et al. 2005). Cataract development usually occurs 2–8 years after the exposure to radiation. The risk of radiation-related cataract formation is dose dependent and may occur with doses of radiation as low as 0.5 Gy (Salvin and Hendricks 2012). Incidence has been reported at 62–100% at doses of >40 Gy (Takeda et al. 1999). Posterior subcapsular cataracts (PSC) are often the initial lens changes, noted as a blockage of the red reflex and easily diagnosed with slit lamp examination. Small PSCs do not cause decreased vision, but as they grow and expand, visual acuity decreases. Occasionally, radiation-related lens changes may appear similar to a senile cataract (Gordon et al. 1995).

32.5.5 Retina

The retina is a light-sensitive neural tissue that lines the posterior portion of the globe and transmits visual input to the brain (Ryan 2006). The inner two thirds of the retina (adjacent to the vitreous) is supplied by the central retinal artery (CRA), which is the first branch of the ophthalmic artery after it leaves the internal carotid artery. The CRA enters the optic nerve posterior to the globe, emerges from the optic nerve head, and divides into branches providing the inner vascular supply of the retina. The central retinal vein is adjacent to the CRA, also exits through the optic nerve head.

After radiation exposure, acute retinal edema has been reported, typically resolving within weeks (Servodidio and Abramson 1993). Radiation retinopathy is a long-term side effect of radiation. Signs and symptoms may appear as early as 6 months after initial treatment though patients with diabetes or risk factors such as concurrent or recent chemotherapy may be predisposed to develop earlier retinopathy (Salvin and Hendricks 2012; Takeda et al. 1999). Radiation retinopathy appears clinically similar to diabetic retinopathy, manifesting as cotton wool spots, microaneurysms, retinal hemorrhages, proliferative retinopathy, and vitreous hemorrhages (Hazin et al. 2009; Servodidio and Abramson 1993; Gordon et al. 1995). The risk of retinal injury is lower at fraction sizes <1.9 Gy/day and total radiation doses

<45–55 Gy (Parsons et al. 1994). Central retinal artery occlusion (CRAO) has also been reported after radiation treatment (Takeda et al. 1999).

32.5.6 Optic Pathway

The optic nerve, or cranial nerve II, transports the retinal ganglion cells (RGCs), which originate in the inner retina, to the chiasm, where they decussate, course through the optic tracts and terminate in the lateral geniculate nucleus. Visual information is then sent to the visual cortex. Disease of the optic nerve is termed optic neuropathy.

Radiation-induced optic neuropathy is a potentially devastating consequence that may occur in patients receiving radiation therapy, often leading to permanent loss of visual function. Radiation-induced optic neuropathy usually presents within 3 years of treatment, peak incidence 12–18 months after treatment. Patients often present with a history of episodic transient visual obscurations followed by painless, sudden loss of vision (Gordon et al. 1995). An afferent pupillary defect and abnormal color discrimination may be noted on examination in involved eye. Depending on the location of radiation-induced injury (anterior or posterior portion of the optic nerve), the optic nerve may appear normal, pale, or edematous in the acute phase. Optic nerve atrophy will always develop within 4–8 weeks of the injury (Hazin et al. 2009; Gordon et al. 1995; Indaram et al. 2015). Radiation optic neuropathy has been found with doses of >50–55 Gy (Servodidio and Abramson 1993; Gordon et al. 1995). The risk of optic neuropathy grows significantly higher at doses greater than 60 Gy (Jeganathan et al. 2011; Shih et al. 2009). The visual pathways are more sensitive to single large doses of radiation than other cranial nerves.

32.5.7 Non-optic Cranial Nerves

Several cranial nerves are important for extraocular muscle function. The oculomotor nerve (cranial nerve III) innervates the superior rectus, inferior rectus, medial rectus, and inferior oblique muscles. In addition, it innervates the pupil and ciliary body, which leads to pupil constriction and accommodation, and the levator palpebrae muscle that elevates the upper eyelid. The trochlear nerve (cranial nerve IV) innervates the superior oblique muscle, and the abducens nerve (cranial nerve VI) innervates the lateral rectus muscle. The cranial nerves exit the brainstem, course through the cavernous sinus, and enter the posterior orbit through the superior orbital fissure (Cioffi 2011). Injury to these cranial nerve leads to strabismus and often double vision.

A childhood cancer survivor study found that survivors who received >5 Gy to the orbit reported an increased risk of double vision. An increased risk was also seen for after >30 Gy to the temporal lobe or posterior fossa. The median onset of the double vision was 2.2 years and incidence increased up to 20 years after diagnosis (Whelan et al. 2010). No specific cause was associated with the diplopia, but the

authors suspected that the diplopia could be due to visual field loss, cranial nerve palsies, and other non-cranial nerve palsy strabismic conditions.

Conventional radiation therapy of lesions in or near the cavernous sinus shows a similar pattern of injury to cranial nerves III, IV, V, and VI compared to radiosurgery. These cranial nerves are known to be fairly radio-resistant and rarely damaged in the course of standard fractionated radiotherapy and radiosurgery. Relatively few complications are encountered to these cranial nerves at single fraction delivering doses up to 40 Gy. A retrospective study by Tishler et al. reported eight patients (total of 62 adult patients) of cranial neuropathies after radiosurgery of lesions near the cavernous sinus, three patients experiencing resolution (Tishler et al. 1993).

32.6 Therapeutic Interventions

32.6.1 Lids and Lacrimal Gland System

Chronic tearing (epiphora) due to the stenosis of the nasolacrimal duct may be treated with nasolacrimal duct dilation, stent placement, or dacryocystorhinostomy for more refractory cases. Malpositioned eyelid margins leading to ectropion or entropion may require surgical intervention. Lacrimal gland injury may lead to DED (see Cornea section below).

32.6.2 Conjunctiva

Tear film composition may be compromised following injury occurs to the conjunctival goblet cells or the glands of Wolfring and Krause, and DED may result (see Cornea section below) (Gordon et al. 1995). Symblepharon, or adhesion of two conjunctival surfaces together (lid adhered to the glove), may occur following widespread conjunctival epithelial injury and lead to limited ocular motility and lid deformity (Servodidio and Abramson 1993). If the lid deformity is severe or if the ocular motility is limited and leading to diplopia, surgical correction of the symblephara may be indicated.

32.6.3 Cornea

DED, also termed keratitis sicca, is due to tear film insufficiency from injury to any of the glands that supply the components of the tear film. Lubricating eye drops (artificial tears) or ointments may be the only treatment required although tear replacement drops may need to be instilled frequently throughout the day (as often as every 15 min). More severe DED may require punctual occlusion, or a unique contact lens that maintains a reservoir of tears against the cornea. The PROSE (Prosthetic Replacement of the Ocular Surface Ecosystem) lens has been used to treat conditions such as radiation keratopathy, Stevens–Johnson syndrome, and

neurotrophic corneal injury caused by cranial nerve 5 injury (Rathi et al. 2012). Sterile corneal ulcerations may also occur and are treated with frequent lubricating tears and bandage contact lenses (Barabino et al. 2005; Servodidio and Abramson 1993). Infectious corneal ulcers require frequent instillation of topical fortified antibiotics (as often as every hour). If an ulcer does not heal and progresses, corneal perforation may develop, which may require emergency corneal grafting to maintain integrity of the eye (Barabino et al. 2005; Gordon et al. 1995).

32.6.4 Iris

Neovascular glaucoma is treated with topical intraocular pressure lowering drops and possibly oral carbonic anhydrase inhibitors (Takeda et al. 1999). Surgical management may be necessary for glaucoma refractory to medical treatments.

32.6.5 Lens

Not all cataracts are vision threatening, and small or peripheral lenticular opacities should be observed. If the cataract significantly obstructs the visual axis, cataract extraction should be considered. Unfortunately, the visual outcomes are not equivalent to cataract extraction in adults, and depends on the age at which the cataract became visually significant (Servodidio and Abramson 1993). If a baby or toddler develops a significant cataract, they are at risk for the development of dense amblyopia, which may persist after the cataract is extracted. Prompt occlusion (patching) therapy after surgery may be necessary to treat and prevent amblyopia in younger children, especially for unilateral cataracts (Medsinge and Nischal 2015). Other postoperative issues such as secondary glaucoma, inflammation, and posterior capsule opacification can also limit vision, and more frequently occur in children compared to adults. Children's eyes also continue to grow both in axial length and corneal curvature over time, so the decision of appropriate power intraocular lens (IOL) can be challenging. Predicting the expected refractive change in the eye is not always possible (Steinert et al. 2004; Danesh-Meyer 2008).

32.6.6 Retina

Proliferative retinopathy due to radiation retinopathy is treated with laser photocoagulation (Servodidio and Abramson 1993).

32.6.7 Optic Pathway and Non-optic Cranial Nerves

No treatment has been found to be successful in treating radiation optic neuropathy though reportedly hyperbaric oxygen may be helpful if initiated soon after the

vision loss is noticed (Salvin and Hendricks 2012; Danesh-Meyer 2008). Intravenous steroids should be considered. There is also known treatment for radiation-induced non-optic cranial neuropathies.

Strabsimus secondary to cranial nerve palsies should be observed for 9 months, awaiting possible spontaneous resolution. Prism glasses or patching may be indicated for the associated double vision. Young children may develop amblyopia from the strabismus. Strabismus surgery can be performed for strabismus secondary to unresolving cranial nerve palsies.

32.7 Prevention

Prevention of radiation effects to the eyes involves limiting the daily and total radiation dose to the eye by delineated and shielding the orbital, ocular, and visual pathway structures when possible. Careful evaluation of 3D radiation approaches with strategic beam placement to avoid unnecessary irradiation of uninvolved normal structures, including the globe, ocular adnexa, and the optic nerves. Computer-guided tomography-based dosimetry can also be calculated to angle the fields to help limit radiation doses (Barabino et al. 2005). Corneal shields may also be useful when using electron therapy near the eye (Gordon et al. 1995; Nelson and Olitsky 2005). Lastly, a good working relationship with an ophthalmologist who is comfortable examining children and is trained in the consequences of ophthalmic sequelae of radiation is vital in the management and treatment of these patients.

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Hearing

33

Paul W. Gidley

Contents

Abstract

Hearing is a fundamental sensory input required for language acquisition and social interaction. Radiotherapy fields that involve the cochlea are associated with hearing loss at dosages over 30 Gy. Cisplatin is known to cause hearing loss in a high percentage of patients, especially when dosages exceed 300 mg/m^2.

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Radiotherapy to the cochlea and cisplatin administration combine to produce hearing loss in most patients. Children with medulloblastoma are at high risk of developing hearing loss due to these factors. Proton beam radiotherapy offers the possibility of minimizing cochlear radiation dose and might help to prevent hearing loss. Predisposing factors, pathophysiology, clinical features, and consequences of hearing loss in the pediatric brain tumor population are discussed. Brief mention is made of therapeutic interventions, prevention, and radiotherapy dose tolerances for this select group of patients.

33.1 Introduction

Hearing is a fundamental sensation and necessary for verbal communication. Hearing is present at birth, and auditory pathways mature during the first years of life. With this maturity comes speech understanding and verbal abilities. Hearing loss affects learning, communication, socialization, school performance, and overall quality of life. Radiation fields that include the cochlea can cause hearing loss when the dose is greater than 30 Gy (Grewal et al. 2010). Hearing loss can be accentuated by cisplatin, which is often used in treatment for medulloblastoma and head and neck cancers.

As an introduction, this section will discuss hearing, audiometry, and the types and grades of hearing loss. Sound can be described based on its pitch or frequency, measured in hertz (Hz); and its intensity or loudness, and measured in decibels (dB). Human hearing ranges from 20 to 20,000 Hz. The human ear can appreciate loudness from −10 to 120 dB.

Hearing is measured by an audiologist using an audiometer and a sound proof booth. The results of testing are recorded on an audiogram. Pure tones at octave intervals beginning at 250 Hz to 20 kHz are used to determine the threshold of hearing. The speech frequencies are considered to be 500–2000 Hz. The audiologist adjusts the intensity of tone in 5 dB steps until the lowest level appreciated by the test subject to find the hearing threshold. Test-retest variability is 10 dB. Changes of 15 dB or more are considered significant.

Sound is presented to the ear with either insert ear phones or circumaural headphones and recorded as an air conduction level. This mode of testing uses the ear canal, eardrum, ossicles, and cochlea, and it gives an overall reading on the function of the ear.

Sound is then presented using a bone conducting vibrator placed either behind the ear or on the forehead. Since bone conducts sound very efficiently to both cochleae, a masking sound is presented to the non-test ear to eliminate it from testing. Bone conduction thresholds give important clues about cochlear function.

The difference between air conduction levels and bone conduction levels is called the air-bone gap and is a measure of conductive hearing loss.

The results for frequencies 500–4000 Hz are averaged to produce a pure tone average (PTA). The 4 kHz level is included to capture high frequency losses that

occur with ototoxicity. Words, actually spondees, can also be used to identify the lowest threshold of speech awareness. This result is recorded as a speech threshold (ST). The speech threshold and pure tone average should agree within 10 dB. Word understanding is tested by using phonetically balanced word lists delivered at 40 dB above threshold hearing which the test subject repeats. The number correctly repeated is recorded as a speech discrimination score (SDS) or word recognition score (WR). This type of testing can be used to accurately assess the hearing in children as young as 5 years old.

Younger children require specialized testing techniques. Toddlers, ages 30 months to 5 years, can be conditioned to perform an act such as dropping a block in a bucket in response to sound. Ear-specific testing can be performed in cooperative children. Neonates to toddlers are tested using evoked potentials. Auditory brainstem responses (ABR) can be used to estimate hearing thresholds for 1–4 kHz range using broadband click noises or lower pitches with a sound pip. This testing takes times and it usually requires mild sedation for young children.

Otoacoustic emission (OAE) is another form of evoked potential testing. Distort product otoacoustic emissions (DPOAE) are widely used to estimate hearing thresholds, from 500 to 6 kHz. This test measures the acoustic response to a tone delivered to the ear. These acoustic responses are generated by outer hair cells. Since ototoxicity affects outer hair cells, this test has gained favor as a means to monitor for hearing during drug exposure. When present, OAE can accurately predict hearing of 30 dB or better. However, middle ear disease, such as otitis media or tympanic membrane perforation, may prevent OAE from being recorded.

Hearing loss has two major forms. Sensorineural hearing loss indicates damage to the cochlea or the auditory nerve. There are several causes of sensorineural hearing loss (SNHL), including genetic defects, infections, tumors, and toxic factors such as medications or radiotherapy. Conductive hearing loss indicates damage to the sound conducting mechanism of the ear, including the ear canal, eardrum, middle ear, and ossicular chain. There are several causes of conductive hearing loss including canal atresia, cerumen impaction, tympanic membrane perforation, middle ear infection, and ossicular abnormalities. Mixed hearing loss is a combination of these two forms of hearing loss.

The severity of hearing loss is grouped into ranges. Normal hearing is −10 to 20 dB. Mild hearing loss is 21–40 dB. Moderate hearing loss is 41–55 dB. Moderately severe hearing loss is 56–70 dB, and severe hearing loss is 71–90, and profound hearing loss is greater than 90 dB.

Hearing loss can also be described by its time of onset. Prelingual hearing loss refers to hearing loss before speech acquisition, and usually connotes children under 5 years of age. Postlingual hearing loss occurs in any person who has already mastered speech.

Radiotherapy is a recognized cause of sensorineural hearing loss. This chapter will describe the effects of radiotherapy on hearing. This discussion will be primary concerned with fractionated radiotherapy. While this textbook is dedicated to pediatric brain tumors, adult population studies will be incorporated and results will be extrapolated from them to illustrate certain clinical points. The topic of hearing loss

related to stereotactic radiotherapy, as in the case of acoustic neuromas, is beyond the scope of this chapter.

33.2 Predisposing Factors

The cochleae are relatively centrally located within the head. This anatomic location makes the cochlea vulnerable to any radiotherapy given for head and neck cancer or brain tumors.

Patients with preexisting sensorineural hearing loss tend to have more rapid and pronounced hearing loss following radiotherapy. These patients might have less "cochlear reserve" to withstand additional injury. Patients with worse pretreatment hearing tend to develop more sensorineural hearing loss following treatment (Honore et al. 2002). Equally, older patients tend to develop more hearing loss than younger patients (Honore et al. 2002; Kwong et al. 1996). This fact has led to the concept of "ear-age" (Fligor et al. 2012).

33.2.1 Cisplatin

The addition of chemotherapy, especially cisplatin, is a major predisposing factor for sensorineural hearing loss and perhaps accounts for 60% of pediatric ototoxic hearing loss (Schell et al. 1989; Brock et al. 2012). Cisplatin (CDDP) generally produces bilateral, irreversible, progressive high frequency (2 kHz and above) SNHL.

Cisplatin causes irreversible, progressive, high frequency hearing loss in about 26–68% of patients (Schell et al. 1989; Op de Beeck et al. 2011). When cumulative doses exceed 400 mg/m^2, up to 90% of young children may suffer moderate to severe hearing loss, requiring rehabilitation with hearing aids (Bertolini et al. 2004; Grewal et al. 2010).

The hearing loss from CDDP is dose related and is inversely proportional to age (Walker et al. 1989). Children are more susceptible to ototoxicity from platinum containing agents than are adults (Grewal et al. 2010). Children under 5 years of age are more sensitive to the effects of cisplatin than children over 15, even controlling for cumulative dose (Li et al. 2004).

Clinically detectable hearing loss might require more than one round of cisplatin. Knight et al. measured the mean time to observable hearing loss by ASHA criteria was 135 days (Knight et al. 2005). Progressive hearing loss might continue for up to 11 years following the last dose of platinum compounds (Bertolini et al. 2004).

Cisplatin ototoxicty is related to the production of reactive oxygen species which triggers apoptosis in cochlear hair cells. Histologic examination of temporal bones treated with cisplatin show loss of inner and outer hair cells, atrophy of the stria vascularis, and degeneration of the spiral ganglion and cochlear nerve (Hoistad et al. 1998).

The combination of young age, high dose of platinum containing agents, central nervous system tumors, and concomitant CNS radiation make children with CNS tumor particularly vulnerable to hearing loss (Grewal et al. 2010).

Children with medulloblastoma are particularly at risk. These tumors account for about 20% of pediatric brain tumors. Treatment includes maximal safe resection, craniospinal irradiation (CSI) followed by a boost to the posterior fossa, and cisplatin-based chemotherapy (Paulino et al. 2010). Five-year survival rates approach 80% in standard risk and 70% in high risk medulloblastomas. Children with high risk tumors typically receive a higher mean cochlear radiation dose than standard risk patients (Paulino et al. 2010).

Progressive hearing loss during treatment often requires cisplatin dose reduction. Cisplatin dose is reduced by 50% for a hearing loss of 40 dB or greater at 4–8 kHz (POG Grade 3 ototoxicity).

