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Adenocarcinoma of the Esophagogastric Junction

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Adenocarcinoma of the Esophagogastric Junction

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To my teacher J. Rüdiger Siewert, Emeritus Professor and Chairman, Department of Surgery, Technische Universität München, Germany, for his 70th birthday

Zurich, Switzerland

Paul M. Schneider, MD
Professor of Surgery

Preface

The Siewert Lesson for Adenocarcinomas of the Esophagogastric Junction: *A Plea for an Order in a Complex Disease*

Adenocarcinomas of the esophagogastric (AEG) junction show an alarming increase in incidence over the last decades in Western industrialized countries. This special volume with contributions from dedicated individuals and friends in the field tries to summarize our current understanding of the etiology, pathogenesis, classification, clinical staging, and state-of-the-art treatment of this modern plague.

In 1987, JR Siewert, Emeritus Professor and Chairman of the Department of Surgery (Fig.) at the Technische Universität München, Germany, inaugurated a therapeutically relevant classification of AEG which is used by many experts and recommended by the International Society for Diseases of the Esophagus and International Gastric Cancer Association. As St. Thomas of Aquino wrote in his *Summa contra Gentiles* (Book I, Chap. 1): "Those ones have to be called wise who put the things into the right order" (author's translation). The "Siewert Classification" is purely based on the anatomic localization of the tumor center, which can be defined by endoscopy using the proximal end of the longitudinal gastric mucosa folds as a pragmatic reference for the endoscopic cardia. AEG include all tumors 5 cm proximal (+5 cm) and distal (−5 cm) of the endoscopic cardia (point zero). An adenocarcinoma of the distal esophagus (>1 to +5 cm), which usually arises from an area of specialized intestinal metaplasia (Barrett's esophagus) is classified as a type I cancer. A type II cancer is a true carcinoma of the cardia (+1 to −2 cm) arising at the esophagogastric junction, whereas a type III cancer (−2 to −5 cm) is a subcardial gastric carcinoma that infiltrates the esophagogastric junction or the distal esophagus from below.

It is noteworthy to mention that the new seventh UICC/AJCC TNM Classification, effective since January 2010, classifies AEG as one group of cancers and finally eliminates meanders like staging regional lymph node metastases at the celiac trunk for Barrett's cancer as systemic metastases (M1a). Even more important is that the new UICC classification of AEG neither eliminates the Siewert classification nor intends to suggest a change in the surgical approach to treat AEG.

For Siewert type I cancers, the standard approach is a transthoracic en bloc esophagectomy with a two-field lymphadenectomy and for the majority of AEG type II and

especially III, a transhiatally extended (i.e., distal esophageal resection) gastrectomy with lymphadenectomy of the lower mediastinum and a systematic abdominal D2-lymphadenectomy is adequate. However, surgeons dealing with type II and III cancers must be prepared to extend a planned transhiatally extended gastrectomy into a transhiatal or transthoracic esophagectomy in case of a positive resection margin at frozen section or if the situation clearly demands an esophagectomy or even esophagogastrectomy.

Local tumor control is still the key to survival and can be achieved by an armada of stage-dependent techniques in experienced centers including endosopic mucosal resections and limited surgical resections for early cancers. For locally advanced tumors, multimodality therapy options are necessary treatment extensions not competing with, but rather amplifying surgical resections.

As a consequence of differentiated diagnostic and therapeutic tools, emerging quality issues involving all aspects of AEG treatment can no longer be neglected, and these patients have to be treated in specialized centers.

Recent developments from molecular pathogenesis to molecular response prediction and early metabolic response evaluation by PET-CT in neoadjuvant treatment protocols as well as sentinel node technology and micrometastases complete our current scientific understanding and efforts in basic and translational research to combat a frequently deadly disease.

We have tried hard to summarize the major aspects of our current understanding of the etiology, pathogenesis, diagnosis, and treatment of a complex disease. At the end, we all should not forget Sepp Herberger's (Coach of the German Football World Champion Team 1954) words: "After the game is before the game."

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Fig. JR Siewert, Emeritus Professor and Chairman of the Department of Surgery at the Technische Universität, Munich, Germany

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1 Epidemiology of Adenocarcinoma of the Esophagus, Gastric Cardia, and Upper Gastric Third

Manuel Vial, Luis Grande, and Manuel Pera

Abstract The incidence of adenocarcinoma of the esophagus and esophagogastric junction (gastric cardia) has risen rapidly over the past three decades in the United States and northern Europe. This increase had been most dramatic among White males. The majority of these cancers arise from Barrett's esophagus. However, less than 10% of the patients with esophageal adenocarcinoma were known to have Barrett's esophagus before. Current evidence indicates that gastroesophageal reflux and obesity are major risk factors for adenocarcinoma of the esophagus. Abdominal obesity, more prevalent in males, and independent of body mass index, seems to be associated with an increased risk of esophageal adenocarcinoma but not of cardia adenocarcinoma. This observation may explain the high male:female ratio observed in esophageal adenocarcinoma. Tobacco use has also been found as a possible risk factor for adenocarcinoma of the esophagus and gastric cardia. Infection with *Helicobacter pylori* and the use of nonsteroidal anti-inflammatory drugs might reduce the risk. On the other hand, low intake of fruits, vegetables, and cereal fibers seem to increase the risk of esophageal adenocarcinoma. Currently, there is no evidence that strongly supports any specific strategy to screen a subgroup of the population at risk for adenocarcinoma of the esophagus or esophagogastric junction. Future strategies to decrease obesity and tobacco use might help to reduce the burden of esophageal adenocarcinoma at least partially.

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1.1 Introduction

Over the past three decades, the incidence of adenocarcinoma of the esophagus (ACE) and esophagogastric junction (EGJ) has increased rapidly in North America and Europe, whereas the frequency of squamous cell carcinoma (SCC) has remained relatively stable or declining in these geographical areas. In this review, we will discuss this epidemiological change as well as the role of different risk and protective factors that have been associated with these cancers.

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1.2 Demographics, Trends, and Geographic Variations of Adenocarcinoma of the Esophagus and EGJ

Data from the Surveillance Epidemiology and End Results (SEER) program in the United States (US) indicated that the incidence of esophageal adenocarcinoma in White males had doubled from the early 1970s to the late 1980s (Yang and Davis 1988). Blot and associates (1991) showed that the increases in the rates of esophageal adenocarcinoma in the US through the 1980s had been in the order of 5–10% per year. By 1990, adenocarcinomas accounted for nearly half of all esophageal cancers among White men (Blot et al. 1993). Based on the incidence trends available from the SEER program through 1998, Brown and Devesa (2002) described that among White males, the incidence of ACE rose from 0.72 per 100,000 population in 1974–1978 to 3.7 per 100,000 population in 1994–1998, an increase of greater than 400%. The rate of increase in esophageal adenocarcinoma in the last 25 years is greater than that of any other solid tumor in the US over the same time interval. The rates of ACE among White females, although much lower than those among White males, increased by more than 300%, from 0.11 per 100,000 population in 1974–1978 to 0.47 per 100,000 population in 1994–1998. In addition, ACE rates increased by more than 100% in Afro-American males, from 0.35 per 100,000 population in 1974–1978 to 0.81 per 100,000 population in 1994–1998; however, the rates of SCC among this population subgroup remain significantly higher (Brown and Devesa 2002). Using more recent nation-wide data (1998–2003) from US population-based cancer registries (NPCR – SEER) with substantially increased population coverage (83%) compared to previous studies, Trivers et al. (2008) found that ACE incidence increased by 2.1% per year. These results indicate a smaller magnitude of increase of ACE than those previously reported. In a recent update from the SEER program assessing the period 2001–2005, ACE represents 55.5% of all esophageal carcinomas in US (Ries et al. 2007).

In a comparison study within the U.S. SEER cancer registry for the years 1973–1998, Kubo and Corley (Kubo and Corley 2002), reported substantial regional, temporal, and ethnic differences between the incidence rates of ACE and adenocarcinoma of EGJ. These authors observed higher incidences of ACE and adenocarcinoma of EGJ in Seattle than Utah (5.3 and 4.0 vs. 2.4 and 2.8 per 100,000 person-years respectively). Association with other variables was also verified (male gender and White population were of predilection in both types of adenocarcinomas in all the studied regions). Crane et al. (2007b), using a population-based medical records database in Olmsted County, Minnesota, report that between the decades of 1971–1980 and 1991–2000 (Fig. 1.1), the incidence of ACE increased significantly from 0.4 to 2.5 per 100,000 person-years, and the incidence of adenocarcinoma of the EGJ also increased from a rate of 0.6 to 2.2 per 100,000 person-years. Similar trends have been reported from Denmark, The Netherlands, United Kingdom (UK), and other northern European countries (Levi and LaVecchia 1991; Moller 1992; Powell and McConkey 1992; Hansson et al. 1993; Reed and Johnston 1993; Powell et al. 2002; Vizcaino et al. 2002; Crane et al. 2007a; Falk et al. 2007). The incidence rates for ACE are the highest in Scotland (>9 cases per 100,000 men) compared with other countries analyzed. Using the recent data provided by the World Health Organization (WHO) over the last two decades, Bosetti et al. (2008) have confirmed a clear upward trend in the incidence of ACE in northern Europe; in Denmark and Scotland the incidence of ACE in men is now higher than that of SCC.

In South Australia, Nguyen et al. (2003) revealed that the incidence of ACE increased

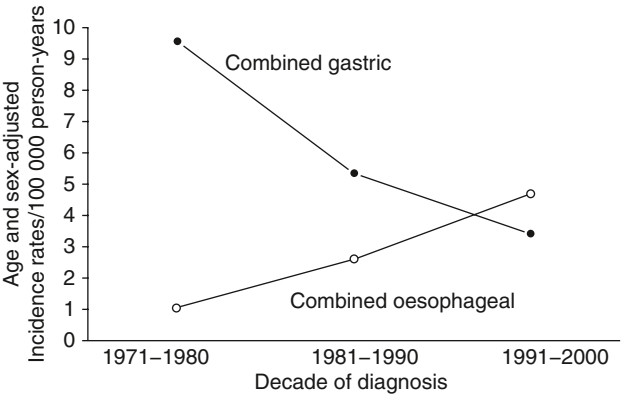

Fig. 1.1 Combined incidence of gastric (proximal, distal, and diffuse) and esophageal (esophagus and EGJ) adenocarcinoma among Olmsted County, Minnesota residents, 1971–2000. Age- and sex-adjusted (to USA white census 2000) rate are per 100,000 person–years. With permission from Crane et al. (2007b)

significantly (close to 140%) in both genders between 1977 and 2000. However, this upward trend has not been confirmed in Asian countries. Yee et al., in a population-based study, reported that in Hong Kong, though a Westernized life-style has been adopted (local prevalence of obesity similar to the US, decreased intake of vegetables, fruits, poultry, but increased consumption of processed meat, fat, beer and liquor) and with an increasing prevalence of gastroesophageal reflux disease (GERD), the incidence of ACE and the ratio of ACE vs. SCC decreased in the period from 1983 to 2003. One possible explanation is that even though the prevalence of GERD is getting more common, Barrett's esophagus (BE) is rare, and 94% of reflux esophagitis were either Los Angeles grade A or grade B esophagitis (Yee et al. 2007).

These observations of esophageal adenocarcinoma are paralleled by rising rates of adenocarcinoma of the EGJ (Blot et al. 1991; Powell and McConkey 1992; Zheng et al. 1993; Botterweck et al. 2000; Falk et al. 2007). Zheng and associates (1993) examined the incidence pattern of adenocarcinoma of the EGJ and distal esophagus in Connecticut between 1955 and 1989. Among males, adenocarcinoma of the EGJ increased during the study period from 0.6 per 100,000 population in 1955–1959 to 3.0 per 100,000 population in 1985–1989. Among females, adenocarcinoma of the EGJ was low (0.1 per 100,000 population) and unchanged during the time period between 1955 and 1969; however, the rate increased from 0.1 per 100,000 population in 1965–1969 to 0.6 per 100,000 population in 1985–1989. In the West Midlands (UK), Powell and McConkey (Powell and McConkey 1990) found that the incidence rate of EGJ tumors increased from 0.7 to 2.0 per 100,000 population between 1962 and 1981. Falk et al. (2007) found similar results in the incidence rate of adenocarcinoma of EGJ in Sweden, with an annual average increase of 2% in both genders between 1970 and 2004.

The causes for this alarming increase in the incidence of adenocarcinoma of the esophagus and EGJ are unclear. Different studies confirm that the increases in the incidence are real and the possibility of anatomic misclassification of adenocarcinoma of the gastric cardia as a possible explanation for the increases in the incidence of esophageal adenocarcinoma, could be ruled out (Devesa et al. 1998; Pohl and Welch 2005; Lindblad et al. 2006).

As we will discuss later, several risks and protective factors for esophageal and EGJ adenocarcinomas, including obesity, tobacco use,

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alcohol, dietary factors, medications, and *H. pylori* infection have been proposed. On the other hand, it is acknowledged that ACE and a portion of EGJ adenocarcinomas arise from long or short segments of BE (specialized intestinal metaplasia), a condition caused by chronic reflux of acid and duodenal contents into the esophagus (Cameron et al. 1997; Pera 2008).

1.3 Age, Gender, and Race

ACE and EGJ show similar epidemiologic characteristics that clearly distinguish them from SCC of the esophagus and from adenocarcinomas of the more distal parts of the stomach. These features include a very high male-to-female ratio at around 7:1 and a higher incidence among Whites compared with Blacks (Kalish et al. 1984; Rogers et al. 1986; Wang et al. 1986; Blot et al. 1991; Powell et al. 2002; Wu et al. 2007b).

Using data from population-based cancer registries aggregates published by the North American Association of Central Cancer Registries (NA-ACCR), Wu et al. (2007b) found that in males, the incidence of ACE in the Black non-Hispanic US population was 25% that of the White non-Hispanic US population (1.42 and 5.71 per 100,000 population, respectively), in the period 1998–2002. This proportion was 41% in females (0.32 and 0.78 per 100,000 population, respectively). They also observed that the incidence of ACE in Hispanic US population was 2.42 and 0.52 per 100,000 in males and females, respectively, with a male:female ratio of 4.6. This ratio was similar to that in Black non-Hispanic population (4.4), but minor to that of White non-Hispanic population (7.3).

Zheng et al. (1993) reported that the male: female ratio of age-adjusted incidence rates in Connecticut is approximately 5.5 for adenocarcinoma of the EGJ. The White:Black ratio for adenocarcinoma of the EGJ has been increasing, mainly due to a more rapid increase in the incidence of adenocarcinoma of the EGJ in Whites (Zheng et al. 1993). The disease, either in the distal esophagus or at the EGJ, mostly affects patients over 50 years of age with the peak at around 55–65 years (Yang and Davis 1988). Devesa et al. (1998) and Crane et al. (2007b) showed that the increasing trends for esophageal and gastric cardia adenocarcinomas varied by age, being more pronounced among older men. Below 65 years, the rates for esophageal adenocarcinoma doubled, whereas the rates for gastric cardia adenocarcinoma increased by 20%. In contrast, above 65 years, there were threefold to fourfold increase in esophageal adenocarcinoma and a 60% increase in gastric cardia adenocarcinoma (Devesa et al. 1998).

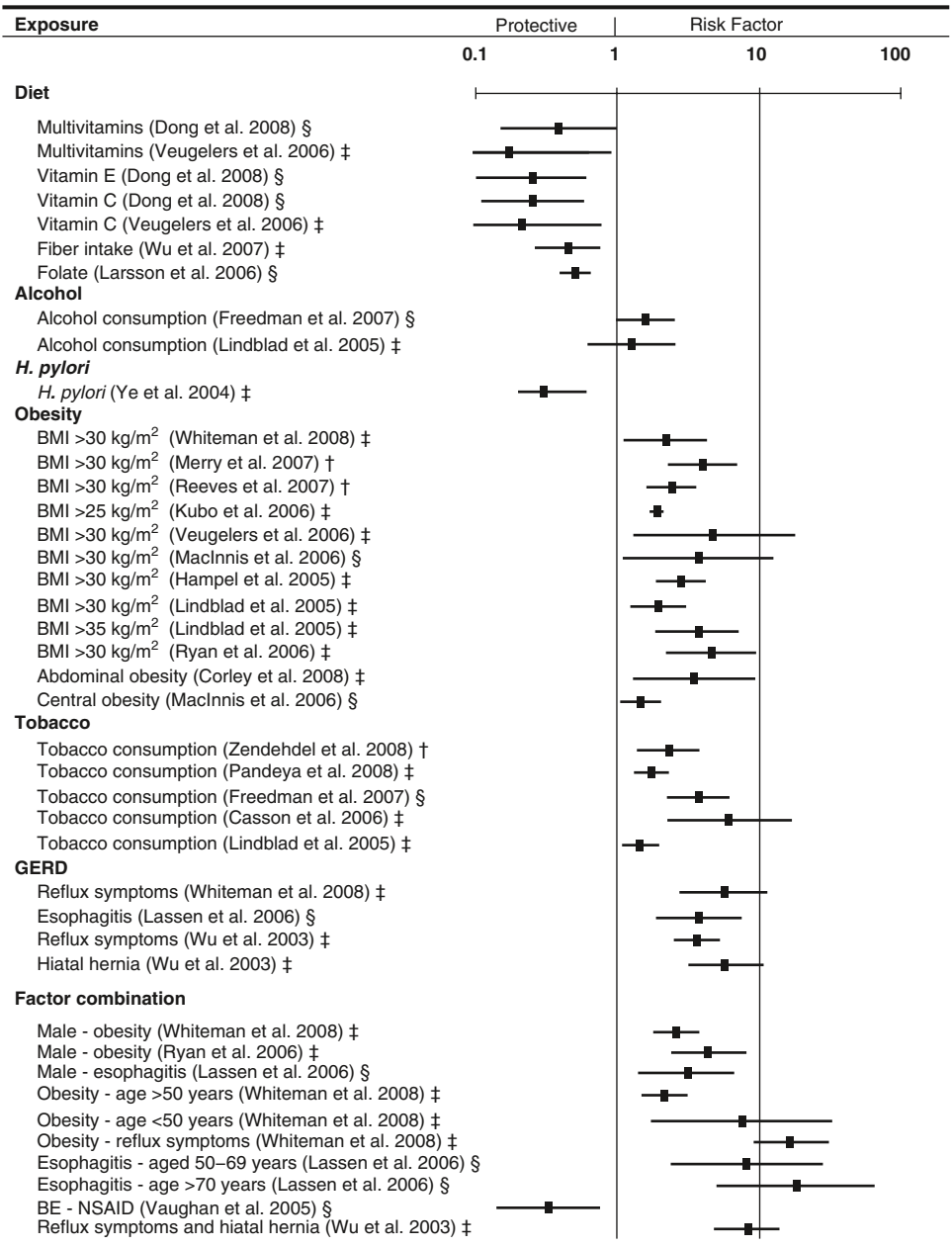
1.4 Gastroesophageal Reflux Disease and ACE and EGJ

Chow and associates (1995) compared 196 patients with ACE or EGJ with 196 matched controls. Significant twofold or greater risks of adenocarcinoma in both the locations were associated with a past history of esophageal reflux, hiatal hernia, esophagitis/ulcer, or dysphagia. The odds ratio increased with the increasing number of these conditions. A population-based, case–control study in Sweden found a strong association between symptomatic GERD and the risk of ACE (Lagergren et al. 1999a). An association, although weaker, was also found for adenocarcinoma of the EGJ, but not for SCC. Among the patients with recurrent reflux symptoms vs. those who had no such symptoms, the odds ratios were 7.7 for esophageal adenocarcinoma and 2.0 for adenocarcinoma of the cardia. In addition, the more frequent, the more severe, and longer-lasting the symptoms of reflux, the greater the risk. Among those with long-standing

severe reflux symptoms, the odds ratios were 45.5 for ACE and 4.4 for adenocarcinoma of the EGJ. The authors noted equally frequent reflux symptoms in adenocarcinoma cases with or without BE. They questioned the role of BE in the carcinogenic pathway. However, 62% of their esophageal adenocarcinomas had BE, which would expect in <1% of asymptomatic individuals and in 3–7% of patients with reflux symptoms and no cancer (Cameron and Romero 2000). In line with the findings of the Swedish Group, three studies (Farrow et al. 2000; Wu et al. 2003b; Whiteman et al. 2008) have found that both frequent GERD symptoms and a history of hiatal hernia were associated with increased risk for esophageal adenocarcinoma (Fig. 1.2). Neither reflux symptoms nor reflux conditions (hiatal hernia, esophagitis) were associated with the risk of adenocarcinoma of the EGJ in a multicenter study (Farrow et al. 2000). The cancer risk to the individual patient with GERD is low, however, because GERD is so common, some 15–20% of adults have reflux symptoms every week (Locke et al. 1997). It has been estimated that a population of 100,000 would include over 10,000 subjects with reflux symptoms, but the incidence of esophageal adenocarcinoma is only about 2.3 per 100,000 per year (Cameron and Romero 2000). BE is the intermediate stage between GERD and adenocarcinoma; progression of BE to invasive adenocarcinoma is reflected histologically by the metaplasia-dysplasia-carcinoma sequence (Cameron 1997). Lassen et al. (2006) retrieved data on endoscopies from five large population-based registers with the aim to estimate the incidence of diagnosed endoscopic esophagitis lesions, and the risk of esophageal adenocarcinoma among patients with previously diagnosed esophagitis. They found that the risk of ACE has increased fivefold in patients with previously diagnosed esophagitis, but most of the adenocarcinomas occurred among patients with BE. Likewise, Murphy et al. (2005) in a population-based cohort, have found that the risk of adenocarcinoma is not elevated in patients with histological evidence of esophagitis without BE. However, we can't, on the basis of symptoms, distinguish those with GERD, with or without BE. Shaheen et al. (2000) believes that until there is a better way of stratifying cancer risk among heartburn patients, decreasing the incidence of esophageal adenocarcinoma among those with heartburn may be difficult. It has been suggested that among 50-year-old men with symptoms of GERD, one time screening endoscopy for BE and adenocarcinoma of the esophagus is probably cost-effective (Cameron and Romero 2000; Inadomi et al. 2003).

1.5 Barrett's Esophagus and ACE and EGJ

BE, an acquired condition secondary to GERD, is a metaplastic change of the lining of the esophagus with the replacement of the normal squamous epithelium by columnar intestinal-type epithelium (Spechler and Goyal 1996; Pera 2008). It is now generally accepted that most, if not all, adenocarcinomas of the esophagus develop from areas of BE (Cameron et al. 1995). The prevalence of BE has been estimated at 3–7% in patients with frequent reflux symptoms undergoing endoscopic examination, compared with 1% in patients having endoscopy for any clinical indication (Cameron et al. 1997). It is currently unclear whether the prevalence of BE is increasing or whether this diagnosis is being made more frequently because of the widespread use of endoscopy. In a population-based study, Conio and Cameron found that the incidence and prevalence of clinically diagnosed BE have increased in parallel with the increased use of endoscopy. The rate of new diagnoses of BE increased 28-fold over the years in the study from 0.37 to 10.5 per 100,000 person-years. The rate of incidence changes of BE was similar to the 22-fold increased utilization of endoscopy over the same years (Conio et al. 2001). Prach



§Hazard Ratio; ‡Odds Ratio; †Relative Risk. Abbreviations: BMI = Body mass index; BE = Barrett's esophagus; NSAID = Non-steroidal anti-inflammatory drug; GERD = Gastroesophageal Reflux Disease.

Fig. 1.2 Protective and risk factors for adenocarcinoma of the esophagus, reported since 2003. Data are presented as mean risk (*square*) and 95% confidence interval (*line*)

(1997) in Scotland, found 1.4 BE cases per 1,000 endoscopies in 1980–1981, with a remarkable increase to 42.7 per 1,000 endoscopies 12 years later. The authors concluded that a real increase in the incidence of BE had occurred. These trends have also been confirmed in the Netherlands and Australia (van Soest et al. 2005; Kendall and Whiteman 2006). Kendall and Whiteman (2006) have reported that while the prevalence of long-segment BE remains unchanged, it is the prevalence of short-segment BE that is increasing, a phenomenon related in part to increased recognition and awareness of this condition.

BE is more common in men than in women, with a male:female ratio of about 2:1. This male predominance increases with the development of Barrett's adenocarcinoma with a ratio of at least 3:1. Mean age at diagnosis in male BE (62.0 years) is lower than that in female BE patients (67.5 years). The same applies to adenocarcinoma, mean ages at diagnosis being 64.7 in males and 74.0 years in females. A recent study in UK suggests that there is an age shift of 20 years in the onset of BE in females that may explain in part the higher incidence of adenocarcinoma in males compared to females. Many females would not survive long enough to progress to symptomatic adenocarcinoma of the esophagus (van Blankenstein et al. 2005).

Autopsy data suggest that the majority of BE cases go undetected in the general population (Cameron et al. 1990). Cameron (1993) estimates that there are about one million persons with BE in the US. Most of them (a "silent majority") do not know that they have the condition and may not be diagnosed unless complications like adenocarcinoma develop. Patients with BE are at risk of developing dysplasia and adenocarcinoma in this metaplastic epithelium. Although the precise risk remains unclear, data from retrospective and prospective studies of patients with BE suggest that the risk of cancer in BE is approximately 0.5% per year (Shaheen et al. 2000). In patients with BE and high grade dysplasia, however, the risk of developing esophageal adenocarcinoma is approximately 6 per 100 patient-years during the first few years of follow-up (Rastogi et al. 2008).

Despite the increased risk of adenocarcinoma, most patients with BE die for other causes (Van der Burgh et al. 1996). For patients with known BE, endoscopic surveillance for early detection of cancer or dysplasia is probably beneficial (Provenzale et al. 1999). However, optimal endoscopic surveillance intervals may change again based on current information showing a lower estimate of cancer incidence (Spechler 2000). Endoscopic surveillance programs are not likely to reduce the death rate from esophageal adenocarcinoma in the general population, because the majority of patients with BE remain undiagnosed. In this line, a series of patients with esophageal adenocarcinomas showed that less than 10% of them were known to have BE before seeking medical attention initially because of symptoms of esophageal cancer (Menke-Pluymers et al. 1992; Chalasani et al. 1998; Bytzer et al. 1999). The lack of GERD symptoms in patients with BE may in part contribute to this observation (GOSPE 1991).

1.6 Obesity

Obesity has assumed epidemic proportions in the US and Europe and is a risk factor for a number of chronic diseases as well as for a number of different types of cancer [colorectum, breast (postmenopausal), endometrium, gallbladder, prostate, bladder, thyroid, and connective tissue] (Carroll 1998; Jacobsen et al. 2001; Samanic et al. 2004; Kuriyama et al. 2005). Five population-based case–control (Chow et al. 1998a; Hampel et al. 2005; Lindblad et al. 2005; Corley et al. 2008; Whiteman et al. 2008), two hospital-based case–control (Ryan et al. 2006; Veugelers et al. 2006), three cohort studies (MacInnis et al. 2006; Merry et al. 2007; Reeves et al. 2007) and two meta-analyses (Hampel

et al. 2005; Kubo and Corley 2006) revealed that excess weight is a strong risk factor for esophageal adenocarcinoma (Fig. 1.2) and that the strength of the association increased with increasing body mass index (BMI). To a lesser extent, excess weight increased the risk of EGJ adenocarcinomas while no effect was seen for gastric adenocarcinoma or esophageal SCC (Chow et al. 1998a; Lagergren et al. 1999b). Kubo and Corley (2006) suggest that the association between BMI and adenocarcinoma is weakest in the EGJ and increases with increasing distance up from the gastroesophageal junction. The positive association between the risk of esophageal adenocarcinoma and the usual BMI was significantly modified by age, with the greatest increase in risk seen among the youngest group (ages <50 years), reaching an OR of 7.5 (95% C.I., 1.7–33.0) (Whiteman et al. 2008). This observation suggests that obesity is particularly important for early-onset tumors, while other risk factors may assume a more prominent role for tumors developing in later years (Chow et al. 1998a). The mechanism by which overweight might affect the risk of ACE and EGJ remains to be identified. One hypothesis suggests that obesity by increasing the risk of hiatal hernia and GERD would presumably increase the risk of BE, which in turn is a precursor lesion for esophageal adenocarcinoma (Brown et al. 1995). However, three studies have shown that obesity *per se* is a strong risk factor for ACE and gastric cardia, independent of reflux (Chow et al. 1998a; Lagergren et al. 1999b; Lindblad et al. 2005). Population-based studies and a meta-analysis have shown that the risk of esophageal and gastric cardia adenocarcinoma increased linearly with increasing BMI and reflux severity, and these risk factors combined in a multiplicative manner (Lagergren et al. 2000c; Hampel et al. 2005; Reeves et al. 2007; Whiteman et al. 2008). Lagergren et al. (2000c) observed than among obese persons (BMI >30 kg/m^2) with reflux symptoms, the odds ratio was 179.2 for esophageal adenocarcinoma and 12.2 for cardia adenocarcinoma compared with lean persons (BMI <22 kg/m^2) without reflux symptoms. However, because the incidence of ACE and gastric cardia is very low, the absolute risk of developing these tumors is still low. These authors also assessed the benefits of endoscopic screening of persons with various combinations of BMI and reflux symptoms. Despite impressive risk estimates, they found no evidence to support general endoscopic surveillance among persons with reflux symptoms. However, in the small group of very obese men with severe symptoms, surveillance might be warranted. In a multicenter population-based case–control study, Engel et al. (2003) found that BMI above the lowest quartile was associated with an attributable risk of 41.1% for developing esophageal adenocarcinoma. Both, Vaughan et al. (2002) in a cohort of patients with BE, and MacInnis et al. (2006) in a population-based cohort study, identified abdominal fat (male-pattern obesity) as a strong predictor of progression to ACE and EGJ, providing an explanation why the incidence of these cancers is substantially higher in males than in females (Lassen et al. 2006; Ryan et al. 2006; Veugelers et al. 2006; Crane et al. 2007b; Falk et al. 2007; Whiteman et al. 2008). More recently, Corley et al. (2008) in a population-based nested case–control study demonstrated that increasing abdominal diameter was strongly associated with an increased risk of ACE, but not with the risk of EGJ cancer. This association was independent of GERD and BMI. Persons with an abdominal obesity pattern have recently been shown to be at risk for BE (Corley et al. 2007; Edelstein et al. 2007). These observations support a potential link between obesity and the sequence BE-ACE. The evidence listed above may support the hypothesis that the increasing prevalence of obesity may be one of the explanations for the rising incidence of esophageal and gastric cardia adenocarcinoma in the western world (Merry et al. 2007). Alternative mechanisms for the BMI-cancer association include potential alterations in endogenous hormone metabolism, such as insulin-like

growth factor, estrogen, glucocorticoids, and insulin (Kubo and Corley 2006; Whiteman et al. 2008). Nevertheless, the case–control design of most studies makes it difficult to be emphatic about temporal association.

1.7 Additional Risk Factors for ACE and EGJ

1.7.1 Tobacco

Tobacco smoking has been found as a possible risk factor for ACE and cardia (Menke-Pluymers et al. 1993; Ahsan et al. 1997; Gammon et al. 1997; Lagergren et al. 2000b; Takesaki et al. 2001; Wu et al. 2001; Engel et al. 2003). In a multicenter, population-based, case–control study conducted in 1997, definitive evidence on the effect of smoking on the risk of esophageal and EGJ adenocarcinomas was added (Gammon et al. 1997). Risk appears to be more than doubled, with a dose-response pattern among smokers. Little reduction in risk was observed until smoking cessation for more than 30 years which is in contrast to the steady decrease in risk observed after quitting for other smoking-related cancers such as cancer of the lung and SCC of the esophagus. Gammon et al. (1997) suggest that smoking may affect an early stage in the induction of esophageal and EGJ adenocarcinomas. Although these data support the role of tobacco as an etiologic factor for adenocarcinomas of the esophagus and EGJ, it does not explain the rising incidence of these adenocarcinomas at times when SCC of the esophagus is not increasing and there is a recent reduction in the prevalence of cigarette smoking (Zhang et al. 1997). Lagergren et al. (2000b) tested the association between tobacco and the risk of ACE and EGJ cancer in a case–control study in Sweden. The risk of ACE with smoking was weak or absent. EGJ adenocarcinoma was dose-dependently associated with smoking (OR = 4.2, 95% CI = 2.5–7.0 among heavy smokers compared with never-smokers). These authors concluded that tobacco smoking does not play an important role in the etiology of ACE. Recently, many others studies (Fig. 1.2) have found an association between smoking and ACE, with an increased risk of 1.45–6.1 (Lindblad et al. 2005; Casson et al. 2006; Freedman et al. 2007; Pandeya et al. 2008; Whiteman et al. 2008; Zendehdel et al. 2008). Whiteman et al. (2008), in a case–control population-based study, found that smoking significantly increased the risk of ACE and EGJ, but there was no evidence of interaction with body mass. Casson et al. (2006) suggest that the susceptibility of some smokers to develop ACE may be genetically modulated. These authors found that this association was seen preferentially in patients with the active allele of either glutathione *S*-transferase M1 or glutathione S-transferase T1 genes.

1.7.2 Alcohol

Several observational studies have failed to find an association between alcohol consumption and risk of ACE and EGJ (Fig. 1.2) (Menke-Pluymers et al. 1993; Gammon et al. 1997; Lagergren et al. 2000c; Takesaki et al. 2001; Wu et al. 2001; Lindblad et al. 2005; Freedman et al. 2007).

1.7.3 Diet and Nutrition

Five case–control studies identified high intake of dietary calories and fat as a strong risk factor for ACE and EGJ (Zhang et al. 1997; Chen et al. 2002b; Mayne and Navarro 2002; Bahmanyar and Ye 2006; Navarro Silvera et al. 2008). Higher intake of meat, particularly red meat, is associated with an increased risk of ACE, while higher intake of meat, particularly poultry, and

high-fat dairy is associated with an increased risk of EGJ carcinoma (Navarro Silvera et al. 2008). Several studies have suggested that some nutrients could be considered as protective factors against esophageal and EGJ adenocarcinoma. This is the case of fruits and fresh vegetables, lutein, niacin, β-carotene, folate, iron, zinc, and vitamins B6, B12, C, and E (Fig. 1.2) (Brown et al. 1995; Zhang et al. 1997; Takesaki et al. 2001; Terry et al. 2001; Chen et al. 2002a; Veugelers et al. 2006; Dong et al. 2008). In the case of folate, a recent meta-analysis calculated a relative risk of 0.5 (0.39–0.65) for ACE (Larsson et al. 2006) A multicenter population-based, case–control study in England and Scotland showed that high BMI in early adulthood and low consumption of fruit are important risk factors for esophageal adenocarcinoma in women (Cheng et al. 2000). These authors found that these two factors accounted for 90% of the risk of the condition in this population. Antioxidants (vitamin C, β−carotene, alpha-tocopherol) have the potential to neutralize the harmful effects of DNA-damaging free radicals, such as those produced by smoking, and these nutrients have generally emerged as protective factors in the previous studies of esophageal SCC (Shklar 1998; Terry et al. 2000b). Terry et al. (2000b) observed that higher intake of antioxidants was associated with similarly decreased risk of esophageal adenocarcinoma. These authors also suggested that the inverse associations of antioxidants with esophageal adenocarcinoma are stronger among sufferers of GERD as well as smokers (Terry et al. 2000b). Five case–control studies showed a protective effect of dietary fiber on the risk of adenocarcinoma of the EGJ and distal esophagus (Brown et al. 1995; Zhang et al. 1997; Terry et al. 2000a; Mayne and Navarro 2002; Wu et al. 2007a). Terry et al. (2001) found a strong inverse association between fiber intake and EGJ adenocarcinoma. This inverse association was driven almost entirely by cereal fiber, and intake of fiber from fruit and vegetables was essentially unrelated to the risk (Terry et al. 2001). There was a protective trend of high fiber intake for adenocarcinoma of the esophagus, but this was not statistically significant. These authors suggest that their findings support the hypothesis that saliva and swallowed air contribute to high nitrosamine concentrations in the most proximal part of the stomach (Terry et al. 2001). Wheat fiber would act as a strong scavenger of nitrites under acidic conditions. Recent studies suggest that lower serum selenium levels may be a risk factor for esophageal adenocarcinoma and gastric cardia cancer (Rudolph et al. 2003; Wei et al. 2004). These authors speculate that selenium may act primarily at later stages of progression toward adenocarcinoma. Evidence from laboratory and population-based studies indicates that some selenium-containing compounds have anticarcinogenetic effects. Results from a cross-sectional study on patients with BE suggest that higher serum selenium levels may be associated with a reduced risk of ACE (Rudolph et al. 2003).

1.7.4 Medications

Lagergren et al. (2000a) investigated whether medications that may promote GERD by relaxing the lower esophageal sphincter (LES) increase the subsequent risk for ACE and gastric cardia. Long-term daily users (>5 years) of any of these medications had an increased risk (incidence rate ratio, 3.8 (95% CI, 2.2–6.4)) compared with persons who had never used these drugs. The association was particularly strong for anticholinergics. Adjustment for reflux symptoms almost eliminated the association, prompting the investigators to suggest that these medications may promote cancer by increasing reflux. These investigators estimated that long-term use of drugs that promote LES relaxation might be responsible for about

10% of esophageal adenocarcinomas. However, since esophageal adenocarcinoma is still a rare disease, the increment in absolute risk in the individual patient after exposure to LES-relaxing drugs is small (Eisen 2000). On the other hand, some evidence had been published in terms that the use of aspirin and other nonsteroidal anti-inflammatory drugs (NSAID) is associated with a 50–90% reduction in the risk of ACE (Funkhouser and Sharp 1995; Corley et al. 2003; Gammon et al. 2004; Hur et al. 2004; Mehta et al. 2005). Vaughan et al. (2005) estimated a hazard ratio of 0.32 (0.14–0.76) for ACE in patients with BE who use aspirin or NSAID (Fig. 1.2). Many of the observational studies listed above have inherent limitations, mostly because not all confounding variables have been taken into account. For instance, the use of aspirin and/or NSAIDs may be associated with certain patient-led behaviors that have an influence on risk. This would then lead to a false association being established between NSAIDs and cancer prevention (Mehta et al. 2005). The role of chemoprevention itself is already being tested in a large randomized study in UK, the ASPirin Esomeprazole Chemoprevention Trial (AspECT) involving 2,500 patients with BE (Das et al. 2008).

1.7.5 *Helicobacter pylori* Infection

The results of a meta-analysis have confirmed quantitatively that *H. pylori* is an important risk factor for noncardial gastric cancer but not for cancer of the cardia (Huang et al. 1998). The risk of gastric adenocarcinoma and its precursor state, atrophic gastritis, is associated particularly with $CagA^+$ compared with $CagA^-$ strains of *H. pylori* (Parsonnet et al. 1997). On the other hand, an inverse relation between $CagA^+$ strains of *H. pylori* infection and risk of esophageal and gastric cardia adenocarcinoma has been observed (Chow et al. 1998b). It has been suggested that the increasing incidence of ACE and EGJ is linked to declining rates of *H. pylori* infection in western countries. Indeed, epidemiological evidence is accumulative that *H. pylori* infection, especially with strains $CagA^+$ is associated with a reduced risk of ACE or EGJ, although a recent population-based case–control study found negative results (Wu et al. 2003a). Recently, in the case-cohort study including 600 gastric cardia adenocarcinoma patients in Linxian (China), a population with low prevalence of BE and ACE, risk of gastric cardia cancer was increased in individuals exposed to *H. pylori* (hazard ratio = 1.64; 95% CI: 1.26-2.14) (Kamangar et al. 2007).

It will be of interest to evaluate whether variations in acidity and the content of refluxate are involved in the mechanism by which *H. pylori* strains may affect the risk of ACE and EGJ (Chow et al. 1998b). A recent study showed that infection with *H. pylori* may reduce the risk of esophageal adenocarcinoma, but these authors think that it is unlikely to do so by atrophy-reduced acidity (Fig. 1.2) (Ye et al. 2004).

1.8 Summary

ACE and EGJ is increasing in US and northern Europe; however, the reasons for this epidemiological change remain unclear. BE represents the precursor lesion for most of these tumors, but the majority of persons with this condition remain unrecognized in the general population. GERD and obesity have emerged as major risk factors for ACE and to a lesser extent for EGJ adenocarcinoma. Although fruits, cereal fibers, and vegetables intake have protective action, there is no evidence that dietary interventions can prevent these cancers. Future strategies to change life-style risk factors may be warranted to reduce at least partially the burden of esophageal adenocarcinoma.

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2 Clinical Classification Systems of Adenocarcinoma of the Esophagogastric Junction

Stefan Paul Mönig and Arnulf H. Hölscher

2.1 Esophagogastric Junction

2.1.1 Introduction

The classification and definition of adenocarcinomas of the esophagogastric junction (EGJ) have not been standardized, and the choice of surgical procedures is still the subject of controversy. In contrast to the decreasing frequency of gastric cancer and squamous cell carcinomas of the esophagus, a number of studies from various western industrialized nations have reported an increased incidence of adenocarcinomas of the esophagus and cardia in the last 30 years. Studies from population-based cancer registries in the United States, the United Kingdom, and Switzerland have indicated a rapid increase in the incidence of adenocarcinoma of the EGJ (Devesa et al. 1998; Bollschweiler et al. 2001, 2002; Sharma et al. 2003). The reasons for this increase remain unclear; however, a number of causes are being discussed, such as the malignant potential of Barrett mucosa and etiologic factors, such as obesity, dietary factors, alcohol, pharmaceutical agents, and tobacco (Bollschweiler et al. 2001).

2.1.2 Definition

Because of the lack of a clear definition and classification, cancer of the EGJ has been considered and treated sometimes as distal esophageal cancer, sometimes as proximal gastric cancer, and sometimes as an entity separate from both esophagus and gastric cancer. The confusion may be in part due to the imprecise definition of the gastric cardia. It is so called, as it is the part of the stomach that is close to the heart, which is "kardia" in the old Greek language (Marsman et al. 2005). Even though anatomists describe the cardia as that zone of the stomach adjacent to the orifice of the tubular esophagus, the orifice can also be defined as the EGJ and the primary problem lies in the precise identification of this junction. The EGJ is localized at the level of the angle of His, the point at which the tubular esophagus joins the saccular stomach, which is not clinically applicable in the preoperative setting. The EGJ is defined differently by anatomists, physiologists,

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endoscopists, and pathologists. Physiologists define the EGJ as the distal border of the lower esophageal sphincter as determined by manometry. Endoscopically, the EGJ is defined as the proximal margin of the longitudinal gastric mucosal folds (Ectors et al. 2005). For the distal margin of the cardia, there is no anatomical landmark. The squamocolumnar junction (Z-line) is the endoscopically visible line formed by the juxtaposition of squamous and columnar epithelia, which has been reported to be located 3–10 mm proximal of the anatomically defined EGJ (Misumi et al. 1989; Takubo et al. 1995; Bombeck et al. 1966). Chandrasoma et al. define the EGJ histologically as the proximal limit of the oxyntic (gastral fundal) mucosa (2007). The maximal length of the cardiac mucosa and oxyntocardiac mucosa, where the cardiac glands are distributed, is reported to average 3–15 mm (Sarbia et al. 2002; Misumi et al. 1989; Ogawa et al. 2001) and the maximal length of the squamous epithelium under which the cardiac glands are distributed has been described to average 1–5 mm (Misumi et al. 1989; Ogawa et al. 2001). The use of the end of the tubular esophagus or proximal limit of the rugal folds to define the esophagastric junction places it at a point that can be over 2 cm proximal to the true EGJ (Chandrasoma et al. 2006) and, therefore, DeMeester and coworkers describe adenocarcinomas of the distal esophagus and "gastric cardia" predominantly as esophageal carcinomas (Chandrasoma et al. 2007).

2.1.3 Different Classification Systems

Most population studies of carcinomas of the esophagus and stomach are based on data collected by cancer registries, which currently use the ICD-O subsite classification (Percy et al. 1990). ICD-O classifies carcinomas in the EGJ as esophagus, subsite "lower third" if the majority of the lesions is in the esophagus and stomach, subsite "cardia" if the lesion is centered on or just distal to the EGJ. However, the fact that the distal extent on the cardia is not defined and the lack of an accurate definition of the cardia have resulted in the misclassification of up to 15% of these carcinomas (Dolan et al. 1999). The TNM classification of the International Union Against Cancer (UICC), the American Joint Committee on Cancer (AJCC) and the Japanese Research Society on Gastric Cancer, differentiates esophageal and stomach cancer, but does not classify separately adenocarcinoma of the esophagastric junction (Sobin and Wittekind 2001; American Joint Commmittee on Cancer 2002). The 7 edition of the TNM classification states an important change in classification of these tumors (Sobin et al. 2009). A tumor the epicenter of which is within 5 cm of the esophagogastric junction and also extends into the esophagus is classified and staged according to the esophageal scheme. All other tumors with an epicenter in the stomach greater than 5 cm from the esophagogastric junction or those within 5 cm of the EGJ without extension into the esophagus are staged using the gastric carcinoma scheme. The definition of the cardia commonly employed in Japan is the area within 2 cm above and below the EGJ (Nishi et al. 1973; Misumi et al. 1989) and tumors whose center is in this area are considered to be cancer of the cardia; such tumors are distinguished from upper gastric cancers.

The Liverpool classification of the EGJ was proposed in 1999 based on the clinocoepidemiological features of over 15,000 carcinomas of the esophagus and stomach (Dolan et al. 1999). In this classification the site of the EGJ is represented by the proximal extent of the gastric rugae (McClave et al. 1987) and carcinomas involving the EGJ are classified as esophageal carcinomas, subsite EGJ. Carcinomas located exclusively in the esophagus and not involving the junction are classified as esophageal, subsite lower third. Carcinomas in the region of the stomach close to the esophagus and not involving the junction are classified as stomach, subsite proximal.

Carcinomas that involve the proximal and distal subsites of the stomach are classified as overlapping, even if they extend to the junction.

A topographical classification of these carcinomas was proposed by Ellis et al. (Ellis 1980; Ellis and Maggs 1981; Ellis et al. 1988). Carcinomas of the cardia in this classification system are defined as carcinomas arising in the upper third of the stomach and involving the EGJ and the lower esophagus. Adenocarcinomas in Barrett's esophagus are not included, even though they may involve the EGJ.

To the present, these different classification systems are not internationally accepted.

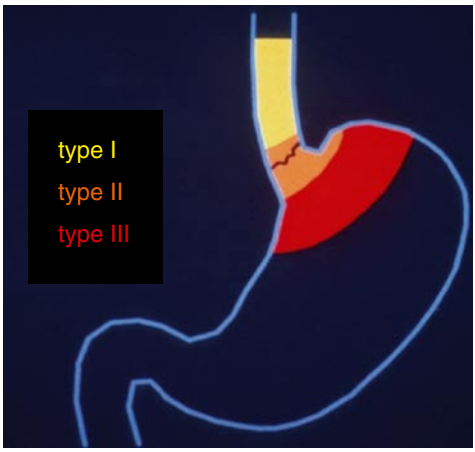

Fig. 2.1 Classification of adenocarcinomas of the esophagogastric junction according to the localization of the center of the tumor. *Type I*: 1 cm above to 5 cm above the cardia; *type II*: 1 cm above to 2 cm below the cardia; *type III*: 5 cm below to 2 cm below the cardia

2.2 Classification of Adenocarcinoma of the EGJ Type I-III

In order to clarify the definition of cancer of the EGJ, Siewert and Hölscher published a topographic-anatomic subclassification of adenocarcinomas of the EGJ in 1987 (Siewert et al. 1987; Hölscher et al. 1995, 2008). The classification was approved at the consensus meetings of the Seventh International Society of Diseases of the Esophagus in 1995 and the second International Gastric Cancer Congress in Munich 1997 (Siewert and Stein 1998).

2.2.1 Definition and Topographical Classification

In this classification the term adenocarcinoma of the EGJ is used to describe all tumors that have their center within 5 cm proximal or distal to the anatomical cardia. Adenocarcinomas of the distal esophagus and subcardial gastric carcinomas are only included if they infiltrate the anatomical cardia. Based on this definition, carcinomas of the EGJ can be classified as three different types according to their location (Fig. 2.1).

Type I tumor (Fig. 2.2):
Adenocarcinoma of the distal esophagus that arises most commonly from the area of specialized intestinal metaplasia of the esophagus (Barrett's esophagus) and infiltrates the EGJ from above.

Type II tumor (Fig. 2.3):
True carcinoma of the cardia that arises from the cardiac mucosa or from short segments with intestinal metaplasia at the EGJ.

Type III tumor (Fig. 2.4):
Subcardial gastric carcinoma that infiltrates the EGJ and the lower esophagus from below.

2.2.2 Diagnosis

Since the assignment of these tumors to the three different types is morphological, based on the anatomic localization of the tumor center, the best way to assign adenocarcinomas of the EGJ to one of these three types is based on a combination of

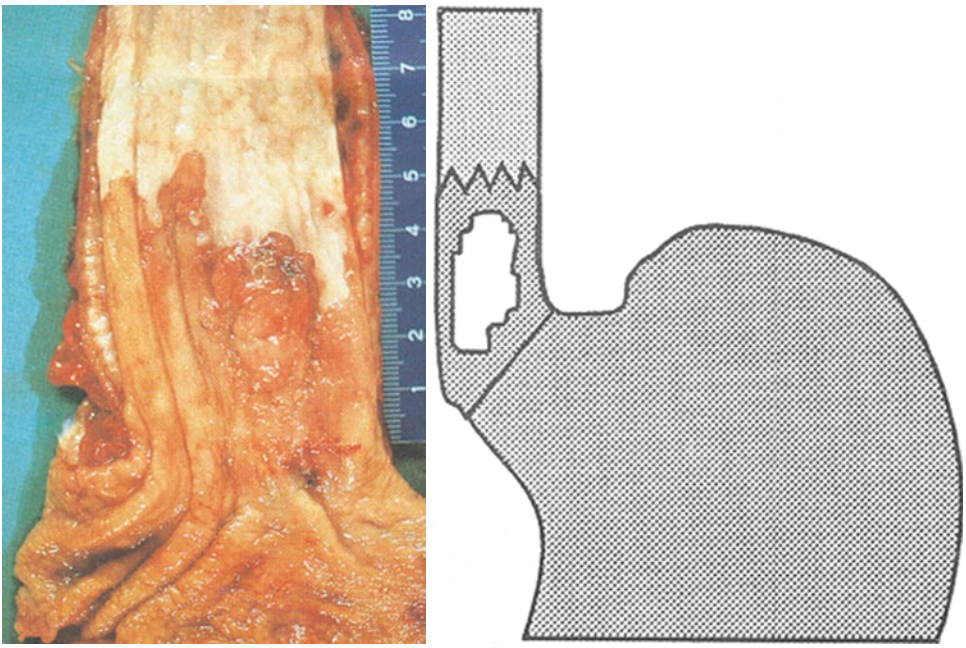

Fig. 2.2 Macroscopic appearance of type I carcinoma of the esophagogastric junction

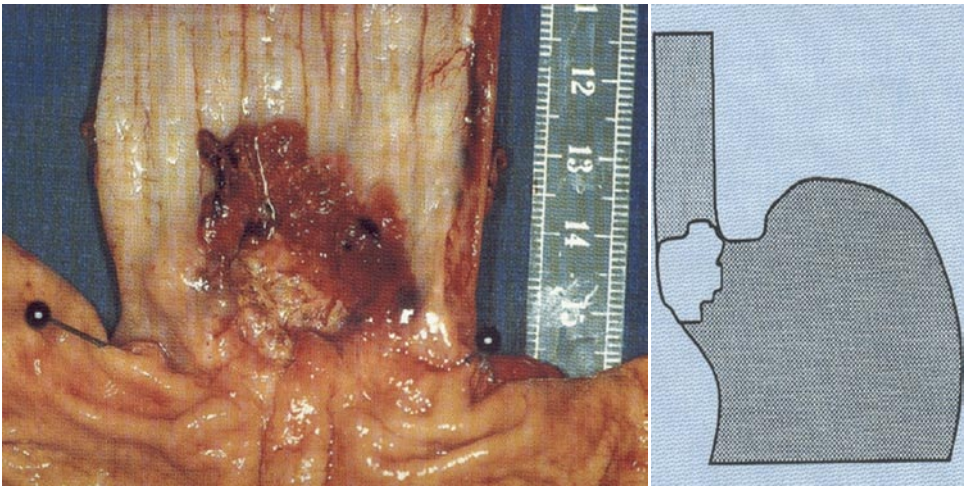

Fig. 2.3 Macroscopic appearance of type II carcinoma of the esophagogastric junction

radiological and endoscopical examination. A thoracic survey radiograph in two planes with contrast visualization of the esophagus and stomach is taken to localize the tumor topographically and anatomically, particularly in relation to the diaphragm. Esophagogastroscopy must be performed in the prograde as well retrograde view to localize the major part of the tumor. CT scans can also be

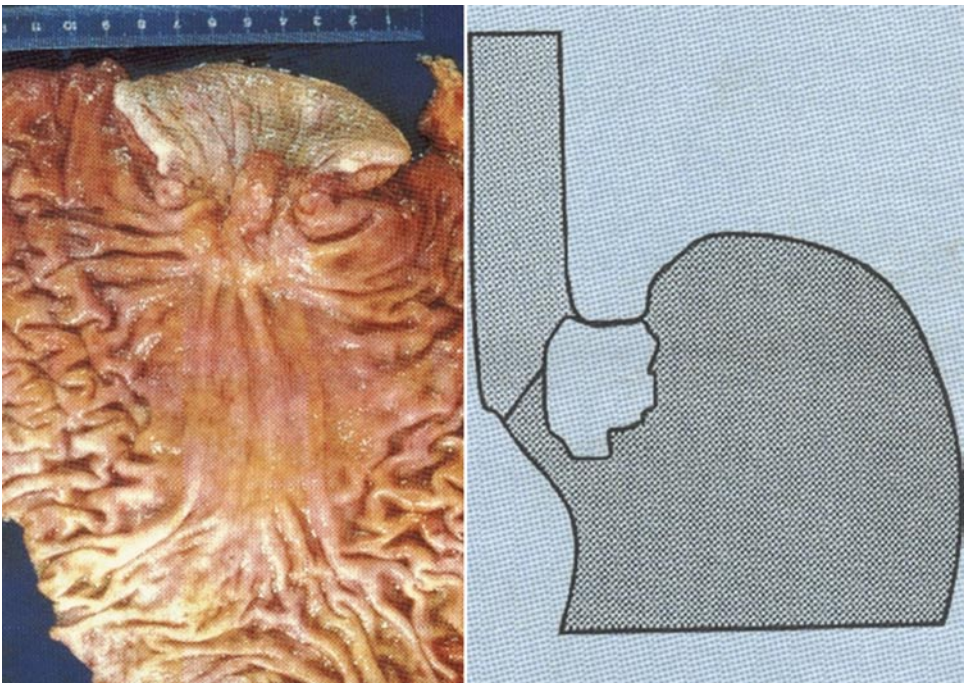

Fig. 2.4 Macroscopic appearance of type III carcinoma of the esophagogastric junction

helpful for the assignment of the tumor. The stringent classification of the adenocarcinoma of the EGJ poses some problems. Very locally advanced tumors obliterate the EGJ, making it difficult to tell whether they originated above or below the junction. The final assignment to one of the three types must be reconfirmed intraoperatively and on the resected specimen, and if necessary, the preoperative assignment has to be revised.