This high survival rate does come at the cost of hearing loss for many of these children. Rates of hearing loss in medulloblastoma patients vary from 13 to 25% (Paulino et al. 2010; Polkinghorn et al. 2011; Fouladi et al. 2008). A large study by Paulino et al., examined hearing results in 44 children with medulloblastoma with a mean follow-up of 41 months (range 11–91 months) (Paulino et al. 2010). They found that only 25% of children developed no hearing loss in either ear. Severe forms of hearing loss, rated as Pediatric Oncology Group (POG) grades 3 and 4 and requiring amplification, occurred in 25% of children. The mean time to development of severe hearing loss was 8.5 months (range 3–77 months). They found 6 out of 11 patients with POG grade 3 or 4 ototoxicity developed a significant unilateral hearing loss. Given that cisplatin causes bilateral hearing loss, the differences in hearing loss between the two ears can be attributed to cochlear radiation dose.

Several different radiotherapy treatment modalities have been described with the intent of minimizing radiation dose to the inner ear (Paulino et al. 2010; Moeller et al. 2011; Jimenez et al. 2013; Lannering et al. 2012; Polkinghorn et al. 2011; Merchant et al. 2008). Proton beam seems to deliver consistently lower cochlear doses while effectively treating the tumor (Moeller et al. 2011; Merchant et al. 2008). While proton beam therapy may carry a higher overall cost than IMRT or other forms of radiotherapy, proton beam therapy may be cost-effective given the reduction in cochlear dose and improved health quality of life results (Hirano et al. 2014; Mailhot Vega et al. 2013). A study by Moeller et al. demonstrated a 5% rate of high grade ototoxicity in a group of 19 patients with a mean follow-up of 12 months (Moeller et al. 2011).

Middle ear effusion or serous otitis media (SOM) is a contributing factor for persistent post-radiation SNHL. Nearly 50% of patients with post-radiation SOM developed persistent SNHL (Kwong et al. 1996).

Timing of cisplatin administration may have an effect on degree of hearing loss. Hearing loss is worse when cisplatin is administered with or directly after radiotherapy (Walker et al. 1989).

Supratentorial tumors and VP shunts are also associated with higher risk for hearing loss with radiotherapy. In children with supratentorial tumors and

ventriculoperitoneal (VP) shunts, hearing loss in the 1–2 kHz may occur with doses less than 30 Gy (Merchant et al. 2004).

33.3 Pathophysiology

This chapter will concern itself with the effects of radiotherapy on the ear, and include information on cochlear-specific radiation effects. Radiotherapy causes several changes to the outer ear, ear canal, middle ear, and cochlea.

33.3.1 Outer Ear

Outer ear and ear canal changes include redness and skin irritation as acute findings. Occasionally, the accumulation of desquamated debris in the canal requires mechanical cleaning. Long-term changes in the ear canal include the loss of the self-cleaning mechanism of the ear, with keratin debris and crusting blocking the ear canal and producing conductive hearing loss.

33.3.2 Middle Ear

The effect of radiation to the middle ear produces a hyperemic and edematous mucosa. Microscopic analysis shows changes in the goblet cells and a transformation of the normal pseudostratified ciliated epithelium to a cuboidal or flattened epithelium. This so-called post-radiation serous otitis media is common after radiotherapy to the nasopharynx and parotid gland, and its incidence has been reported to be as high as 26% (Wang et al. 2009).

33.3.3 Inner Ear

Radiation-induced sensorineural hearing loss is a dose-dependent, progressive, permanent, and late effect. The rate of SNHL may be as high as 24–36% after radiation doses of 60 Gy (Kwong et al. 1996; Merchant et al. 2009; Mujica-Mota et al. 2014).

The cochlea is more sensitive to radiotherapy than the brain or the auditory nerve (Bohne et al. 1985; Low et al. 2009). The basal turn of the cochlea is particularly at risk. Histopathologic examination of the irradiated cochlea reveals damage to the organ of Corti and atrophy of the basilar membrane, spiral ligament, and stria vascularis (Leach 1965; Schuknecht and Karmody 1966; Asenov et al. 2007; Hoistad et al. 1998). These changes are greater than seen in age-matched controls. Outer hair cell loss, mainly in the basal turn and sometimes in the middle turn, has

been described. This finding would correspond to the high frequency loss seen in these patients, particularly the 4 kHz frequency (Asenov et al. 2007).

The mechanism of cell death appears to be related to reactive oxygen species (ROS) and necrosis. Dose-dependent production of reactive oxygen species (ROS) has been demonstrated at 1 h post-irradiation in a cochlear inner ear cell line (Low et al. 2006). ROS might explain the high frequency loss seen in post-irradiation patients since outer hair cells in the basal turn have less antioxidant capacity than do cells in the apical turn (Rybak and Whitworth 2005).

Cochlear hair cells do not divide; cell damage causes permanent loss of these cells. On the basis of in vitro experiments, epithelial cells die as a result of apoptosis (Low et al. 2006). Cochlear hair cells are more susceptible to the damaging effects of radiation than are spiral ganglion cells of the eighth cranial nerve (Winther 1969). However, the direct damage of radiation on cochlear hair cells would produce a sudden hearing loss, and this does not explain the delayed and long latency period seen with radiation-induced sensorineural hearing loss (Mujica-Mota et al. 2014).

The activation of p53 is a recognized pathway for apoptotic cell death and is a dose-dependent process (Chao et al. 2000). The p53 activation starts 72-h post-irradiation and is dose dependent.

Non-apoptotic pathways might include p53-independent mechanisms or caspase-independent programmed cell death mechanisms (Low et al. 2009). The sphingomyelin-ceramide pathway is a dose-dependent, p53-independent apoptotic pathway which is prominent in epithelial cells 24 h following radiation-induced DNA damage (Kolesnick 2002; Kim and Shin 1994). This pathway is not found in cochlear hairs cells, but it is in vascular endothelial cells, which are found in the stria vascularis (Paris et al. 2001). It is possible that vascular effects in the stria vascularis combined with induced inflammatory changes for radiotherapy account for the relatively long latency period seen with radiation-induced sensorineural hearing loss.

The semicircular canals can have vesiculations and perilymphatic hemorrhages, but the sensory epithelium in the cristae and the vestibular nerve fibers may be unaffected (Asenov et al. 2007).

Williams et al. reported on 100 children with brain tumors (Williams et al. 2005). They identified a 27% cumulative incidence of 20 dB or greater hearing loss in the speech range by the fifth year after radiotherapy. The cumulative incidence increases up to 50% within 9 years. None of these patients received chemotherapy. The mean radiation dose was 54 Gy (range 36–70 Gy) and the time to onset ranged from 14 to 102 months (mean 49 months) (Williams et al. 2005).

A similar longitudinal study by Hua et al. reports a 14% incidence of hearing loss occurring within 3–5 years (Hua et al. 2008). Hearing loss was found to be dose related, being low for 30 Gy or less and increased for doses greater than 40–45 Gy. Hearing loss was greatest at 6–8 kHz.

Moeller et al. found that the use of proton beam radiation for childhood medulloblastoma resulted in a low risk of hearing loss at 1 year (Moeller et al. 2011).

33.4 Clinical Presentation

Hearing loss manifests in children with speech delay, poor academic performance, and poor socialization. Patients with hearing loss have difficulty in understanding speech, especially in a noisy background. Difficulty understanding speech over the telephone (since no visual cues are available) and elevated television volume are other symptoms of hearing loss.

Hearing is important from birth. It has long been known that children born with hearing loss have great difficulty in catching up to age-matched peers. Early identification of hearing loss has been the thrust of neonatal hearing screening programs. This same concept applies to children who will receive potentially ototoxic cancer treatment. Pretreatment audiograms are essential to establish a baseline and to identify any preexisting hearing loss which might place the child at a higher risk of developing further hearing loss.

The hearing loss from radiotherapy affects hearing above 4 kHz than in the speech range (Mujica-Mota et al. 2013). Hearing loss in levels greater than 4 kHz may not be readily apparent to the child or parent. High frequency hearing (2–4 kHz) is important in word recognition. Consonant are high frequency sounds. As high frequency hearing is lost, word understanding begins to suffer (Kwong et al. 1996). This fact is especially important in children who are learning to speak and read and write.

Serial audiograms over time show a progressive hearing loss, affecting all frequencies (Mujica-Mota et al. 2013).

Hearing loss seems to occur in two time frames (Talmi et al. 1989). Early-onset sensorineural hearing loss begins either during or immediately following radiotherapy. Late-onset SNHL occurs several months to years following radiotherapy. Kwong et al. identified hearing loss within an average of 4 months of finishing radiotherapy, range 0–48 months (Kwong et al. 1996). Ninety percent of SNHL in their study was documented within 2 years. Transient SNHL is also reported; however, SNHL that persists longer than 1 year is unlikely to improve with time (Kwong et al. 1996).

Hearing loss following radiotherapy is progressive and primarily high frequency. Due to the slowly progressive nature of this hearing loss, long-term follow-up is necessary to understand fully its magnitude. A 12-month follow-up is probably too short for an accurate evaluation of SNHL incidence (Leighton et al. 1997).

Hua et al. studied 78 children with brain tumors treated with radiotherapy alone and identified a hearing loss rate of 14% (Hua et al. 2008). They found no hearing loss in children with a cochlear mean dose of 30 Gy or less. If the cochlear mean dose was greater than 50 Gy, then hearing thresholds increased to 40–60 dB, equal to a moderate or moderately severe sensorineural hearing loss. They found that hearing losses were greatest for the highest frequency range (6–8 kHz). If the cochlear mean dose reached 59.4 Gy, the probability of high frequency hearing loss was 37% at 5 years. They identified that hearing changed slowly from normal

to moderately severe over 18 months; but permanent hearing loss occurred at mean time of 3.4 years (range 3–5 years) (Hua et al. 2008).

A large study of 100 children with brain tumors treated with radiotherapy only showed that 27.4% of children developed hearing loss at any frequency in the 0.5–2 kHz range (Williams et al. 2005).

Several grading scales have been developed to describe and document ototoxicity (Table 33.1) (Brock et al. 1991; Chang and Chinosornvatana 2010; Brock et al. 2012; National Cancer Institute: Common Terminology Criteria for Adverse Events, Version 4.03; Schmidt et al. 2007). These scales are important in comparing results of clinical trials and for monitoring adverse events. The grading systems do have drawbacks. The scales are designed based on audiometric results. However, some children are too young or too ill for routine audiometry. Some children are tested with either auditory brainstem response (ABR) or otoacoustic emissions, and these test results are not easily translated into the grading scales. Furthermore, the effect of otitis media, which is common in childhood and is especially common following radiotherapy, must be accounted for when reviewing hearing data.

There are three grading scales that are not appropriate for reporting hearing loss. Radiation Therapy Oncology Group criteria considers subjective hypoacusis as an adverse effect, and it does not require the distinction between conductive and SNHL (Cox et al. 1995). The European Organization for Treatment of Cancer does not include the category "ear" in late adverse effects (Cox et al. 1995). Late Effects Normal Tissue Task Force Subjective, Objective, Management, and Analytical scale includes objective and analytical evaluation tools, but the use of an audiogram is up to the discretion of the treating physician (Mujica-Mota et al. 2013; Pavy et al. 1995).

33.5 Consequences

Hearing loss has an impact on speech understanding, academic performance, socialization, and quality of life. Mild bilateral hearing loss of 15–25 dB can have an impact on academic performance, and roughly 40% of children with this degree of hearing loss may have to repeat a grade (Bess et al. 1998). Overall, cross-sectional analysis of survivors childhood brain tumors have a greater need for special education, lower college attendance rates, fewer close friends, and higher unemployment rates than age-matched controls (Gurney et al. 2009). The exact role that hearing loss plays in these children is unclear from this type of survey.

Children with clinically significant hearing loss should be evaluated by an audiologist and assessed for assistive listening devices or hearing aids (Lafay-Cousin et al. 2013). Appropriate amplification is important for speech development and language acquisition. In the regular school setting, use of preferential seating or an FM system may help children with hearing loss. Children with learning deficits might require special schooling with more direct or one-on-one teaching.

Table 33.1 Compilation of grading scales for pediatric ototoxicity

Grade	Brock, 1991 (Brock et al. 1991)	Muenster classification, 2007 (Schmidt et al. 2007)	Chang and Chinosornvatana, 2010 (Chang and Chinosornvatana 2010)	National Cancer Institute CTCAE v. 4.0, 2010 (National Cancer Institute: Common Terminology Criteria for Adverse Events, Version 4.03)	International Society for Pediatric Oncology Boston, Brock et al., 2012 (Brock et al. 2012)
0	<40 dB at all frequencies	<10 dB at all frequencies	<20 dB at 1000; 2000; 4000 Hz		≤20 dB HL at all frequencies
1	>40 dB loss at 8000 Hz	>10 dB to <20 dB loss at all frequencies	**1a** >40 dB at any freq 6000–12,000 Hz	Shift or loss of 15–25 dB, two freq, one ear	>20 dB HL (i.e., 25 dB HL or greater); SNHL above 4000 Hz (i.e., 6 or 8 kHz)
			1b >20 and <40 dB at 4000 Hz		
2	>40 dB loss at 4000 Hz and above	**2a** >20 to <40 dB loss at >4000 Hz	**2a** ≥40 dB at 4000 Hz and above	Shift or loss of 25–90 dB two freq, one ear	>20 dB HL SNHL at 4000 Hz and above
		2b >40 to <60 dB loss at >4000 Hz	**2b** >20 and <40 dB at any freq below 4000 Hz		
		2c >60 dB loss at >4000 Hz			
3	>40 dB loss at 2000 Hz and above	**3a**- >20 to <40 dB loss at <4000 Hz	≥40 dB at 2000 or 3000 Hz and above	>20 dB bilateral or >30 dB unilateral loss in speech frequencies or use of hearing device	>20 dB HL SNHL at 2000 Hz or 3000 Hz and above
		3b- >40 to <60 dB loss at <4000 Hz			
		3c- >60 dB loss at <4000 Hz			
4	>40 dB loss at 1000 Hz and above	>80 dB loss at <4000 Hz	≥40 dB at 1000 Hz and above	Audiologic indication for cochlear implant	>40 dB HL (i.e., 45 dB HL or more); SNHL at 2000 Hz

dB decibels, *Freq* frequency, *Hz* Hertz, *CTCAE* common terminology criteria for adverse events

33.6 Therapeutic Interventions

33.6.1 Amifostine

Amifostine is an organic thiophosphate compound with cytoprotective properties used to prevent hematologic, renal, neural, and mucosal complications of chemotherapy without attenuating antitumor effects (Kemp et al. 1996; Glover et al. 1986, 1987). It is administered before and during cisplatin infusion as a twice daily dose of 600 mg/m^2. It has a very short half-life of just 8 min, and infusions must be timed immediately before cisplatin administration. Amifostine can cause hypocalcemia, and close calcium monitoring is required. Amifostine has been studied in children with average risk medulloblastoma and found to be effective at reducing the risk of severe (grade 3 or 4) ototoxicity (Fouladi et al. 2008). The active metabolite of amifostine, WR-1065, acts as a scavenger of ROS and binds to platinum agents to prevent and reverse DNA platination (Treskes et al. 1992).

Long-term hearing loss following radiation and cisplatin has been reported (Knight et al. 2005; Merchant et al. 2004; Bertolini et al. 2004). Amifostine seems to protect against cisplatin ototoxicity over time, perhaps for as long as 3 years (Fouladi et al. 2008).

Other agents that have been studied to prevent cisplatin-related ototoxicity include sodium thiosulfate (Muldoon et al. 2000; Dickey et al. 2005; Madasu et al. 1997), sodium salicylate (Hyppolito et al. 2006), and *n*-acetylcysteine (Dickey et al. 2005; Low et al. 2008).

33.6.2 Steroids

Drugs can be administered as intratympanic therapy to avoid any potential systemic effect. Intratympanic administration has been used successfully for many years to deliver relatively high doses of steroids to the inner ear, by way of absorption or diffusion through the round window membrane. Steroids have been studied experimentally to identify a role for preventing radiation or chemotherapy ototoxicity. Early results show some promise, but this mode of therapy has not been adopted for widespread use.

33.6.3 Hearing Aids

The role of hearing aids has been described under *Consequences*.

33.6.4 Cochlear Implants

Cochlear implants in children have a long history of success for many different causes of hearing loss. There are published reports of children receiving cochlear

implants after treatment for rhabdomyosarcoma (Torkos et al. 2002), medulloblastoma (Roland et al. 2010), and nasopharyngeal carcinoma (Chua and Tan 2007). Success rates for hearing rehabilitation seem to be equal between irradiated and nonirradiated ears (Soh et al. 2012). Even ears affected with osteoradionecrosis have been successfully implanted with good speech recognition (Adunka and Buchman 2007).

33.7 Prevention

Limiting the radiation dosage to the cochlea is the best form of prevention of hearing loss. Improved target localization using fiducials or daily imaging might reduce set uncertainty and decrease the change that the cochlea is included in the target volume (Hua et al. 2008). Highly conformal planning and delivery techniques, such as IMRT or proton beam therapy, can also help to minimize cochlear dose.

Close monitoring of dose and hearing levels is important when cisplatin is being prescribed. Dose modification or drug elimination is required when significant hearing impairment is reached. While cisplatin has a proven track record of efficacy for many tumors, the search for targeted agents is prompted by the hope of avoiding side effects, such as ototoxicity or nephrotoxicity. Until new, effective chemotherapeutics agents are developed, children with brain tumors will still suffer hearing loss when cisplatin is delivered along with radiotherapy.

33.8 RT Dose Tolerance Guidelines

Information on the tolerance dose to the cochlea in children are largely lacking. Most information comes from adult studies that are extrapolated to children. The tolerance dose to the cochlea with a probability of 5% complication within 5 years has been reported to be 60 Gy (Emami et al. 1991). The tolerance dose to the cochlea with a probability of 50% complication rate within 5 years is 70 Gy (Emami et al. 1991). These figures might need to be reevaluated in the light of more recent studies, especially taking into account the effect of concomitant chemotherapy.

Pan et al. observed significant hearing loss ($\geq$10 dB change) at 2 kHz and higher frequencies in adult patients when the dose was 45 Gy or greater (Pan et al. 2005). Chen et al. reported that dosages higher than 48 Gy are associated with hearing loss at 4 kHz in the majority of adult patients when radiotherapy is given with chemotherapy (Chen et al. 2006).

The threshold dose in children for auditory toxicity after radiation is reported to be within the range of 35–45 Gy (Merchant et al. 2004; Hua et al. 2008). Dosages less than 30 Gy have little effect on hearing (Merchant et al. 2004; Linskey and Johnstone 2003; Hua et al. 2008). Consistent with this fact is the finding from Thibadoux et al. who studied 61 children with acute lymphoblastic leukemia who received 24 Gy of craniospinal radiation but no chemotherapy. None of these children developed hearing loss at 3 years (Thibadoux et al. 1980). The dose threshold

might be lower in children with supratentorial tumors and ventriculoperitoneal (VP) shunts, perhaps as low as 30 Gy (Merchant et al. 2004).

The TD50/5 for acute reactions of the middle ear has been estimated to be 40 Gy and for chronic otitis media to be 65–70 Gy (Emami et al. 1991). Wang et al. reported that the rate of middle ear effusions could be diminished if the dose to the middle was kept under 34 Gy and the dose to the isthmus of the Eustachian kept under 53 Gy (Wang et al. 2009). In an earlier study, Wang et al. demonstrated that the rate of otitis media with effusion was related to radiation dose given to the isthmus of the Eustachian tube (Wang et al. 2007). When dose to the isthmus was kept below 52 Gy and the dose to the middle ear was kept below 46 Gy, the rate of otitis media with effusion was decreased in their study population of nasopharyngeal patients (Wang et al. 2007).

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Vascular Late Effects of Cranial Radiation

34

Christine Hill-Kayser and Louis Constine

Contents

Abstract

Many pediatric cancer survivors have received cranial radiation as part of multimodality treatment, most commonly those with leukemia and primary tumors of the central nervous system. The effects of radiotherapy on the developing vascular system may be significant, in summary causing the vessels to appear prematurely aged and fragile. As a result of these changes, survivors are at risk for vascular pathologies that include ischemic stroke, vascular malformations such

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as Moyamoya, aneurysm, and cavernoma, hemorrhage, necrosis, complicated migraines, and other, rarer, syndromes. Certain factors including age, genetic predisposition, and radiation dose and volume may contribute to risk of such pathologies. There is an increasing role for prevention through modifiable risk factors including metabolic factors. Treatment of vascular pathologies arising after radiotherapy remains similar to that recommended for de novo vascular disease.

34.1 Introduction

Cranial radiotherapy has the potential to cause permanent damage to brain and neck vasculature, putting survivors of pediatric cancers requiring this treatment at risk for numerous related late effects. These may include, but are not limited to, cerebrovascular events (both ischemic stroke and hemorrhage), veno-occlusive syndromes, vascular malformations, and tissue necrosis. Recent investigations suggest that the vascular systems of survivors of childhood cancer may appear prematurely aged, with survivor arteries demonstrating smaller arterial lumens, increased carotid intima-media thickness, plaque formation, and stiffness compared to control groups (Vatanen et al. 2015; Krystal et al. 2015). These characteristics likely drive the development of vasculopathies.

The effects of this frailty of the vascular system may be far reaching and cause significant disability. Neurocognitive late effects are discussed elsewhere in the text; however, the intimate association of vascular health and neurocognitive function should not be overlooked. This relationship may be obvious, as in the case of infarcts or bleeds that limit cognition, or more subtle: vascular effects in the hippocampal region have recently been associated with neurocognitive decline in patients having received cranial radiotherapy (Farjam et al. 2015), and strategies to restore hippocampal capillary density may provide cognitive recovery (Warrington et al. 2013). In a similar fashion, vascular pathology may have major effects on other systems, including visual and auditory. This chapter will discuss the pathophysiology and clinical presentations of the major vasculopathies associated with cranial radiation in pediatric patients, as well as modifications that may be made to limit them.

34.2 Types of Vascular Pathologies Observed in Survivors After Cranial Radiation

34.2.1 Ischemic Stroke

Most data regarding stroke incidence in survivors of childhood cancer have been published using the Childhood Cancer Survivorship Study database (CCSS). The group of patients surveyed as part of the CCSS was diagnosed with cancer as children between 1970 and 1986, and have been followed with surveys since; siblings

are used as a control group responding to the same survey questions. The relative risk of stroke within the entire CCSS cohort is 9.8 times higher than that of the sibling control group (Oeffinger et al. 2006).

Not surprisingly, groups of patients who received radiotherapy to the head or neck (those with acute lymphoblastic leukemia (ALL), Hodgkin lymphoma, and primary brain tumors) had the highest stroke risk of all groups within the CCSS (Bowers et al. 2005, 2006). Risk of stroke in survivors of Hodgkin lymphoma is increased by 5.6-fold compared to siblings, likely due to risk associated with radiation to the mediastinum and/or neck, and resultant atherosclerosis and early aging of vessels. This treatment is associated with carotid arterial disease. Within the group of CCSS patients studied who have survived acute lymphoblastic leukemia, the relative risk of cerebrovascular event is elevated over siblings by sixfold in patients who had cranial radiotherapy, compared to fourfold in those who received only chemotherapy (Bowers et al. 2006). This implies that both modalities (in addition, potentially, to disease) contribute to stroke risk, but that radiotherapy portends risk above chemotherapy alone.

These risks are multiplied further in patients who have survived central nervous system (CNS) malignancies, particularly those treated with radiotherapy and receiving >50 Gy brain radiotherapy. The standard doses for many primary pediatric brain tumors (including gliomas, medulloblastoma, and ependymoma) exceed 50 Gy. The CCSS data suggest that this population may be at a risk for stroke that approaches a 40-fold increase compared to siblings. This risk may be particularly high for patients who received radiotherapy to the Circle of Willis (Campen et al. 2010), as is the case for many survivors of common pediatric tumors of the CNS.

For all patients who have received cranial radiation, risk of stroke appears to persist even after recovery, as expected, with a cumulative incidence of recurrent stroke 38% at 5 years, and 59% at 10 years after first stroke in CCSS survivors of leukemia and/or CNS tumors who received cranial radiotherapy (Mueller et al. 2013a, b).

34.2.2 Vascular Malformations

34.2.2.1 Veno-Occlusive Disease and Moyamoya

Moyamoya syndrome translates to “puff of smoke” in Japanese and refers to a typical radiographic appearance that includes progressive narrowing of large vessels and subsequent development of collateral vessels. Most commonly, Moyamoya is characterized by occlusion of larger cerebral arteries and formation of small vessels that form a net via anastomoses (Rogers 2003). Moyamoya is by no means a syndrome specific to patients who have received cranial irradiation and can occur idiopathically or in the setting of neurofibromatosis 1 (Rosser et al. 2005); however, a recent literature review by Wang and colleagues demonstrated 46 reported cases of Moyamoya in childhood cancer survivors who received cranial radiation over a 40-year period (1967–2007). The most common tumor types were gliomas, followed by medulloblastomas, mimicking the frequency of CNS tumor types

requiring radiation in children. Most (75%) received radiation at age <9 years, and interval to development of Moyamoya was 3 years (Wang et al. 2014). Other groups have found that Moyamoya-like vasculopathy may be associated with radiation to tumors in the suprasellar region, proximal to the Circle of Willis (Morris et al. 2009). These authors identify patients having received at least 45 Gy for craniopharyngioma, optic gliomas, and germ cell tumors to be at particular risk, with a similar time to development of 3 years. They suggest that radiotherapy contributes to narrowing of the internal carotid arteries, and subsequent development of collateral blood vessel formation; however, it is important to note that incidence of Moyamoya may be increased in patients with suprasellar tumors even in the absence of radiotherapy, likely from compression of arterial blood flow (Desai et al. 2006; Aoiki et al. 2002).

Not surprisingly, children with NF1 who receive cranial radiation (most commonly for optic glioma) may be at particularly high risk of development of Moyamoya, with documentation of development at lower radiation dose (18–39 Gy) (Kestle et al. 1993; Kikuchi et al. 2007).

34.2.2.2 Aneurysm

Vessel aneurysms have been reported after cranial radiation, with histopathologic changes in vessel walls that include inflammatory cells and degenerated smooth muscle (Lucas and Mack 2014; Nanney et al. 2014). A recent review of the literature demonstrated a total of 46 patients with 69 intracranial aneurysms in irradiation fields reported between 1978 and 2013 (Nanney et al. 2014). Among reported aneurysms, 55% presented with some form of hemorrhage. These were identified in adult cancer survivors, with increased risk of rupture correlating with increasing age; the risk of aneurysm formation in childhood cancer survivors is not well described. Having said this, post-radiation aneurysm tissue appears to resemble that of other post-radiation vascular malformations, and it is reasonable to assume that children having received cranial radiotherapy may be at increased risk of aneurysm formation compared to peers due to endothelial cell damage, even if these risks remain relatively low.

34.2.2.3 Cavernous Malformations and Telangiectasias

Cavernous malformations and telangiectasias likely represent forms of vascular injury along a spectrum, ranging from dilated vessels with stagnant blood (cavernous malformation), to exposed capillaries within normal parenchymal tissue (telangiectasia) (Partap 2012). The risk of cavernoma in children exposed to cranial radiation is 1–4%, and is likely highest for children with a preexisting vascular malformation that was present prior to radiotherapy. The largest pediatric series describes 10 of 297 pediatric survivors with cavernoma at a median of 37 months after radiotherapy (Burn et al. 2007). Telangiectasias are reported in 20% of leukemia and brain tumor survivors (Koike et al. 2004). For the most part, these lesions are observed on routine surveillance imaging.

34.2.3 Hemorrhage

In the specific population of pediatric cancer survivors, cerebral hemorrhage has been described as an extension of other radiation-induced vascular complications, including ischemic stroke, vascular malformation, and Moyamoya. Wang and colleagues suggest that, because pediatric cancer survivors are less likely than adults to suffer from hypertension and amyloid angiopathy (the most common causes of cerebral hemorrhage in the general adult population), cerebral hemorrhage in this unique population is likely to arise from other vasculopathies, specifically vascular malformations (Wang et al. 2014). These authors suggest that radiation-induced cerebrovasculopathy is a predisposing factor for cerebral hemorrhage in this particular population. To this end, vascular malformations that result from fragile, sclerotic vessels may be at increased likelihood of rupture for the reasons of the existence of these qualities within the walls of abnormal vasculature themselves.

A review of the literature by the same authors identified 31 cases of cerebral hemorrhage in pediatric cancer survivors after cranial radiation over a 40-year period, with a median time to development of 7.5 years. Their review did not identify dose and/or temporal relationships between vascular malformation and subsequent development of hemorrhage.

34.2.4 Necrosis

Radiation necrosis is a feared late complication of cranial radiotherapy that is thought to arise as a result of microvascular damage (Coderre et al. 2006). Characterization of necrosis may be complicated by varied terminology, difficulty with identification on various imaging modalities, and lack of histopathology. The symptoms that it causes are related to location and severity, and clinical manifestations may range from absent to severe disability and even death. Although first described over 30 years ago, radiation-induced brain necrosis has received recent attention in the literature. In a recent series of cases by Indelicato and colleagues, patients with symptomatic necrosis specific to the brainstem were described as having both focal T2 prolongation and contrast enhancement within areas of concern; these findings were not consistent with vascular distribution (Indelicato et al. 2014). A separate review by Plimpton and colleagues demonstrated five cases of radiation necrosis in 101 children who received radiation for solid brain tumors, with median time to onset of 1.2 months (Plimpton et al. 2015). Three children were symptomatic and successfully managed with steroids and bevacizumab. Indelicato's group specifically examined brainstem necrosis and found a 2-year cumulative incidence of any brainstem toxicity of 3.8% in 313 patients who received >50.4 Gy(RBE) proton therapy to the brainstem (Indelicato et al. 2014).

These two recent studies demonstrate similar rates of brain necrosis regardless of modality employed. Concern for increased risk of brainstem and other brain necrosis associated with proton beam irradiation has been raised and this topic remains

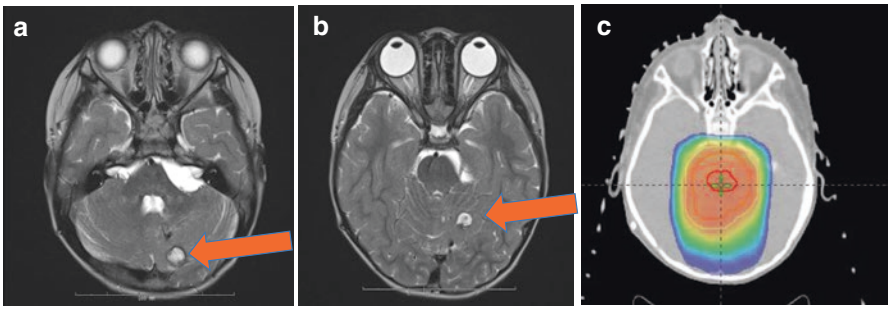

Fig. 34.1 Multiple cavernous malformations observed on routine surveillance imaging in a young child approximately 18 months after completion of radiotherapy for anaplastic ependymoma of posterior fossa. Cavernomas are indicated by *orange arrows* in panels **a** and **b**. Dose distribution is shown in panel **c**

under investigation; however, currently no comparative data exist to suggest that proton irradiation portends increased risk when Quantitative Analyses of Normal Tissue Effects in the Clinic (QUANTEC) and Childrens' Oncology Group (COG) dosimetric guidelines are respected and safe planning is undertaken by a team with experience and understanding of unique aspects of this technology. Indelicato and other groups suggest that particular care should be undertaken when radiotherapy is delivered to very young children (<3 years), those receiving multiagent chemotherapy, and those with atypical teratoid rhabdoid tumors (Indelicato et al. 2014, Kralik et al. 2015), as risk of symptomatic necrosis may be highest in patients with these characteristics. If these associations prove to be true, observations regarding proton therapy may be confounded by the fact that very young children are unlikely to receive radiotherapy with any modality other than protons due to severe neurocognitive deficits that may be observed when X-ray-based therapy is delivered to very young children. Indeed, Freund and colleagues have published models implying reduction in risk of necrosis with use of proton therapy compared to X-ray-based arc therapy, and this stands in contrast to other groups who raise concern of increased risk associated with higher radiobiologic equivalent dose with proton therapy, particularly at the distal beam edge (Freund et al. 2015). Active studies regarding this controversial topic remain underway (Fig. 34.1).

34.2.5 Other Vascular Effects of Cranial Radiotherapy

Mineralizing microangiopathy is a process that affects small vessels and can lead to calcification of the basal ganglia. Radiation dose of 15 Gy has been associated with increased risk of development on autopsy studies (Okuno et al. 1985), and its incidence has been demonstrated to be 17% in childhood leukemia survivors having received cranial radiation (Rajakulasingam et al. 1979).

Superficial siderosis is a rare vascular complication that results from recurrent hemorrhage and hemosiderin deposition into the subarachnoid space (Koeppen

et al. 1993). It is characterized by deafness (sensorineural) and ataxia, as well as myelopathy, and is associated with radiation for tumors in the posterior fossa and/or spinal column (Fearnley et al. 1995).

Complicated migraines may occur after completion of treatment with radiotherapy doses over 50 Gy (Bartleson et al. 2003). Some authors suggest that these may result from radiation damage to the trigeminovascular system that triggers a neurovascular headache. Symptoms can last hours to days and are generally reversible.

34.3 Risk Factors, Prevention, and Treatment

34.3.1 Risk and Prevention

Risk factors for radiation-induced cranial vasculopathy fall into two major categories. Some, such as age and genetic predisposition, exist at the time of radiation delivery and have the potential to impact decision-making regarding use of radiation, as well radiation modality, dose, and volume. Age at the time of radiation appears to play a role in risk of development of vascular complications, with very young age (<3 years) increasing risk of radiation-induced brain necrosis and older age increasing risk of vascular malformation and stroke. As discussed earlier, physicians delivering radiotherapy to very young children, particularly those receiving multiagent chemotherapy, may elect to reduce radiation dose slightly until necrosis risk is better understood, but this should be done with caution to avoid compromising tumor-related risks. Studies are underway investigating dose de-escalation in certain pediatric tumors, including ALL, germ cell tumors, and medulloblastoma, and the results of these may favor decreasing overall radiation dose and may in turn contribute to decreased risk of vasculopathy; however, this is not recommended outside of a clinical trial at this time. Along the same lines, certain tumor locations, such as proximity to brainstem and Circle of Willis, may pose particular risk to vessels, both by physical compression and radiation risk resulting from treatment. Although research interests exist in decreasing radiation margins as well as dose as discussed above, these modifications are not recommended outside of a clinical trial.

Neurofibromatosis is certainly associated with increased risk of vasculopathy, even in the absence of malignancy (Rosser et al. 2005; Hersh 2008), likely due to mutations in neurofibromin that compromise the integrity of the endothelial and smooth muscle cells of blood vessels; radiotherapy may further this risk by causing vascular damage to already compromised vessels. Decision-making regarding use of radiotherapy, particularly in low grade gliomas, when other treatment modalities may exist with efficacy equal to that of radiation, may alter the risk benefit ratio in this specific population.

Other risk factors for vasulopathies, such as certain metabolic factors, may be modifiable at the time of radiation and anytime thereafter into survivorship. Low levels of high-density lipoprotein (HDL) (Lo et al. 2016) and hypertension (Mueller et al. 2013a, b) are associated with increased risk of stroke in survivors after cranial

radiation, and growth hormone (either supplemented or endogenous) may play a preventive role (Lo et al. 2016). Increased physical activity has been indirectly linked to decreased vascular disease with endothelial colony forming cells, serving as biomarkers of vascular injury, being decreased after cranial radiotherapy but increased by physical activity (Pradhan et al. 2015). Perhaps in best summary, Partap and colleagues point out that metabolic abnormalities that are common in survivors after cranial radiation, including hypothalamic obesity, growth hormone deficiency, hypogonadism, hypothyroidism, low HDL, insulin resistance, and sedentary lifestyle in all likelihood contribute to risk of vascular abnormalities and events that are initiated by radiation damage. Many of these are modifiable and warrant close follow-up and treatment whenever possible; these may be best delivered in a dedicated survivorship clinic with expertise caring for growing survivors of pediatric brain tumors.

Also supporting the need for close follow-up by informed clinicians, recurrent headache has been observed to predict for development of cerebral ischemia in children treated for brain tumors with radiotherapy. Patients who repeatedly report severe headaches may be targeted for stroke prevention and monitoring (Kranick et al. 2013).

34.3.2 Treatment

In general, treatment of vascular disorders occurring in children after cranial radiation is similar to standard treatments for the disorders themselves. Ischemia may be treated with efforts for rapid reperfusion and rehabilitation from deficits. Generally, cavernous malformations and telangiectasias may be watched closely, with intervention recommended if rapid growth or symptoms (headache, bleeding, seizures) are observed. Complicated migraine headaches may be addressed with anticonvulsants, as well as headache prevention with hydration, nutrition, and avoidance of vasoconstrictors (Morris et al. 2009). One group notes that aneurysms found in fields previously exposed to radiation may be inherently weaker than other aneurysms and may also have a higher likelihood to rupture, recommending that more aggressive treatment be considered for this particular group of patients (Lucas and Mack 2014). This recommendation is complicated by the inherently increased risk of repair of radiated vasculature, and warrants further study. No firm treatment recommendations are available for other vascular malformations or Moyamoya. Antiplatelet prophylaxis has not proved beneficial; surgical revascularization for Moyamoya may provide benefit in certain scenarios (Fung et al. 2005). Radiation necrosis may be treated with systemic steroids in combination with bevacizumab, and this combination supports recovery in some cases (Plimpton et al. 2015).