2.2.3 Biological and Clinical Variations

Although all adenocarcinomas arising in the vicinity of the EGJ share a number of common epidemiological and morphological features, a series of observations in the recent literature provides justification for such a classification (Siewert and Stein 1998).

Epidemiology based on surgical studies shows marked differences in sex distribution, Barrett's mucosa, Laurén category, degree of differentiation (grading), and long-term survival between type I, II, and III carcinomas (Siewert et al. 2005; Hölscher et al. 1995).

In a series of 1,346 patients with adenocarcinomas of the EGJ, Siewert demonstrated a preponderance of the male patients with type I tumors compared to type II or III carcinomas (Siewert et al. 2000; Nakamura et al. 2002). The presence of intestinal metaplasia (Barrett's esophagus) adjacent to the tumor could be demonstrated in 77% of the type I carcinomas (Siewert et al. 2005), but only in 10% of type II and in 2% of type III tumors. More than 80% of type I carcinomas showed a so-called intestinal growth pattern according to the Laurén classification system, whereas more than 60% of type III carcinomas had a diffuse growth pattern and

more than 70% of these type III tumors were undifferentiated (G3/4).

Long-term survival analysis showed a markedly better prognosis for patients with type I carcinoma than patients with type II and III carcinomas, with type III having the worst prognosis (Siewert et al. 2005). Siewert ascribes the poor prognosis for the type III carcinomas to the high prevalence of diffuse type carcinomas and the frequent presence of lymphatic spread in the type III carcinomas. In contrast to this result, Yuasa et al. (2006) from Japan described a higher rate lymph node metastasis, an increased risk of hepatic recurrence, and a lower 5-year survival in type II compared with type III cancer. However, these comparisons were not performed between T categories, but only between the whole groups.

2.2.3.1 Lymphatic Metastasis

The current discussion concerning the extent of resection in patients with adenocarcinoma of the EGJ is focused beside the luminal extent of resection primarily on the adequate extent of lymphadenctomy. Lymph node dissection should be based on the knowledge of the lymphatic system draining these regions, actual incidence of lymph node metastases, and the effect on survival.

In a microscopic analysis of adenocarcinomas of the EGJ, Siewert et al. described that invasion of lymph nodes by type I tumors was less frequent than in type II and III tumors and that lymph node involvement had prognostic impact (Siewert et al. 2005; von Rahden et al. 2005). This difference in lymph vessel involvement between type I and typeII/III carcinomas leads to the hypothesis that, based on a chronic inflammatory process type I adenocarcinoma, leads to a degeneration of lymphatic vessels over time, and therefore, lymphatic metastases begin later in type I tumors than in II and III tumors. However, again these comparisons were not performed between the T-stages of type I, II, and III, but only for the whole groups.

Akiyama showed that in esophageal carcinomas the distribution of lymph node metastases is widespread in the area between the superior mediastinum and the celiac region, and therefore, proposed lymph node dissection of the whole length of the posterior mediastinum, superior gastric region, and celiac region (Akiyama et al. 1981). Aikou and Shimazu (1989) described only in 6.6% suprabifurcal lymph node metastases in type I carcinoma and in cardia carcinoma no positive lymph nodes in this region. Griffin et al. (1990) found a low incidence of cervical recurrence after radical esophagectomy with two-field lymphadenectomy in patients with adenocarcinoma of the esophagus. In contrast to these results, Altorki found metastasis of the cervical lymph nodes in 27% of patients with adenocarcinoma of the lower esophagus after three-field lymphadenectomy (Altorki and Skinner 1997). Lerut reported lymphatic spread to cervical nodes in 26% of patients with adenocarcinoma of the lower esophagus and 18% of patients with adenocarcinoma of the EGJ after three-field lymphadenectomy (Lerut 1998; Lerut et al. 2004). These results indicate that tumor cells of type I esophageal carcinoma can spread to the thoracic and even to cervical lymph nodes and toward the abdomen. Contrary to type I carcinomas, type II and type III carcinomas have lower rates of lymphatic spread to the mediastinum and higher rates to abdominal compartment I and II (Dresner et al. 2001). Lymphoscintigraphic studies confirm these results (Cense et al. 2004). Tachimori found that there was lymph node involvement in the lower mediastinum in 19% of patients with adenocarcinoma of the cardia involving the esophagus (type II), and Wang found lymph node metastases of the inferior paraesophageal region in 18% of the patients with cardia carcinoma (Tachimori et al. 1996; Wang et al. 1993). In our series the incidence of

lower mediastinal lymph node metastases in type II and III carcinomas was 11% or 13%, similar to that reported by Aikou (10%) (Aikou and Shimazu 1989; Mönig et al. 2002). In summary, type I cancer shows more frequent lymph node involvement in the upper mediastinum with metastasis to lymph nodes of the tracheal bifurcation and above. On the other hand, in type II and III carcinomas lymph node metastasis is more frequently found in the lower mediastinum and in the area of the celiac trunk. Thus, there are pronounced differences between the pattern of lymph node metastasis between type I and types II and III tumors, whereas lymph node metastasis is similar in types II and III.

2.2.4 Surgical Consequences

The aim of the surgical therapy is the complete resection (R0-resection) of the primary tumor and adequate lymphadenectomy. The type I adenocarcinoma represent a distal esophageal cancer and consequently is treated by transthoracic en bloc esophagectomy including mediastinal lymphadenectomy (Fig. 2.5). A prospective controlled Dutch trial has demonstrated that for type I carcinoma the transthoracic esophagectomy leads to better overall survival than the transhiatal approach (Hulscher et al. 2002; Hulscher and van Landschot 2005; Omloo et al. 2007).

A randomized trial from Japan showed that the 5-year survival of 37.9% for the left side transthoracic surgical approach for type II and III carcinomas was inferior to the 5-year survival rate of 52.3% for the transhiatal extended gastrectomy approach (Sasako et al. 2006). Similar results, showing that for Type II carcinoma extended total gastrectomy was superior to the esophagectomy, were obtained in a multicenter trial in France (Sauvanet et al. 2005). Similar to type II carcinomas, subcardial adenocarcinomas of type III are also treated by transhiatal extended gastrectomy with distal esophageal resection, which according to the R0 resection rate has been shown to be adequate for this entity (Fig. 2.5).

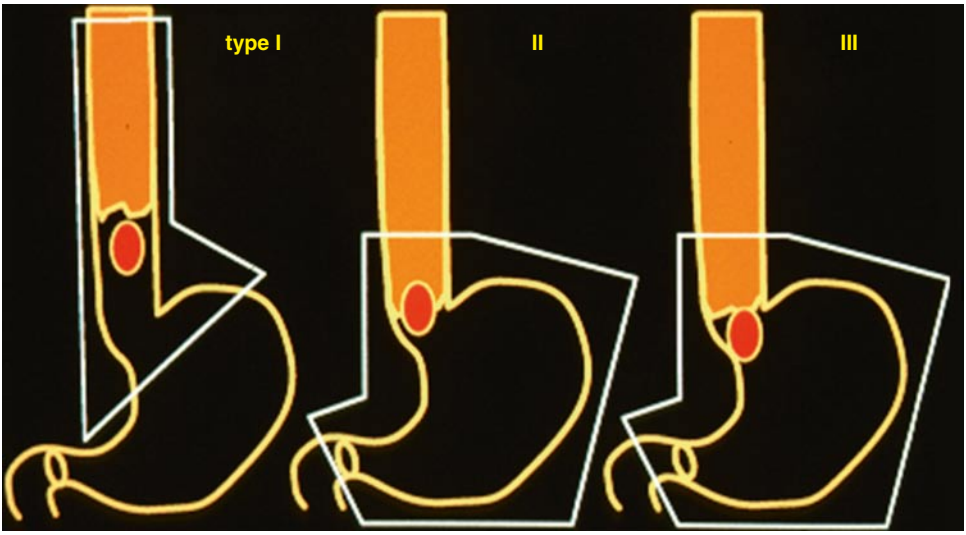

Fig. 2.5 Extent of resection in type I, II, and III adenocarcinoma of the esophagogastric junction. *Type I*: transthoracic esophagectomy; *type II/III*: transhiatal extended gastrectomy

2.3 Conclusions

In summary, the topographical classification of the EGJ originally introduced by Siewert and Hölscher in 1987 is now accepted in many centers in the world. The classification is easy to apply and has shown that there is a difference between type I, II, and III carcinomas. There have been a large number of publications reporting results from epidemiological, histopathological, and therapeutic trials based on this classification. The analysis of these trials has allowed comparison of treatment results for the various tumor types from different oncology centers resulting in evidence-based recognition that type I tumors are best treated using a transthoracic resection, while transhiatal extended total gastrectomy is adequate for type II and III tumors.

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3 Histopathologic Classification of Adenocarcinoma of the Esophagogastric Junction

Stephan E. Baldus

3.1 Introduction

In contrast to squamous cell carcinomas of the esophagus as well as adenocarcinomas of the distal or middle third of the stomach, the incidence of adenocarcinomas in the distal esophagus or EG junction increased continuously during the last decades. Initially, most of these cancers were thought to represent either esophageal or gastric carcinomas (especially the so-called "carcinomas of the cardia"). However, it became clear that the pathogenesis of these cancers exhibits differences. While most of the "true" adenocarcinomas of the distal esophagus arise predominantly on the basis of Barrett's metaplasia developing in the clinical setting of gastroesophageal reflux disease, the etiology of cancers of the cardia and the subcardial stomach remained unclear. In addition, the histopathological discrimination of these three types of adenocarcinoma remained difficult and arbitrary in a substantial part of the cases, especially if residual Barrett's epithelium could not be detected. On the other hand, surgical experience led to the conclusion that differentiated surgical approaches may be necessary depending on tumor stage and localization (Stein et al. 2000, 2003). On this background, Siewert et al. (Siewert et al. 1987; Siewert and Stein 1998) introduced a clinical topographic classification of carcinomas of the esophagogastric junction, which was based on the combination of contrast radiogram, endoscopy with orthograde and retroflexed view of the esophagogastric junction, computer tomography, as well as intraoperative observations. According to this classification, adenocarcinomas of the esophagogastric junction were defined as tumors which have their center within 5 cm proximal or distal to the endoscopic cardia. They are divided into three types (I–III) according to their location. Type I represents adenocarcinomas of the distal esophagus with the tumor center located more than 1 cm above the endoscopic esophageal junction. Type II carcinomas ("true" carcinomas of the cardia) are those having their center located within 1 cm oral and 2 cm aboral of the junction. Type III represents subcardial adenocarcinomas with the tumor center located more than 2 cm below the esophagogastric junction.

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3.2 Definition of the Esophagogastric Junction

The classification of the adenocarcinomas of the esophagogastric junction mainly depends on the definition of the esophagogastric junction itself. Anatomically, it represents the region where the tubular esophagus joins the stomach. Endoscopically, the esophagogastric junction is defined as the level of the most proximal end of the gastric folds (Boyce 2000). On the other hand, the esophagogastric junction is histologically defined as the squamocolumnar junction (SCJ or Z-line). However, the junction between squamous epithelium of the esophagus and gastric (cardiac) epithelium may occur at or up to about 2 cm above the anatomical junction. While in normal individuals the tubular esophagus is lined by squamous epithelium, it may also be lined by columnar epithelium especially in patients with hiatus hernia and gastroesophageal reflux disease. During the last years, controversies started with regard to the gastric cardia. According to the traditional definition, the gastric cardia starts at the squamocolumnar junction; however, its distal end is ill-defined.

Histologically, it is characterized by tubular glands containing mucus-secreting cells. In the transition zone between cardia and gastric fundus, parietal (oxyntic) cells are also present as solitary cells or as small cell groups. Therefore, the extent of the exclusively mucus-secreting epithelium is variable (de Nardi and Riddell 1997). These traditional definitions were questioned by Chandrasoma and coworkers in several studies. In one of them (Chandrasoma et al. 2000), a cardia-type mucosa was not observed in 3/7 pediatric patients at autopsy. The authors developed the hypothesis that cardia-type mucosa represents an early histologic manifestation of gastroesophageal reflux. According to their theory, an abnormal columnar-lined esophagus is characterized by the presence of cardia-type mucosa, oxynto-cardia-type mucosa, and intestinal metaplastic epithelium between gastric oxyntic mucosa and esophageal squamous epithelium (Chandrasoma et al. 2001). In consequence, the proximal limit of gastric oxyntic mucosa defined by histology should represent the true esophagogastric junction (Chandrasoma et al. 2006). However, in numerous further autopsy studies on embryos, fetuses, and infants (Kilgore et al. 2000; Glickman et al. 2002; Derdoy et al. 2003; de Hertogh et al. 2003), a columnar epithelium representing fetal or infant cardia-type mucosa could be observed in all individuals investigated. Its length was rather short (0.3–0.6 mm) at or after birth (de Hertogh et al. 2003) and varied in pediatric patients between 1–4 mm (Kilgore et al. 2000) or 0.1–3 mm (Derdoy et al. 2003). These data underline that cardia-type mucosa represents a normal histological structure at least during fetal and infant development. The length of cardia-type epithelium, especially in adults, may increase in patients with gastroesophageal reflux disease and extend proximally above the level of the anatomic esophagogastric junction into the distal esophagus (Glickman et al., 2002; Odze 2005). Apart from this controversy, if cardia-type mucosa represents a normal or a metaplastic epithelium, further aspects make the definition of "true carcinomas of the cardia" as a special subgroup problematic. In this context, the observations that cardia-type mucosa can also be found in the distal esophagus, that it rarely extends more than 2–3 mm below the squamocolumnar junction (Ormsby et al. 2000; Kilgore et al. 2000), and that the proximal stomach is predominantly lined by oxyntic epithelium (Chandrasoma 1997; Oberg et al. 1997) have to be mentioned. Therefore, an adenocarcinoma located in the anatomical region of the cardia must not be histogenetically derived from true cardia-type epithelium. Taking into consideration the discussion of these problems and controversies, a new WHO classification of tumors of the esophagogastric junction was introduced in 2000.

3.3 WHO Classification of Tumors of the Digestive System

3.3.1 General Principles

The WHO Classification of Tumors of the Digestive System (Hamilton and Aaltonen 2000) defines adenocarcinomas of the esophagogastric junction as "adenocarcinomas that straddle the junction of the esophagus and stomach." Adenocarcinomas confined to the distal esophagus, which are mostly Barrett's carcinomas, are designated as "adenocarcinomas of the esophagus." Gastric adenocarcinomas have to be confined to the stomach and do not cross the esophagogastric junction. In summary, the definition of these three tumor types is now based on their localization.

According to the WHO classification, the following guidelines should be applied:

1. "Adenocarcinomas that cross the esophagogastric junction are called adenocarcinomas of the EG junction, regardless of where the bulk of the tumor lies.
2. Adenocarcinomas located entirely above the esophagogastric junction as previously defined are considered esophageal carcinomas.
3. Adenocarcinomas located entirely below the esophagogastric junction are considered gastric in origin. The use of the ambiguous and often misleading term "carcinoma of the cardia" is discouraged. Depending on their size, these should be called carcinoma of the proximal stomach or carcinoma of the body of the stomach."

3.4 Histopathologic Subtypes

Adenocarcinomas of the distal esophagus derive from Barrett's mucosa in the vast majority of the cases. Histologically, they typically exhibit a tubular and/or papillary pattern and are mostly well or moderately differentiated (Paraf et al. 1995). However, signet-ring cell carcinomas and mucinous adenocarcinomas also occur in a minority of the cases.

Four types of adenocarcinomas of the esophagogastric junction are described in the WHO classification: papillary, tubular, mucinous, and signet-ring cell carcinomas. The latter two types are only rarely observed in the esophagus and the EGJ, and their frequency is considerably higher in the stomach (Wang et al. 1986). As a special tumor type, "pylorocardiac carcinoma" characterized by tall epithelial cells with a clear or pale cytoplasm and basal or central nuclei was described earlier (Mulligan and Rember 1954), but other authors found this pattern difficult to distinguish from other types of gland-forming adenocarcinomas (Stubbe Teglbjaerg and Vetner 1977). Two other rare types of carcinomas have to be encountered: the adenosquamous carcinoma seems to result from a dual differentiation leading to a mixture of glandular and squamous elements. Furthermore, the mucoepidermoid carcinoma of the esophagus should be distinguished. It arises from the mucous paraesophageal glands and resembles salivary gland tumors. The two components are more separated and the nuclear pleomorphism is increased.

3.5 Precancerous Lesions and Histogenetic Aspects

With regard to the etiology of adenocarcinoma of the distal esophagus, the decisive role of chronic gastroesophageal reflux and the consecutive development of Barrett's mucosa and Barrett's-associated intraepithelial neoplasia has been established (Lagergren et al. 1999; Mueller et al. 2000; Goldblum 2003; Fléjou 2005).

According to the WHO classification (Hamilton and Aaltonen 2000), all specimens

containing Barrett's epithelium should be assessed as negative, positive, or indefinite for intraepithelial neoplasia (formerly the so-called "dysplasia"). If intraepithelial neoplasia is present, it should be classified as "low-grade" (synonymous with mild or moderate dysplasia) or "high-grade" (synonymous with severe dysplasia and carcinoma in situ). The criteria applied for the grading of intraepithelial neoplasia comprise cytological as well as architectonical features (Schmidt et al. 1985; Antonioli and Wang 1997; Hamilton and Aaltonen 2000; Odze 2006). Since interobserver agreement on the grading of intraepithelial neoplasia is poor, in some European and most Far Eastern countries (Odze 2006) the so-called Vienna classification (Schlemper et al. 2000) has also been applied (Table 3.1). In the esophagogastric junction, intestinal metaplasia and intraepithelial neoplasia of the cardia-type epithelium are also observed and have been regarded as precancerous conditions (DeMeester and DeMeester 2000, DeMeester 2006). Obviously, both may also be related to gastroesophageal reflux disease. However, intestinal metaplasia of the cardia is only observed in a minority of the patients with Barrett's esophagus (Pereira et al. 1998). Furthermore, columnar epithelium-lined esophagus with specialized intestinal metaplasia was most commonly seen in Caucasian patients with reflux, whereas intestinal metaplasia at the esophagogastric junction was found in Caucasians with reflux and in African Americans without reflux with similar frequencies (Chalasani et al. 1997). Demographically, patients with intestinal metaplasia at the esophagogastric junction are different from patients with Barrett's esophagus. They have a higher prevalence of *Helicobacter pylori* infection and a lower prevalence of dysplasia as compared to Barrett's esophagus (Hirota et al. 1999; Sharma et al. 2000). Especially, the role of intestinal metaplasia in the context of Helicobacter infection remains unclear at the moment, particularly if it is concomitant with gastroesophageal reflux (Vigneri et al. 2000; Voutilainen and Sipponen 2001; Malfertheiner and Peitz 2005; Odze 2006). In summary, at least some clinical and pathological features indicate that Barrett's mucosa and intestinal metaplasia of the cardia-type epithelium represent two potentially different clinical processes. Barrett's mucosa and intestinal metaplasia of the cardia can be usually distinguished on the basis of H&E sections (Sarbia et al. 2004). In addition, various attempts were made in the past to evaluate whether additional immunohistochemical markers (especially cytokeratins or mucins) can help to discriminate both conditions. In 1999, Ormsby et al. reported that Barrett's mucosa shows a typical superficial CK20 staining as well as a strong CK7 staining of both superficial and deep glands in nearly all cases. On the other hand, this pattern was not observed in gastric cardia specimens with the evidence of intestinal metaplasia. During the following years, numerous other groups performed similar immunohistochemical investigations. As reviewed recently (Nurgalieva et al. 2007), only 8 of 15

Table 3.1 Vienna classification of gastrointestinal epithelial neoplasia (Schlemper et al. 2000)

Category 1	Negative for neoplasia/dysplasia
Category 2	Indefinite for neoplasia/dysplasia
Category 3	Noninvasive low-grade neoplasia (low-grade adenoma/dysplasia)
Category 4	Noninvasive high-grade neoplasia
	4.1 High-grade adenoma/dysplasia
	4.2 Noninvasive carcinoma (carcinoma in situ)[a]
	4.3 Suspicion of invasive carcinoma
Category 5	Invasive neoplasia
	5.1 Intramucosal carcinoma[b]
	5.2 Submucosal carcinoma or beyond

[a]Noninvasive indicates absence of evident invasion

[b]Intramucosal indicates invasion into the lamina propria or muscularis mucosae

comparative studies reported significant differences in cytokeratin staining patterns between Barrett's esophagus and intestinal metaplasia of the cardia with a high sensitivity (89–100%) and specificity (83–100%) for long-segment Barrett's esophagus and lower estimates for short-segment Barrett's esophagus, and seven studies showed no significant differences and a very low sensitivity. In conclusion, the role of cytokeratin immunohistochemistry in differentiating Barrett's esophagus, especially short-segment Barrett's esophagus, from intestinal metaplasia of the cardia remains controversial. In this context the definition of "positivity" and the subjectivity in the interpretation of the results obviously play an important role (Younes 2005).

Furthermore, adenocarcinomas of the distal esophagus, esophagogastric junction, and proximal stomach were also investigated immunohistochemically in order to evaluate possible histogenetic differences. However, most of them exhibited a $CK7^+/CK20^+/MUC1^+$ phenotype irrespective of the presence or absence of Barrett epithelium, which suggests a similar histogenesis of these tumors (Flucke et al. 2003). Other authors also observed that CK 7/20 profiles have no role in distinguishing tumors of the three locations (Gulmann et al. 2003), whereas another group (Taniere et al. 2002) reported that a $CK7^+/CK20^-$ pattern is highly suggestive of an esophageal origin as compared to an origin from the proximal stomach. Similarly, a $CK7^+/CK20^-$ profile was shown in 87.5% of type I, but only 35% of type II adenocarcinomas according to the Siewert classification (Mattioli et al. 2007). On the other hand, Driessen et al. (2004) observed an identical cytokeratin expression pattern $CK7^+/CK20^-$ in most esophageal and cardia adenocarcinomas. Therefore, the question of a particular histogenesis of the different types of adenocarcinomas of the EGJ as reflected by cytokeratin expression remains controversial.

3.6 Prognostic Aspects of Histopathologic Classification

In an analysis of 96 patients with Barrett's-associated adenocarcinoma (Torres et al. 1999), older patient age, higher pathologic stage (including depth of invasion and lymph node status), infiltrative growth pattern, perineural invasion, vascular invasion, and the absence of a peritumoral lymphoid infiltrate were associated with shortened survival according to univariate survival analysis in the entire cohort and in patients without chemoradiation, with the exception of infiltrative growth pattern (in the nonchemoradiation group). Subcategorization of lymph nodes according to the number involved with metastases had no further effect on prognosis. However, subcategorization of T1 tumors into T1a and T1b reflected differences in prognosis. Using multivariate analysis, only older patient age and the absence of a peritumoral lymphoid infiltrate were found to be statistically associated with poor survival independent of stage.

Another study (Fontana et al. 2003) involving 100 patients with carcinomas of the esophagogastric junction (5 type I, 54 type II, and 41 type III according to the Siewert classification) investigated the prognostic value of various histopathological classifications, Siewert's topographical classification as well as TNM classification. Summarized, histopathologic lassifications according to WHO, Laurén (1965) and Goseki et al. (1992) as well as Siewert's topographical classification did not reveal any differences with regard to survival probability. Only the TNM staging system, and particularly lymph node positivity, represented predictors of survival. Previously, Jakl et al. (1995) identified only residual tumor and depth of penetration as independent predictors of survival in multiple regression analysis of a series of 125 patients with resected "carcinomas of the cardia," whereas lymph node involvement and Laurén's classification did not

show additional significance. As compared with distal gastric carcinomas, the poor prognosis of proximal gastric cancers relied on the more advanced age and tumor stage at the moment of presentation as well as on the higher postoperative morbidity (Pacelli et al. 2001).

3.7 UICC Classification and Grading

Adenocarcinomas of the esophagus or stomach should be staged according to the new seventh edition of the UICC classification (Sobin et al. 2010), as shown in Tables 3.2 and 3.3. Carcinomas of the esophagogastric junction the epicenter of which is within 5 cm of the esophagogastric junction and thus also extend into the esophagus are classified and staged using the esophageal scheme. Tumors with an epicenter in the stomach greater than 5 cm from the esophagogastric junction are classified and staged using the gastric carcinoma scheme (Sobin et al. 2010). Compared to the previous sixth edition of the TNM classification, some pT and pN categories of the classifications of both esophageal and gastric cancers were revised. Furthermore, metastases of esophageal and esophagogastric junction carcinomas to celiac lymph nodes are no longer staged as pM1a.

Differentiation of adenocarcinomas of the distal esophagus, esophagogastric junction, or stomach should be graded as well, moderately or poorly differentiated.