The current *COG Long-Term Follow-Up Guidelines* recommend an annual neurologic examination in patients with a history of ≥18 Gy cranial irradiation, with brain MRI with diffusion-weighted imaging and magnetic resonance angiography recommended as clinically indicated (www.survivorshipguidelines.org). The utility

of carotid ultrasonography for screening for stenosis is unclear in the population of patients treated with radiotherapy to the neck. This screening tool is not recommended in the general population (LeFevre and U.S. Preventive Services Task Force 2014) as risks of interventions are felt to outweigh potential benefits; however, conclusions from the general population cannot necessarily be applied to this high-risk population. For patients who encounter radiation-associated vascular disease, treatment should focus on modifiable risk factors that may prevent evolution of vasculopathy and/or development of further injury, as well as the supportive treatments outlined above.

34.4 Future Directions

Many cooperative group and institutional studies are currently investigating the safety of radiation dose reduction as well as volume reduction (in the form of reduced margin expansions) for children who require brain and neck radiotherapy. Some tumors that are historically treated with craniospinal or whole brain radiation, such as medulloblastoma, may prove to be curable with treatment to the posterior fossa or tumor bed only for certain patients, and the promise of this approach grows as genetic characterization is increasingly available: Current studies are investigating decreased radiation volumes and doses based on genetic characterization. Providing that these efforts do not compromise cure, they may contribute to reduction in vascular risk in the future and our worth pursuing—CCSS data suggest that stroke hazard may increase by up to 5% with every 100 Gy increase in radiation dose (Mueller et al. 2013a, b), and reduction in doses may well contribute to decreased vascular late effects. Changes in technique for treatment of Hodgkin lymphoma—treatment of involved nodes rather than involved fields—have been demonstrated to decrease carotid artery dose substantially, with predicted stroke risk much less than would be associated with a conventional mantle field (Moraldo et al. 2013). Advances in technology that allow reduction in normal tissue exposure may also contribute to this; for example, use of particle therapy to avoid the low dose radiation "bath" to the normal brain that is imposed by use of IMRT will hopefully allow elimination of risk to vessels in the areas of the brain distant from tumor. Finally, better understanding of vascular risk and increased understanding of systemic markers that imply poor vascular health may assist clinicians in offering directed, preventive care to patients at the highest risk for these potentially devastating late effects.

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Second Neoplasms After Successful Treatment for Pediatric Central Nervous System Tumors

35

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Contents

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Abstract

As survival rates following treatment for pediatric central nervous system tumors continue to improve, it is now clear that survivors of childhood cancer are at risk for a wide range of health, neurocognitive, social, and psychiatric issues. Perhaps the most significant and damaging complication facing survivors of childhood cancers is diagnosis of a second neoplasm. The development of a second neoplasm is a multifactorial process that is influenced by cancer histology, genetics, treatment technique and intensity, and environmental factors. These are a group of histologically diverse cancers that can occur at any location in the body with varied latency times. Many secondary malignant neoplasms have an extremely poor prognosis. While radiotherapy dose and field design been associated with second neoplasm development, new treatment strategies and technologies such as proton therapy have the potential to significantly reduce this devastating complication of treatment. As our ability to understand and quantify the factors that influence risk improve, models accurately predicting individual risk may be incorporated into treatment selection.

35.1 Introduction

There has been a dramatic improvement in outcomes of children treated for cancer in the United States over the last 30 years. Cancers of the central nervous system (CNS) represent almost 20% of all childhood cancers. While the gains made do not approach those in cancers such as acute lymphoblastic leukemia (ALL), 5-year survival rates have still increased by 20% from 1975 (Smith et al. 2010). It is now evident that children cured of their primary CNS tumors are at risk for a wide array of health, neurocognitive, social, and psychiatric issues (Armstrong 2010; Oeffinger et al. 2006). Perhaps the most significant and damaging complication for these cancer survivors is a diagnosis of a second neoplasm (SN) after successful cure.

Classification of a subsequent neoplasm can be difficult. A SN is a second tumor occurring near the original treatment site, of a different histological type, and after a reasonable amount of time has passed since primary therapy. These can be benign tumors such as a cavernoma and meningioma, or secondary malignant neoplasms (SMNs) such as a glioma.

There appears to be an increasing number of SN seen in survivors of childhood cancer (Maule et al. 2008; Peterson et al. 2006). Given the temporal nature of developing a SN, the increasing long-term survival of children with CNS tumors would seemingly partially account for this observation (Fig. 35.1). Development of a SN is a multifactorial event (Fig. 35.2) (Travis et al. 2012), resulting from a combination of genetic predisposition, susceptibility to therapy (including age at treatment), treatment type and intensity, time since completion of therapy, and the other exogenous factors such as smoking and obesity.

Outcomes of patients treated for a SMN after a childhood CNS tumor are almost universally dismal (Carret et al. 2006; Neglia et al. 2006; Paulino et al. 2008; Taylor

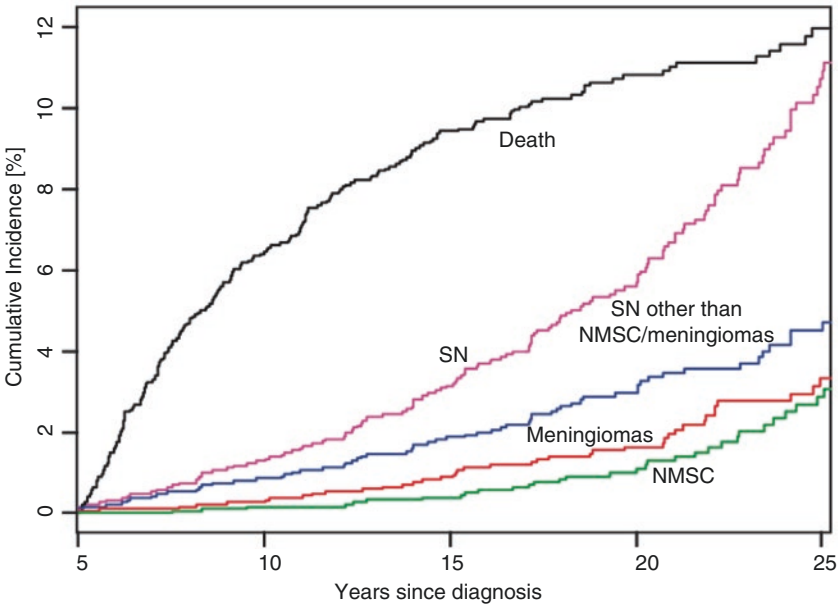

Fig. 35.1 Cumulative incidence of second neoplasms with death as a competing risk (Armstrong et al. 2009)

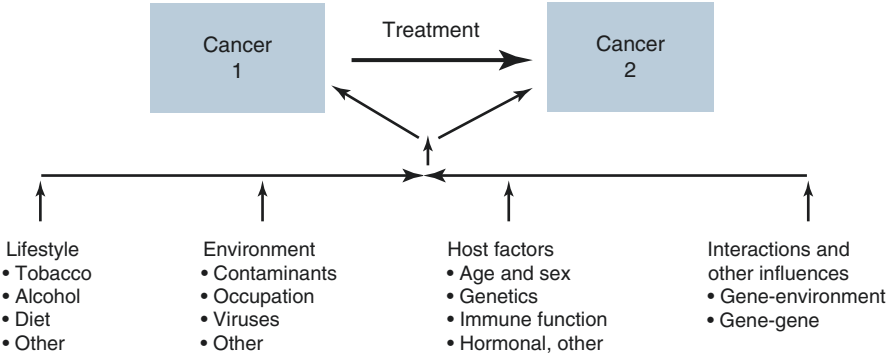

Fig. 35.2 Etiologic factors involved in multiple cancer development (Travis et al. 2012)

et al. 2009; Walter et al. 1998). Patients have often been treated with the maximum amount of tolerable therapy for their primary disease and have few treatment options available. Therefore, it is important to take any steps possible to mitigate the risk of SMNs during primary therapy for a CNS tumor while preserving chance of cure and to perform active long-term surveillance in survivors of childhood CNS tumors.

With therapies rapidly changing and our genetic understanding of secondary cancers still in its infancy, it can be difficult to predict risk in children undergoing treatment for CNS tumors. Nevertheless, as multimodality therapy becomes more common, and our ability to support children through more intensive treatment regimens improves, survival rates will continue to increase, and SNs will become an increasingly important clinical entity.

35.2 Genetic and Familial Factors Influencing the Risk of Second Neoplasms

Just as with primary tumors of the CNS, the etiology of SNs in children is multifactorial. While cancer therapies do play a role (see below), it is becoming increasingly apparent that genetic factors contribute as well (Kony et al. 1997; Korones et al. 2003; Kuenzle et al. 1994; Little et al. 1998; Salminen et al. 1999). Salminen and colleagues examined the Finnish Cancer Registry from 1953 and 1994 and found that patients diagnosed with primary CNS tumors were at a higher risk for SNs when treated with surgery alone. Patients treated without radiotherapy had a standard incidence rate (SIR) of 2.0, suggesting that host factors including genetic predisposition may contribute to SMN formation (Salminen et al. 1999). Cardous-Ubbink and colleagues demonstrated an even higher risk of secondary malignancy among a child only cohort treated with surgery alone in Amsterdam (SIR 13) (Cardous-Ubbink et al. 2007). Children with CNS tumors may be especially at risk. Little and colleagues examined a cohort of 4400 patients treated for childhood cancer and found first CNS tumor was found to predict for second tumor of the CNS compared to other locations of first primary (Little et al. 1998). When examining patients with any genetic syndrome they found a RR of 8.28 for development of SN of the CNS. This association was not found to be statistically significant when removing patients diagnosed with neurofibromatosis 1 (NF1), likely because of the large number of participants with this diagnosis in this study (Little et al. 1998).

There are several well-described familial tumor syndromes that predispose children to a higher risk of CNS tumors (Table 35.1) (Pan and Prados 2003). Children with familial syndromes are included in large SN analyses from the Childhood Cancer Survivorship Study (CCSS), the British Childhood Cancer Survivor Study (BCCSS), and the Surveillance, Epidemiology, and End Results (SEER) database. Children diagnosed with a primary CNS neoplasm are not routinely screened unless clinically indicated, making the true incidence of SN difficult to determine. Children with these familial syndromes can make up as much as 20% of participants in some series (Tsui et al. 2015; Kony et al. 1997), and rates may be higher when all genetic causes are considered (Broniscer et al. 2004). Various case series have associated the occurrence of SMNs with specific genetic syndromes in children with primary brain tumors (Garwicz et al. 2000; Kingston et al. 1987; Little et al. 1998; Meadows et al. 1985; Stavrou et al. 2001; Torres et al. 1997).

Table 35.1 Familial tumor syndromes of the CNS

Syndrome	Characteristic CNS lesion	Characteristic skin lesion	Opthalmologic feature	Chromosome	Gene	Protein
NF-1	Optic pathway glioma, brainstem glioma	Café-au-lait spots, axillary freckling	Lisch nodule	17q11	NF1	Neurofibromin
NF-2	Bilateral acoustic neuroma, multiple meningiomas	NF-2 plaque, subcutaneous schwannomas		22q12	NF2	Merlin
Retinoblastoma	Pineoblastoma		Leukokoria	13q14	Rb1	Rb1
Von-Hippel-Lindau	Hemangioblastoma of the cerebellum/ spine		Retinal angioma	3p25	VHL	VHL
Tuberous Sclerosis	Subependymal giant cell astrocytoma, subependymal nodule, cortical tuber	Ash-leaf spots, adenoma sebceum, Shagreen patch Ungal fibroma	Retinal astrocytoma	9q34, 16p13.3	TSC1, TSC2	Hamartin, Tuberin
Stuge-Weber	Leptomeningeal angiomatosis, cortical calcifications, hemispheric atrophy	Port-Wine nevus	Choroidal hemangioma, glaucoma			
Turcot	Glioblastoma, brain tumor polyposis type 1 and 2, medulloblastoma			5q21	APC	
Gorlin (nevoid basal cell carcinoma)	Medulloblastoma	Basal cell carcinoma		9q22.3	PTCH	
L'hermitte-Duclos/Cowden	Dysplastic gangliocytoma of the cerebellum	Facial trichilemmoma		10q23.3	PTEN	
Li-Fraumeni	Malignant gliomas, PNET			17q (between exon 5 and 9)		P53

NF neurofibromatosis, *PNET* primary neuroectoderm tumor
Adapted from: Pan 2003

The association between NF1 and SN is well known (Garwicz et al. 2000; Kingston et al. 1987; Little et al. 1998; Meadows et al. 1985; Sharif et al. 2006; Friedman and Birch 1997). Children with NF1 have both an increased risk for brain tumor development and possibly an increased susceptibility to treatments such as radiotherapy (Sharif et al. 2006). Especially at risk are patients who have developed an optic pathway glioma (OPG). One cohort of patients with OPG had a 20% rate of second tumors when treated without radiotherapy, and 50% rate for patients treated with radiotherapy (Sharif et al. 2006). Other studies have estimated the risk to be between 11 and 52% (Korones et al. 2003; Kuenzle et al. 1994). Nevoid basal

cell carcinoma syndrome (NBCCS) has also been described as being found in higher than expected incidences in patients diagnosed with SMNs after treatment of a primary CNS tumor (Albrecht et al. 1994; Kingston et al. 1987; Stavrou et al. 2001).

There is an increased genetic risk of SN development for some patients independent of familial cancer syndromes. Kony and colleagues performed a case-control study of 25 patients diagnosed with SMNs out of 649 children treated at a single institution. Patients with family members who had early onset of cancer had an odds ratio (OR) for subsequent SMN development of 4.7 (Kony et al. 1997). A genetic susceptibility to treatment may contribute to this elevated risk. Flint-Richter and colleagues examined 525 families and discovered that patients who developed a meningioma after cranial radiation for tinea capitis had a higher rate of first-degree family members with meningioma (11%) compared to those who did not develop a meningioma after radiation therapy for tinea capitis (1%) suggesting a genetic predisposition (Flint-Richter and Sadetzki 2007).

Further evidence is supplied from the CCSS. Friedman and colleagues examined siblings of patients enrolled in the CCSS diagnosed with a primary CNS neoplasm and noted a trend for a higher SIR of cancer diagnosis. This rate was higher for siblings (SIR of 2.4) and offspring (SIR of 15.0) of CCSS study participants who were diagnosed with a SN themselves (Friedman et al. 2005). This association is not observed in parents, children, or siblings of patients diagnosed with childhood cancer who did not develop a SN when accounting for known cancer hereditary syndromes (Olsen et al. 1995, 2009; Sankila et al. 1998; Winther et al. 2001; Friedman et al. 2005). Apart from rare hereditary cancer syndromes, pediatric cancer itself does not seem to be a marker of increased risk in families; however, it does seem that some children who develop a SN may have an unknown genetic predisposition. Our knowledge of familial cancer syndromes is not complete, and there are certain patient families that are likely at an increased risk for cancer that is not yet attributable to a named syndrome.

35.3 The Effects of Cancer Therapies on Neoplasm Development in the Central Nervous System

Today, children diagnosed with a primary malignancy of the CNS will receive a wide variety of cancer treatments, each with its own profile of adverse events and risk for long-term complications. Increasingly, many children are being treated with bimodality or trimodality therapy; this has contributed to the truly historic gains made in survival after treatment.

Radiotherapy is the most common cancer therapy implicated in increasing the risk of SNs. However, some systemic treatment regimens used for primary CNS cancer can increase the rate of SMNs, either alone or in combination with radiotherapy (Duffner et al. 1998; Relling et al. 1999; Walter et al. 1998). In addition to the increased risk seen with intravenous chemotherapy, intrathecal methotrexate has been shown to increase the rate of SMNs in the CNS in survivors of childhood cancer independent of the effects of other risk factors (Taylor et al. 2010).

35.3.1 Increased Risk in Healthy Individuals

Fractionated radiotherapy has been shown to induce malignant brain tumors in non-human primates at a high rate after 35 Gy delivered over 2 weeks (Lonser et al. 2002). Data in humans are limited, however, examining patients treated with therapeutic radiation for noncancerous diseases of the head and neck as well as survivors of the atomic bomb yield some insights. Even though the carcinogenic effects of ionizing radiation to induce non-CNS tumors has been recognized for some time, the potential for SNs of the CNS was recognized much later.

Our understanding of neoplasm development after exposure to total body ionizing radiation therapy comes mainly from survivors of the atomic bomb detonations in Japan. Although an increased risk of developing any cancer is seen (Peterson et al. 2006), specifically identifying the risk of CNS tumors, is difficult given the small number of cases. Still, an association has been shown between radiation exposure and non-brain nervous system tumors in atomic bomb survivors (Thompson et al. 1994). In addition to atomic bomb exposure, therapeutic radiation exposure for various benign conditions, including ankylosing spondylitis, tonsillitis, and tinea capitis, in childhood has been associated with increased incidence of CNS tumors (Darby et al. 1987; Shore et al. 2003; Shore-Freedman et al. 1983).

In one of the largest reported experiences, approximately 20,000 Israeli adults and children were treated with therapeutic radiotherapy to the head for tinea capitis between 1948 and 1960. Shortly after treatment, researchers began following this cohort to better understand ionizing radiation's effects on otherwise healthy brains and meninges. After 40 years of follow-up, Sadetzki and colleagues reported the outcomes of over 10,000 of these children matched with sibling and population controls and found an increased risk of SN with exposure to therapeutic radiotherapy (Sadetzki et al. 2005). This elevated risk was found to be dependent on the dose received, as well as age at delivery. An excessive relative risk (RR) of 4.63/Gy and 1.98/Gy were reported for benign and malignant CNS tumors, respectively. This translated to an excess absolute risk (EAR) of 0.48/Gy and 0.34/Gy per 10,000 person years. Younger children were at increased risk. The risk of developing a malignant brain tumor was 3.56/Gy for children 4 and younger and only 0.47/Gy for children over the age of 10 at the time of radiation exposure.

35.3.2 Increased Risk in Individuals with Non-CNS Neoplasms

An increased incidence of SNs of the CNS has been observed in children with leukemia who receive prophylactic cranial irradiation to mitigate the high risk of CNS leukemia relapse (Bhatia et al. 2002; Hijiya et al. 2007; Jenkinson and Hawkins 1999; Loning et al. 2000; Neglia et al. 1991; Nygaard et al. 1991; Perkins et al. 2013). Various individual institution and large database outcomes are shown in Table 35.2. Taken together, the data strongly demonstrate that even in children without primary CNS cancer, cranial irradiation appears to increase the risk of SNs in the brain.

Table 35.2 Selected series describing secondary malignancy risk after childhood leukemia

Author	Institution	*N*	Years	Cranial XRT	Interval since treatment	Standardized incidence ratio for CNS tumors	Cumulative risk of any second malignancy	Predictive factors
Neglia	Children's Cancer Study Group	9720	1972–1988	NR	0.3–13.2	21.7[a]	2.5% at 15 years	XRT, age ≤ 5
Nygaard	Nordic	981	1958–1985	58.4%	7.5–16.5	26.7 (5.5–78.1)[b]	2.9% at 20 years (8.1% with XRT)	XRT
Jenkinson	National Registry of Childhood Tumors (UK)	3961	1962–1987	87%	NR	23 (11–43)[c]	0.5% at 10 years[c]	XRT
Loning	German Childhood Cancer Registry	5006	1979–1995	77.2%	1–15	18.6 (9.8–29.4)	3.3% at 15 years (1.0% for CNS)	XRT, age ≤ 7
Bhatia	Children's Cancer Group	8831	1983–1995	38%	1.1–15.8	10.1 (5.9–16.2)	1.18% at 10 years (0.82% for CNS)	Males, XRT, relapse
Hijiya	St. Jude	2169	1962–1998	NR	1.7–31.7	31.8 (19.7–47.6)	10.85% at 30 years (1.17% at 15 years for CNS excluding meningioma)	No SS

NR not reported, *SS* statistically significant
[a]Ratio of observed vs. expected
[b]SIR for patients treated with radiotherapy only, SIR was 0 for patients not treated with radiotherapy
[c]Malignant tumors only

Children diagnosed with primary CNS tumors will likely need surveillance following successful therapy. It is important to remember that diagnostic scans using ionizing radiation, such as CT scans, have been shown to independently increase the risk of SMN for children without cancer. Increased risk of leukemia and CNS tumors were primarily observed, with the risk rising with increased cumulative childhood dose and younger age at exposure (Mathews et al. 2013; Pearce et al. 2012).

35.3.3 Increased Risk in Individuals with CNS Neoplasms

35.3.3.1 Radiotherapy

External beam radiotherapy was one of the first identified risk factors for SN development, but interpretation is difficult. The accepted dose prescriptions and treatment volumes vary widely for different primary CNS tumors. Dose level, targets,

and technology used to shape distribution can vary from institution to institution, by clinical trial randomization, and by era the child was treated for the first malignancy. These issues complicate the elucidation of the role of radiotherapy dose and volume in population-based series of patients treated over extended periods of time or between institutions that used different approaches.

Armstrong and colleagues found that the use of radiotherapy for the primary CNS tumor to be predictive of secondary neoplasm risk in their examination of a cohort of children in the CCSS treated for CNS primaries (Armstrong et al. 2009). When the authors further analyzed patients by dose of radiation received, they found that at 25 years after diagnosis, children who received 50 Gy or more had a 7.1% (95% CI 4.5–9.6%) cumulative incidence of CNS-SNs compared to 1.0% (95% CI 0–2.3) for no radiation exposure ($p < 0.001$). Those who received less than 50 Gy radiation had an intermediate cumulative incidence of 5.2% (95% CI 2.1–8.3). This correlation with a high radiation dose was also shown by others and suggests a dose response (Chojnacka et al. 2014; Vinchon et al. 2011). There is emerging evidence in pediatric cancers that while radiation therapy increases the risk of SN, the contribution of radiation therapy is not seen until after 5 years (Svahn-Tapper et al. 2006). It is not known if this delayed risk is seen in specifically in patients with primary CNS tumors.

These data showing a potential dose response for secondary malignancy risk in children with primary CNS tumors is consistent with the findings of Neglia and colleagues who demonstrated a dose response in children diagnosed with primary cancer from any site that subsequently developed a CNS secondary neoplasm (Fig. 35.3). They demonstrated a linear relationship for excessive RR and calculated

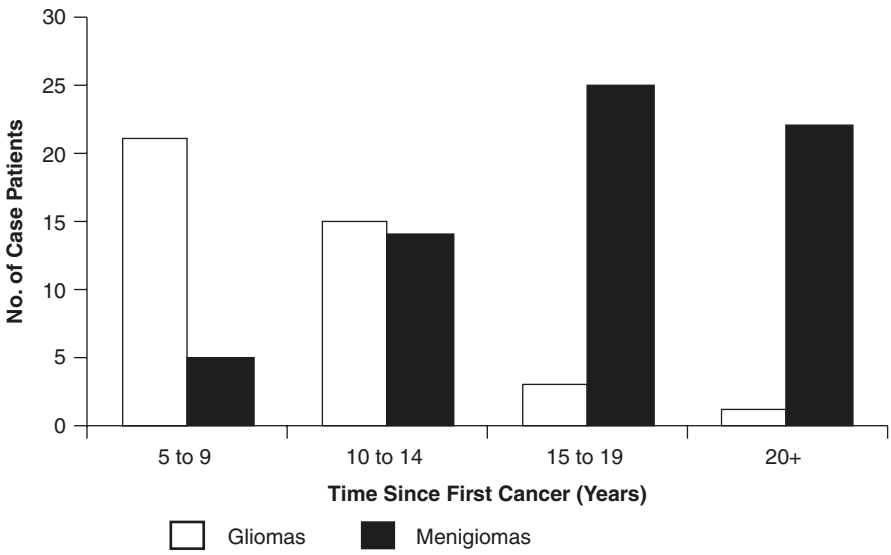

Fig. 35.3 Relative risk of subsequent gliomas and meningioma within the Childhood Cancer Survivor Study cohort by radiation dose (Neglia et al. 2006)

a slope of 0.33 per Gy for secondary gliomas and 1.06 per Gy for secondary meningiomas (Neglia et al. 2006). A slope of 0.69 per Gy was calculated for all secondary CNS tumors. Radiation therapy dose was also found to be predictive of second neoplasms of the CNS in the BCCSS as well (Taylor et al. 2010). Taylor and colleagues demonstrated an elevated RR of 5.1 per Gy for secondary meningiomas and 0.08 per Gy for glioma/PNETs. Both age at exposure and genetic susceptibility influence these risks (Taylor et al. 2010).

35.3.3.2 Cytotoxic Chemotherapy

More children are receiving cytotoxic chemotherapy for cancer treatment than ever before. Chemotherapy such as alkylating agents and topoisomerases are commonly thought to have the potential to promote SMNs in children. Other antimetabolite therapies have been implicated as well (Relling et al. 1999; Klein et al. 2003). Examining the influence of chemotherapy is difficult in large registries of patients given the often-limited information available; still, some information can be gleamed from these databases. In an analysis of the US SEER cancer registry, the most important risk factor for developing a SMN in 5-year survivors of childhood primary CNS cancer was the era in which the primary cancer was diagnosed and treated (Peterson et al. 2006). Compared to patients treated before 1979, patients treated after 1985 had a 6.7 fold increase in risk. Even after controlling for the use of radiotherapy, treatment era was the most important factor. This trend has been observed in other studies as well; with some studies report that chemotherapy alone or in conjunction with radiotherapy increases risk of SN (Maule et al. 2008; de Vathaire et al. 1999; Guerin et al. 2007). Noting that high dose chemotherapy was first used for the treatment of brain tumors in children in the late 1980s, the authors question if chemotherapy is increasing the rates of secondary malignancies either as a sole agent, or more likely, in combination with radiotherapy (Peterson et al. 2006).

Multi-institutional clinical trials and single institutional series can examine chemotherapies effect on SMNs among more homogenous treatment populations or with more detailed records than can be done with population-based studies. Duffer and colleagues reported the results of a Pediatric Oncology Group (POG-8633) study in which children younger than 3 years of age with malignant brain tumors received prolonged postoperative chemotherapy with delayed radiotherapy (Duffner et al. 1998). Participants received vincristine, cyclophosphamide, cisplatinum, and etoposide for 12 or 24 months depending on age. For children treated when younger than 2 years, the authors report a 18.9% cumulative risk of SN at 8 years. This very high rate of SN, especially SMN, is partially a result of the young age at which the children were treated and the amount of chemotherapy they received over the study period (Duffner et al. 1998). This variation in susceptibility to the secondary neoplastic potential of radiation therapy may be related to the increased proliferation of tissues in younger children or the comparatively high number of undifferentiated stem cells. Additionally, young children's tissues are exposed to growth hormones at a higher level and for greater amounts of time, possibly leading to increased cancer propagation (Tubiana 2009).

Series of older children have demonstrated high rates of SN formation as well, albeit not as high as that seen in the POG Study. In the Children's Oncology Group (COG) A9961 trial, children with average risk medulloblastoma were treated with craniospinal irradiation and chemotherapy. Patients had a cumulative incidence of second neoplasms of 4.2% at 10 years (Packer et al. 2013). Similarly, patients treated as part of the German HIT '91 trial for medulloblastoma were found to have an overall rate of second malignancies of 4.3%(von Hoff et al. 2009). While all patients received cranial spinal irradiation, patients treated on the more aggressive sandwich arm developed more second malignancies than patients treated with maintenance chemotherapy (6.3% vs. 2.6%).

Given the increasing reports of high rates of SMNs in the literature, Tsui and colleagues examined 2779 patients treated at St. Jude Children's Research Hospital for a primary CNS tumor from 1985 to 2012 (Tsui et al. 2015). While they noted a cumulative incidence of second neoplasms for patients with medulloblastoma or PNET treated with multimodality therapy of 12.0% at 20 years, they did not see any difference in those patients treated when they compared the patients to a similar group of patients who received radiotherapy alone. There was, however, a statistically significant difference favoring more SNs in the multimodality arm when examining the cumulative incidence at 10 years (Tsui et al. 2015). This suggests that the addition of chemotherapy may change the temporal pattern of SN development, but not the ultimate number, which has been suggested by other series (You et al. 2013). When examining all patients with primary CNS tumors, no difference was seen on multivariate analysis between patients treated with chemoradiation or radiation alone (Tsui et al. 2015).

It is possible, therefore, that chemotherapy influences the development of SNs by potentiating the influence of radiotherapy. Garwicz and colleagues performed a nested case-control study of children treated for cancer in five Nordic countries (Garwicz et al. 2000). While the risk of a SMN was not increased by chemotherapy alone, the interaction of chemotherapy with radiation therapy was found to be statistically significant at all radiation dose levels. While this was demonstrated in a population that comprise all childhood cancer diagnoses (with 20% primary CNS), we do not yet have enough data to fully extrapolate this finding to children with primary CNS cancer given that there have been conflicting findings reported in the literature. For example, Broniscer and colleagues reported on the St. Jude Children's Research Hospital Experience and did not find an increased risk of second malignancies among patient with primary CNS cancer who received chemotherapy or a combination of chemotherapy and radiotherapy (Broniscer et al. 2004).

35.3.4 Other Risk Factors

Other factors could contribute to the development of second cancers. Inskip and Curtus demonstrated that children with PNET tumors had higher rates of SMNs compared to other CNS histologies using the US SEER database (Inskip and Curtis 2007). Children diagnosed with a primary astrocytoma had a SIR of 13 (95% CI

5.4–25) for development of a SN compared to a SIR of 45 (95% CI 19–88) for PNET (Inskip and Curtis 2007). Confirming earlier reports (Chojnacka et al. 2014; Duffner et al. 1998; Broniscer et al. 2004), Tsui and colleagues demonstrated that younger children, especially those younger than 5 years of age were at a higher risk for SNs, but no differences were seen for sex or race (Tsui et al. 2015). This finding in children less than 5 years of age agrees with the dose response established for secondary gliomas by Negila discussed previously (Neglia et al. 2006). In a cohort of patient who received cranial radiation for CNS tumors, Vichon and colleagues demonstrated a higher cumulative incidence in boys when compared to girls (Vinchon et al. 2011). Care must be taken in interpreting this finding given the heterogeneous study populations and often-conflicting results.

35.4 Second Neoplasms Following Childhood Central Nervous System Tumors

35.4.1 Incidence of Second Neoplasms in Survivors of Childhood Central Nervous System Tumors

It has been known for some time that children treated for primary CNS malignancies are at risk for SNs (Mann et al. 1953). While many of the first reported cases were from single institutions with limited ability to determine true incidence after treatment (Kantar et al. 2004; Makidono et al. 2009; Soffer et al. 1989; Strojan et al. 2000; Amirjamshidi and Abbassioun 2000), investigators are now using large multi-institutional and multinational series to examine the question (Cardous-Ubbink et al. 2007; Friedman et al. 2010; Inskip and Curtis 2007; Jazbec et al. 2004; Jenkinson et al. 2004; MacArthur et al. 2007; Olsen et al. 2009; Reulen et al. 2011; Meadows et al. 1985; Rosso et al. 1994). These larger series allow for identifications of more subtle risk factors.

Table 35.3 shows results from selected recent publications examining the rates of second malignancies in population studies of children diagnosed with a primary CNS cancer (Jenkinson et al. 2004; Cardous-Ubbink et al. 2007; Inskip and Curtis 2007; MacArthur et al. 2007; Olsen et al. 2009; Reulen et al. 2011; Armstrong et al. 2009; Hammal et al. 2005). Standard incidence rates of any SN following treatment for a childhood CNS tumor have been reported as 1.6–17.4 compared to the general population. In addition to differences in practice patterns and treatment, these rates vary widely based on length of follow-up, inclusion of benign tumors, and surveillance methods used.

The majority of data for survivors of primary CNS cancer comes from subgroups of large cohort population studies of all childhood cancers. Relatively few published reports have focused only on children diagnosed with a primary CNS tumor outside of single institution or cooperative group-based studies (Peterson et al. 2006; Maule et al. 2008; Armstrong et al. 2009). One such large group is the CCSS. This cohort was constructed to evaluate health outcomes in 5-year survivors of various childhood cancers including primary CNS tumors. Patients were treated at one of several

Table 35.3 Selected large population studies examining the rates of secondary neoplasms in survivors of a primary childhood CNS tumor

Study	Year published	Years enrolled	Number of patients with primary CNS tumors	% of patients who received cranial RT	Observed # of SN	Standardized incidence ratio	Excess absolute risk[a]
British Childhood Cancer Survivor Study (UK)	2011	1940–1991	4111	NR	338	2.7 (2.4–3.2)	12.2
Childhood Cancer Survivors Study	2009	1970–1986	1877	77	151	4.1 (3.2–5.2)	NR
Nordic[b]	2009	1943–2005	10,970	NR	78	1.6 (1.3–2.0)	NR
US SEER	2007	1973–2002	4806	55.5	69	6.3 (4.9–8.0)	15.3
British Columbia	2007	1970–1995	438	NR	9	5.1 (2.7–9.6)	16.9
Dutch	2007	1966–1996	109	NR	9	17.4 (6.98–35.8)	53.6
Northern Region Young Persons Malignant Disease Registry (UK)	2005	1968–1999	745	NR	14	6.1 (3.3–10.2)	NR
National Register of Childhood Tumors (UK)	2004	1962–1968	4009	NR	55	4.7 (3.66–6.2)	10
France and UK	1999	Before 1985	722	84	15	5 (3–9)[c]	14

[a]Per 10,000 person years
[b]Denmark, Finland, Iceland, Norway, Sweden
[c]Observed/expected

institutions in the United States or Canada and were treated between 1970 and 1986. Over 14,000 participants were enrolled (Friedman et al. 2010).

Armstrong and colleagues examined a 1877 patient cohort of children with primary CNS cancer included in the larger CCSS cohort (Armstrong et al. 2009). Astrocytoma and glial tumors were the most common primary cancer histologies. Most patients were treated with surgery followed by radiotherapy alone (41.6%) or chemotherapy and radiotherapy (27.0%), although some patients underwent surgery alone (26.0%). For patients receiving radiation therapy, 51.8% received a dose of 50 Gy or more and 36.8% received spinal radiation therapy. The authors determined

that the cumulative incidence of all SNs was 10.7% (95% CI 8.8–12.6%) at 25 years from diagnosis (Armstrong et al. 2009). When non-melanoma skin cancer and meningiomas were excluded, the cumulative incidence was 4.5% (3.3–5.7%). Rates of specific SN are shown in Table 35.4. In comparison to other CCSS participants, those with primary CNS cancers had a higher rate of secondary CNS tumors and a lower rate of breast cancer. Since radiotherapy has been shown to increase the risk of secondary CNS tumors in survivors of any childhood cancer (Neglia et al. 2006), this is likely a result of higher rates of CNS directed radiotherapy in children with CNS primary compared to those diagnosed with cancers involving other sites.

Table 35.4 shows selected single institution cohorts and cooperative group-based studies examining rates of SN in patients with primary CNS malignancies (Duffner et al. 1998; von Hoff et al. 2009; Vinchon et al. 2011; Packer et al. 2013; Tsui et al. 2015). Cumulative incidences range from 3.0% to 18.9%. These rates vary widely depending on follow-up, type of chemotherapy used, and age of patients undergoing treatment. A sizable majority of patients included in these series received radiotherapy and some series consisted only of patients who received cranial irradiation. Vinchon and colleagues examined all children who received radiotherapy at a single institution in France since 1970 (Vinchon et al. 2011). They calculated a cumulative incidence of secondary neoplasms of 8.9% at 10 years. This rate was likely higher than some previously reported studies because all patients received cranial irradiation and follow-up was long. A large number of the SNs were cavernomas that have shown a strong association with cranial irradiation (Burn et al. 2007; Duhem et al. 2005; Lew et al. 2006; Strenger et al. 2008; Heckl et al. 2002).

Table 35.4 Selected single institution and multi-institutional studies examining the rates of secondary neoplasms in survivors of a primary childhood CNS tumor

Institution	Year published	Years enrolled	Primary cancer	Number of patients	% of patients who received cranial RT	Cumulative incidence	Latency time	Risk factors
St. Jude	2015	1985–2012	Any CNS	2779	75.6	3.0% (4.6–7.7) at 10 years	7.7 years	XRT
COG A9961	2013	1996–2000	Medulloblastoma	421	100	4.2% (1.9–6.5%) at 10 years	5.8 years	NR
Lillie FR	2011	1970–2010	Any CNS	552	100	8.9% at 10 years	13.1 years	Males, XRT dose,
HIT '91	2009	1991–1997	Medulloblastoma	280	100	12 of 280 developed SN[a, b]	8 years	Sandwich Arm
POG	1998	1986–1990	Any CNS	198	NR	18.9% (0–70%) at 8 years	4.75 years	Young Age[c]

FU follow-up, *NR* not reported

[a]Not a cumulative incidence

[b]8 of 12 SN developed in more intensive sandwich chemotherapy arm, no statistics are provided

[c]4 of 5 second malignancies occurred in children younger than 2 years at diagnosis

Table 35.5 Common second neoplasms after treatment for primary CNS tumors

Author (year)	Sites of increased risk for second neoplasm (SIR)
Tsui et al. (2015)	Any CNS (49.7) Glioma (57.2) Soft Tissue Sarcoma (29.3) Thyroid (20.9) Bone (16.3) Leukemia (13.6)
Reulen et al. (2011)	Glioma (12.3) Bone (8.7) Digestive (3.6) Genitourinary (1.6)
Armstrong et al. (2009)	Any CNS (25.3) Thyroid: (11.2) Soft Tissue Sarcoma (8.4)
Maule et al. (2008)	All Non-CNS (2.25) Other Endocrine (13) Thyroid (11) Soft Tissue Sarcoma: (7.7) Colon (5.0) NHL (4.3) Leukemia (2.8)

SIR standardized incidence ratio, *NHL* Non-Hodgkin lymphoma

Many of the large population-based cohorts include patients treated very long ago (some in the 1940s) and with older treatments and techniques than are not used today (Armstrong et al. 2009; Maule et al. 2008; Peterson et al. 2006; Cardous-Ubbink et al. 2007; Friedman et al. 2010; Inskip and Curtis 2007; Jazbec et al. 2004; Jenkinson et al. 2004; Olsen et al. 2009). Defining the rate of SNs in the modern era is difficult; often 10–20 years of follow-up is needed to construct an accurate rate. Tsui and colleagues examined patients treated for a primary CNS tumor at St. Jude Children's Hospital in the "modern era" (between 1985 and 2012) (Tsui et al. 2015). The authors report a cumulative incidence of SNs of 3.0% at 10 years, and 6.0% at 20 years.