Table 3.2 UICC classification of carcinomas of the esophagus and EG junction (7th edn 2010)

T – primary tumor	
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma in situ/high-grade dysplasia
T1	Tumor invades lamina propria, muscularis mucosae, or submucosa
	T1a Tumor invades lamina propria or muscularis mucosae
	T1b Tumor invades submucosa
T2	Tumor invades muscularis propria
T3	Tumor invades adventitia
T4	Tumor invades adjacent structures
	T4a Tumor invades pleura, pericardium, or diaphragm
	T4b Tumor invades other adjacent structures such as aorta, vertebral body, or trachea
N – regional lymph nodes	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastases
N1	Metastasis in 1–2 regional lymph nodes
N2	Metastasis in 3–6 regional lymph nodes
N3	Metastasis in 7 or more regional lymph nodes
M – distant metastasis	
M0	No distant metastasis
M1	Distant metastasis

3.8 Histopathologic Regression Grading after Neoadjuvant Therapy

During the last years, the concept of neoadjuvant (radio-)chemotherapy with regard to carcinomas of the esophagus, esophagogastric junction, and the stomach has developed rapidly (Schneider et al. 2005; Cunningham et al. 2006; Halliday et al. 2007; Ott et al. 2008). Recently, the United Kingdom National Cancer Research Institute (NRCI) Medical Research Council Adjuvant Gastric Infusional Chemotherapy (MAGIC) trial demonstrated a significantly improved progression-free and overall survival for patients with operable gastric or lower esophageal adenocarcinomas, who received a perioperative regimen of infused epirubicin,

Table 3.3 UICC classification of carcinomas of the stomach (7th edn 2010)

T – primary tumor	
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma in situ: intraepithelial tumor without invasion of the lamina propria, high-grade dysplasia
T1	Tumor invades lamina propria, muscularis mucosae, or submucosa
T1a	Tumor invades lamina propria or muscularis mucosae
T1b	Tumor invades submucosa
T2	Tumor invades muscularis propria
T3	Tumor invades subserosa
T4	Tumor perforates serosa or invades adjacent structures
T4a	Tumor perforates serosa
T4b	Tumor invades adjacent structures
N – regional lymph nodes	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastases
N1	Metastasis in 1–2 regional lymph nodes
N2	Metastasis in 3–6 regional lymph nodes
N3	Metastasis in 7 or more regional lymph nodes
N3a	Metastasis in 7–15 regional lymph nodes
N3b	Metastasis in 16 or more regional lymph nodes
M – distant metastasis	
M0	No distant metastasis
M1	Distant metastasis

cisplatin, and fluorouracil (ECF) (Cunningham et al. 2006). Consequently, perioperative chemotherapy in stage II and stage III esophageal and gastric cancers is suggested as a new standard of care in the Western World (Ott et al. 2008; Siewert et al. 2007). Since clinical response evaluations according to WHO criteria applying endoscopy, endoscopic ultrasound, and re-biopsy (Schneider et al. 2008) have been shown to be highly inaccurate, an objective morphologic response evaluation should be performed after surgery. In 1994, Mandard et al. established a tumor regression grading system using five grades: TRG1 (complete regression) with the absence of residual cancer and fibrosis extending through the different layers of the esophageal wall; TRG2 characterized by the presence of rare residual cancer cells scattered through the fibrosis; TRG3 exhibiting an increase in the number of residual cancer cells, but fibrosis still predominating; TRG4 shows residual tumor outgrowing fibrosis; and TRG5 is characterized by the absence of regressive changes. Subsequently, systems of tumor regression were introduced for gastric (Becker et al. 2003) as well as esophageal (Baldus et al. 2004; Schneider et al. 2005) cancer, which are based on the estimated percentage of vital residual tumor cells (VRTC). In the latter study, the degree for histomorphologic regression was classified into four categories (Schneider et al. 2005): grade I, >50% VRTCs; grade II, 10–50% VRTCs (partial response); grade III, nearly complete response (NCR) with <10% VRTCs; and grade IV, complete response (pCR, ypT0). Both studies demonstrated that tumor regression was significantly correlated with prognosis. With regard to gastric carcinoma, the accuracy of regression grading may be improved by adding additional staging variables such as tumor size and lymphatic vessel involvement. Regarding esophageal cancer, lymph node status represented an additional prognostic parameter for patients with complete resections (R0) following neoadjuvant radiochemotherapy. Therefore, a response classification system including tumor regression as well as lymph node metastases was proposed (Schneider et al. 2005), as shown in Table 3.4. In conclusion, the application of a regression classification based

Table 3.4 Response Classification System proposed for Esophageal Cancer (Schneider et al. 2005)

Class I	Minor histomorphologic regression (VRTC >10%)
a	With lymph node metastases
b	Without lymph node metastases
Class II	Major histomorphologic response (VRTC <10%)
a	With lymph node metastases
b	Without lymph node metastases

on two parameters could lead to an improved objective evaluation of the effectiveness of treatment protocols, accuracy of staging and restaging modalities, as well as molecular response prediction.

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The Pathogenesis of Barrett's Metaplasia and the Progression to Esophageal Adenocarcinoma

4

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Abstract The most important risk factor for the development of Barrett's esophagus is the reflux of both gastric and duodenal contents into the esophagus. The reason why Barrett's metaplasia develops only in a minority of patients suffering from gastroesophageal reflux disease remains unknown.The exact mechanism behind the transition of normal squamous epithelium into specialized columnar epithelium is also unclear. It is likely that stem cells are involved in this metaplastic change, as they are the only permanent residents of the epithelium. Several tumorigenic steps that lead to the underlying genetic instability, which is indispensable in the progression from columnar metaplasia to esophageal adenocarcinoma have been described. This review outlines the process of pathogenesis of Barrett's metaplasia and its progression to esophageal adenocarcinoma.

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4.1 Introduction

Over the past 50 years, more insight has been gained into the pathophysiology and molecular pathways associated with the development of Barrett's esophagus and esophageal adenocarcinoma. Gastroesophageal reflux disease (GERD) has now been recognized as the most important risk factor for the onset of Barrett's metaplasia and esophageal adenocarcinoma. Environmental, dietary, and genetic factors are also likely to play an important role. However, the exact mechanism underlying the transition from normal squamous epithelium towards metaplastic epithelium has not been elucidated yet. The identification of stem cells in the normal squamous esophageal epithelium has led to speculations about the contribution of these cells in the metaplastic process, as these cells are the only permanent residents of the epithelium. Recently, some studies that have shed new light on the molecular and cellular basis of Barrett's esophagus have been published.

This review gives an overview of the pathogenesis of Barrett's metaplasia and its progression towards esophageal adenocarcinoma. The risk factors for the development of Barrett's esophagus as well as the different theories concerning the cell of origin of Barrett's metaplasia

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are reviewed. Finally, a summary of the tumorigenic steps that are involved in the development of esophageal adenocarcinoma is given.

4.2 Normal Esophageal Epithelium

The luminal surface of the normal esophagus is lined by stratified squamous epithelium of the nonkeratinizing type (Geboes and Desmet 1978; Seery 2002). This epithelium can histologically be divided into two zones: (1) a luminal "differentiated zone" consisting of progressively flattened, terminally differentiated keratinocytes, and (2) a basal "generative" zone. Within the latter, a basal layer (single layer of cells next to the basal membrane) and several epibasal layers (variable number of cell layers above the basal layer) can be distinguished (Fig. 4.1). At regular intervals along the epithelium, the lamina propria invaginates and forms papillary structures within the epithelium. Subsequently, in the basal layer two components can be distinguished: the interpapillary basal layer (IBL) covering the interpapillary zone and a papillary basal layer (PBL) overlying the papillae (Fig. 4.1) (Seery 2002). Shedding of epithelial cells occurs when cells have migrated from the basal zone towards the esophageal lumen (Jankowski et al. 1992).

To maintain epithelial integrity, the rapidly proliferating esophageal mucosa is repopulated by a limited number of stem cells present in the generative basal zone. These stem cells divide, replace the stem cell compartment itself, and generate transit amplifying cells (differentiating daughter cells that enter the epibasal layer) (Slack 2000). It has been observed that the process of low proliferation and asymmetric cell division (giving rise to one stem cell and one transit amplifying cell) specifically characterizes the IBL (Seery and Watt 2000).

It is hypothesized that another stem cell population might also account for the reconstitution of the surface epithelium. This population is thought to reside in the tubuloalveolar glands that are present in the submucosal layer of the esophageal epithelium (Seery 2002). Although there is no direct evidence for the existence of these stem cells, an analogy can be drawn with the epidermis in which the stem cells are located not only in the interfollicular epithelium, but also in the bulge region of the hair follicle (Cotsarelis et al. 1990; Rochat et al. 1994).

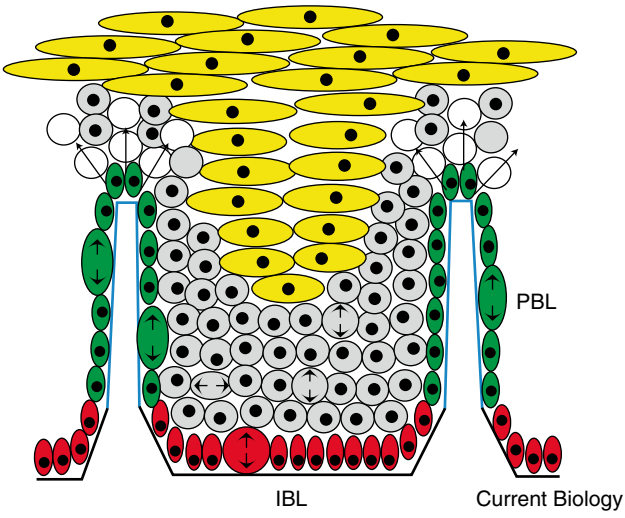

Fig. 4.1 Schematic representation of the organization of the human esophageal epithelium. The interpapillary basal layer (IBL) cells constitute the stem cell compartment (*red*). Transit amplifying cells are proposed to reside in the papillary basal layer (PBL in *green*) and epibasal layers (*gray*). Suprabasal cells that can no longer divide and are undergoing terminal differentiation are shown in *yellow*. *Arrows* indicate the direction of cell movement. Reprinted from Seery and Watt (2000) with permission

4.3 Pathogenesis of Barrett's Metaplasia

4.3.1 Development of Barrett's Esophagus: Congenital vs. Acquired

Columnar epithelium in the intrathoracic part of the gastrointestinal tract in combination with an ulcer and esophagitis was first described in 1950 by Norman Barrett, a British surgeon (Barrett 1950). However, he misinterpreted the condition as a tubular intrathoracic stomach. Also, he was convinced that this was due to a congenitally short esophagus (Barrett 1950). Johns hypothesized that this condition might be due to a premature cessation of the physiologic replacement of the columnar ciliated epithelium (which lines the esophagus during embryogenesis) by stratified squamous epithelium, starting around 22 weeks of gestation (Barrett 1950; Johns 1952). In his opinion, this was a congenital disorder. However, arguments against this congenital theory include the fact that the squamous replacement of the fetal columnar epithelium begins in the mid esophagus and progresses toward each end (Johns 1952). The cervical region appears to be the last to lose its embryonic lining, which is contradictory to the fact that the columnar epithelium in a Barrett's esophagus is always found in the lower esophagus (Park et al. 2003). In 1953, Allison and Johnstone demonstrated that the columnar epithelium was located proximal to the lower esophageal sphincter (LES), and thus it was recognized definitively as an abnormality of the esophageal mucosa (Allison and Johnstone 1953). Furthermore, the association between columnar lined epithelium and GERD was recognized, and this led to the concept of an acquired condition. Moersch et al. and Hayward were the first to suggest that the columnar lining might be an acquired condition due to reflux esophagitis that destroys the squamous epithelium (Moersch et al. 1959; Hayward 1961). This concept was broadly accepted when Bremner et al. (1970) showed columnar cell regeneration in the distal esophagus in an experimental model of chronic gastroesophageal reflux.

4.3.2 Definition of Barrett's Metaplasia

Three histological types of columnar epithelium in the esophagus have been described: a gastric fundic type composed of chief and parietal cells; a junctional type composed of mucous glands without parietal cells, and a specialized type with intestinal characteristics including mucous glands and goblet cells (Paull et al. 1976). These three types are nowadays referred to as oxyntocardiac mucosa, cardiac mucosa, and intestinal metaplasia, respectively (Chandrasoma et al. 2003). It is only intestinal metaplasia that has been recognized as a premalignant condition, which is included in the definition of a Barrett's esophagus: a condition in which the normal squamous epithelium of the distal esophagus is replaced by specialized columnar epithelium, which is characterized by the presence of intestinal metaplasia (Haggitt 1994; Sampliner 1998). Metaplasia refers to the conversion of one cell type to another during postnatal life and might be the effect of conversion of tissue-specific stem cells (Tosh and Slack 2002). Goblet cells, which are barrel-shaped and have a distended, mucin-filled cytoplasm that stains positively with Alcian blue are characteristic for intestinal metaplasia.(Haggitt et al. 1988; Haggitt 2000).

4.3.3 Gastroesophageal Reflux Disease

There are many risk factors associated with the development of a Barrett's esophagus. GERD is considered to be the key risk factor (Fass et al. 2001; Wild and Hardie 2003). Chronic GERD is characterized by various conditions, including

nonerosive and erosive esophagitis, ulceration, and strictures of the esophagus. It has been reported that approximately 10% of patients with GERD-symptoms develop a Barrett's esophagus (Winters et al. 1987; GOSPE 1991; Tytgat 1995). Furthermore, increased age (Cameron and Lomboy 1992; Johansson et al. 2007), male sex (Blot et al. 1991; Vizcaino et al. 2002), and Caucasian race (Devesa et al. 1998) are general risk factors for Barrett's esophagus as described in several epidemiologic studies.

4.3.3.1 Pathophysiology

Esophageal exposure to refluxed gastric contents is considered to be the major factor in the development of reflux esophagitis and Barrett's esophagus. Animal models have demonstrated that gastric acids are involved in injuring the esophageal mucosa (Bremner et al. 1970; Gillen et al. 1988). In humans, patients with a Barrett's esophagus typically have greater esophageal acid exposure based on 24-h pH monitoring when compared to patients with esophagitis, or normal subjects (Iascone et al. 1983; Stein et al. 1992; Neumann and Cooper 1994; Singh et al. 1994). A direct relationship between the severity of esophageal mucosal injury and the degree and frequency of refluxed acid exposure has been reported (Iascone et al. 1983). Furthermore, it has been found that patients with Barrett's esophagus have a significantly longer exposure time to a pH lower than 4 than patients with esophagitis (Vaezi and Richter 1996). Interestingly, there is a clear correlation between the length of the columnar lined esophagus and the severity of reflux (Csendes et al. 1993). However, one study showed that in a group of patients with a Barrett's esophagus that was followed-up for more than 7 years, the length of the Barrett's segment did not change (Cameron and Lomboy 1992). It has been hypothesized that the transformation of squamous epithelium into columnar metaplasia does not occur after intestinal metaplasia has developed (Chandrasoma and DeMeester, 2006). In other words, the occurrence of intestinal metaplasia in cardiac mucosa might act as a break for further columnar transformation of squamous epithelium by reflux. Nevertheless, this hypothesis is still unproven, and further research is needed in this field.

Acid injury involves the ability of H^+ ions to enter the cytoplasm of the esophageal epithelial cell with subsequent cell death. In the normal situation, the apical membrane of the epithelial cells is not permeable to acid (Khalbuss et al. 1995). When luminal acidity is sufficiently high, intercellular junctions are damaged and widening of the intercellular spaces is observed (Hopwood et al. 1979; Carney et al. 1981). Subsequently, H^+ ions are able to penetrate into the cell through the basolateral membrane. The intracellular acids lead to cell death and, finally, to ulceration once the necrosis affects a large area.

Pepsin is a digestive enzyme, secreted as pepsinogen and activated into pepsin by gastric acid. Pepsin is considered to be harmful as it may cause erosive esophagitis in an acidic environment by increasing the cell permeability to H^+ ions (Safaie-Shirazi 1977; Jankowski et al. 1992). However, the exact role of pepsin in damaging the esophageal mucosa has not been explored extensively thus far.

Besides the effect of gastric acids and pepsin, excessive reflux of duodenal contents into the esophagus also contributes to the development of Barrett's metaplasia. Bile reflux or alkaline reflux are terms that are often used to describe the reflux of duodenal contents, which consists of conjugated and unconjugated bile salts, lysolecithin, and pancreatic enzymes such as trypsin. The term "alkaline reflux" suggest a pH >7, although it has been reported that the majority of esophageal bilirubin exposure occurs when the pH is between 4 and 7 (Kauer et al. 1995). Therefore, the term duodenogastroesophageal reflux (DGER) may be more appropriate, referring to the retrograde reflux of

duodenal contents (bile and pancreatic fluid) into the stomach as well as the esophagus. It is believed that both pancreatic enzymes and bile salts are able to induce severe esophagitis (Kivilaakso et al. 1980; Harmon et al. 1981).

Trypsin is a pancreatic enzyme that is responsible for the lysis of proteins. It is thought to affect intercellular substances causing shedding of epithelial cells (Salo et al. 1983). Trypsin can cause substantial injury to the esophageal mucosa at alkaline pH. The role of lysolectihin, another component of duodenal juice, is less understood.

Bile salts are conjugated with either taurine or glycine when secreted by the liver. The conjugation process makes bile acids more soluble in an acidic environment (range pH 2–7) by lowering the Pk_a dissociation constant (Buttar and Wang 2004; Guillem 2005); an environment in which synergistic damaging effects from gastric acids and conjugated bile salts have been described (Vaezi and Richter 1995; DeMeester 2001). However, acidification of bile salts to a pH of less than 2 leads to irreversible precipitation and inactivation of the bile salts. At neutral or alkaline pH, conjugated bile salts cause only minimal injury. However, this is in contrast with trypsin and unconjugated bile salts, which have the greatest potential to damage the esophageal mucosa under alkaline circumstances (Nehra et al. 1999).

It has been suggested that in a moderately acidic gastric environment (range pH 2–7), as can occur with the use of acid-suppression medication, bile salts are partially soluble and are potentially harmful to mucosal cells (DeMeester and DeMeester 2000). For conjugated bile salts to remain completely harmless in a patient with GERD taking acid-suppression medication, a gastric pH of at least 7 must be aimed for during day and night (DeMeester and DeMeester 2000). Hence, incomplete acid suppression may allow esophageal mucosal damage to occur while the patient is asymptomatic (Kauer et al. 1995).

Several studies using combined pH and bile-reflux monitoring in nonoperated GERD patients, suggest increasing amounts of both acid reflux and DGER with increasing severity of esophageal lesions (Champion et al. 1994; Caldwell et al. 1995; Kauer et al. 1995; Vaezi and Richter 1995; Marshall et al. 1997; Dixon et al. 2001). Two consecutive studies showed that the highest bilirubin concentration and percentage of time with pH <4, were seen in patients with Barrett's esophagus, followed by patients with esophagitis, and controls (Vaezi and Richter 1995, 1996). The results of these studies are supportive of a synergistic activity of acid and bile reflux. Moreover, simultaneous esophageal exposure to both acid and DGER was the most prevalent reflux pattern (95%) in patients with a Barrett's esophagus (Vaezi and Richter 1996). Reports on esophageal aspirates have shown conflicting results with regard to the role of DGER: some studies could detect an increased amount of bile acids in patients with Barrett's esophagus, whereas other studies could not confirm this (Sital et al. 2006). However, aspiration techniques have been criticized because of the short aspiration periods and intrinsic limitations of these techniques (Vaezi and Richter 1995). The overall results of animal studies, esophageal monitoring, and aspiration studies (Richter 2000; Sital et al. 2006) suggest a synergistic role for gastric and bile acids in the etiology of a Barrett's esophagus.

4.3.3.2 Role of Inflammation and Oxidative Stress

Increased exposure of the normal esophageal mucosa to (duodeno) gastroesophageal reflux results in mucosal damage and tissue inflammation. The mucosal inflammatory response is characterized by specific cytokine and chemokine profiles. The nuclear factor-kappa B (NF-kB) pathway is thought to play a pivotal role in this response: NF-kB comprises a family of transcription factors that regulates the host inflammatory and immune responses by increasing the expression of many genes that are involved in

the inflammatory reaction (Yamamoto and Gaynor 2001). Subsequently, increased levels of cytokines including TNF-α, interleukin (IL)-1β, IL-6, and IL-8 can also directly activate the NF-kB pathway, thus establishing a positive autoregulatory loop that can amplify the inflammatory response and increase the duration of chronic inflammation (Yamamoto and Gaynor 2001). Inappropriate activation of NF-kB has been linked to a variety of inflammatory and neoplastic conditions (Barnes and Karin 1997; Yamamoto and Gaynor 2001).

The cytokines that are released in response to GERD may thus contribute to the activation of the NF-kB pathway in these patients. Moreover, NF-kB was found to be upregulated in Barrett's epithelium (Abdel-Latif et al. 2005; O'Riordan et al. 2005).

Gastric acid and bile salts can activate the arachidonic acid pathway, which controls inflammation. Cyclooxygenase-2 (COX-2) is a key enzyme of this pathway, and catalyzes the conversion of arachidonic acids into prostaglandins. COX-2 is usually not detectable in normal tissues, but can be induced in processes like inflammation and carcinogenesis (Buskens et al. 2003). Also, it has been shown that activation of NF-kB can lead to an increase in COX-2 (Yamamoto et al. 1995). An in vitro study showed that COX-2 is functionally active in Barrett's esophagus: treatment with a COX-2 inhibitor diminished cell growth, whereas proliferation could be restored by treatment with prostaglandin (Buttar et al. 2002). A gradually increased COX-2 expression has been reported from normal squamous epithelium toward Barrett's metaplasia and esophageal adenocarcinoma (Wilson et al. 1998; Shirvani et al. 2000; Morris et al. 2001). Moreover, an increased COX-2 expression seems to be related with a reduced survival in patients with esophageal adenocarcinoma (Buskens et al. 2002; Mobius et al. 2005).

Chronic inflammation can also induce the production of reactive oxygen species: highly reactive free radicals that are generated as products of oxygen degradation during injury. These free radicals have an important role in the inflammation process. They may damage DNA by causing mutations, induce the production of proinflammatory cytokines, and produce growth factors for epithelial cells (Jones et al. 2000). Under normal conditions, cells are protected from reactive radicals by antioxidant defense systems. When oxidative stress (an imbalance between oxidant production and the antioxidant capacity of the cell) arises, these defense systems promote the expression of antioxidants (Mates et al. 1999). In patients with reflux esophagitis and Barrett's esophagus, it has been demonstrated that mucosal damage is associated with increased oxidative stress, characterized by an enhanced free radical proportion and decreased antioxidant activity (Wetscher et al. 1995; Jimenez et al. 2005). Also, one study suggested the lower levels of the antioxidant vitamin C found in patients with a Barrett's esophagus, supporting the hypothesis of oxidative stress being important in the pathogenesis of metaplastic epithelium (Fountoulakis et al. 2004).

4.3.3.3 GERD-Related Factors

Since not all patients with GERD develop a Barrett's esophagus, it implicates that additional risk factors play an important role. As we will discuss below, genetic predisposition, presence of a hiatal hernia, a low esophageal sphincter pressure, obesity, and dietary patterns have been described to contribute to this risk. It should be kept in mind that most of these factors are related to the severity of GERD and still cannot fully explain why only the minority of patients with GERD will develop Barrett's esophagus. Indirect evidence for a possible genetic susceptibility comes from a study that has reported an increased prevalence of GERD among family members of patients with Barrett's esophagus or esophageal adenocarcinoma (Romero et al. 1997). It is

hypothesized that an unknown susceptibility gene is inherited in an autosomal dominant fashion with incomplete penetrance, as not all individuals in these families develop Barrett's esophagus or esophageal adenocarcinoma (Sappati Biyyani et al. 2007). It has been suggested that a tumor suppressor gene is involved (Drovdlic et al. 2003). In this model, germline mutations in the gene predispose to neoplasia, and once the second allele is lost or mutated (i.e., a "second hit" caused by environmental factors like chronic GERD), cancer may develop. Furthermore, polymorphisms (specific variant alleles) of different genes that may be associated with an altered esophageal cancer risk have been described (Hiyama et al. 2007). For example, polymorphisms in the genes involved in carcinogen metabolism, DNA repair, and cell cycle control have been correlated with the presence of Barrett's esophagus and esophageal adenocarcinoma (Hiyama et al. 2007).

Interference with the physiologic function of the esophagogastric junction can occur in two conditions: dysfunction of the LES and the presence of a hiatal hernia (Buttar and Falk 2001).

A defective LES causes an increased acid exposure in the distal esophagus and can be found in over 95% of patients with a Barrett's esophagus (Stein et al. 1991). In the presence of an incompetent LES, ineffective clearance function due to motility disorders of the esophageal body further prolongs the time the esophagus is exposed to gastric contents (Stein and Siewert 1993).

A hiatal hernia may contribute to GERD by a variety of mechanisms (Mittal and Balaban 1997). First, clearance of acid from the esophagus is impaired; gastric acid may be trapped in the hernial sac and can subsequently be refluxed in the esophagus during a swallow-induced relaxation (Mittal et al. 1987). Second, esophageal emptying can be impaired when an irreducible large hiatal hernia is present (Sloan and Kahrilas 1991). Finally, a large hiatal hernia causes a widening of the esophageal hiatus that may impair the ability of the crural diaphragm to function as an external sphincter (Sloan et al. 1992). It has been reported that the presence of a hiatal hernia is a risk factor in the development of a Barrett's esophagus (Conio et al. 2002), and metaplastic epithelium has been observed more often in patients with a hiatal hernia than in those without it (Aste et al. 1999).

Obesity could increase the risk for the development of a hiatal hernia and provoke reflux through an elevated intraabdominal pressure. Increased body mass index (BMI) is known to be a risk factor for GERD (Hampel et al. 2005), but it remains unclear whether the increased risk for Barrett's esophagus associated with BMI is mediated by GERD directly or whether there is a higher risk regardless of reflux. A recently published meta-analysis provided evidence that increasing BMI does not present an increased risk of Barrett's esophagus above what would be expected from GERD alone (Cook et al. 2008). However, it was commented that the BMI does not take into account the distribution of fat within the body (Moayyedi 2008). Markers of central obesity (visceral fat) like the waist–hip ratio could be more reliable in the determination of a possible independent relationship between obesity and the development of a Barrett's esophagus (Yusuf et al. 2005).

Diet is a modifiable risk factor that may influence cancer risk through several mechanisms. Studies of fruit and vegetable intake are consistent with a protective role for antioxidants against the development of a Barrett's esophagus. A case–control study revealed that diets rich in fruits, vegetables, and fish were inversely associated with Barrett's esophagus, whereas this risk in persons following Western dietary patterns (high in fast food and meat) may be adversely associated (Kubo et al. 2008). But again, the fact that the association between diet and Barrett's esophagus is mediated by GERD, cannot be excluded.

Dietary nitrate is another component that may promote the development of Barrett's esophagus as a consequence of GERD. Nitrate is secreted by the salivary glands (that derive nitrate from the

entero-salivary recirculation of dietary nitrate), and is converted into nitrite by oral bacteria. When the swallowed saliva enters the acidic gastric environment, the nitrite is converted into nitrous acid and nitrosating species, which can form potentially carcinogenic compounds (see Fig. 4.2). However, this process is inhibited by the vitamin ascorbic acid, which is actively secreted in the gastric juice (Schorah et al. 1991), thereby reducing these compounds to nitric oxide. Although this action of ascorbic acid inhibits the luminal generation of the potentially carcinogenic nitrosating species, it has been shown that nitric oxide can also rapidly diffuse into the adjacent epithelium, resulting in nitrosative stress in the epithelial cells (Fig. 4.2) (Iijima et al. 2003). It has been reported that in the case of severe GERD, this process occurs in the esophageal lumen rather than the cardia, as saliva encounters gastric acids at a more proximal location (Suzuki et al. 2005). However, the clinical significance of this nitrosative chemistry in the distal esophagus during acid reflux remains unclear. It has been suggested that high concentrations of nitric oxide causes oxidative stress, which may contribute to carcinogenesis (Liu and Hotchkiss 1995). Moreover, the same authors hypothesized that the increase in the incidence of adenocarcinoma of the distal esophagus and gastric cardia might be related to the increased dietary content of nitrates (McColl 2005).