The most commonly reported SNs in the previously discussed studies have been intracranial (Olsen et al. 2009; Reulen et al. 2011; Armstrong et al. 2009), however, not all SNs occur in the CNS. Maule and colleagues examined an international cohort of childhood survivors of CNS cancer from 13 population-based centers (Maule et al. 2008). The author's goal was to identify the rate of non-CNS tumors in these patients. The cumulative incidence at 45 years was 3.30% for the development of any non-CNS SN. Table 35.5 shows specific extracranial SNs that patients were found to be at risk for.

35.4.2 Increasing Rate of Secondary Neoplasms

Many large population-based databases are showing an increase in the incidence of SN. While this may partially be attributable to the increase in number of cases and

longer follow-up, these factors do not completely explain this phenomenon. This unexplained increase may be a product of increasing rates of multimodality therapy, more widespread use of intensive therapy, widespread availability of higher resolution imaging, or increasing provider knowledge about survivorship and the risk of second malignancy. Regardless of the reason, SN diagnosis will continue to become a more important issue in the treatment of pediatric patients with primary CNS tumors. Future treatment strategies will require maintaining or improve cure rates, while using technological and pharmacological innovation to reduce the rates of secondary effects of cancer treatment.

35.4.3 Time from Initial Diagnosis to Diagnosis of Second Neoplasm

Time to development of a SN is varied, however, observed rate of SNs increase with increased follow-up (Armstrong et al. 2009; Maule et al. 2008; Vinchon et al. 2011; Hijiya et al. 2007; Goshen et al. 2007). Series report median times to development of 5.8–21 years for children treated for CNS tumors (Packer et al. 2013; Peterson et al. 2006; Tsui et al. 2015; Vinchon et al. 2011; Armstrong et al. 2009; Broniscer et al. 2004; Devarahally et al. 2003; Duffner et al. 1998; Maule et al. 2008; von Hoff et al. 2009). Multiple factors may influence the time to development in these series including: histology, primary malignancy, sex, radiation dose, and radiation field design (Paulino et al. 2008, 2009). Secondary neoplasms of different histologies tend to occur at different time intervals from treatment, with gliomas occurring at a shorter time interval after treatment than meningiomas (Fig. 35.4) (Neglia et al. 2006).

Paulino and colleagues performed a review of the available literature and discovered that although the median latency time from treatment to development of a radiation-associated malignant glioma was 8.75 years (Fig. 35.5), the proportion of SNs occurring within 10 years differed between patients treated for leukemia or lymphoma (81%), solid tumors (59%), and benign conditions (18%) (Paulino et al. 2008). This agrees well with two other studies which report a median time to development of 9 years (Elsamadicy et al. 2015; Neglia et al. 2006), with 82% of cases occurring in 15 years (Elsamadicy et al. 2015). In Paulino's review, radiotherapy field design was also found to impact on latency time. In patients receiving whole brain or craniospinal radiotherapy, 72.5% of radiation induced malignant gliomas occurred within 10 years of initial radiotherapy, compared to only 51.2% of patients treated with local fields. Other series have reported median latency intervals of 8–17.4 years for malignant gliomas (Bowers et al. 2013). Taylor and colleagues found that the latency time to development of glioma after childhood cancer was dependent on grade of the SMN, with low grade tumors developing a mean 15.5 years for low grade tumors and 21.0 years for high grade tumors (Taylor et al. 2010).

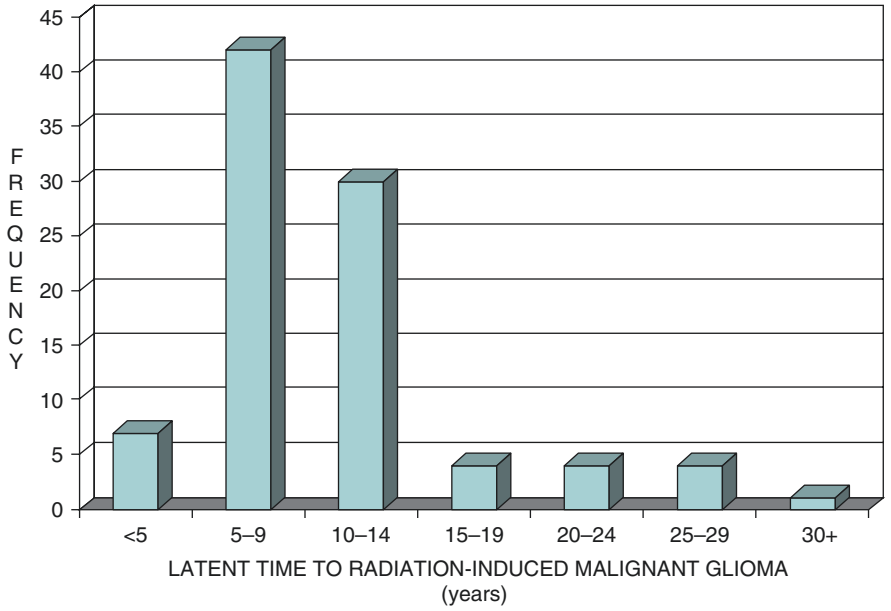

Fig. 35.4 Time to development of subsequent gliomas or meningiomas in the Childhood Cancer Survivor Study cohort from original cancer diagnosis (Neglia et al. 2006)

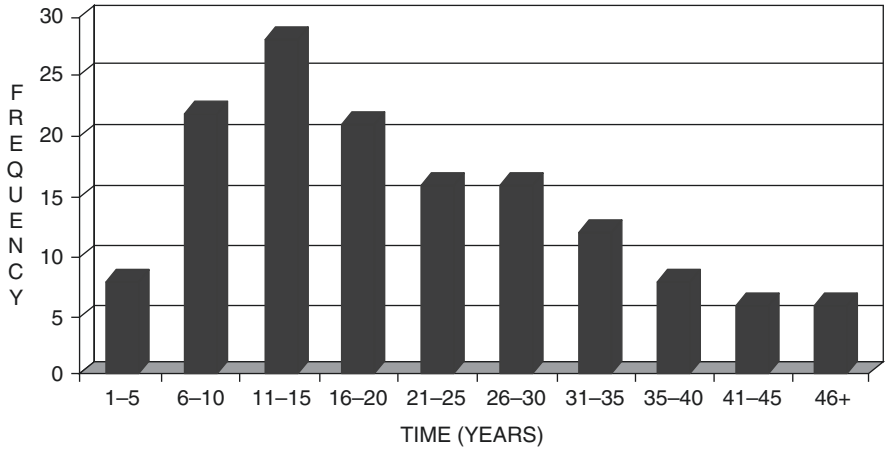

Fig. 35.5 Number of cases and latency time to develop radiation induced malignant glioma (Paulino et al. 2008)

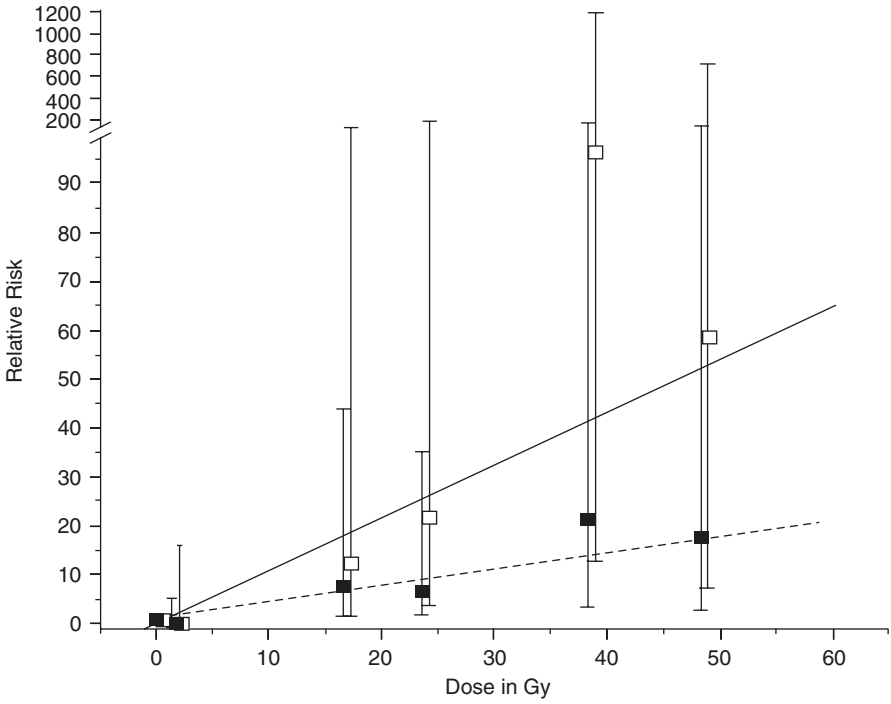

Fig. 35.6 Number of cases and latency time to develop radiation-associated meningioma (Paulino et al. 2009)

Meningiomas remain a lifelong issue for survivors of pediatric brain tumors (Fig. 35.6). Even survivors who have not developed a meningioma 20 years after diagnosis of first cancer have a 5.3% incidence of meningioma in the following decade (Armstrong et al. 2009). In an analysis of the available literature of radiation-associated meningiomas, Paulino and colleagues found that latency time was shorter for males than females (Paulino et al. 2009). Similar to malignant gliomas, the authors observed shorter latency times for patients originally treated for leukemia (14.9 years) compared to brain tumors (20.2 years) and benign conditions (32.1 years). Other studies have reported long median latency times for childhood cancer survivors who develop subsequent meningiomas ranging from 12 to 23.1 years (Ghim et al. 1993; Hijiya et al. 2007; Neglia et al. 2006; Taylor et al. 2010; Vinchon et al. 2011; Walter et al. 1998).

35.4.4 Common Second Neoplasm Histologies

The most common sites of SN in children diagnosed with primary CNS tumors closely mimic the sites at risk for age- and sex-matched healthy individuals. These children are however, at a much higher risk for specific cancers that appear very

rarely in healthy children. Children in the CCSS diagnosed with primary CNS neoplasms most commonly develop non-melanoma skin cancers such as squamous cell and basal cell carcinoma. These cancers make up 43.9% of all diagnosed subsequent cancers. When examining cancers that are more common in survivors of childhood CNS cancer compared to the general population, CNS tumors are the most common site of SMNs in this cohort (Armstrong et al. 2009). Common sites of SN after treatment for primary CNS tumors are shown in Table 35.5.

35.4.4.1 Within the CNS

Meningiomas were some of the first secondary tumors noted by clinicians (Mann et al. 1953). It is now clear the meningiomas remain a lifelong risk for patients treated with cranial radiation therapy (Paulino et al. 2009). Survivors of childhood CNS tumor are at a greater risk for developing meningiomas, and those meningiomas that develop are more commonly higher grade (grades 2 and 3) than would be expected in a healthy population. In addition to meningiomas, gliomas were quickly recognized as a particularly grim SN. In a recent analysis, the SIRs of astrocytoma/glial tumors and malignant meningiomas were 24.3 and 714.7, respectively (Armstrong et al. 2009). Glial tumors that do develop are more often a higher grade than would be expected for the patients age (Taylor et al. 2010).

35.4.4.2 Outside the CNS

While CNS malignancies remain the most common (Svahn-Tapper et al. 2006; Cardous-Ubbink et al. 2007; Inskip and Curtis 2007; Jazbec et al. 2004; Olsen et al. 2009; Armstrong et al. 2009; Amirjamshidi and Abbassioun 2000), it is becoming clearer that these SNs may develop outside the CNS, especially in patients who received systemic chemotherapy or craniospinal irradiation. The CCSS and other series commonly identify survivors of childhood CNS tumors at risk for thyroid (Armstrong et al. 2009; Maule et al. 2008; Tsui et al. 2015) (SIRs of 11–20.9), soft tissue sarcomas (Armstrong et al. 2009; Maule et al. 2008; Tsui et al. 2015) (SIRs 7.7–29.3), and other extracranial sites. Maule and colleagues' study of 13 population-based centers examined only second neoplasms outside the CNS (Maule et al. 2008). They identified standardized incidence ratios for other endocrine cancer (13), non-Hodgkin lymphoma (4.3), leukemia (2.8), and colon cancer (5.0) (Maule et al. 2008). Elevated incidences of GI cancer as well as GU cancers were also seen in the primary CNS cohort of the BCCSS (Reulen et al. 2011).

35.5 Treatment Outcomes Following Secondary Neoplasms of the Central Nervous System

As discussed previously, common secondary tumor histologies include meningiomas, gliomas, schwannomas, and PNETs (Neglia et al. 2006; Taylor et al. 2010; Pettorini et al. 2009). These tumors can present a management challenge for clinicians, especially when the primary malignancy originated from the CNS or initial treatment involved radiotherapy to the head or brain. Patients often receive aggressive treatment upfront including maximal safe surgical resection, high dose

radiation therapy or extended field radiation therapy, and increasingly aggressive chemotherapy. These interventions leave few options for patients who develop a tumor in a similar location after a short latency time and ultimately poor survival, especially in patients with SMNs. Children with SNs in the CNS as a result of an underlying genetic syndrome may have even worse outcomes (Taylor et al. 2009). Still, given the relatively small absolute numbers of developing a SN, in the CCSS annual death rates from SN do not surpass those from disease recurrence or progression until 30 years after treatment (Armstrong et al. 2009).

35.5.1 Gliomas

In their study of 247 second primary CNS tumors among participants in the BCCSS, Taylor and colleagues found a 5-year overall survival rate of 19.5% (95% CI 8.6%–33.7%) following diagnosis of subsequent glioma (Taylor et al. 2009). Grade of the glioma was the only factor found to predict survival. Other studies confirm grade as a poor prognostic factor in secondary gliomas. Reported 5-year overall survival rates in these studies range from 0 to 19.5%(Carret et al. 2006; Neglia et al. 2006; Paulino et al. 2008; Taylor et al. 2009; Walter et al. 1998; Romeike et al. 2007). The vast majority of reports of secondary gliomas are in children who have been exposed to cranial radiation (Carret et al. 2006; Neglia et al. 2006; Taylor et al. 2009; Walter et al. 1998; Salvati et al. 2008). Although treatment options are often limited and depend on the original treatment and latency time, re-irradiation has been attempted for secondary malignant gliomas (Carret et al. 2006; Paulino et al. 2008). Carrett and colleagues examined patients from 17 institutions participating in the Canadian Pediatric Brain Tumor Consortium (Carret et al. 2006). They identified 18 patients who developed a high-grade glioma following a previous childhood cancer. Patients had a median survival of 9.75 months from diagnosis of secondary glioma. Eight of eighteen patients received re-irradiation, and they did not see improved outcomes for patients treated with radiation, likely because of the small number of patients included in the study (Carret et al. 2006). When larger numbers were examined, differing results were found by Paulino and colleagues who examined the literature for reported cases of radiation induce malignant gliomas (Paulino et al. 2008). In 85 reported cases, the authors found that median survival was 11 months for all patients. The authors found that patients treated with re-irradiation had a 2-year survival rate of 20.5% compared to 3% for those who did not (Paulino et al. 2008). Care must be taken when interpreting these findings, as complete patient data was not available, multivariate analysis was not used, and treatment selection may rely heavily on performance status in these patients.

35.5.2 Meningiomas

Compared to childhood cancer survivors who develop malignant gliomas, children diagnosed with a secondary meningioma have better outcomes. Series report overall

survival rates ranging for 69 to 100%(Ghim et al. 1993; Taylor et al. 2009; Walter et al. 1998; Goshen et al. 2007; Hijiya et al. 2007). For participants in the BCCS, 5-year survival rates following the diagnosis of a subsequent meningioma was similar between men and women (84.0% vs. 81.7%) (Taylor et al. 2009). Both meningioma grade and presence of an underlying genetic syndrome were found to effect survival. Reported 5-year survival rate was much better 84.3% for low grade meningiomas compared to 57.3% for high grade meningiomas (Taylor et al. 2009). The majority of secondary meningiomas are low grade and solitary (Ghim et al. 1993; Paulino et al. 2009). Treatment often consists of surgical resection (Ghim et al. 1993), but this can be difficult in cases in which multiple meningiomas can occur in one patient or there are indications for adjuvant therapy when radiation has already been given as part of the treatment of the initial neoplasm (Sugden et al. 2014).

35.6 Risk Reduction Strategies

As more becomes known about the risk of SN in survivors of childhood cancer, strategies are being developed to potentially mitigate this risk. Currently, the emphasis is on developing strategies and technologies to specifically reduce the additional risk of therapeutic radiation exposure (the most commonly identified risk factor).

Radiation exposure has been shown to be a risk factor for second neoplasm formation. Furthermore, a dose relationship has been demonstrated with both the overall prescribed dose (Neglia et al. 2006; Taylor et al. 2010), and estimated dose to individual organs (Guerin et al. 2007). With such a strong relationship in the literature, efforts are being made to reduce the overall radiotherapy dose, radiation target size, and integral dose spillage for patients treated with radiotherapy.

One obstacle to achieving these clinically meaningful reductions in SNs by altering radiotherapy target volumes is that our models are not yet accurate in predicting an individual patient or organ's true risk. While small areas are fit models reasonably well, in larger organs, it is unclear if whole organ dose, partial organ dose, or point dose are more important predictors (Nguyen et al. 2008).

Examining a cohort of 4581 children treated for any cancer in France and the United Kingdom, Diallo and colleagues observed that the majority (66%) of SMN occurred in the beam bordering region (Diallo et al. 2009). Rates of SMN were lower distant to the beam (22%) and much lower in the radiation beam path (12%). Authors concluded that this high incidence along the edge of the field was seen because the dose is often not high enough to kill cells, but not low enough to avoid normal tissue effect (Diallo et al. 2009).

This result is worrisome as more clinicians are using techniques such as Tomotherapy and intensity modulated radiotherapy (IMRT) that increase the amount of tissue exposed to this intermediate dose (Hall 2006; Kry et al. 2005). These techniques are being used more frequently in the treatment of children, including those with primary CNS tumors, in order to deliver a more conformal high dose region, and potentially reduce early and late effects. The increased integral dose that accompanies these techniques is of uncertain clinical significance. Further complicating

the issue, a modulated field will require a greater number of monitor units to deliver the same dose (Klein et al. 2006). Newer techniques that modulate the beam will lead to higher amounts of machine leakage subsequently causing higher total body dose for pediatric patients (Hall 2006). In the first report of second malignancies following IMRT for pediatric malignancies of any kind, Casey and colleagues report a cumulative incidence rate of 3.3% (95% CI 1.0–7.8%) (Casey et al. 2014) that appears in line with previous reports of 2D and 3D conformal techniques (Cardous-Ubbink et al. 2007; Friedman et al. 2010; Hammal et al. 2005; Inskip and Curtis 2007; Jazbec et al. 2004; Jenkinson et al. 2004; MacArthur et al. 2007; Meadows et al. 2009; Olsen et al. 2009; Reulen et al. 2011; Gold et al. 2003).

Particle therapies, such as proton therapy, are gaining interest as a way to improve high dose conformity while avoiding low dose spillage seen with extreme modulation of photon beams. There is increasing use of proton therapy for childhood malignancies, especially tumors of the brain and spine, in part because of a theoretically reduced risk of SN. Using the spread out Bragg peak (SOBP), proton therapy has reduced low dose volumes, particularly along the distal beam axis. This dosimetric attribute of proton therapy can be especially useful when sensitive organs lay past the target volume (shown in Fig. 35.7) (Amsbaugh et al. 2012).

In the first comparative analysis of second cancer incidence rates in patients treated with proton or photon radiotherapy, Chung and colleagues matched 558 patients treated with proton irradiation to patients included in the SEER database (Chung et al. 2013). After adjusting for sex, age, primary site, and year of diagnosis, proton therapy was associated with less development of second malignancies (HR 0.52, 95% CI 0.32–0.85). Given the small number of children under 18 years old included, further analysis will need to be done to confirm the result in the pediatric population.

Several authors have reported on the SN potential of craniospinal irradiation with protons compared with photons (Miralbell et al. 2002; Mu et al. 2005; Newhauser et al. 2009). The estimated cancer risk was 7.1 fold higher using photons, even when neutron scatter was accounted for (Newhauser et al. 2009). While the low dose regions of a proton therapy plan are often considerably smaller than a photon plan for the same patient, modern planning systems do not take into account neutron scatter, which is generated. Techniques, such as passive scattering proton therapy, can produce large numbers of incident neutrons, which may or may not be clinically significant (Moteabbed et al. 2014). Scanning beam proton therapy is one commonly used technique that limits the amount of neutron scatter and is increasing being pushed for in pediatric patients (Hall 2006).

As we collect clinical data on new techniques such as IMRT and proton therapy and new strategies such as incorporating second malignancy risk into our treatment planning process we will learn more about the clinical benefits of these theoretically beneficial approaches. Still, our understanding of SNs will always be based on techniques that were used 15–20 years before given the long latency time involved to see the full effects. It is likely that regardless of any mitigation strategies we develop, SN will continue to represent a significant risk after treatment for a primary CNS malignancy of childhood.

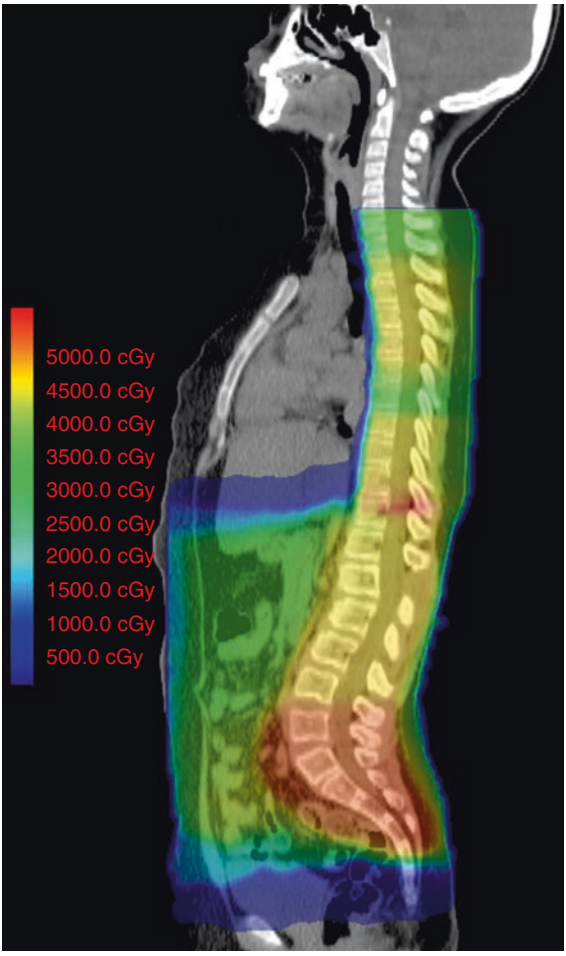

Fig. 35.7 Comparison of photon and proton dose distributions in a child (Amsbaugh et al. 2012)

Conclusions

Considering the risk of SN development when treating children with CNS tumors will continue to gain importance as outcomes for primary treatment continue to improve. Development of a SN after treatment is a multifactorial process that depends on primary disease, patient and tumor genetics, and treatment for the primary disease. Treatment and genetic factors can interact to greatly alter the risk of a SN. Children are at risk at sites both inside and outside the CNS. While some second malignancies are benign or easily treatable, some SMNs bear a grave prognosis.

A better understanding of treatment factors that contribute to SMN risk is allowing researchers to use current technologies for the first time to reduce risk of secondary cancers. Still newer technologies, including radiotherapy planning

and particle therapy are beginning to accrue more clinical outcome data, making them attractive treatment strategies for those that have access. As we gain a better understanding of the influence of systemic therapy on secondary cancer risk, treatment approaches may be designed with the risk of second malignancy in mind.

While cure of pediatric primary CNS cancer will always be the most important aim of treatment, as our knowledge of SNs continues to grow we will be able to better understand which patients are at increased risk. Great gains may be made as we continue to better understand the genetic risk factors associated with SN development. Combining this understanding of genetic risk factors with a detailed dosimetric understanding of radiotherapy's dose-volume-response relationship is imperative to construct better models for SN development. As these models improve, they may be incorporated into the consultation process to predict a child's individual risk of SN development, allowing families to make more informed decisions about treatments.

Hopefully, post-treatment surveillance and survivorship programs will continue to be developed with the risk, location, and timing of secondary malignancies in mind. Although difficult given small patient numbers and a heterogeneous population, more research is needed to develop treatment strategies for patients who are diagnosed with SMNs.

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Afterword

36

Edward C. Halperin

Contents

Abstract

The diagnosis and treatment of childhood central nervous system tumors raises profound ethical and theological questions including the problem of evil, the physician's religious license to heal, and the "slippery slope" problem of informed consent. This chapter explores these three questions.

36.1 Introduction

One of the first lessons taught to medical students at the beginning of their core pediatrics clinical rotation is that "children are not little adults." Clinical issues of feeding, growth, and development as well as the spectrum of diseases and the details

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of their management in children are not recapitulations of what is learned in the core medical school adult internal medicine rotation. While there are many similarities between adult and pediatric medicine and surgery, there are sufficient differences to render pediatrics a distinct intellectual discipline. Similarly, in neuro-oncology there are significant differences in the spectrum of diseases treated and the details of disease management between children and adults.

Regarding issues related to medical ethics and theology associated with neuro-oncology there are, similarly, many areas in common between adults and children. The concepts of beneficence, non-malfeasance, justice, and the right of self-determination are applicable in both adults and children. There are, however, important distinctions in children compared to adults in the realms of ethics and theology related to neuro-oncology just as there are in other aspects of the clinical management of central nervous system (CNS) tumors.

In this chapter, I will explore three of these issues. If the reader expects unequivocal answers to the profound ethical and theological questions posed by pediatric CNS tumors, then he/she will be disappointed. The great philosophers and theologians of the Western tradition have often come up short responding to some of the questions we shall consider in the next few pages. Surely, therefore, the efforts of this radiation oncologist to grapple with these same profound issues will pale in comparison. I have come to believe over many years of clinical practice, however, that becoming is often superior to being. Simply making the effort to grapple with difficult questions is often very rewarding. Also, it is also often perfectly fine, when dealing with "the big questions" of medicine, to conclude "I don't know" or "I'm not sure." People who seem to be absolutely sure about the answers, when dealing with issues such as "What is truth?", "What is justice?", "What is the right thing to do?", or "Is there a G-d and, if so, what is His intent?" are, to my mind, a little bit frightening. Better, I think, to say "the world is a complicated place and in grappling with the big questions I often really don't know the answer." Uncertainty in reference to biomedical ethics and theology is both normal and healthy.

36.2 The First Problem: The Logical Problem of Evil

> [Your] eyes are too pure to see evil, You cannot look upon injustice. Why do You gaze upon traitors, why are You silent while the wicked one swallows up one more righteous than him?
>
> And You have made man like the fish of the sea, like the crawling creatures over which no one rules. All are caught up in the net. (*Habbakuk* 1:13–15)

It is generally thought that the formulation of the logical problem of evil is attributable to the ancient Greek philosopher Epicurus (341 BCE–270 BCE). Epicurus felt that the goal of philosophy was to attain a happy, tranquil life of inner peace, freedom from fear, and absence of pain. "We declare pleasure to be the beginning and end of the blessed life." (Epicuraenism 1994) He viewed the universe as infinite and eternal and events as the result of the motions and interactions of atoms moving in empty space (Epicuraenism 1994; Kekes 1990; Sacks 2011; Tooley 2005). The gods dwell in intermundial spaces and are neither concerned by human affairs nor intervene in them (Schwartz and Goldstein 1990).

Why do bad things, like brain tumors, afflict innocent children if there is an all-powerful, all-merciful, all-knowing G-d? This is called "the problem of evil" and the "Epicurean paradox" is succinct summary.

> Is G-d willing to prevent evil, but not able?
> Then He is not omnipotent.
> Is He able, but not willing?
> Then He is malevolent.
> Is He both able and willing?
> Then whence cometh evil?
> Is he neither able nor willing?
> Then why call him G-d? (Mark 2001)

The vexation of the problem of evil was stated by the physician-philosopher Maimonides (1135–1204):

> It is something which pains the heart and troubles the mind. From it alone many throughout the generations have been drawn to completely reject belief. It is the fact that we see in the world crooked judgment, the righteous suffering while the wicked enjoy a good life. People say: "Why do these men succeed in their ways, while that one and that one, who appear to be righteous, are destroyed?" This is the root of rebellion within every nation and tongue (Schwartz and Goldstein 1990)

The extent to which there is a correspondence in our lives between "righteousness and happiness, and between misery and sin, is a recurrent problem" in the Bible (Hertz 1996). A clear statement of earthly reward for good deeds and punishment for bad is found in Deuteronomy 11:13–25, albeit in a largely agricultural context that would make perfect sense in a culture in which life and death depended upon the success of the harvest.

> ...if ye shall hearken diligently upon My commandments which I command you this day... that I will give the rain of your land in its season...that thou mayest gather in thy corn, and thy wine, and thine oil. And I will give grass in the fields for thy cattle…and [if] ye turn aside and serve other gods, and worship them; and the anger of The Lord be kindled against you, and He shut up the heaven, so that there shall be no rain, and the ground shall not yield her fruit; and ye perish quickly from off the good land which the Lord giveth you…

While Deuteronomy and Ezekiel declare that people get what they deserve in this life, the books of Job, Jeremiah, Habakkuk, the Psalms, and Ecclesiastes "point out how often it goes well with the wicked and ill with the righteous" (Hertz 1996).

36.3 Scientific Rationalizations, Evil, and Childhood Cancer

Oncologists repetitively encounter distressing situations. It is common for oncologists to develop scientific rationalizations to explain these situations and cope with them. Consider the following examples:

> "The patient in room 102 has metastatic bronchogenic carcinoma. He is, however, 79 years old and he smoked two packs of cigarettes per day for the last 60 years."

"The patient in room 104 has locally advanced squamous cell carcinoma of the larynx and is in severe pain and cannot control his secretions. He is, however, 65 years old and he smoked two packs of cigarettes per day for the last 45 years and averages one or two six-packs of beer per day. Alcohol and tobacco are well-known causative agents of squamous cell carcinoma of the head and neck."

"The patient in room 106 has stage IV squamous cell carcinoma of the cervix. She is 50 years old. Her medical history shows early onset of sexual activity, multiple sexual partners, and repetitive venereal infections."

What doctors are doing when they invoke known carcinogenic agents related to lifestyle choices (cigarette smoking, drinking alcohol, sexual behavior) is "explaining why this patient has advanced cancer." Somehow it makes physicians feel better to give the distressing cases in hospital rooms 102, 104, and 106 the gloss of "I know why this happened."

Consider, in contrast, a few cases on the pediatric oncology floor:

"The patient in room 202 has medulloblastoma with leptomeningeal dissemination at presentation. He is 9 years old."

"The patient in room 204 is dying of infiltrative pontine glioma which progressed promptly in spite of external beam radiotherapy and chemotherapy. He is 8 years old."

"The patient in room 206 is dying of supratentorial glioblastoma multiforme which progressed promptly in spite of surgical resection, postoperative radiotherapy, chemotherapy, and biological therapy. He is 15 years old."

There is no lifestyle choice the pediatric neuro-oncologist can invoke to "explain" the patients in rooms 202, 204, and 206. These children did not smoke, drink, or engage in unsafe sex which resulted in them having advanced CNS tumors.

As a pediatric radiation oncologist, I first encountered this problem as a young faculty member. I faced resistance from anesthesiologists when they were asked to come to the radiotherapy department to anesthetize children for daily radiotherapy. "Why are you doing this?", the anesthesiologists would ask. "Aren't all of these children going to die?" This opposition was not dissimilar from what was faced by the pioneering pediatric medical oncologists who began to actively treat childhood leukemia with chemotherapy after World War II. Colleagues would denounce them for "poisoning children who everyone knows have hopeless diseases and ought to be allowed to die in peace."

I began to wonder why anesthesiologists didn't object to anesthetizing adult patients for repeat coronary artery bypass graft surgery or for lobectomies for lung cancer? In both situations, the 5-year survival was worse than for most of the children that they were being asked to anesthetize for radiotherapy. I came to realize that many anesthesiologists were deeply upset by seeing children with cancer. They felt that cancer in children "made no sense" and implied that "the world is a random place with no order and no justice."

Unable to "explain" pediatric CNS tumors other than invoking the actions or inaction of oncogenes and tumor suppressor genes, the pediatric oncologist, the anesthesiologist, and the child's parents are bereft of a rationalization. There is "no one to blame." It is not uncommon for people to refer to this state as "being angry

with G-d. Why did this catastrophe befall this child? He did nothing to deserve this!" Faced with this conundrum, how does the doctor have the emotional strength to get up every morning and go to work?

The American botanist Asa Gray (1810–1888), overlooking the centrality of random events in evolution, felt that natural selection was directed by G-d. John Dewey called this "design on the installment plan." In a May 22, 1860 letter to Asa Gray, Charles Darwin struggled with the concept that one could delineate a rational design to evil.

> …I cannot see as plainly as others do, and as I should wish to do, evidence of design and beneficence on all sides of us. There seems to me too much misery in the world. I cannot persuade myself that a beneficent and omnipotent G-d would have designedly created the *Ichneumonidae* with the express intention of their feeding within the living bodies of Caterpillars, or that a cat should play with mice. Not believing this, I see no necessity in the belief that the eye was expressly designed. On the other hand, I cannot anyhow be contented to view this wonderful universe, and especially the nature of man, and to conclude that everything is the result of brute force. I am inclined to look at everything as resulting from designed laws, with the details, whether good or bad, left to the working out of what we may call chance. Not that this notion at all satisfies me. I feel most deeply that the whole subject is too profound for the human intellect. A dog might as well speculate on the mind of Newton. (Darwin 1919)

36.4 Common Responses to the Problem of Evil

Any practicing clinician will encounter multiple approaches to the problem of evil (Kekes 1990; Mark 2001; Eisen 2004; Kushner 1978). They include:

- Suffering is redemptive. There is a reason for this child having a brain tumor. It is through suffering and martyrdom that we achieve real self-understanding and Divine Grace. Suffering is not an absolute evil. Insofar as suffering educates and purifies it may be viewed as an instrument of Divine Love (Darwin 1919). In Deuteronomy 8:5 we read, for example, that "as a man chasteneth his son, so The Lord thy G-d chasteneth thee." The pathway of suffering may be interpreted as a necessary road.
- G-d must know what is best. There is a good reason for this child to have a malignancy. Maybe you and I cannot understand it but G-d is doing what is best. "The Creator, His actions are perfect, for all His ways are judgment. He is a G-d of faith, and there is no injustice; righteous and straight is He." (Deuteronomy 32:4) Clinicians will see this sort of language, from time to time, when their patients die. Language associated with the death of a child such as "she has been called home" or referring to funerals as "homecoming ceremonies," "G-d needed little Johnny more than we did so He called him to be by his side," or the promise that there is an afterlife which is superior to this one and, by entering into it, the child is better off are all manifestations of the "Divine Father Knows Best" point-of-view.
- G-d does the best He can but is not fully able to prevent the suffering of the innocent. G-d joins with His people in their suffering (Kushner 1978).

- There is a good god and a bad god. There is a G-d and there is Satan. Sometimes, the forces of good are in ascendancy and sometimes the forces of evil are in ascendancy. When children get sick, the evil god or force or spirit is in ascendancy (Kushner 1978).
- Things just happen. There is no G-d. Humans are the result of evolution. Oncogenes and suppressor genes and their biologic consequences have arisen through evolutionary biology like everything else in life. Sometimes, this means that children get brain tumors. We just have to deal with it. There is no point in deep theological speculation: sometimes the weather is bad, sometimes there are earthquakes and people get killed, sometimes lightning strikes a dry forest and animals are immolated by forest fires, and sometimes children get brain tumors. This response to the Epicurean paradox is to simply conclude that an omnipotent, omniscient, and omnibenevolent G-d does not exist (Eisen 2004). There are, however, several obvious flaws in the paradox. It is not obvious that there is an all-powerful and perfectly good G-d and it is, furthermore, not obvious that if there is such a G-d that G-d's existence guarantees the nonexistence of evil (Kekes 1990; Mark 2001; Alexander 1997).

36.5 Believing, Accepting Evil, and Responding to Evil

An expression of a willingness to subjugate the problem of evil to a belief in the ultimate righteousness of G-d, even if humans cannot understand the divine purpose, is found in the Talmud's approach to blessings. There are many benedictions which are mandated to be said when partaking of life's pleasures such as food or drink and a special blessing to be said when one of life's events produces rejoicing. It is curious, however, that there is also a mandated blessing for occasions of sorrow or catastrophe. What is the lesson of this requirement to bless an event which a person would normally interpret as an evil occurrence? The Talmudic scholar, Adin Steinsaltz, writes

> This obligation to bless evil occurrences...reflects an outlook on life. Where other faiths believed in dualism or in two divinities, one creating only good and the other generating evil, Judaism always believed in the one all-embracing entity. This viewpoint also found expression in the daily prayer and in the benedictions recited in the event of catastrophe, recalling the words of Isaiah…"I form the light and create darkness; I made peace and create evil, I the Lord do all these things." (Isaiah 45:7) (Steinsaltz 1976)

This citation from the prophet Isaiah is particularly powerful insofar as it explicitly states that the creation of evil is the work of a monotheistic G-d. It is, perhaps, the most straightforward response of a person of faith to the Epicurean paradox: To say that a person does believe in a G-d, that this G-d creates good and evil, and it is beyond human understanding to grasp why and, therefore, the best response is acceptance.