Helicobacter pylori infection causes a chronic gastritis that is associated with the development of intestinal metaplasia and cancer (Malfertheiner and Peitz 2005). *H. pylori* does not infect the esophagus, and its presence is not associated with an increased risk of Barrett's esophagus. In fact, some data suggest that gastric *H. pylori* infection may protect the esophagus from the effects of acid reflux by decreasing gastric acidity due to gastric atrophy (Chow et al. 1998; Bahmanyar et al. 2007). In fact, *H. pylori* infection might be associated with an increased risk of esophageal adenocarcinoma in patients in whom it causes high acid secretion secondary to an antrum-predominant, nonatrophic gastritis, but it might be associated with a reduced risk when the infection induces gastric atrophy (Bahmanyar et al. 2007). Therefore, the pattern of gastric colonization induced by

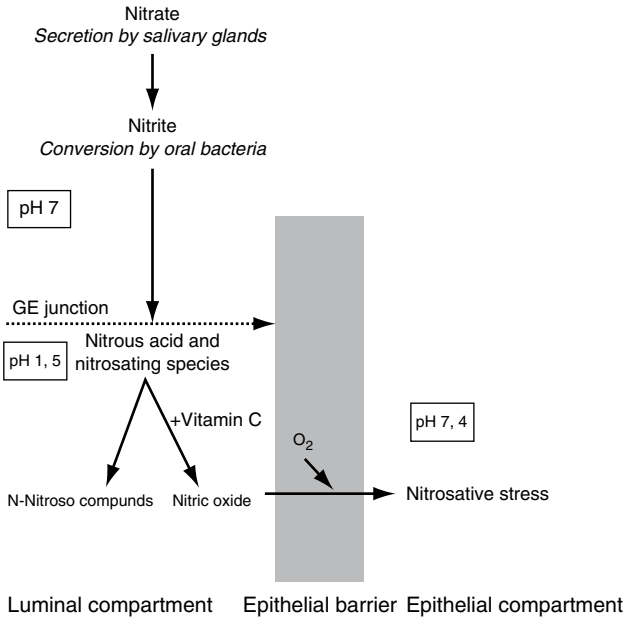

Fig. 4.2 Chemical reaction occurring at the gastroesophageal junction when nitrite in saliva encounters acidic gastric juice. Adapted from Iijima et al. (2003)

H. pylori infection may be the determinant of the effects of the infection on reflux disease.

4.3.4 Cell of Origin of Barrett's Metaplasia

It has now been generally accepted that Barrett's esophagus is an acquired condition as a consequence of GERD. Although the process of GERD and its contributing risk factors are well described, the exact mechanism underlying the transition from normal squamous epithelium into metaplastic columnar epithelium has not been identified yet. However, there are several theories with regard to the cell of origin that gives rise to the metaplastic change of the epithelium.

4.3.4.1 Upward Migration of Gastric Epithelium

Initially, upward cell migration from the gastric epithelium into the distal esophagus to reconstitute the reflux-damaged squamous epithelium was favored (Allison and Johnstone 1953; Bremner et al. 1970). However, it was demonstrated in animal studies that the development of a columnar esophagus is not hindered when there is a mucosal defect separating the distal esophagus from the transitional zone at the gastroesophageal junction (Gillen et al. 1988; Li et al. 1994).

Furthermore, Barrett's metaplasia may include a variety of epithelial cells (including goblet and neuroendocrine cells) that are not found in the proximal stomach. Therefore, it was hypothesized that the cell giving rise to the columnar mucosa is intrinsic to the esophagus itself.

4.3.4.2 Transdifferentiation

Another possibility is the direct conversion of differentiated cells into another cell type in the absence of cell proliferation, a process called "transdifferentiation." It is based on the normal developmental process whereby the esophagus undergoes a columnar to squamous cell transition at 18 weeks of gestation (Montgomery et al. 1999). Furthermore, it has been shown that during the development of the mouse esophagus, squamous cells arise directly from columnar cells independent of cell division and apoptosis (Yu et al. 2005). It is assumed that the reverse transdifferentation (from squamous to columnar epithelium) could account for the generation of Barrett´s metaplasia in the context of GERD. However, this extrapolation of data may not be valid, as the embryological maturation of the esophagus may be quite different from the pathological development of metaplastic epithelium.

4.3.4.3 Transitional Zone Theory

The transitional zone theory states that the cells at the gastroesophageal junction undergo cellular migration and colonize the gastric cardia or distal esophagus in response to damaging luminal agents during reflux. This theory was based on the identification of a cell with features of both squamous and columnar epithelium that had been identified with scanning electron microscopy at the transitional zone between the normal squamous esophageal epithelium and the columnar epithelium of Barrett's esophagus (Shields et al. 1993; Sawhney et al. 1996). These newly colonized cells can express either a columnar or a squamous phenotype depending on their location (esophagus or cardia) (Fass and Sampliner 2000) and can maintain a growth advantage due their resistance to the luminal components. Furthermore, cells that express both squamous and columnar cytokeratin markers have been identified at the squamo–columnar junction (Boch et al. 1997) Similarities exist between the structure of the GEJ and transitional zones in other areas of the body such as the

cervix uteri, which shows cells of high plasticity in the transitional zone (Smedts et al. 1993).

4.3.4.4 De-Novo Metaplasia

More than 20 years ago, it has already been hypothesized that GERD induces esophagitis with destruction of squamous epithelium and ulceration, and that the ulcer is reepithelialized by multipotential undifferentiated stem cells (Spechler and Goyal 1986). The prevailing hypothesis today is that Barrett's esophagus develops when GERD damages the superficial layers of the esophageal squamous epithelium, thereby exposing stem cells in the basal layers of the epithelium to toxic agents that stimulate an abnormal differentiation (Jankowski et al. 1999). As a result of chronic epithelial damage possibly induced by bile reflux and inflammatory conditions, the stem cells undergo a phenotypic or metaplastic change that will eventually lead to Barrett´s stem cells. It has been reported that a similar change can be observed during the process of mucinosis in the squamous mucosa of the vagina, which can be seen in atrophic vaginal epithelium in postmenopausal women (Koike et al. 1990; Sodhani et al. 1999). At this location, there is little known about the exact cause and the clinical significance of these metaplastic cells.

4.3.4.5 Duct Cell Metaplasia

Columnar cells covering a Barrett's esophagus may also originate from ductal cells of esophageal submucosal glands (Gillen et al. 1988; Wright 1996). It has been suggested that stem cells exist in the glandular neck region of the esophageal submucosal gland ducts similar to those found within the bulge region of the hair follicle (Fitzgerald 2006). Therefore, it is believed that after ulceration or damage, stem cells may grow out to form a new gland, giving rise to a duct by which the glandular cells are carried to the surface. The basis for this mechanism is the ulcer associated cell lineage: the development of a new cell lineage from mucosal stem cells that occurs adjacent to the region of ulceration in the gastrointestinal tract (Hanby and Wright 1993). Peptides related to the maintenance of mucosal integrity (i.e., the two trefoil peptides pS2 and human spasmolytic polypeptide that contain three-fold shaped ("trefoil") cysteine-rich domains) are associated with this process and their expression was also reported in the metaplastic epithelium of Barrett's esophagus (Hanby et al. 1994). However in rats, in which no glandular structures are located in the esophageal epithelium, reflux can still trigger a similar transition into a Barrett's like metaplastic epithelium (Pera et al. 2000).

4.3.4.6 Bone Marrow Stem Cells

Apart from tissue-specific stem cells, it is now known that bone-marrow derived stem cells that circulate in the blood have such a degree of plasticity that they can also give rise to diverse epithelial cells (Bjerkvig et al. 2005). Recently, a study reported on the contribution of bone marrow stem cells to the development of Barrett's esophagus in an animal model. Female rats were given a high dose of irradiation, followed by reconstitution of their bone marrow and immune systems through bone marrow transplants of male rats. Furthermore, both severe esophagitis and intestinal metaplasia were induced by esophagojejunostomy. The study revealed that after 8 weeks, the male adult progenitor cells of bone marrow origin could be detected in the esophageal epithelial cells, thereby contributing to the esophageal regeneration and metaplasia in this model of Barrett's esophagus (Sarosi et al. 2008). However, the authors have already pointed out that the

possibility of fusion of the donor's bone marrow cells with the host's epithelial cells instead of the transdifferentiation into esophageal epithelial cells cannot be excluded (Sarosi et al. 2008).

Overall, it can be concluded that the exact origin of the cells involved in the transition from a normal squamous epithelium into a metaplastic Barrett's epithelium has not been identified yet. However, it is most plausible that stem cells are involved in this process, as they are the only permanent residents of the epithelium.

4.3.5 Transformation into a Columnar Epithelium

To date, only few studies have reported on the transformation of normal squamous esophageal cells into columnar epithelial cells from a molecular point of view. A recent study investigated the role of the bone morphogenetic protein (BMP) pathway in the metaplastic transformation process both in vivo and ex vivo (Milano et al. 2007). The study was based on the finding of the same group that the BMP-4 gene was abundantly expressed in Barrett's esophagus and esophagitis as a result of GERD (van Baal et al. 2005). BMP-4 is a protein belonging to the transforming growth factor (TGF)-β family that is involved in controlling cellular differentiation, migration, and proliferation. In general, BMPs are induced during inflammation and injury. The BMP-pathway proved to be overactivated in esophagitis and Barrett's esophagus when compared to controls. Moreover, in ex vivo experiments, it was shown that the differentiation of normal squamous cells toward a columnar cell type was induced by BMP-4, which was particularly illustrated by changes in cytokeratin expression patterns. Therefore, it was suggested that the BMP-pathway could play a role in the transdifferentiation of normal squamous esophageal cells into columnar cells (Milano et al. 2007).

Another study investigated the role of retinoic acid in the transition between squamous and columnar cell types (Chang et al. 2007). Retinoic acid (RA) is a powerful inducer of differentiation during embryogenesis and activates a number of cell-signaling pathways that are involved in determining the fate of the embryonic cells (Hay and Zuk 1995; Gronemeyer and Miturski 2001). Indeed, one of the target genes of RA is the homeobox gene Cdx2 (encoding for a so-called homeodomain transcription factor that is specifically involved in the regulation of the patterns of development, the morphogenesis), which is likely to induce a change in the cell differentiation status (Eda et al. 2003). In the esophagus, Cdx2 expression is observed in the areas of specialized intestinal metaplasia and this expression seems to be enhanced after exposure to various bile acids (Eda et al. 2003; Phillips et al. 2003; Moons et al. 2004; Lord et al. 2005; van Baal et al. 2008). Interestingly, one of the components of the bile refluxate (lithocholic acid) has been demonstrated to influence the efficiency of retinoic acid (Radominska-Pandya and Chen 2002). In this study, it was shown that ex vivo exposure of squamous biopsy specimens to both retinoic acid and lithocholic acid caused columnar differentiation. Conversely, an ex vivo Barrett's esophagus biopsy specimen could be transformed into a squamous-appearing epithelium through the inhibition of retinoic acid (Chang et al. 2007). These observations implicate a retinoic acid-induced transformation to metaplastic epithelium. However, follow-up is needed by in vivo experiments.

4.3.6 Clonal Expansion

Barrett's esophagus has been described as a clonal proliferative disorder: clonal fields of abnormal cells populate the metaplastic epithelium, with each field having potential clonal alterations in DNA content (ploidy), mutations,

or deletions (Maley and Reid 2005). After the initiation of a metaplastic stem cell, a stage of clonal expansion takes place, which may lead to rapid colonization of the adjacent mucosa (Atherfold and Jankowski 2006). Under conditions such as ongoing GERD, it is thought that this stem cell divides to produce two metaplastic stem cells instead of one stem cell and one differentiating transit amplifying cell (Atherfold and Jankowski 2006). Gland bifurcation is thought to be the consequence of this mechanism (Schmidt et al. 1999) (see Fig. 4.3). These bifurcating glands will divide again thereby producing a large group of epithelial cells with a common genotype (clonal expansion). This process has also been shown to occur in the colon, thereby offering support to this theory (Greaves et al. 2006).

4.4 Progression to Esophageal Adenocarcinoma

Patients with a Barrett's esophagus have a higher risk of developing esophageal adenocarcinoma when compared to the general population (Cameron et al. 1985; Tytgat 1995). Two meta-analyses showed that the overall estimate of cancer incidence in Barrett's esophagus varies between 6 and 7 cases per 1,000 person–years (0.6–0.7% per year) (Thomas et al. 2007; Yousef et al. 2008). Another recently published systemic review focused on the incidence of esophageal adenocarcinoma in patients with histologically proven high-grade dysplasia who were undergoing surveillance. An average incidence rate of 6.6/100 patient-years (range 2.3–10.3)

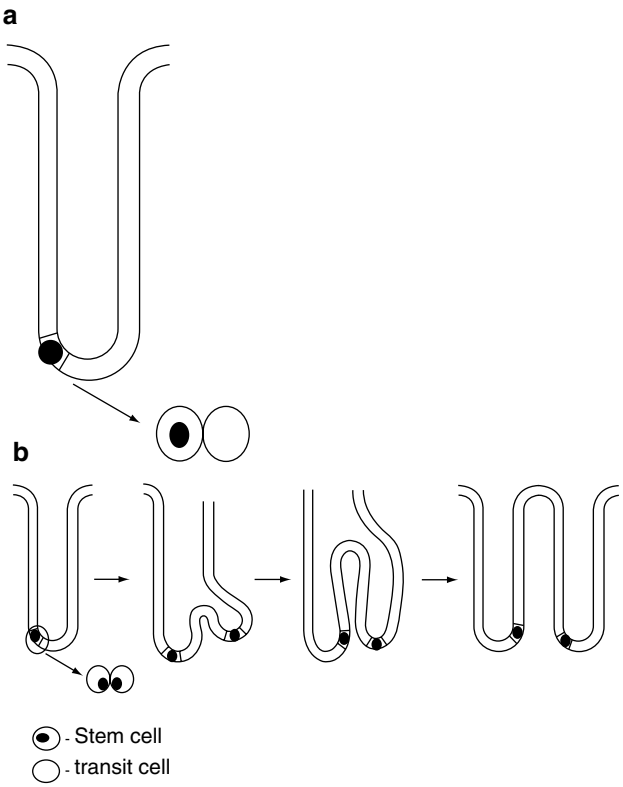

Fig. 4.3 Role of stem cell number in controlling glandular phenotype. (**a**) Stem cell division results in one transit cell and one stem cell, which causes gland homeostasis. (**b**) Stem cell division results in two stem cells, which causes gland bifurcation. Adapted from Jankowski et al. (2000)

was found (Rastogi et al. 2008). However, one study showed an inverse relationship between study size and reported cancer risk in the setting of Barrett's esophagus, with small studies reporting much higher risks of cancer than larger studies (Shaheen et al. 2000). This finding suggests publication bias, which might have led to an overestimated cancer risk in patients with Barrett's esophagus in the literature.

It is generally accepted that the development of esophageal adenocarcinoma follows a metaplasia – dysplasia – carcinoma sequence, which is characterized by a number of genetic and epigenetic changes (Jankowski et al. 1999). Currently, the histologic finding of high-grade dysplasia remains the most reliable predictor of progression to esophageal adenocarcinoma. Also, genetic changes linked to this progression may be used as biomarkers (Williams et al. 2006; Kerkhof et al. 2007).

4.4.1 Hallmarks of Cancer Progression

In the development of an invasive carcinoma, six essential steps have been described: self-sufficiency in growth, insensitivity to antigrowth signals, evading apoptosis, limitless replicative potential, sustained angiogenesis, and ability for invasion and dissemination (Hanahan and Weinberg 2000). In Barrett's carcinogenesis, there is a clear documentation for all of these biological characteristics, which has been summarized previously (Wijnhoven et al. 2001; Morales et al. 2002; Lagarde et al. 2007). Here, an overview of the most important molecular changes during the progression from metaplasia to dysplasia and, ultimately, invasive carcinoma is given.

4.4.1.1 Self-Sufficiency in Growth

The cell cylce is divided into G1 (first gap), S (DNA synthesis), G2 (second gap), and M (mitosis) phase. In G1, cells reach a key restriction point at which they either enter the S-phase and complete the cell cycle, or exit the cycle and become quiescent (G0) (Souza et al. 2001). Growth signals are required for cells to leave the G0 phase and progress through the restriction point. Growth-signaling molecules bind to the receptors on the cell surface, thereby activating intracellular pathways involving the activation of growth regulatory molecules, including cyclins D1 and E. Cyclin D1 is a key regulator of cell cycle progression, particularly at the transition from G1- to S-phase (Murray 2004). Expression of cyclins D1 and E has increased in neoplastic cells in Barrett's esophagus (Arber et al. 1996; Sarbia et al. 1999; Bani-Hani et al. 2000; Lin et al. 2000).

Several growth factors have been associated with the metaplasia – dysplasia – carcinoma sequence in esophageal adenocarcinoma. The epidermal growth factor (EGF) as well as TGF-α bind to the EGF receptor to stimulate cell proliferation (Singh and Harris 2005). Overexpression of the EGF receptor has been reported to correlate with tumor progression and a poor differentiation grade (al-Kasspooles M et al. 1993; Yacoub et al. 1997; Wilkinson et al. 2004; Wang et al. 2007).

Besides the EGF receptor, it has been shown that the hepatocyte growth factor (HGF) receptor (also known as Met) is overexpressed in both dysplastic epithelium and esophageal adenocarcinoma (Herrera et al. 2005). Activation of Met causes decreased apoptosis and enhanced proliferation, angiogenesis, and invasion (Herrera et al. 2005; Jiang et al. 2005). Another study has identified Met expression as an independent prognostic risk factor in patients with esophageal adenocarcinoma: patients with high Met expression had a reduced survival and were more likely to develop distant metastases and local recurrences compared to patients with low Met expression (Tuynman et al. 2008). Interestingly, inhibition of COX-2 has been shown to downregulate Met expression both in vitro and in vivo (Herrera et al. 2005; Tuynman et al. 2005).

4.4.1.2 Insensitivity to Antigrowth Signals

In normal tissue, multiple antiproliferative signals operate to maintain cellular quiescence and tissue homeostasis. These growth-inhibitory signals are received by cell surface receptors linked to intracellular signaling pathways. Proliferation can be blocked by two distinct mechanisms: cells may be forced out of the active cell cycle into the G0 phase or cells may be pushed towards a permanent growth arrest characterized by differentiation. The Retinoblastoma (Rb)-pathway plays an important role in this process. Changes in genes that normally block Rb-phosphorylation (i.e., p16 and p53) have been identified. Loss of heterozygosity (LOH), mutations, or promoter hypermethylation of the p16 gene have been reported in up to 80% of patients with a Barrett's esophagus (Klump et al. 1998). Furthermore, p16 alterations are recognized as early molecular lesions associated with clonal proliferation within metaplastic epithelium (Maley et al. 2004).

The adenomatous polyposis coli (APC) gene is a tumor suppressor gene that blocks cell proliferation by binding cellular signal proteins and by inducing differentiation. The prevalence of mutations in the APC gene is low in esophageal adenocarcinoma compared with colon cancer (Powell et al. 1994); on the other hand, LOH on chromosome 5q (where the APC gene is located) occurs frequently (Boynton et al. 1992; Kawakami et al. 2000).

Cell cycle progression of normal epithelial cells is inhibited by TGF-β (acting as a negative growth factor), whereas malignant epithelial cells are often insensitive to the growth-inhibitory effects of TGF-β. Indeed, TGF-β responsiveness is reduced during all stages of the metaplasia – dysplasia – carcinoma sequence, resulting in an impaired TGF-β signaling. Loss of expression of the functional receptor for TGF-β is associated with adenocarcinoma of the esophagus (Garrigue-Antar et al. 1996; Souza et al. 1996). During subsequent tumor progression, TGF-β can be overexpressed, and may contribute to tumor invasion and systemic tumor spread. In esophageal adenocarcinoma TGF-β overexpression is associated with advanced tumor stage (von Rahden et al. 2006).

4.4.1.3 Evading Apoptosis

The ability of tumor cell populations to expand in number is determined not only by the rate of cell proliferation, but also by the rate of cell apoptosis (programmed cell death). Apoptosis can be regulated through several pathways that are activated by DNA damage. The protein p53 activates one of these pathways: DNA damage results in the accumulation of p53 which stops the progression of the cell cycle until the genetic damage has been repaired or apoptosis has been induced (Giaccia and Kastan 1998; Prives and Hall 1999; Robert et al. 2000). Mutations, LOH, and deletions of the p53 gene have been reported in the majority of patients with esophageal adenocarcinomas (Younes et al. 1993; Hamelin et al. 1994; Kyrgidis et al. 2005). Moreover, p53 mutations were associated with poor tumor differentiation grade, reduced disease-free survival, and reduced overall survival (Ribeiro et al. 1998; Ireland et al. 2000; Schneider et al. 2000; Casson et al. 2003).

4.4.1.4 Limitless Replicative Potential

In normal cells, the replicative potential is limited by the length of telomeres (ends of chromosomes). During each cell cycle, a loss of 50–100 base-pair telomeric DNA of each chromosome is noted. After a certain number of divisions, the telomeres are too short to protect chromosomes from degradation, and the cell is triggered to exit from G1 into a permanent growth-arrested G0-state. To reach a state of unlimited replication, tumor cells must stabilize the length of their

telomeres. In 85–95% of human cancers, stabilization of telomeres is achieved by the reactivation of telomerase (which can impede telomere degradation) (Shay and Bacchetti 1997). Increasing levels of telomerase are observed along the metaplasia – dyplasia – carcinoma sequence (Lord et al. 2000). Furthermore, it has been presumed that telomere dysfunction contributes to genomic instability in human cancer (De Lange 2005).

4.4.1.5 Sustained Angiogenesis

Angiogenesis is required to maintain tumor growth as oxygen and nutrients supplied by the vasculature are crucial for the development and progression of a malignant tumor. Tumor angiogenesis is a multistep process. The initial step requires the release of angiogenic factors that stimulate endothelial cell proliferation and migration. The most potent angiogenic molecules belong to the vascular endothelial growth factor (VEGF) family, and are secreted by almost all solid cancers. Several groups have reported that, compared with the normal squamous epithelium of the esophagus, a higher level of expression of VEGF-A can already be observed in nonneoplastic Barrett's epithelium, with a further increase in high-grade intraepithelial neoplasia and superficial cancer (Couvelard et al. 2000; Auvinen et al. 2002; Mobius et al. 2003). The switch towards an angiogenic state appears to be an early event in the progression toward esophageal adenocarcinoma. However, no prognostic role of the increased expression of VEGF in patients with invasive esophageal cancer has been established yet.

4.4.1.6 Tissue Invasion and Dissemination

Abnormalities in cell–cell adhesion molecules play an important role in the process of invasion and dissemination of tumor cells. The principle functions of these molecules are to hold cells together and mediate cell–cell interactions. For example, E-cadherin on the surface of all epithelial cells is linked to the actin cytoskeleton through interactions with catenins in the cytoplasm (especially β-catenin), and is able to form bridges with other cells. In epithelial cancers, a disrupted cell–cell adhesion might lead to metastases (Christofori and Semb 1999; Wijnhoven et al. 2000). A significant reduction of E-cadherin expression has been shown as the Barrett's metaplasia – dysplasia – carcinoma sequence progresses (Bailey et al. 1998). Furthermore, it has been reported that a reduced expression of both E-cadherin and β-catenin correlates with decreased patient survival in esophageal adenocarcinoma (Krishnadath et al. 1997; Nair et al. 2005).

Loss in epithelial cell–cell contact is thought to play a pivotal role in the process by which epithelial cells acquire motile properties that are required for invasion. This process is called the epithelial to mesenchymal transition (EMT) (Thiery 2002). During EMT, epithelial cell–cell contact is decreased by the downregulation of cytoskeletal components and the cell morphology becomes more fibroblast-like with the upregulation of mesenchymal markers (Thiery 2003). It has been shown that EMT promotes cellular motility and invasion in a range of tumor cells in vitro. TGF-β is an important inducer of EMT (Thiery 2003), and one immunohistochemical study confirmed its role in EMT in patients with esophageal adenocarcinoma (Rees et al. 2006). However, more evidence is needed to support these limited data.

4.4.2 Genetic Instability

The tendency for these six tumorigenic steps to occur is increased by a general underlying phenomenon of genetic instability. Exposure to (duodeno-)gastroesophageal reflux has been shown to cause nonspecific DNA damage

(Olliver et al. 2005), and the most prominent gene abnormality that promotes mutagenesis in response to DNA damage is the loss of the p53 tumor suppressor protein. Epigenetic changes (i.e., hypo- or hypermethylation of DNA) may also result in genetic instability, which has been reported in the development of esophageal adenocarcinoma (Eads et al. 2001). Aneuploidy (abnormal nuclear DNA content) does not correlate with any single mutation, but reflects widespread DNA changes due to genomic instability (Morales et al. 2002). Several studies showed that aneuploidy in Barrett's epithelium is associated with the risk for progression to malignancy, and that the prevalence of aneuploidy increases with the degree of dysplasia (Menke-Pluymers et al. 1994; Galipeau et al. 1996; Montgomery et al. 1996).

4.5 Summary

Barrett's esophagus is an acquired condition in which the normal squamous epithelium of the esophagus has been replaced by specialized (intestinal-type) columnar epithelium. Reflux of both duodenal and gastric contents is thought to be the causative factor. Several factors that promote GERD, including dysfunction of the LES, the presence of hiatal hernia, obesity, dietary patterns, and *H. pylori* infection have been described. The refluxate induces several changes in the esophageal epithelium at the cellular and molecular level. The reason why only a minority of patients suffering from GERD develops Barrett's epithelium remains unknown. Despite recent progress in our understanding of some pathophysiologic observations in Barrett's esophagus, we have not been successful in identifying the key steps in cellular transformation. It is most plausible that stem cells are involved in this process, as they are the only permanent residents of the epithelium. Obviously, further research in this field is required that should focus on revealing the stem cells involved in the development of Barrett's esophagus, in order to achieve better understanding of this complex process.

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5 Differences in the Molecular Biology of Adenocarcinoma of the Esophagus, Gastric Cardia, and Upper Gastric Third

Kuno Lehmann and Paul M. Schneider

Abstract Adenocarcinoma of the distal esophagus, gastric cardia, and upper gastric third are grouped in type I-III by the Siewert classification. This classification is based on the endoscopic localisation of the tumor center, and is the most important diagnostic tool to group these tumors. On a molecular level, there is currently no marker that would allow to differentiate the three different types. Furthermore, the Siewert classification was not uniformly used in the recent literature, making interpretation and generalization of these results difficult. However, several potential targets have been identified that may help to separate these tumors by molecular markers, and are summarized in this chapter.

5.1 Introduction

The incidence of cancer at the gastroesophageal junction is rising in the US and in Europe (Devesa et al. 1998). The increase of these junction tumors was accompanied by a simultaneous decrease of noncardia tumors of the stomach (Botterweck et al. 2000). A clinical classification of carcinomas of the gastroesophageal junction exists according to Siewert, distinguishing between type I (distal esophagus), type II (true cardia), and type III (subcardial tumors) (Siewert and Stein 1998). This classification is based on endoscopic appearance and defines the cardia as a zone of 2 cm at the proximal end of the longitudinal folds.

The clinical management of type I tumors includes, as for esophageal carcinomas, a transthoracic esophageal resection and a mediastinal and coeliacal lymphadenenectomy. Type II and III tumors are treated by abdominal, transhiatal extended gastrectomy with a D2 lymphadenenctomy (Stein et al. 2000; von Rahden et al. 2006).

Known prognostic factors are a complete (R0) resection and involvement of lymph nodes. Type I tumors metastasize to lymph node compartments in the mediastinum, whereas type II and III tumors spread mainly into the celiac compartment. A study with 145 patients found a significantly increased rate (24% vs. 7%) of micrometastasis in type II and III tumors compared with type I tumors (Mueller et al. 2000). A significant impact on survival for micrometastasis was observed in type I and II tumors in a series of 85 patients (Schurr et al. 2006).

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5.2 Microsatelite Instability (MSI) and Loss of Heterozygosity (LOH)

By comparing MSI and LOH by genomic hybridization, a significant difference was found on locus 14q31–32.1. This mutation occured more often in Barrett-related adenocarcinoma than in cardia cancer (van Dekken et al. 1999). This result was not confirmed by a following study and many others did not succeed in demonstrating any significant differences by genomic hybridization (El-Rifai et al. 2001; Marsman et al. 2004; Menke-Pluymers et al. 1996; Weiss et al. 2003; Yanagi et al. 2000). A comparative analysis using microarrays showed some differences between the two types but concrete and reproducible results must follow (Chang et al. 2004).

5.3 Difference in Phenotype on Histology and Immunohistochemistry

A prospective analysis of 1,346 patients observed intestinal metaplasia (Barrett's esophagus) adjacent to the tumor in 76.9% of the specimens and in 97.4% after neoadjuvant chemotherapy. In contrast, only 2% of the type III tumors exhibited this growth pattern. Similarly, 81% of the type I but only 39% of the type III tumors had an intestinal growth pattern (Siewert et al. 2005) (Table 5.1).

Cytokeratin (CK) 7 and 20 are structural proteins of the cytoskeleton. Intestinal cells express CK20, lining the glandular surfaces and crypts. CK7 is a marker of differentiated intestinal cells. A typical CK20/CK7 expression pattern was observed in long-segment Barrett's esophagus compared to the gastric cardia (Couvelard et al. 2001; Ormsby et al. 1999). This pattern was not seen in intestinal metaplasia in the stomach (Shen et al. 2002). The expression rate of the CK7/CK20 pattern may be lower in patients with a short-segment Barrett's esophagus (Liu et al. 2005). For the distinction of benign lesions, the value of the CK7/CK20 expression pattern is still under discussion (Nurgalieva et al. 2007).

For the differentiation of junctional carcinomas, the literature is also controversial; a positive predictive value of 87% was found for the CK7/CK20 phenotype in 85 cases. This sharp edged difference is supported by other studies (Mattioli et al. 2007; Taniere et al. 2002). But in several publications, no important difference in CK7/20 staining between esophageal and cardia cancer was observed (Driessen et al. 2004; Flucke et al. 2003; van Lier et al. 2005).

Mucin peptide core antigens were identified as markers for the progression of dysplasia in Barrett's esophagus (Arul et al. 2000). MUC1

Table 5.1 Clinical differences between esophagogastric junction tumors according to Siewert's classification

Clinical Phenotype	Type I	Type II	Type III
age	60	61	64
male/female ratio	10:1	5:1	2:1
intestinal metaplasia	76-97%	6%	1%
high grade (G3-4) tumors	54%	60%	73%
intestinal growth pattern (Laurén)	81%	55	38%
lymph node spread	mediastinal	celiac	celiac
pN+	55%	66%	79%
micrometastases	24%	24%	7%
gastroesophageal reflux	strong	+	weak
Helicobacter pylori	none	+	strong
previous cancer	++	+	++
survival after 5/10 years	50/40%	40/35%	25/20%

and MUC6 helped to differentiate intestinal metaplasia originating from a Barrett's esophagus only in some studies (Flucke et al. 2003; Glickman et al. 2003).

5.4 Differences in the Hallmarks of Cancer

Self-sufficiency in growth signals, insensitivity to antigrowth signals, evasion of apoptosis, limitless replicative potential, sustained angiogenesis, and tissue invasion are called the hallmark capabilities of cancer cells (Hanahan and Weinberg 2000). The tumor cell achieves these capabilities in a multistep process by mutation of genes leading to a gain or loss of function of gene products. Candidate genes for progression of Barrett's esophagus to adenocarcinoma have been described (Fitzgerald 2006; Morales et al. 2002). In the following sections, we will discuss important candidate genes and factors that are involved and may be different between type I, II, and III tumors of the esophagogastric junction (Table 5.2).

Table 5.2 Molecular differences between esophagogastric junction tumors according to Siewert's classification. A stronger association is represented by (+), and a weaker association by (–)

Molecular Markers	Type I	Type II	Type III
CK7/20 pattern	+		–
MUC 1/6	+		–
p53	+	+	–
COX-2	+	–	
APC hypermethylation		+	–
loss of p16	+	+	–
phosphorylated Rb		+	–
MAPK	–	+	+
b-catenin redistribution	+	–	

5.5 Self-Sufficiency in Growth Signals

In gastric cancer, chronic infection with *Helicobacter pylori* (Hp) is a known risk factor for the development of gastric carcinoma. Chronic Hp infection induces mitogen-activated protein kinase (MAPK) activity and subsequently activates mitogenic pathways (Kacar et al. 2007). Type II esophagogastric carcinomas showed a significantly higher rate of gastric Hp infection, compared to type I carcinomas (Mattioli et al. 2007). In contrast, chronic gastric Hp infection was associated with a statistically reduced risk for esophageal carcinoma and was not associated with cardia cancer in other studies (Anderson et al. 2008; Kamangar et al. 2006; Ye et al. 2004).

In Barrett's esophagus, repeated exposure to bile salts induces an increased proliferation (Kaur et al. 2000). Activation of proliferative signals by bile exposure involves inflammation-associated signaling pathways I kappaB kinases beta (IKK beta), tuberous sclerosis complex 1 (TSC1), and mammalian target of rapamycin (mTOR) downstream effector S6 kinase (S6K1) (Yen et al. 2008) or nuclear factor kappa B (Abdel-Latif et al. 2004) and c-myc (Tselepis et al. 2003). Bile reflux is also associated with intestinal metaplasia in the gastric cardia (Dixon et al. 2002). The localization of metaplasia may be related to the severity of reflux and the function of the lower esophageal sphincter (Csendes et al. 2002).

5.6 Insensitivity to Antigrowth Signals

Antigrowth pathways block proliferation or can induce a quiescent stage. Hypermethylation of the p16 gene, controlling the transition of the G2/S

phase, is a mechanism of neoplastic progression in esophageal neoplasia (Bian et al. 2002; Klump et al. 1998). Loss of p16 staining on immunohistochemistry was also significantly more frequent in cardia compared to noncardia gastric cancer (Kim et al. 2005). Hypermethylation of the APC locus may also contribute to esophageal cancer progression (Eads et al. 2000). APC mutations were observed to be significantly more in cardia than in distal gastric carcinomas (Tajima et al. 2007). Studies comparing the differences among all three types of junctinal tumors are lacking.

5.7 Evasion of Apoptosis

An important cell cycle control mechanism and potential switch to apoptosis is mediated by p53 (Levine 1997). Mutation-positive status for p53 has been shown to be a marker of progression to malignancy and an independent prognostic factor for patients after complete resection of a Barrett's carcinoma (Schneider et al. 1996, 2000). Mutations of p53 seem to occur in a similar frequency in distal esophageal and cardia carcinomas (Ireland et al. 2000). In more distal gastric carcinomas, this mutation is much less common (Flejou et al. 1999).

Increased expression of cyclooxygenase Type 2 (COX-2) is an important prognostic factor in Barrett's carcinoma (Buskens et al. 2002; Wilson et al. 1998). This expression was significantly weaker in cardia carcinoma than in the distal esophagus (Buskens et al. 2003; Marsman et al. 2004).

The enzyme 15-Lipoxygnase (15-LOX-1) showed a decreased expression in esophageal carcinoma. An upregulation of the enzyme and induction of apoptosis by NSAIDs could be demonstrated in vitro (Shureiqi et al. 2001). In gastric carcinoma cells, inhibition of 15-LOX-1 also induced apoptosis by upregulation of the enzyme (Wu et al. 2003).

5.8 Limitless Replicative Potential

Normal cells lack telomerase, the enzyme required to replicate the last 50–200 basepairs of the genome. Thus, every replication cycle shortens this region, finally inducing a growth-arrested G0 stage. Most human cancer cells reactivate telomerase; this was also observed in esophageal adenocarcinoma (Morales et al. 1998) and in gastric carcinomas (Gulmann et al. 2005). No difference was observed for the expression in both types of cancers and a diagnostic value seems improbable as this mutation occurs early in carcinogenesis (Barclay et al. 2005).

5.9 Sustained Angiogenesis

Expression of vascular endothelial growth factor (VEGF) is an essential and early step in the carcinogenesis of Barrett's adenocarcinoma (Auvinen et al. 2002; Couvelard et al. 2000). This was also shown for early gastric cancer (Cabuk et al. 2007). Expression of VEGF was a marker of progression and had a prognostic impact on disease free survival and overall survival in patients with gastric cancer (Kolev et al. 2007). There is a correlation of COX-2 expression and VEGF. Inhibition of COX-2 resulted in a decreased lymphangiogenesis in an experimental model (Iwata et al. 2007).

5.10 Tissue Invasion

The glycoprotein e-cadherin on the cell surface mediates the anchoring of cells via intracellular catenins and the actin cytoskeleton. Significant reduction of e-cadherin expression is a step in the dysplasia-adenocarcinoma sequence of Barrett's

esophagus (Bailey et al. 1998). Beta-catenin plays a structural role by binding to cadherins at the intracellular cell surface. It also has a role in downstream signaling by the wnt pathway and mediates transcriptional activation in a complex with lymphoid enhancer factor/T cell factor (Lef/Tcf) (Novak and Dedhar 1999). One study showed a significantly increased nuclear accumulation of beta-catenin in patients with esophageal adenocarcinoma, compared to patients with gastric cardia cancer (Marsman et al. 2004).

5.11 Conclusion

The anatomical classification by Siewert is safe and easily applicable and translates in a different surgical strategy for type I compared to type II and III carcinomas. The classification is nowadays widely, but not uniformly used. This makes interpretation of some results difficult.

Two major risk factors are identified for the development of adenocarcinoma in the gastroesophageal region: Gastroesophageal reflux and Hp infection. Gastroesophageal reflux has clear association with Barrett's carcinoma, the association with cardia carcinoma is only suspected. For gastric adenocarcinoma – and type III tumors are considered as such – there is a clear association with chronic Hp infection. This association seems less probable for type II carcinomas.

At the moment, the literature fails to show a clearcut molecular differentiation between the three types. Differences between distal esophageal (type I) and gastric (type III) carcinomas are partially established. These genes include p16 and p53. Cardia carcinomas (type II) differ from type I tumors in the expression of COX-2 and from type III tumors in APC mutational status.

Immunohistochemical discrimination by cytokeratin (CK7 and CK20) or mucin phenotype is considered to be controversial, although some studies showed promising results.

Further molecular differentiation of the three tumor types is mandatory and should follow a uniform classification.

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6 Clinical Staging of Adenocarcinoma of the Esophagogastric Junction

Julia Cordin, Kuno Lehmann, and Paul M. Schneider

Abstract Tumors of the esophagogastric junction are among the most frequent and cause lethal cancers. Patients often do not present until late in the disease when the tumor is sufficiently large to cause obstruction or invasion of the adjacent structures, and thus becomes symptomatic. Preoperative staging is critical to select those patients whose disease is still locally confined for curative surgery. Ideally, clinical staging should accurately predict tumor invasion, lymph node involvement, and distant metastases. Upper endoscopy establishes the tumor diagnosis by multiple biopsies and defines the tumor type (Siewert I-III), based on tumor localization in relation to the endoscopic cardia. Preoperative TNM staging has a strong impact on treatment strategy. Endoscopic Ultrasound (EUS) determines the T category, and to a lesser extent, the presence of lymph node metastases. Multislice Computed Tomography (CT) and ^{18}Fluorodeocxglucose Positron Emission Computed Tomography (^{18}FDG-PET-CT) provide further information, especially about systemic metastases. Diagnostic laparascopy is suggested in advanced (CT3/4) Siewert type II-III tumors to exclude peritoneal carcinomatosis. This chapter summarizes current staging modalities and their accuracy in clinical practice.

6.1 Introduction

Tumors of the esophagogastric junction are among the most frequent and lethal cancers. In addition, their incidence is increasing (Botterweck et al. 2000). Patients often do not present until late in the disease when the tumor is sufficiently large to cause obstruction or invasion of the adjacent structures, and thereby becomes symptomatic. Preoperative staging is critical to select those patients whose disease is still locally confined for curative surgery. Ideally, clinical staging should accurately predict tumor invasion, lymph node involvement, and distant metastases.

6.2 Establishing the Diagnosis

Upper endoscopy with multiple biopsy-sampling establishes the diagnosis (Lerut et al. 2006). The procedure enables tissue diagnosis

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and visualizes the upper gastrointestinal tract, if the endoscope can pass the tumor. Early-stage cancers appear endoscopically, as superficial, elevated, flat, or ulcerated lesions. Advanced lesions can impose as strictures, ulcerated masses, circumferential masses, or large ulcerations (Japanese Gastric Cancer Association 1998). Although the endoscopic visualization of a large, suspect mass is nearly pathognonomic for cancer, biopsies are mandatory to confirm the diagnosis. Taking multiple biopsies increases the diagnostic accuracy as shown in a series including patients with esophageal and gastric cancer (Graham, et al. 1982). The accuracy for the first biopsy was 93%, and increased to 95% for four, and 98% for seven biopsies.

6.3 The Tumor Center Localization Determines the Classification

Upper endoscopy enables the diagnosis of cancer, and also classifies adenocarcinoma of the esophagogastric junction. Adenocarcinomas of the gastric cardia have distinct pathological and clinical characteristics as compared to distal gastric tumors (MacDonald 1972). However, adenocarcinoma of the gastric cardia and the distal esophagus also show many similarities and were also classified as one group of tumors (Kalish et al. 1984). The use of different classification systems made a comparison of epidemiology, diagnosis, management, and outcome difficult. This confusion is mainly due to the borderline location of these tumors between the distal esophagus and the stomach, the ambiguous use of the term "cardia carcinoma," and the lack of clear UICC recommendations for classification and staging of these tumors (Hermanek and Sobin 1997).

Siewert and colleagues established a classification for adenocarcinoma of the esophagogastric junction (AEG) that is now widely accepted and used (Siewert et al. 1987; Siewert and Stein 1998). AEG tumors were defined by a tumor center within 5 cm proximal or distal to the endoscopic cardia. This "endoscopic cardia" is defined as the area where the longitudinal gastric folds end. The Siewert classification of AEG divides them into three types (Fig. 6.1). The location of the AEG does influence the prognosis and affects the therapeutic management (Siewert et al. 1998). Until now, AEG type I has been staged like esophageal cancers and AEG type II and type III like gastric cancers. The new 7th edition of the UICC TNM classification stages adenocarcinoma of the esophagogastric junction (Siewert type I-III) as one clinical entity alike esophageal cancers. Lymph nodes at the celiac trunc are considered regional lymph nodes (see chapter 3).

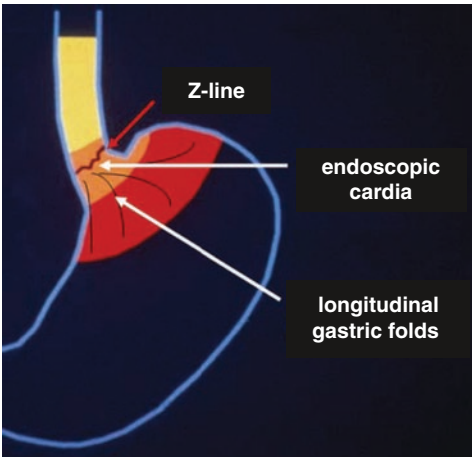

Fig. 6.1 Siewert classification of AEG. Type I (*yellow*): Adenocarcinoma of the distal esophagus with the tumor center more than 1 cm above the endoscopic cardia. These tumors generally originate from an area of Barrett's metaplasia in the esophagus. Type II (*orange*): True carcinoma of the cardia (tumor center from 1 cm above to 2 cm below the endoscopic cardia), arising from the cardiac epithelium or a short segment with intestinal metaplasia. Type III (*red*): subcardial gastric carcinoma infiltrating the cardia ± distal esophagus from below (tumor center 2–5 cm below the endoscopic cardia)

6.4 Preoperative TNM Staging Defines Further Treatment Strategies

The main goal of preoperative TNM staging is to select patients with early disease for limited surgery, and to avoid unnecessary radical surgery in patients with systemically (M+) advanced disease. Depending on the tumor stage, current treatment options for esophageal and gastric cancer range from endoscopic mucosal resection (EMR) to preoperative chemoradiation followed by esophagectomy or transhiatally extended gastrectomy (Lerut et al. 2001). Evaluation of the T-category is critical for AEG tumors. Only T1 tumors are considered as early cancers. In patients with categories T1-2 at presentation, primary resection and lymph node dissection is the treatment of choice, and is potentially curative. Extension into the esophageal adventitia results in a locally advanced T3 carcinoma, which is still resectable, but usually asks for multimodality treatment (preoperative neoadjuvant chemotherapy or chemoradiation). Invasion of the tumor into adjacent organs, such as aorta, diaphragm, liver, or pancreas, indicates T4 disease. Approximately 80% of patients in Western countries have locally advanced disease at the time of diagnosis. Neoadjuvant chemotherapy or chemoradiation may improve the rate of curative resections and potentially overall survival (Cunningham et al. 2006).

Approximately, 50% of patients have metastatic disease at presentation. With a few exceptions (e.g., single organ metastasis), no curative treatment is available and local tumor therapy is applied exclusively for palliation of symptoms (Lerut et al. 2006).

According to the current UICC/AJCC classification, metastatic disease is subdivided into M1a (metastases to nonregional lymph nodes) and M1b (distant organ metastases) for AEG Siewert type I (Greene et al. 2002). In the new UICC/AJCC classification, AEG Siewert Type I-III will be staged identically and lymph node metastases to the celiac trunk will be classified as regional lymph node metastases and will no longer be classified as M1a for Siewert Type I tumors.

6.5 Imaging Techniques for AEG

Currently, the most frequently used imaging techniques for the clinical staging of AEG are endoscopic ultrasound and multislice CT of the chest and abdomen. The ^{18}FDG-PET or the combined ^{18}FDG-PET/CT is not yet widely available. Barium studies may suggest the presence of adenocarcinoma of the esophagogastric junction and help defining unclassified AEG (e.g., impassable tumor stenosis), but are not routinely performed. The MRI may play a role in selected patients with suspected liver metastases.

6.6 Endoscopic Ultrasound (EUS)

EUS is nowadays the most precise imaging technique to evaluate the depth of tumor invasion (uT) and to a lesser extent, lymphatic (uN) involvement (Bentrem et al. 2007; Kienle et al. 2002). The ability to display distinct wall layers is the particular advantage of EUS in the staging of esophageal and gastric cancer. EUS at 7.5 MHz (conventional EUS) produces a five-layer image (superficial mucosa, mucosa, including the lamina muscularis mucosae, submucosa, muscularis propria, adventitia/serosa) of the organ wall (Messmann and Schlottmann 2001). Accurate staging of early AEG is helpful if a local therapy like EMR is planned. The risk for positive regional lymph nodes is below 5% if the tumor is limited to the mucosa (T1a). Deeper infiltration to the submucosa (T1b) will raise this risk to >20% (Katai and Sano 2005; Stein et al. 2005). Subsequently, higher invasion grades (uT2-3) frequently show

the involvement of the regional lymph nodes. Mucosal tumors (T1a) are frequently undetectable in conventional EUS. Therefore, there is a high chance for a submucosal infiltration (T1b), if the 7.5 MHz EUS is positive (Kelly et al. 2001).

EUS can also be performed with a high-frequency (up to 30 MHz) miniprobe-EUS, which is able to demonstrate up to nine different layers. This kind of EUS is primarily used to distinguish disease involving the mucosa from disease penetrating into the submucosa. A successful differentiation of mucosal and submucosal cancers is hereby possible in 84% (Murata et al. 1996). With high-frequency EUS (20–30 MHz), correct identification of T1a ranges from 70 to 100%. A clear disadvantage of high-frequency EUS compared to conventional EUS is its lower depth of penetration. Therefore, high-frequency EUS cannot be used for lymph node staging and assessment of locally advanced tumors (Murata et al. 2003). The accuracy of conventional EUS in differentiating lower T-categories uT1/T2 from advanced categories uT3/T4 in gastric and esophageal cancers were 93% and 91% in very experienced hands, respectively. Some studies, however, showed a lower accuracy for T-staging in the daily clinical routine and it is obvious that reported accuracies are clearly lower in more recent studies (Meining et al. 2002). Unfortunately, the accuracy of EUS is highly dependent on the experience of the examiner and showed only a rather modest performance in some studies (Meining et al. 2003; Polkowski et al. 2004).

In general, EUS tends to overestimate the depth of tumor infiltration, when inflammatory reactions or edema is present. This is likely the reason for the low accuracy (50% or less) of EUS to predict histopathologic response to neoadjuvant therapy (Beseth et al. 2000; Schneider et al. 2008). Furthermore, local advancement of the disease may lead to stenosis, which is already a rather poor prognostic sign (Hiele et al. 1997). In this condition, the accuracy of T-staging falls below 50% (Lerut et al. 2006). The accuracy of EUS staging appears to be better in Siewert type I than type II/III cancers (Byrne and Jowell 2002).

EUS can assess structures up to a distance of approximately 5 cm from the probe. This allows assessment of the regional lymph node involvement. EUS is probably more accurate to assess regional lymph nodes than CT (Kienle et al. 2002) (Table 6.1). To improve specificity, EUS can be combined with fine-needle aspiration (FNA). This is a highly sensitive method to assess lymph nodes (Fritscher-Ravens et al. 2000). Despite this, FNA can lead to false negative results due to sampling

Table 6.1 Assessment of the lymph node involvement by CT, EUS, and ^{18}FDG-PET

Reference	Tumor type	*n*	CT		EUS		^{18}FDG-PET	
			Sens (%)	Spec (%)	Sens (%)	Spec (%)	Sens (%)	Spec (%)
Flamen et al. 2000	E	39	22	96	63	88	39	97
Kim et al. 2001	E	53	15	97			52	94
Kienle et al. 2002	B	117	84	47	84	71		
Romagnoulo et al. 2002	E	48	53	86				
Hunerbein et al. 2003	B	97			71	71		
Wu et al. 2003	E	86	77	79	68	75		
Yoon et al. 2003	E	81	11	95			30	82
Polkowski et al. 2004	G	88	84	50	68	64		

The table shows sensitivity and specificity for multislice CT, EUS, or PET in patients with gastric (G), esophageal (E), or both esophageal and gastric cancer (B). Adapted from (Weber and Ott 2004)

errors, and rarely to false positive results, when the needle passes through the primary tumor.

Overall, conventional EUS at 7.5 MHZ appears to be an acceptable local T-staging modality that allows a reasonably safe stratification for primary resection for uT1/2 tumors and neoadjuvant treatment for uT3/4 tumors. Its value in the prediction of lymph node involvement is limited even in experienced hands. The future role of the miniprobe is rather questionable since EMR is now frequently used as a combination of a staging and treatment modality and therefore makes high frequency EUS unnecessary. EUS-guided FNA of lymph nodes should be performed only if clinical consequences are drawn from this examination.

6.7 Computed Tomography (CT)

Today, multislice, contrast-enhanced CT is probably the most frequently used staging modality for adenocarcinoma of the esophagogastric junction. The introduction of multislice computed tomography (CT) into clinical radiology constitutes a major improvement in CT technology. It will most likely widen the scope of CT endoscopy, CT angiography, and multiplanar imaging in the near future. The advantages over helical CT have been quantitative, mainly in terms of increased image acquisition speed which provides acquisition of a large volume of the body and an optimal contrast between vessels, tumors, and various tissues. Therefore, new challenges are faced that require the development of novel strategies in order to take full advantage of the increased capabilities of multislice CT in its current form and future generations of CT scanners (Gretschel et al. 2004).

CT is of limited value for loco-regional staging. It is not capable of differentiating the depth of primary tumor invasion and often leads to overestimation of T2 tumors as T3 or even T4 tumors, especially in AEG type II and III. Although CT can detect enlarged lymph nodes, the sensitivity, specificity, and accuracy for nodal disease are low (Table 6.1). The accuracy for the prediction of lymph node metastases is between 62 and 73% and therefore within the range of conventional EUS (van Vliet et al. 2008). Thus the major role of CT is the detection of tumors infiltrating adjacent structures and predominantly systemic metastases at the most common sites (liver, lung). The reported values for the sensitivity of CT for the detection of distant metastases vary from less than 50% to more than 90% (Kinkel et al. 2002; van Vliet et al. 2008). However, a major drawback of all noninvasive imaging modalities including multislice CT is the limited sensitivity for the detection of small metastases on the peritoneum.

For good quality CT examination of the upper gastrointestinal tract, up to 1,500 mL of water should be used as a negative contrast medium (Horton and Fishman 1998). Intravenous contrast medium is necessary and data acquisition at the time of peak enhancement of the liver enables optimal contrast between tumor and normal mucosa.

In conclusion, CT clearly has its role in the detection of metastases at the most common sites (liver, lung, lymph nodes) and the identification of locally advanced tumors (T3/T4) in AEG types I-III (Fig. 6.2).

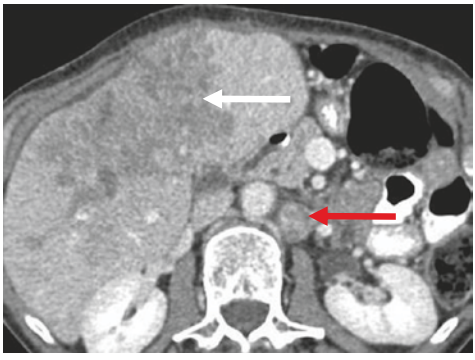

Fig. 6.2 CT image of metastases in AEG type III. The CT scans shows diffuse metastases in the liver (*white arrow*) and a large para-aortic lymph node metastasis (*red arrow*)

6.8 ^{18}Fluorodeoxyglucose Positron Emission Tomography (^{18}FDG-PET)

^{18}FDG-PET is unique in its ability to visualize areas of increased metabolic activity within tissues. It is based on the application of the glucose analog 2-deoxy-2-(18F)-fluoro-D-glucose (^{18}FDG). ^{18}FDG is preferentially taken up by tumor cells due to their high metabolic turnover, but cannot be metabolized inside the cell. The detection of lesions by ^{18}FDG-PET is dependent on the size and ^{18}FDG uptake. Therefore, even very small lesions, with a diameter of less than 1 cm can be visualized, if the metabolic activity of the tissue is high. In contrast, large tumor masses can be falsely negative if the tumor is metabolically inactive (De Potter et al. 2002; Stahl et al. 2003). Usually, AEG show a high ^{18}FDG-uptake.

PET has a limited role in evaluating the T-category because of its inability to differentiate between individual organ layers. Compared with ^{18}FDG-PET or CT, EUS was more accurate for T-staging (Lowe et al. 2005). For loco-regional N-staging, ^{18}FDG-PET has a limited value due to its low sensitivity of 20% (Flamen et al. 2000; Lerut et al. 2000). However, there is still additional information due to a high specificity of the ^{18}FDG-PET (Chen et al. 2005). Results for N-staging by ^{18}FDG-PET are summarized in Table 6.1.

The ^{18}FDG-PET, however, increases the diagnostic accuracy for distant metastases (Heeren et al. 2004; Meltzer et al. 2000). For the detection of liver metastases, ^{18}FDG-PET shows a specificity of 85% and is therefore more sensitive than CT and ultrasound (Kinkel et al. 2002).

Furthermore, the assessment of tumor response by ^{18}FDG-PET has been shown to correlate with histopathologic tumor regression and patient survival in patients with AEG tumors (Ott et al. 2006; Weber et al. 2001). Responders were defined as those with a >35% decrease in the metabolic activity of the tumor tissue. Residual ^{18}FDG uptake after chemo-radiotherapy shows residual tumor tissue and is associated with a poor prognosis.