An interesting extension of thoughts concerning this assertion of acceptance of the inevitability of evil comes from the work of Joseph Soloveitchik. To simplify his very

erudite and thoughtful exposition of the problem: There is evil in the world. Humans ask "Why?". If one believes in a G-d beyond all human comprehension, how can one presume to have any language to engage in a conversation with an entity beyond human comprehension about "Why?". Therefore, rather than spend useless time and energy posing an unanswerable question, the only proper response for the ethical person is to spend less time pondering "Why?" and more time taking action to deal with the evil (Sacks 2011; Sokol 1999). The physician treating a child with a brain tumor and the parents of that child can be paralyzed by dwelling on the cosmic and unanswerable question: "Why did this catastrophe befall this innocent child?". Better to say, "In the grand scheme of the world, I have no idea why this evil befell this particular innocent child. Philosophers and theologians, throughout recorded time, have pondering this problem and not reached a satisfactory conclusion. What I know for certain, however, is that there is nothing I did to cause it but it is within my power to do something about it: diagnose, treat, comfort, and support; and that is what I am going to do." We will explore this point of view in more detail later in this chapter.

36.6 Does Everything Happen for a Reason?

> Who trusted G-d was love indeed
> And love creation's final law-
> Tho' nature, red in tooth and claw
> With ravine, shriek'd against his creed –
> Canto 56
> In memoriam A.H.H.
> Alfred, Lord Tennyson

A young mother dies in a tragic automobile accident, leaving behind a grieving husband and their 3-year-old son. Six years later, the child develops medulloblastoma and is cured by a combination of surgery, radiotherapy, and chemotherapy. While the child is hospitalized, the patient's father meets and falls in love with one of the nurses caring for his son. They marry and form a loving new family unit. One of the patient's aunts says at the wedding, "See, everything happens for a reason. My nephew's illness occurred to bring together this couple."

Where do beliefs like this come from? For those whose lives are deeply associated with a faith tradition, a belief that events like the occurrence of the medulloblastoma are purposefully designed by G-d helps make sense of the world. Many atheists, however, also believe in "fate"—that events in life happen for a reason and there is an underlying order to our lives. The tendency to see a meaning in life's events is probably associated with a powerful drive in humans to make sense of events by appealing to goals, desires, and intentions. While paranoid people (who obsess over other people's hidden motives and intentions) and highly empathic people (who think a lot about the emotions of others) are particularly likely to believe in fate, many people do. People find it reassuring to think that there are no random events. Rather, it is more comforting to believe that what we experience in life is part of an unfolding plan (Banerjee and Bloom 2014).

In clinical medicine, however, there is a serious danger in either the physician or the patient's family being guided by the belief that "everything happens for a reason." Such beliefs tend to make people think that the status quo or "letting things take their course" are acceptable because they are "part of the plan." Indeed, for some the viewpoint that "everything happens for a reason" means that we live in a fundamentally fair place where goodness is rewarded and bad behavior punished (Banerjee and Bloom 2014). Consider, for example, another way of telling our opening story: A young mother dies in a tragic automobile accident, leaving behind a grieving husband and their 3-year-old son. Six years later, the child develops medulloblastoma and is treated with surgery. The child's father is convinced that his infidelity during his marriage caused the death of his wife and the development of medulloblastoma in his child. He declines postoperative chemoradiotherapy so that his son "will not be made to suffer because there is a reason he got this tumor" and the child dies within 10 months of diagnosis. While the child is hospitalized for terminal care the patient's father meets and falls in love with one of the nurses caring for his son. They marry and form a loving new family. One of the patient's aunts says at the wedding, "See, everything happens for a reason. My nephew's illness and death occurred to bring together this couple."

It is important for physicians and nurses, when faced with the assertion "everything happens for a reason," to remind parents that events more often unfold in a favorable manner when individuals work hard to make them do so (Banerjee and Bloom 2014). As John F. Kennedy concluded his 1961 inaugural address: "With a good conscience our only sure reward, with history the final judge of our deeds, let us go forth…asking His blessing and His help, but knowing that here on earth G-d's work must truly be our own" (Kennedy 2013).

36.7 An Alternative Approach to the Problem of Evil

> On the contrary, this is the way it should be, that one has difficulty understanding G-d, Blessed is He. This is fitting and proper for Him; it is in accord with His greatness and exaltedness. From the very fact of His greatness—that He is exalted far above our minds—it certainly follows that it is impossible for us to understand or grasp how G-d, Blessed is He, conducts the world. Therefore it is inevitable that we should be puzzled by Him. If His conduct followed the rules of our intelligence, then His mind would be like our mind. (*Reb Nachman of Breslav*) (Mark 2001; Osler 1921)

Up to this point in our discussion, we have been discussing aspects of the typical formulations and responses to the problem of evil. The usual form of the solution is to either deny the existence of evil or to cede ground on claims about G-d's omniscience, omnipotence, or omni-benevolence. There are, however, other approaches. Let us consider a particular interesting one.

One can distinguish aspects of human life as being either those of fate or control of destiny. When a brain tumor afflicts a child and the family is in the fate mode, the viewpoint that they are being acted upon by external forces, the first response is to feel "crushed, unable to make sense of anything that has befallen him, unable to

make sense of life as a whole...struggling to understand the cosmos and G-d's role in its governance…the struggle often leads to a denial of evil, to the claim that all is really good." (Sokol 1999) People in this mode of thought feel themselves being acted upon by a wholly external dynamic, like a cork tossed on the waves of the ocean, subject to fate not of their own making and nearly impossible to understand.

Let us contrast this with someone who has adopted a control of destiny mode of thought. "While from G-d's perspective all suffering might well be justified, and therefore good, human beings are incapable, for metaphysical reasons, of adopting G-d's perspective...the only humanly possible response to suffering is to acknowledge its evil. To deny the existence of evil may well be metaphysically true but metaphysical truth is humanly false, and...humanly useless." (Sokol 1999) Joseph Solovetchik writes that "Man is born like an object, dies like an object, but possesses the ability to live like a subject, like a creator, an innovator who can impress his own individual seal upon his life...and enter into a creative, active mode of being. Man's task in the world...is to transform fate into destiny…an existence of compulsion, perplexity and muteness into an existence replete with a powerful will, with resourcefulness, daring and imagination." (Sokol 1999)

Restated, there is no value in having a conversation about the motivations of a monotheistic all-powerful, all-knowing, and all-merciful G-d. Humans have no language whatsoever to engage in such a conversation or understand the motivations and actions of such a G-d (Sacks 1993). The psychiatrist and Concentration Camp survivor Victor Frankel explained it as follows:

> [Does] an ape that was being used to develop poliomyelitis serum—and for this reason punctured [by hypodermic needles] again and again—… ever be able to grasp the meaning of its suffering.[?] … of course it would not; for with its limited intelligence it could not enter into the world of man, i.e., the only world in which its suffering would be understandable. Then I pushed forward with the following question: "And what about man? Are you sure that the human world is a terminal point in the evolution of the cosmos? Is it not conceivable that there is still another dimension possible, a world beyond man's world; a world in which the question of and ultimate meaning of human suffering would find an answer?" (Schwartz and Goldstein 1990; Frankl 1992)

The only rational response is action (Sacks 2011). "To respond to suffering actively, creatively, and productively, by honestly confronting the horrors of suffering, rather than self-deceptively shoving them under some thick metaphysical carpet." (Sokol 1999) Those who are suffering must learn from experience to empathize with the others who are suffering and act upon that empathy.

How does this approach help a clinician caring for a child with a brain tumor? It may be of use to formulate the problem of evil in the following way: Neither the parents of a child with a brain tumor nor the doctor taking care of that child gain anything by investing time and energy into cosmic debates over the origin of evil. They should simply accept that evil does exist. If they are people of faith, then they can conclude that if there is a G-d humans are incapable of discerning G-d's motives. It's fine to discard statements such as "there really is a divine good in this child having a brain tumor, we just can't understand what it is" and replace them

Fig. 36.1 The Hebrew Letter Bet

with "I don't understand why this happened to this child and I never will, but what I do know is that I can do something about dealing with this tumor and I had best get about doing it."

A charming Biblical commentary illustrates this point of view. The book of Genesis begins with the word Bereshit or "In the beginning." Why, the commentary wonders, does the text of the Bible begin with the Hebrew letter Bet, the second letter of the alphabet? Wouldn't it have made more sense to begin the creation of the world with the first letter of the alphabet, Aleph, either because it is the first letter or because the letter is associated with the oneness of G-d? Perhaps the answer is to be found in the shape of the letter (Fig. 38.1). Imagine a person standing on the base line of the letter and remember that Hebrew is read from right to left. The only opening in the letter is at the front. Therefore, the role of humans is not to seek to know what is above you, it is unknowable. Similarly, it is not to speculate on what is below you, it is also unknowable. Your only choice is to go forward—to emphasize the primacy of action. Abstruse theological discussions are less important than taking action in this world (Szlakmann 1990).

36.8 The Second Problem: The Problem of the Physician's "License to Heal"

For a person who believes that we live in a world governed by an all-powerful, all-knowing, all-just, and all-merciful monotheistic G-d, then all of life's events and the natural world are part of the Divine will. CNS malignancies, therefore, as a natural event, may also be construed as part of the Divine will. Some people of faith, therefore, conclude that human interference with illness is, at best, hubris and, at worst, a direct attempt to interfere with Divine will and, therefore, blasphemous. By what right can a physician presume to try and effect the course of a fellow human's illness against the deliberate designs of Providence? (Jakobovits 1959) This concept is referred to as either "the right to heal" or "the license to heal."

The problem of the alleged defiance of the will of G-d does not, of course, only apply to the physician's license to heal. Consider, for example, the lightning rod. By the seventeenth and early eighteenth centuries, many people had observed lightning

and its destructive capabilities. Trees and buildings were felled and/or burned and animals and humans were killed or injured by lightning strikes. To many observers at the time the destruction wrought by lightning must be caused by G-d's wrath directed against humans for their misdeeds (Dray 2005).

To the modern reader, explaining lightning or disease or, for that matter, earthquakes and floods as the punishment of a wrathful G-d might seem strange. However, to our forebears these events seemed to make sense if they were attributed either to a wrathful G-d or to a battle between the forces of G-d and Satan. Rather than the world being one of complete moral chaos, the world could be at least be understood in terms of either Divine punishment or Divine v. Satanical combat.

When understood in the context of his times, therefore, it is not surprising that Benjamin Franklin's invention and implementation of lightning rods as a means of protecting people and property was viewed, by many of his contemporaries, as interfering with the Will of G-d. By what right did a mere human aspire to snatch lightning from the heavens and transmit it, via a grounded electrical conducting cable, to the earth? Some Christian ministers of Franklin's time attributed other natural disasters such as earthquakes as Divine punishment for Franklin's invention. On the other hand, many others lauded Franklin for his use of observation and reason to understand and address the problem of lightning strikes (Dray 2005).

Using human reason to treat childhood brain tumors or inventing the lightning rod raise similar theological questions and have been debated on analogous terms. Societal attitudes toward the ill person have gone through several phases in the Western heritage. Among ancient Semitic civilizations, the ill person was burdened with an odium insofar as some people felt that illness was an atonement for unrighteousness. In Ancient Greece, illness destroyed the idea of the perfect harmony and balance of health (Jakobovits 1959). With the rise of Christianity, suffering assumed the character of purification and a mean of achieving grace. Martyrdom was redemptive.

There are three major approaches taken to deal with the theological problem of the physician's license to heal. One is to reject medicine altogether. Suffering is to be borne. Any attempt to ameliorate and treat disease is an attack on the Divine scheme of life. Sir William Osler, in his 1913 series of lectures later collected in the book *The Evolution of Modern Medicine*, seeks to explain why, after the fall of the Roman Empire, "the light of [medical] learning burned low, flickering almost to extinction. How came it possible that the gifts of Athens and Alexandria were deliberately thrown away?" (Osler 1921) Osler lays some of the blame on the collective societal trauma of the destruction of Rome and the devastating effects of the plague. He places, however, considerable blame on medieval Christianity's position on the question of the license to heal. Consider, Osler writes, the change wrought by Christianity.

> The brotherhood of man, the care of the body, the gospel of practical virtues formed the essence of the teaching of the Founder—in these the Kingdom of Heaven was to be sought; in these lay salvation. But the world was very evil, all thought that the times were waxing late, and into men's minds entered as never before a conviction of the importance of the four last things—death, judgment, heaven and hell. One obstacle alone stood between man and

> his redemption, the vile body, "this muddy vesture of decay," that so grossly wrapped his soul...the wisdom of the Greeks was not simply foolishness, but a stumbling block in the path. Knowledge other than that which made a man "wise unto salvation" was useless. All that was necessary was contained in the Bible or taught by the Church…The new dispensation made any other superfluous. As Tertullian said: Investigation since the Gospel is no longer necessary. (Dannemann, Die Naturw., I, p. 214.) This attitude of the early Fathers toward the body is well expressed by [Saint] Jerome. "Does your skin roughen without baths? Who is once washed in the blood of Christ needs not wash again." In this unfavorable medium for its growth, science was simply disregarded, not in any hostile spirit, but as unnecessary. (Osler 1921)

A second approach to the problem of the license to heal is to ask: Is there any less moral justification for curing illness by the use of human intelligence than there is for using human intelligence to derive methods for irrigating the soil to improve crop yields or to put a roof over one's head? Maimonides, for example, responds to people who think that one can restore a person's faith by reducing their reliance on human cures.

> According to this worthless and corrupt opinion, any person who is hungry and goes for bread and eats it, though he will doubtless be healed from that grave illness (the illness of hunger), would have to be considered in lacking in faith and reliance on his G-d. (Jakobovits 1959)

A third approach to the problem of the physician's license to heal is to assert that while disease may be the result of a Divine visitation, there is an additional divine sanction wherein G-d grants man the right and responsibility to cure. Biblical injunctions to not "stand idly by the blood of your fellow" (Leviticus 19:16) and if a person is injured in a quarrel then the individual causing the injury must cause the injured party "to be thoroughly healed" (Exodus 21:18–19) are cited in the Talmud to justify the physician's license to heal. "If any human saves a single soul…[it is as] if he had saved the entire world." (Sanhedrin 37a) and "from [the verses in Exodus and Leviticus it is derived] that the physician is granted permission to cure." [Baba Kamma 85a] (Jakobovits 1959) Maimonides concludes

> Free will is bestowed on every human being...a man's actions are in his own hands; no compulsion is exerted. He is constrained by nothing external to him…[Wealth] should be extended for noble purposes, and to employ the maintenance of the body of the preservation of life, so that its owner may obtain a knowledge of G-d, insofar as that is vouchsafed to man. From this point of view, the study of medicine has a very great influence on the acquisition of the virtues and of the knowledge of G-d, as far as on the attainment of true spiritual happiness. Therefore, its study and acquisition are pre-eminently important religious activities. (Nuland 2005)

36.9 The Third Problem: The Problem of Informed Consent and the Slippery Slope

The irradiation of a brain tumor of childhood often, of necessity, creates a risk of a decrement in IQ, impairment in neuroendocrine function, and the chance of radionecrosis of brain tissue. The treating physician will, therefore, seek to obtain

informed consent from the child's parents for therapy in the context of these risks and will often quote probabilities of these injuries. For example, "If we treat this tumor with the proposed course of surgery, radiotherapy, and chemotherapy, there is an X% chance of the loss of Y IQ points by your child, a Z% chance of abnormal hormone function which will necessitate endocrine therapy, and a Q% chance of necrosis of brain tissue which could cause further IQ loss, seizures, or death. In return for these risks, there is a B% chance of curing the tumor. Do I have your permission to treat your child?"

Because of the way in which consent is commonly sought, the child's parents are placed in the position of making value judgements in the context of incomplete information. No one knows for certain, for example, what the IQ will be at age 21 of a 4-year-old. One can estimate the likely IQ based upon the IQs of the biological parents, the IQs of siblings, and the educational and social opportunities likely to be afforded to the child—but the prediction remains imprecise. Asking parents, therefore, to decide if they can accept a likely decrement of X IQ points when they do not know what number they are subtracting X from is asking a great deal. Obviously, the loss of, say, 5 IQ points from someone whose IQ was going to be 130 has considerably less social and economic consequences than the loss of 5 IQ points from someone whose IQ was going to be 85. Furthermore, IQ loss might be placed in social context by parents. If a child's parents have aspirations that the child will follow the footsteps of a father who is a nuclear engineer and a mother who is a cardiac anesthesiologist, then the loss of IQ points will be given a different value that if the parents are both unskilled laborers and have aspirations for their child that he/she becomes an unskilled laborer.

At what point does IQ loss, neuroendocrine impairment, or the risk of radionecrosis become "too much" such that someone would either recommend against treatment or a parent might decline to give consent for treatment? Some might say, "All life is of infinite value. There is no impairment which makes a life not worth saving and not worth living. Therefore, we will accept any risk of any injury if there is a possibility of preserving life." Others might say, "No, there are certain types of injuries of certain extent which are more than I feel are consistent with a quality of life worth living."

If one adopts the later point-of-view, then where does one draw the line to determine under what circumstances life is worth saving and living? Is it worth saving a life if the child's IQ is likely to be 70 but not 50? What about 70 but not 69? This type of reasoning engenders great fear in some people because it harkens to the expression "life unworthy of life." This phrase was used by the Nazi government of Germany to justify, initially, the execution of children with congenital malformations, the mentally retarded, and psychiatric patients. Ultimately, it formed the Nazi logic for the mass slaughter of those religious and racial groups deemed by Hitler's government to be "unworthy of life."

Giving informed consent for cancer treatment in children, where the treatment engenders a risk of late effects, creates the so-called slippery slope ethical dilemma. If there are a set of possible treatment complications which might lend someone to deem these complications "unacceptable," then are we launched down a "slippery slope" wherein many types of human life will be deemed "unworthy of life." Aren't

judgements about what complications are unacceptable entirely subjective? Where does one draw the line and how firm is that line?

Physicians must take great care not to impose their own subjective value systems on parents. The opinion of the doctor regarding the value placed on IQ loss or neuroendocrine impairment can play a role in decision-making regarding informed consent for treatment. The opinion of the doctor, however, must not supplant the value system of the child's parents and other family members.

Conclusion

In this chapter, we have explored the ethical and theological problems related to childhood CNS tumors and their treatment: the problem of evil and responses to it, the problem of the physician's license to heal, and the problem of obtaining informed consent in the context of the "slippery slope." The author hopes the reader found the exposition of these problems of interest even though he finds himself as incapable as his far more distinguished historical predecessors of unequivocally "solving" them.

Note Some of the material in this chapter has been previously published by the author, in a different form, in "The Problem of Evil and Childhood Cancer" and "Common Responses to the Problem of Evil" in Halperin EC, Chapter 1, "The Cancer Problem in Children", in Constine LS, Tarbell NJ, Halperin EC (editors). Pediatric Radiation Oncology, Sixth Edition. Philadelphia: Wolters Kluwer, 2016, and is used in this chapter with the gracious permission of Wolters Kluwer of Philadelphia, Pennsylvania.

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