In the future, the combined ^{18}FDG-PET/CT may improve the accuracy of lymph node staging and the assessment of distant metastases by combining the advantages of two modalities (Fig. 6.4). However, a comparative study on that topic is currently not available.

6.9 MRI

There is little benefit of magnetic resonance imaging (MRI) in routine staging of AEG. The few studies that exist mostly compare multislice CT with MRI. These studies did not show a substantial benefit of one over the other method (Anzidei et al. 2009; Wang et al. 2000). The same was found for the staging of regional lymph nodes. MRI did not improve the already weak accuracy of multislice CT (Sohn et al. 2000). Thus, for the staging of the T and N categories, MRI does not add any benefit. However, MRI may play a role for metastatic disease, mostly for liver metastases and helps to differentiate malignant from benign lesions. The choice of the contrast media during the MRI scan is important (Gretschel et al. 2004). The use of contrast media containing supramagnetic iron oxide particles (SPIO) facilitates the detection of low-vascularized liver lesions like metastases, and thereby enhances the diagnostic sensitivity (Kim et al. 2003) (Fig. 6.3).

6.10 Staging Laparoscopy Excludes Peritoneal Disease

Peritoneal carcinomatosis is an important problem in patients with AEG type II and particularly III. The incidence ranges from 7% in a large Japanese series including many early stages

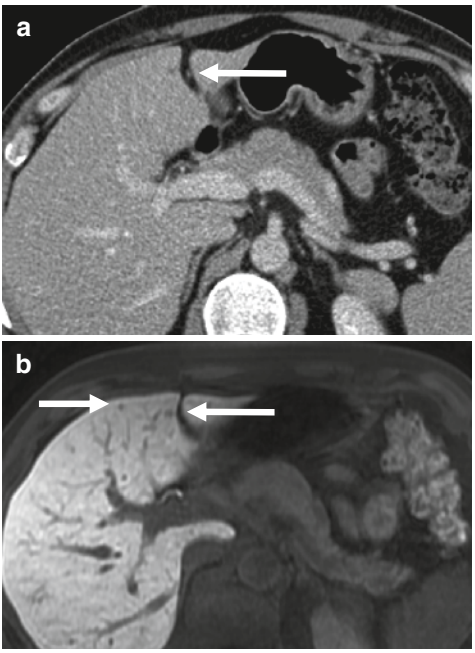

Fig. 6 3 CT and MRI Image of liver metastases. The CT (**a**) and MRI (**b**) scans show the same level in the same patient at identical time points. One lesion was hardly visualized by CT (**a**, *arrow*). By MRI, two lesions were found at the same level and appeared well demarcated (**b**, *arrows*)

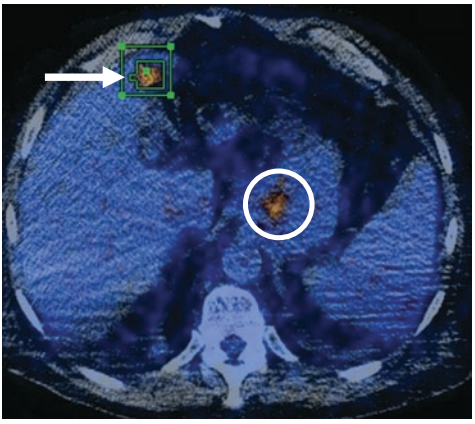

Fig. 6.4 Image of a ^{18}FDG-PET/CT. ^{18}FDG PET/CT images of a patient with an AEG type II, showing ^{18}FDG-uptake of the primary tumor (*circle*) and a single lesion in the liver (*arrow*)

(Maruyama et al. 2006) up to 56% in Western studies, where single cells were detected by immuno-histochemistry (Benevolo et al. 1998; Jonas et al. 2004). Small intraabdominal tumor deposits may not be visualized by abdominal imaging, because of the limited resolution of the conventional imaging methods such as CT, ^{18}FDG-PET, and MRI. Therefore, laparoscopy has been increasingly used for staging and exploration of intraabdominal disease in AEG Type II, and especially Type III tumors to avoid unnecessary laparatomy (D'Ugo et al. 1996; Hunerbein et al. 1995). Laparoscopy can be combined with diagnostic lavage cytology in the absence of ascites. This offers improved accuracy in the detection of intraabdominal tumor spread than CT (Chang et al. 2009). In general, staging laparoscopy is recommended in patients with locally advanced (uT3/4) AEG type II and III tumors where a neoadjuvant treatment is planned (Rau and Hunerbein 2005). Without preoperative chemotherapy, the laparoscopy can be performed in the setting of the planned primary resection. In patients with known metastatic disease, laparoscopy is unnecessary.

6.11 Conclusion

In conclusion, to establish the diagnosis for suspected adenocarcinoma of the esophagogastric junction, multiple biopsies during upper endoscopy are recommended. Endoscopy is crucial for the classification of AEG types I-III according to Siewert. The minimum staging requirement for an AEG type I-III is a CT of chest and abdomen with oral and intravenous contrast medium, preferentially as a multislice CT. In many centers, conventional EUS is performed in addition to CT and provides the uT category, and reasonably discriminates between T1/2 and T3/4 categories. In early AEG type I cancers, EMR is now frequently used as a combination

of a staging and treatment modality. In case of a submucosal cancer (pT1b) EMR/ESD is just diagnostic and a surgical resection is generally necessary. To exclude systemic metastases, a multislice CT or ^{18}FDG-PET/CT should be performed. MRI with supramagnetic iron oxide particles may be helpful in identifying liver metastases. A staging laparoscopy is recommended for occult peritoneal carcinomatosis in all locally advanced (uT3/4) AEG type II and III tumors, especially if neoadjuvant treatment is planned or within the setting of the planned primary resection.

Our current staging procedure consists of EUS and multislice CT. Within a prospective trial, we perform ^{18}FDG-PET-CT to evaluate its usefulness in detecting regional and extraregional lymph node metastases and systemic metastases. Diagnostic laparoscopy and lavage cytology is performed in all patients with cT3/T4 AEG type II-III to rule out occult peritoneal carcinomatosis prior to neoadjuvant chemotherapy or in the setting of a planned primary resection.

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7 Endoscopic Mucosal Resection for Staging and Therapy of Adenocarcinoma of the Esophagus, Gastric Cardia, and Upper Gastric Third

Henriette Heinrich and Peter Bauerfeind

Abstract Minamally invasive endoscopic resection techniques allow definitive histological staging for dysplasia and early cancer and in many cases curative treatment. In Barrett's esophagus with High Grade Dysplasia (HGD) or early mucosal cancer, endoscopic mucosal resection (EMR) should be considered both as diagnostic and therapeutic first line procedure, with the possibility to repeat the procedure in case of residual Barrett's dysplasia or mucosal cancer. In early cancer of the the submucosa, surgical resection should be discussed. Endoscopic submucosal dissection (ESD) is a useful therapeutic option for HGD or early cancer in the squamous epithelium of the esophagus or in the stomach when en bloc resection is needed in large lesions.

7.1 Introduction

Over the recent years, improving endoscopic imaging techniques allowed the early detection of neoplasia in the upper gastrointestinal tract. With this, minimally invasive endoscopic resection (ER) techniques have been developed allowing curative treatment in many cases and definite histological staging in all cases. This option has gained importance as radical esophageal resection and gastrectomy are associated with a significant mortality and morbidity. Since only a part of patients with HGD progess to cancer over the years, the less invasive ER offers great advantage over surgical resection.

In contrast to surgical resection, ER does not allow local lymph node resection, which makes careful selection of patients with minimal risk of lymph node metastases necessary.

Generally, endoscopic treatment is indicated for superficial lesions, which are limited to the mucosa (m1–m3), and therefore, have a low risk of lymphatic involvement. Lesions with high risk of lymph node involvement, meaning deep infiltration of the submucosa, poor cancer differentiation, and lymph or vascular invasion, are an indication for surgery (Pohl et al. 2008).

There are no randomized controlled studies to make a statement on whether surgery or endoscopic treatment is preferable in early neoplastic lesions of the upper gastrointestinal tract (Green et al. 2009). Nevertheless, ER is not only minimally invasive, therapeutic, and possibly curative, but also a useful diagnostic tool. In contrast to ablative methods like photodynamic therapy and argon plasma coagulation,

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ER allows complete histologic workup of the resected specimen with special focus on the risk factors mentioned above.

7.2 Staging and Marking Before ER

Local staging by endoscopic ultrasound is mandatory before ER. Initial decision between endoscopic techniques or surgery is based on the invasion depths. T1 and T2 tumors can be very well distinguished by this method (Pohl et al. 2008). The presence of local lymph nodes has to be determined by endoscopic ultrasound before ER, since final histology is frequently changed by ER (Hull et al. 2006). If multiple or very large lymph nodes are found, EUS, CT or PET-CT may be considered before ER. Computed tomography (CT) is only useful for ruling or distant metastases. With PET-CT, biologically active local metastasis might be found. Both may change the decision from ER to surgery in few cases. EUS-guided FNP of local lymph nodes might be difficult to interpret since a positive finding may be caused by cells from the esophageal or gastric wall. The crucial differentiation between T1m and T1sm by EUS is, on the other hand, hard to make. However, histology of the resected specimen will finally tell the truth (Pohl et al. 2008). The injection of fluid (saline, diluted epinephrine, and others) to lift the mucosa from the muscularis propria is necessary for CAP-assisted ER and ESD. There is evidence that the type of submucosal lifting relates to the infiltration depth in colorectal cancers (Kato et al. 2001). This also applies to neoplastic lesions of the upper gastrointestinal tract, although solid data are lacking.

Identification of multifocal neoplasia and disease-free margin is of critical importance. This can be achieved by advanced imaging techniques like high resolution endoscopy including narrow band imaging. Conventional chromoendoscopy with agents such as indigo carmine might also be used. In the stomach, spraying acetic acid combined with narrow band imaging is frequently applied. Lugol staining is used for squamous cell carcinoma or high-grade dysplasia in the esophagus (Curvers et al. 2008; Pouw and Bergman 2008).

Coagulation marks 2–5 mm outside the lateral margins of the target lesion are helpful to avoid incomplete resection because of impaired view due to bleeding during ER (Pouw and Bergman 2008).

7.3 Endoscopic Resection Techniques

In general, two different ER techniques, piecemeal and the en bloc resection with several technical modifications, can be distinguished.

For piecemeal resection, the CAP technique creating a pseudopolyp by lifting the mucosa by fluid injection, suction into a cap and its resection by a diathermy snare, or the combination of rubber band ligature and diathermy snare can be used (Inoue and Endo 1990). The CAP technique also allows en bloc resection of smaller lesions, mostly those smaller than 2 cm. Endoscopic submucosal dissection (ESD) allows the en bloc removal of larger lesions, and more precise histological evaluation of lateral margins of the obtained specimen. After marking the resection area by coagulations marks and lifting the mucosa by injection of fluid, incision of the mucosa around the lesion, regardless of its diameter, is performed. The mucosa is then removed in one piece by submucosal en bloc dissection with an electrosurgical knife (Miyamoto et al. 2002). Various compositions of the injected fluid and dissection techniques are used frequently, changed and adapted by the groups using these methods. Advent of new equipment, such as new dissecting devices (e.g., hybrid knife), also changes the procedures rapidly. Thus, no standards for the different ER methods are established yet. ESD is best

established for early cancer of the stomach and for early squamous cell cancer of the esophagus.

Piecemeal resection is technically easier, faster, and allows resection of larger lesions, but theoretically bears the risk of higher recurrence rates, which could be due to insufficient overlap of resection areas with consecutive remnants of neoplastic tissue.

7.4 Results of ER

Results of ER are usually reported as completeness of resection or relapse of Barrett's metaplasia/dysplasia or cancer. However, relapse or incomplete resection after ER may not represent failure of treatment since repetitive ER is frequently necessary and may finally result in an overall success. A more useful endpoint of ER is probably death from oesophageal or stomach cancer. It was shown that patients with Barrett's cancer often die from other reasons before Barrett's cancer became relevant (van der Burgh et al. 1996).

In addition, definite local staging after ER is an important result of this procedure, which allows careful selection of those patients who really benefit from surgical resection.

7.5 Results in Early Barrett's Adenocarcinoma or HGD

ER is a safe and effective method of resection of superficial lesions with high-grade dysplasia and early intramucosal cancer (IMC) limited to the mucosa, where risk of lymph node or vessel involvement has been reported to be less than 2% (Pouw and Bergman 2008; Ginsberg 2008; Larghi et al. 2007). Studies show a technical success rate ranging between 70 and 100% (Larghi et al. 2007; Soehendra et al. 2006; Seewald et al. 2003; Peters et al. 2006; Siddiqui and Gerke 2008; Gondrie et al. 2008).

Technical success, however, is largely defined by the selection of the patients and the experience of the examiner. Technical failure of ER in the hand of an experienced examiner usually means that surgery is anyway necessary. Recurrence of HGD or IMC seems to be a more valid outcome measure, reported to be 0–30% (May et al. 2002a, b). However, recurrence does not imply failure of ER, since second or multiple retreatments were shown to be successful.

Few data on long-term success with respect to mortality from Barrett's cancer are available, but some show favorable results (Pech et al. 2008; Giovannini et al. 2004). However, most reports have only small case numbers and short follow-up. Only one study reports results after 5 years with no deaths among 349 patients, including a majority with IMC (Pech et al. 2008). The pathologist plays an important role as distinction of HGD and IMC underlies a substantial interobserver variability (Odze and Lauwers 2008). Thus, long-term results might be affected by the pathologist and most guidelines recommend a second opinion on histological diagnosis.

ESD is not yet used in Barrett's HGD or IMC, except for case reports (Rosch et al. 2004). Accordingly, no short and long-term results are available. However, large Japanese series on ESD in squamous cell carcinoma have shown that this method is feasible in the esophagus (Fujishiro et al. 2006) and shows long-term advantage compared to piecemeal resection (Ishihara et al. 2008). ESD might be a good alternative in large IMC, but it will be difficult to show that cancer-free survival or necessity for surgery is improved compared to EMR. Taking into account the excellent results of piecemeal resection technique, it seems very unlikely that ESD will prove its superiority in the near future.

In HGD, the benefit of ER has to be compared with the natural history of HGD. A recent

metaanalysis showed that HGD transforms into cancer with a rate of 6.6/100 patient years (Rastogi et al. 2008). Thus, any intervention for HGD has to compete with this rather low risk of cancer. Furthermore, after transformation into cancer, well-established treatment options are available, especially if detected at an early stage. These considerations are also the reason why surgery should not be considered as the first-line treatment for HGD in Barrett's esophagus.

7.6 Complications of ER in Barrett Esophagus

Stricture is the most important complication, ranging between 0 and 70% in the published series (Soehendra et al. 2006; Giovannini et al. 2004). It will appear in almost all patients with circumferential ER. Thus, circumferential ER should be limited to a short segment (less than 3–5 cm). Most authors claim that circumferential ER in one session should be avoided and the remaining Barrett should be resected in a second session after healing of the first ER. However, scar formation makes the second resection more difficult and increases the risk of perforation. The combination of ER and radio frequency ablation (BARRX) offers an alternative for circumferential ablation with less risk of stricture formation (Shaheen et al. 2009).

Strictures are treated by standard bougienage technique. Short intervals (days) between bougienage sessions seemed to be most effective; controlled data are lacking. Treatment of stricture by removable stents is only successful in some patients (Holt et al. 2004). Biodegradable stents may be useful for stricture treatment; however, only case reports are available yet (Saito et al. 2008). Bleeding frequently occurs during ER, but it is rarely a problem after the procedure. More important is perforation that is reported to occur between 1 and 7% of the cases. After ER, frequently some air bubbles in the mediastinum are seen in CT-scan without clinical importance. However, larger perforations may occur partly due to insufficient separation of the layers or after repeated EMR and scar formation. These cases can be treated successfully with clips or stents and antibiotic treatment. Surgery is reported to be necessary only in very few cases as most complications can be handled endoscopically (Larghi and Waxman 2007).

ESD in the esophagus is mainly performed in Japan for squamous cell cancer. Risk for perforation or stricture seems similar as in EMR (Fujishiro et al. 2006). There are no data on complications for ESD in Barrett HGD or IMC.

7.7 ER for HGC or Early Cancer at the Esophagogastric Junction

HGD or early cancer at the esophagogastric junction is either included in studies reporting ESD for early gastric cancer (Chung et al. 2009) or in EMR studies for Barrett's neoplasia. In a recent Japanese series, 41 patients with ESD at the esophagogastric junction out of 2,011 patients with ESD for early gastric cancer were identified in order to evaluate the risk of stricture (Coda et al. 2009). The authors report a 17% risk of strictures; all patients were successfully treated by balloon dilatation. No reliable results on long-term outcome in this small subgroup are available. However, it seems unnecessary that these patients should be treated differently. Results are most likely similar to those in the esophagus or the stomach. ER is an attractive curative method also for neoplasia at the esophagogastric junction, despite few controversial opinions (von Rahden et al. 2006).

7.8 ER for Gastric Neoplasia

Japan is the country where ER and ESD for gastric neoplasia are best established. Well-differentiated elevated or flat adenocarcinomas <20 mm and depressed lesions with a size <10 mm and no sign of ulceration are an indication for endoscopic treatment.

Lymph node metastases were found in depressed cancers in <80% when submucosal infiltration was present (Abe et al. 2002).

In early gastric cancer a review of a large database of more than 5,000 patients who underwent gastrectomy with D2 level lymph node dissection showed that IMCs and small cancers (<3 cm) infiltrating the upper third of the submucosal layer (sm1) have a minimal incidence of lymph node metastases compared to mortality risk from surgery (Gotoda 2008). These results led to expanded criteria for the suitability for ER in early gastric neoplasia including ulcerative lesions with a size of 21 mm or greater, as well as cancers confined to the mucosa and small cancers invading the upper submucosal layer (sm1). In comparing ER and surgery for small differentiated gastric carcinomas, the disease specific 5-and 10-year survival rates of both therapy options are 99%. After ER, local recurrence rates are between 2 and 35% and correlates with the number of obtained specimens. All local recurrences could be cured endoscopically or surgically (Ono 2006; Uedo et al. 2006).

The most common complication of ER and ESD is bleeding (8%). Perforation is not common with ER for early gastric carcinoma, but ESD bears a risk of up to 4% (Gotoda 2008).

ESD offers the possibility to better resect large and ulcerative lesions, further reducing the need for gastrectomy (Gotoda 2008).

A study by Goto et al. showed complete resection rates for early gastric cancer in 91% and en bloc resection in 96%.The 5-year disease specific survival rates were reported to be as high as 100%, which could make ESD an alternative method to gastrectomy for the treatment of early gastric carcinoma (Goto et al. 2009).

7.9 Conclusion

In the last few years ER was used in a considerable number of patients with HGD or early cancer in Barrett's esophagus and stomach. ER allows conclusive histology in most cases, changing the pre-ER biopsy results in many patients. Curative results are amazingly good, but only few data on long-term results are available. In all cases of HGD it should be considered as first choice treatment. In early cancer it allows definite histology and may be followed by other treatment modalities such as surgery. In HGD or IMC of Barrett's esophagus, piecemeal resection by cap technique or rubberband ligation seemed to be a safe and successful method with low risk of local relapse, or later, lymph node metastases. Local relapse can successfully be treated endoscopically in most cases. ESD might be an attractive alternative in some patients with neoplastic Barrett's esophagus, but its clinical advantage over piecemeal resection remains to be shown. In gastric HGD or early cancer en bloc resection should be attempted in all cases. Therefore, ESD is necessary in large lesions.

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8 Surgical Strategies for Adenocarcinoma of the Esophagogastric Junction

Marc Schiesser and Paul M. Schneider

Abstract This chapter summarizes the surgical strategies for adenocarcinomas of the distal esophagus, gastric cardia, and subcardial gastric cancer invading the cardia ± distal esophagus known as adenocarcinomas of the esophagogastric junction (AEG). The different surgical approaches according to the tumor origin, localization, and tumor stage are addressed with particular attention to the extent and type of resection and appropriate lymphadenectomy (LAD). The classification of AEG according to Siewert is helpful for the selection of the surgical strategy. While type I tumors benefit from a transthoracic en bloc esophagectomy including a two-field LAD, type II and III tumors can be treated by an extended total gastrectomy with a transhiatal resection of the distal esophagus and LAD of the lower mediastinum and the abdominal D2 compartment. Limited resections appear to be possible for early tumor stages in selected cases of type I–III tumors.

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8.1 Introduction

The incidence of adenocarcinomas of the esophagus and gastric cardia is rising in the western world as a result of widespread gastroesophageal reflux and other risk factors (Pera et al. 2005). Recommendations for the surgical management of these tumors are needed to improve the patients' prognosis. To establish the resection strategy for an adenocarcinoma of the esophagogastric junction (AEG), the surgeon has to know what type of tumor he/she is confronted with, since the different tumor types warrant different surgical strategies to achieve an optimal outcome. In addition, the surgeon has to consider the pattern of lymph node metastases of the given tumor in order to plan the appropriate extent of lymphadenectomy (LAD). Prior to the introduction of the Siewert classification in 1987 (Siewert et al. 1987), studies about adenocarcinomas around the anatomical cardia included various types of tumors, and as a consequence, led to a lot of misinterpretation of the data in this field. The Siewert classification has to be seen as an attempt to introduce a systematic order that makes results comparable. The Munich group has published their results of 1,602 patients with AEG treated according to this classification (Siewert et al. 2000; Feith et al. 2006). Although

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this classification has been controversially discussed, it remains the best currently available for these kind of tumors. Since its introduction, it has been used by many centers throughout the world and served as a guide for the surgical approach. In addition, the classification has been adopted by the International Gastric Cancer Association and the International Society for Diseases of the Esophagus (Siewert and Stein 1998). Over the years, it has become clear that the different tumor types warrant different surgical strategies to optimize the patients' outcome (Fig. 8.1). In this chapter, we focus on the adaptation of the surgical strategy for the different types of AEG. Staging issues and the results of neoadjuvant therapy are not part of this review.

The Siewert classification is purely based on the anatomic localization of the tumor center, which can be defined by endoscopy using the proximal end of the longitudinal gastric mucosa folds as a pragmatic reference for the endoscopic cardia (point zero). The AEG includes all tumors 5 cm proximal (+5 cm) and distal (−5 cm) of the endoscopic cardia (point zero). An adenocarcinoma of the distal esophagus (>1 to +5 cm), which usually arises from an area of specialized intestinal metaplasia (Barrett's esophagus), is classified as a type I cancer. A type II cancer is a true carcinoma of the cardia (+1 to −2 cm) arising immediately at the esophagogastric junction. A type III cancer (−2 to −5 cm) is a subcardial gastric carcinoma that infiltrates the esophagogastric junction or the distal esophagus from below. The difference to a pure proximal gastric cancer is the infiltration of the cardia ± distal esophagus. Type I to III tumors exhibit epidemiological and histopathological differences. While there is a predominance of males in type I cancers (approximately 10:1), this coefficient drops to 2:1 in type III cancers. The prevalence of Barrett's metaplasia is over 90% in type I cancers, 5–10% in type II cancers, and less than 1% in type III cancers. Furthermore, there is an increased proportion of dedifferentiated G3 or G4 tumors and diffuse type tumors according to Laurén in type III cancers compared to the type I tumors (Lauren and Nevalainen 1993).

Besides the classification of the tumor, one has to consider the pattern of lymph node metastases of the given tumor entity. The distinguished

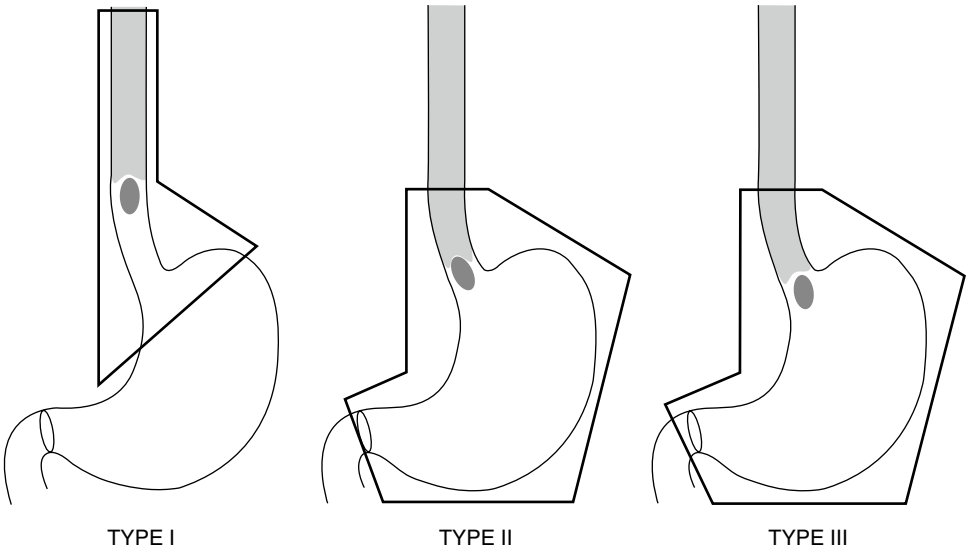

Fig. 8.1 Extent of resection for AEG type I, II, and III (from *left* to *right*)

lymph node metastases pattern of the different tumor types is a cornerstone for the surgical strategy and the extent of LAD. Lymphographic studies showed that the main lymphatic pathways originating from the lower esophagus (type I tumors) advance both up into the mediastinum and down to the celiac axis. Lymphatics from the gastric cardia and subcardial region (type II and III tumors) preferentially spread to the celiac axis (Aikou and Shimazu 1989). In addition, there are retroperitoneal lymphatics, which drain directly to the supra and infrapancreatic nodes and nodes at the left renal vein. These anatomical features should be considered. The extent of the LAD will be discussed in detail for the different tumor types.

8.2 Surgical Strategies for AEG Siewert Type I

AEG Type I carcinomas (in the vast majority Barrett's cancer) are esophageal cancers. The surgical strategy for these tumors is based on the lymph node metastases pattern and the localization of the tumor in the distal esophagus. For AEG type I tumors, a subtotal resection of the esophagus is frequently mandatory (Fig. 8.1). In general, there are two major resection strategies, which are recommended for the type I tumors: the transthoracic en bloc resection and the transhiatal resection, first described by Grey Turner in 1933. There is limited evidence available to demonstrate a clear advantage of one of the two procedures. However, a randomized clinical trial (RCT), which compared the two techniques, showed a 10% survival benefit (29% vs. 39%) for the transthoracic group (Hulscher et al. 2002; Omloo et al. 2007). This finding was confirmed in the 5-year follow-up data, with a reported survival benefit of 14% for type I tumors (51% vs. 37%) in the transthoracic group (Omloo et al. 2007). The significant effect was dependent on the number of positive lymph nodes in the resection specimen. If less than eight positive lymph nodes were present, the disease-free survival benefit was significantly higher in the transthoracic group (23% vs. 64%, $p=0.02$). More than eight positive lymph nodes were associated with a poorer outcome, indicating the presence of a systemic disease as a possible explanation. One shortcoming of this study was the higher proportion of stage IV patients in the transthoracic group (15% vs. 7%), which might be responsible for the relatively modest statistical benefit of the transthoracic technique in the whole study population. Overall, the results highlight the importance of an accurate lymph node staging and resection, which is only possible with a transthoracic en bloc resection of the esophagus. The significantly increased pulmonary morbidity, which has been observed in the transthoracic approach (57% transthoracic vs. 27% transhiatal, $p<0.001$), did not result in a higher perioperative mortality (4% transthoracic vs. 2% transhiatal, n.s.) and can be minimized in experienced centers, as convincingly demonstrated in this trial.

The extent of the LAD for adenocarcinomas and squamous cell carcinomas of the esophagus has been controversially discussed for many years. To describe the extent of the LAD, we use the classification published by Fujita et al. in 2003, which represents the classification of the ISDE consensus conference from 1994. In brief, standard LAD involves the lower mediastinal and upper abdominal nodes, which can be achieved by a transhiatal resection. Extended LAD (two-field LAD) includes the resection of the subcarinal, right paratracheal/upper mediastinal nodes, and left tracheobronchial nodes to the upper border of the aortic arch (entrance of the left recurrent laryngeal nerve), in addition to the standard procedure. The total LAD or extended two-field LAD involves the resection of the bilateral recurrent laryngeal nerve nodes. A three-field LAD includes the resection of the cervical ± supraclavicular nodes. The various extents of LAD for esophageal cancer including AEG type I are shown in Fig. 8.2.

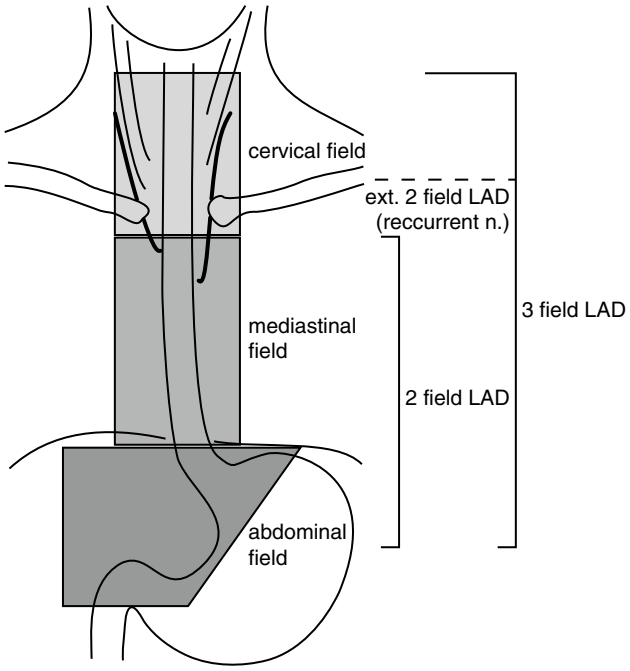

Fig. 8 2 Classification of lymphadenectomy by different fields for esophageal cancers including AEG type I tumors

The extent of lymph node metastases in R0 resected patients is an important prognostic factor in patients with squamous cell cancer, as well as adenocarcinoma of the esophagus (Siewert et al. 2001; Hofstetter et al. 2007). Type I tumors do predominantly metastasize into the paraesophageal nodes in the lower mediastinum and into the upper abdominal lymph nodes (Schuhmacher et al. 2007). However, it has been shown that 15.6% of the patients demonstrate positive nodes higher in the mediastinum at the tracheal bifurcation and in the upper mediastinum (Schroder et al. 2002). Complete resection of these lymph nodes allows accurate staging and might prevent recurrent disease originating from lymph node metastasis within this area. This is important since mediastinal recurrence is seen in up to 21% of the patients according to Dresner and Griffin (2000). In patients following transhiatal esophageal resection, recurrent disease is still locoregional in 44% of the patients (Hulscher et al. 2000).

There is some evidence that suggests an independent correlation between the number of removed lymph nodes and survival after esophagectomy (Peyre et al. 2008a). For all these reasons, a two-field LAD is performed on a routine basis in our institution for type I tumors (Fig. 8.2).

Despite the predominant spread of type I tumors into paraesophageal and upper abdominal nodes, cervical lymph node metastases in type I cancers have been described. Lerut et al. (2004) found in his three-field LAD study 26% positive cervical lymph nodes in type I tumors and 18% positive cervical lymph nodes in type II tumors. This number is comparable to the rate of cervical lymph node metastases of distal squamous cell carcinomas (Nishihira et al. 1998) and has been confirmed by Altorki et al. (2002). The prevalence of cervical lymph node involvement is T-category dependent and more frequent in advanced disease (Altorki et al. 2002; Lerut et al. 2004). According to Lerut et al., the prevalence of involved cervical nodes is higher than

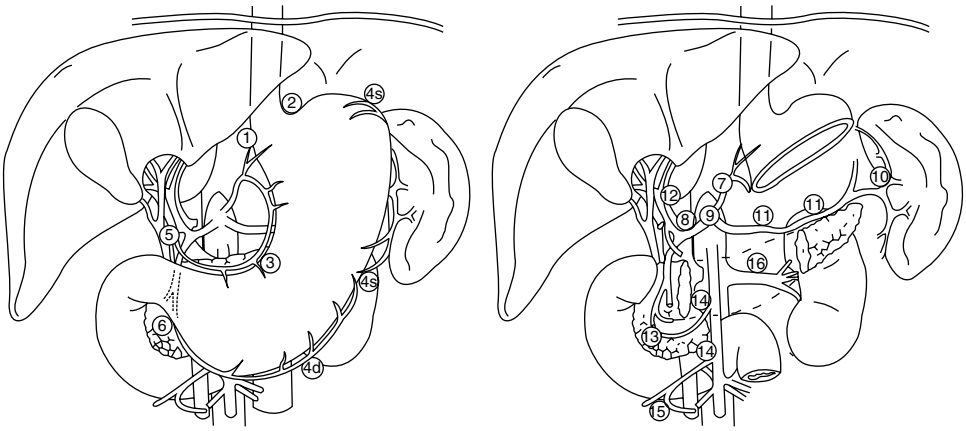

Fig. 8.3 Extent of abdominal lymphadenectomy for AEG type II and III tumors. D2-LAD encompasses stations 1–6 (compartment I) that are shown on the *left* and 7–12 (compartment II) on the *right*. Station 16 (*left* renal vein) is recommended to be removed in addition to compartment II nodes because of direct retroperitoneal channels from the cardia/fundus region

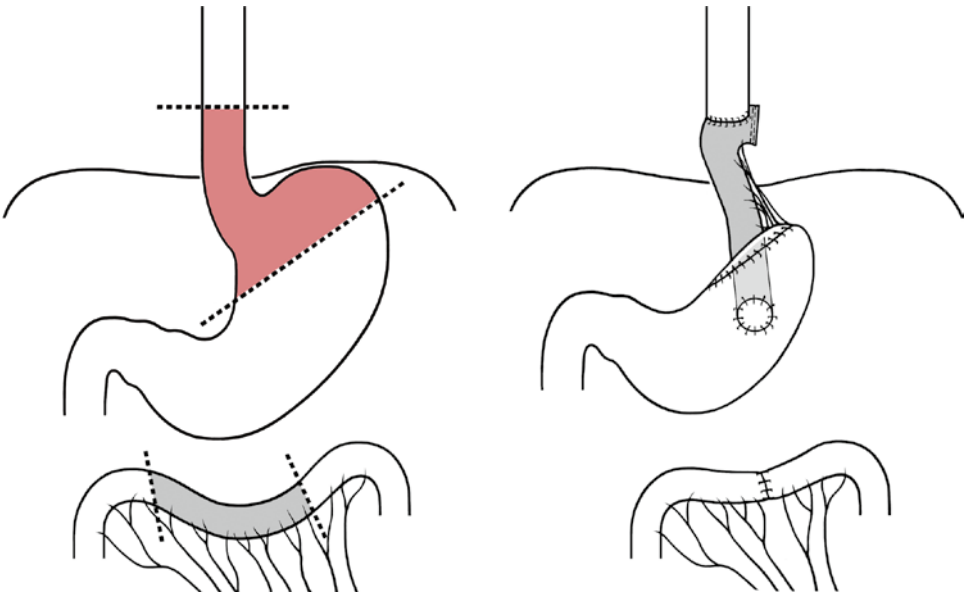

Fig. 8.4 Limited resection for early AEG type I or II using a reconstruction with isoperistaltic jejunal interposition according to Merendino and Dillard (1955)

expected regardless of the type and localization of the tumor. The 5-year survival rate of patients with positive cervical lymph nodes was very poor (13% vs. 31% in the node negative patients), despite the extensive 3-field LAD in this study (Lerut et al. 2004). In contrast, Altorki et al. found a remarkable 5-year survival rate of 25% in cervical node positive patients with

adenocarcinoma of the distal esophagus (Altorki et al. 2002). Trials in squamous cell esophageal carcinomas showed similar results. A small Japanese RCT showed no significant survival benefit in patients with esophageal squamous cell cancer undergoing three-field LAD. There was only a trend toward an improved 5-year survival rate of 83% in the three-field compared to 65% in the two-field LAD group (Nishihira et al. 1998). The associated morbidity of a three-field and extended two-field LAD is high (Nishihira et al. 1998; D'Journo et al. 2005). It consists of recurrent nerve palsy (56% in the Nishihira trial) and pulmonary complications (33% in the Lerut trial and 19% in the Nishihira trial) (Nishihira et al. 1998; Lerut et al. 2004). Dresner and Griffin (2000) found a low incidence of cervical recurrence (6%) in patients following R0 resection without three-field LAD and suggested that a more extensive LAD was unlikely to change the prognosis. In summary, the prevalence of cervical lymph node metastases in Siewert type I and II tumors is higher than expected and appears to be identical to distal squamous cell cancers (see Table 8.1). The value of a routine three-field LAD, however, is still unclear and is associated with at least a higher morbidity.

Therefore, we perform an extended two-field or three-field LAD only in selected cases with a high suspicion of involved lymph nodes in the preoperative staging, e.g., FDG avid lymph nodes in the PET/CT scan. EUS-guided fine needle aspiration for suspicious cervical lymph nodes (e.g., in PET/CT) can be performed prior to surgery to confirm the diagnosis. For all other patients without suspicious findings in the staging, the additional morbidity seems to be too high and the survival benefit too low to advocate for an extended two-field or three-field LAD on a routine basis.

Table 8.1 Prevalence of positive cervical lymph nodes in distal esophageal cancer

	Adenocarcinomas	Squamous cell carcinoma
Altorki et al. (2002)	37% (18/48)	34% (11/32)
Lerut et al. (2004)	26% (16/62)	16% (4/16)

Another controversy is the relevance of positive celiac lymph nodes. Hofstetter et al. (2007) showed that esophageal cancer patients with regional or celiac lymph node involvement did have a better prognosis compared to nonregional involvement (common hepatic artery nodes, splenic artery nodes, and retroperitoneal nodes). The current AJCC/UICC-TNM staging classification considers celiac node involvement as an M1a category. As a consequence, in some institutions these patients receive definitive chemoradiation. According to the results of Hofstetter et al., the survival curves of patients with regional lymph node involvement were identical to patients with celiac lymph node involvement, with a 3-year survival rate of 24% vs. 23%. On the contrary, nonregional lymph node involvement and the number of involved lymph nodes were poor prognostic factors, with a 3-year survival rate of 0% for nonregional lymph node involvement and 63%, 31%, and 13% for 0, 1–3, and more than 3 involved lymph nodes, respectively (Hofstetter et al. 2007). These results have been confirmed in a large multicenter study that assessed the impact of involved lymph nodes on survival and risk of systemic disease. The frequency of systemic disease increased from 16% in patients without nodal involvement to 93% in patients with 8 or more involved lymph nodes (Peyre et al. 2008b).

The upcoming new AJCC/UICC-TNM classification starting in January 2010 will no longer consider celiac node involvement as an M1a stage for patients with Siewert type I cancer, and patients with suspicious or positive celiac nodes should, therefore, not be withdrawn from surgery at all.

For all the above mentioned reasons, the preferred surgical strategy in our institution for AEG type I cancers is a transthoracic en bloc

resection with a two-field LAD (Figs. 8.1 and 8.2). It is important to ensure the complete resection of Barrett's mucosa within the esophagus for the prevention of recurrent disease (D'Journo et al. 2009). If necessary, this has to be confirmed with intraoperative endoscopy and frozen section. For high-risk patients with a potentially resectable cancer, a transhiatal approach is a valid alternative to the transthoracic approach in order to minimize perioperative morbidity (Hulscher et al. 2002; Portale et al. 2006). This approach is beneficial in patients with impaired pulmonary or cardiac function. To objectively assess the extent of the patient's comorbidities and associated risk, we suggest to use the composite score from Bartels et al. (1998).

8.2.1 Reconstruction

There are two main reconstruction techniques for patients undergoing esophageal resection for type I tumors. While a high intrathoracic anastomosis can be performed after a transthoracic resection of the esophagus, the transhiatal resection requires a cervical anastomosis. The advantage of the cervical anastomosis is the better control of potential leakages. However, the leakage and stenosis rate is substantially higher using this technique. The leakage rate of the cervical anastomosis has been reported to be 25% in patients with primary resection and 31% in patients with salvage esophagectomy following radiation dosages exceeding 60 Gy from the very experienced National Cancer Center Group in Tokyo (Tachimori et al. 2009). In addition, the need for repetitive dilatations of an anastomotic stenosis is a very common problem in patients with a cervical anastomosis (Scheepers et al. 2009). The preferred reconstruction after esophagectomy in our view is, therefore, a gastric tube with a high intrathoracic anastomosis in the posterior mediastinum (in analogy to Ivor-Lewis but as high above the level of the azygos vein as possible). This technique results in fewer leakages and stenoses (Holscher et al. 2003). We recommend an intraoperative dilatation of the pylorus. A pylorotomy or pyloroplasty is not necessary at all and adds additional risks. As an alternative to a gastric tube, one can also use colon with the arterial supply from the arteria colica sinistra or arteria colica media in patients, where the stomach is not available for the reconstruction, e.g., patients with previous gastric resections (Motoyama et al. 2006). Functional results appear to be poorer than with a gastric conduit (Cense et al. 2004). The preferred route of reconstruction is orthotopic in the posterior mediastinum (Nakajima et al. 2007).

In selected cases, a two-stage procedure can be performed using the retrosternal route with a cervical anastomosis a few weeks after the initial esophagectomy. This route is less likely associated with a mediastinitis in case of leakage (Stein et al. 2001). It is, however, inferior in terms of functional outcome (Nakajima et al. 2007). Taken together, a two-stage strategy is a valuable alternative for high-risk patients, in which a resection and reconstruction at the same time seem to be too much of a burden for the patient.

A newer alternative reconstruction strategy is a supercharged jejunal loop with dual blood supply from the distal vascular pedicle and a proximal microvascular anastomosis to cervical vessels, preferentially if the stomach and colon are not available for reconstruction (Peyre et al. 2008a). This procedure should only be performed in expert hands in selected cases in order to achieve a good quality of life.

8.2.2 Limited Resection

In early Barrett's cancer that is restricted to the mucosa (pT1a), endoscopic mucosal resection (EMR) or endoscopic submucosal dissection (ESD) is possible and can be used as a combination of an invasive staging procedure and a

definitive therapy (Pech and Ell 2009). Lymph node metastases are very rare or absent at this early stage (Schuhmacher et al. 2007; Holscher et al. 1997). If the EMR is not performed adequately, high local recurrence rates and endoscopic re-resections have been reported in the past (Ell et al. 2000) (see separate chapter in this edition). Tumors, which do invade the submucosa (T1b) following EMR or according to high-frequency endosonography (miniprobe), have positive lymph nodes in up to 41% of the patients depending on the depth of submucosal infiltration (Bollschweiler et al. 2006) and should not be treated by EMR/ESD unless the patient is in poor condition. In general, a transthoracic en bloc resection including an adequate lymphadenectomy should, therefore, be performed in all pT1b tumors.

As an alternative, a limited resection followed by reconstruction according to Merendino and Dillard (1955) can be discussed. Using this approach, Stein et al. reported excellent results with survival rates in type I and II tumors that did not differ from transthoracic or transhiatal esophageal resections (Stein et al. 2000). Limited resection was performed through a transabdominal approach with wide anterior splitting of the diaphragmatic hiatus and included a resection of the distal esophagus, esopaghogastric junction, and proximal stomach. Lymphadenectomy comprised an en bloc removal of all lymphatic tissue in the lower posterior mediastinum, along the cardia, the proximal two thirds of the lesser curvature, the fundus, and along the common hepatic and splenic artery toward the celiac axis. Multicentric tumor growth or associated high-grade dysplasia was observed in 60.6% of the resection specimens. It has to be stressed that the complete Barrett's mucosa has to be resected in order to prevent recurrence. For this reason, limited resections are not possible in long segment Barrett's metaplasia. Lymph node metastases or micrometastases were present in none of the 38 patients with tumors limited to the mucosa (pT1a) vs. 10 of the 56 (17.9%) patients with tumors invading the submucosa (pT1b). Lymph node metastases were prognostic, but the pT1a/pT1b category and the surgical approach were not. Limited resection with jejunal interposition appears to be safe in selected cases, prevents gastroesophageal reflux, and is associated with a good quality of life. Attention to technical details of limited resection and jejunal interposition is, however, required to avoid complications, poor functional results, and the need for reintervention. New technologies for accurate prediction of the presence and pattern of lymphatic spread, e.g., sentinel node techniques and artificial neural networks, may allow a further reduction of the invasiveness of surgical resection without compromising cure rates. So far, no data are available from randomized controlled trials, and as a consequence, this therapy option cannot be considered as a standard procedure and should be performed within prospective trials.

8.2.3 Minimal Invasive Operation Techniques

Minimal invasive techniques such as a thoracoscopic resection of the esophagus have been recently reported (Schuchert et al. 2008; Nguyen et al. 2008). A cervical anastomosis is usually performed with this technique, with the known problems of this type of anatomosis. More recently, first results are reported with the thoracoscopic/laparoscopic Iwor-Lewis esophagectomy (Nguyen et al. 2008; Bizekis et al. 2006). The laparoscopic preparation of the gastric tube and lymphadenectomy is safe and seems to be a real alternative for the open abdominal approach (Holscher et al. 2007). Randomized data to support these techniques are however not available, and therefore, it cannot be currently regarded as a standard procedure. So far these techniques should be performed within prospective controlled trials, but have to be considered as very promising.

8.3 Surgical Strategies for AEG Siewert Type II and III

While the type II tumor is a true cardia cancer, the type III tumor originates from the subcardial region and infiltrates the cardia ± esophagus from below. Type II and especially III tumors have a worse prognosis compared to type I tumors (Fig. 8.5) and typically spread into the paracardial and perigastric lymph nodes (Siewert et al. 2000; Feith et al. 2006). Paraesophageal lymph node metastases are less common (8–15%) and metastases at the tracheal bifurcation are thought to be rare (1%) (Schuhmacher et al. 2007). The standard resection technique for these tumors suggested by Siewert is, therefore, a total gastrectomy with a transhiatal resection of the distal esophagus (Fig. 8.1), lymphadenectomyof the lower mediastinum, and a D2 LAD (including lymph node station 16 at the left renal vein; Fig. 8.3) (Siewert et al. 2000). The preferred reconstruction is a Roux-en-Y reconstruction with 60 centimeters of jejunum between the esophagojejunostomy and the Roux-en-Y anastomosis in order to prevent bile reflux. Pouch reconstructions are contraindicated in this situation with a supradiaphragmal anastomosis.

The real lymph node metastases rate in the upper mediastinum and cervical lymph node stations has only been assessed by few trials. Lerut et al. have challenged the concept of rare upper mediastinal and cervical lymph node involvement by reporting 17% positive lymph nodes in type II tumors (Lerut et al. 2004). The transhiatal approach allows a resection of the esophagus and lymph nodes up to the inferior pulmonary vein and less frequently up to the tracheal bifurcation. For the abdominal extent of lymphadenectomy, the value of the D2 LAD has been a matter of debate over decades between the Western and Asian world. The large Dutch RCT, however, showed a significant survival benefit for patients with a D2 LAD in stage III A (Bonenkamp et al. 1999). Therefore, we recommend a systematic D2 LAD as a standard technique in every patient (Fig. 8.3). Despite different results in Japanese and Western patients, it is likely that the lymphatic spread pattern and the biological behavior of these tumors are the same within the two populations (Gall and Hermanek 1985). For that reason, it is also likely that Western patients could benefit from the distinctive Japanese data about lymph node metastases pattern in gastric cancer. In 1989, Maruyama analyzed the lymph node metastases pattern of 1931 patients with gastric cancer and found a clear correlation between

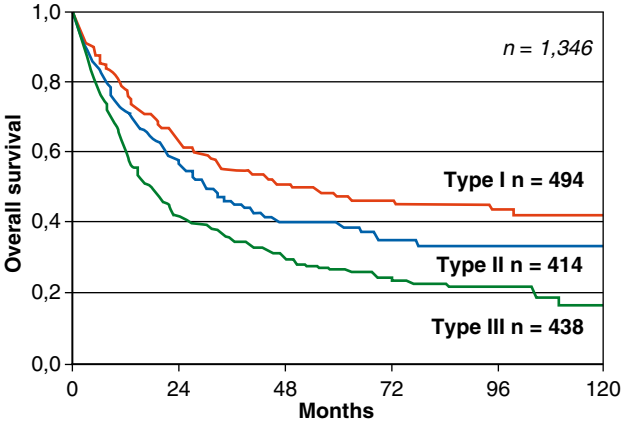

Fig. 8.5 Survival rates for AEG I–III (modified from Siewert et al. 2007) JACS)

the localization of the tumor and the involved lymph nodes (Maruyama et al. 1989). The incidence of true skip node metastases was rare, and the most frequently involved lymph nodes for proximal cancers were the perigastric lymph nodes, the lymph nodes along the left gastric artery, the celiac trunk, the splenic artery, and the splenic hilum. Therefore, Maruyama advocated the resection of these nodes in cancers arising in the proximal stomach. Another reason for a systematic D2-LAD is the inaccuracy of the currently available imaging and staging modalities that cannot reliably determine the presence of lymph node metastases. The additional morbidity associated with the lymphadenectomy can be minimized in experienced units and should not be an argument against the performance of a D2 LAD (Kulig et al. 2007).

A special feature of type II and III tumors is the possibility of a direct retroperitoneal spread into the lymph node stations superior and inferior to the pancreas, as well as into the area of the left renal vein (station 16, see Fig. 8.3). These lymph nodes should be resected at least if they are suspicious in the staging imaging.

In the past, different surgical approaches such as the left thoracoabdominal approach have been proposed as an alternative to gastrectomy with a transhiatal resection of the distal esophagus (Fig. 8.1). Sasako et al. performed a RCT in 2005 to compare the left thoracoabdominal approach vs. the abdominal transhiatal approach for Siewert type II and III cancers (Sasako et al. 2006). They found no survival benefit using the thoracoabdominal approach. The morbidity, however, was significantly increased in the thoracoabdominal group (49% vs. 34%). In a randomized trial from the Netherlands, there was also no benefit from a transthoracic resection over a transhiatal resection for AEG type II (Omloo et al. 2007). These results were confirmed in a French multicenter trial (Sauvanet et al. 2005). Together, these data suggest that the thoracoabdominal approach is clearly not necessary for most AEG Siewert type II and III tumors unless the extent of esophageal infiltration makes transhiatal distal esophageal resection impossible.

Splenectomy has been advocated in the past and was part of a radical en bloc lymphadenectomy. However, splenectomy did not improve survival, and in contrast, resulted in a higher perioperative morbidity rate and mortality (Bonenkamp et al. 1999; Griffith et al. 1995). In addition, the immunologic defense properties of the spleen are compromised. Therefore, splenectomy should be avoided whenever possible.

It has been a matter of ongoing debate whether there is only an arbitrary difference between the AEG type II and III tumors. Yuasa et al. analyzed the disparity between Siewert type II and III cancers and observed a different lymph node metastases pattern and a different 5-year survival rate in favor of type II tumors in patients who underwent R0 resections (Yuasa et al. 2006). According to Siewert and Yuasa, the type III cancers exhibit a poorer survival rate compared to type II cancers (Siewert et al. 2000). Therefore, both groups consider the type II and III carcinomas as a distinct clinical entity with different outcome (Fig. 8.5). One reason for a potential bias in this observation is the likelihood that c/p T1 type III carcinomas that do not extend to the cardia are grouped within gastric cancers of the proximal third, and therefore, will not be classified as AEG Siewert type III. In other words, the early type III carcinoma is recognized as a proximal gastric cancer by the endoscopist and pathologist and will not occur in the cohort of AEG's. This is probably one explanation why the percentage of T1 tumors in type III cancers is always low, as it is the case in the large cohort from Munich with only 7% T1-categories in type III cancers compared to 14% in type II cancers. Therefore, the lower proportion of T1 categories might be one of the reasons for a poorer prognosis in these patients.

A more important factor for a true difference between type II and III tumors is the higher percentage of G3/4 or diffuse type cancers,

according to Laurén, in AEG type III compared to type I and II tumors (Lauren and Nevalainen 1993).

Survival curves for AEG types I-III form the largest published series and are displayed in Fig. 8.5 and clearly demonstrate the particularly poor survival for AEG type III.

8.3.1 Limited Resection

Unlike in the western world, the proportion of upper-third gastric cancer in Japan has not increased over the last decade. On the other hand, they do have an increasing proportion of early gastric cancers (Ozawa et al. 1998), which is the result of widespread screening programs. The analysis of patients with upper-third gastric cancer treated with standard Japanese D2 total gastrectomy in the 1980s showed that metastases in the distal perigastric nodes were rare, and the patient's outcome was excellent with a 5-year survival rate approaching 90%. Therefore, Japanese surgeons proposed a limited surgical strategy for early gastric cancer of the upper third using proximal gastrectomy and distal esophageal resection and reconstruction with isoperistaltic jejunal interposition according to Merendino and Dillard (1955) (Fig. 8.4). The spleen is preserved, but the suprapancreatic lymphatic nodes (station11) are removed. Katai et al. published the results of 45 patients including Siewert types II and III patients treated with this strategy and reported excellent results with a 5-year survival rate of 90%. In the report by Stein et al., early Siewert type II tumors were also included with excellent prognosis (Stein et al. 2000).Therefore, limited resections in early cancer of the upper gastric third and AEG Siewert type II and III seem to be a valuable alternative in selected cases (Katai et al. 2003) and should be performed within prospective controlled trials.

8.3.2 Minimal Invasive Techniques

Minimal invasive techniques such as laparoscopic total gastrectomy are technically feasible, but are not standard of care yet (Bo et al. 2009). Minimal invasive distal gastrectomies are preferentially performed in Japan in early gastric cancers of the distal third (Kitagawa et al. 2005a). Technical problems may occur if a distal esophageal resection is necessary and particularly in obese patients, where laparoscopic lymphadenectomy tends to be more difficult. Currently, this technique plays a minor role in AEG II and III.

8.3.3 Sentinel Node Technique

AEGs do have a distinct lymphatic spread pattern (Maruyama et al. 1989), and it has been shown that if only one lymph node is positive in type I tumors, it is located in the posterior inferior mediastinum in 95% of patients (Schuhmacher et al. 2007). Efforts have been undertaken to implement a sentinel lymph node technique in analogy to other solid tumors (e.g., breast cancer). Especially in the context of limited resection, it is attractive to consider the use of a sentinel node technique in order to determine the extent of lymphadenectomy. However, the sentinel lymph node technique is not yet established in the clinical routine and is not considered a standard treatment option. The accuracy of the sentinel node technique is T-stage dependent (Aikou et al. 2001) and a high rate of skip metastases in the D2 compartment has been described at least in gastric cancer patients (Kitagawa et al. 2005b). A combined marking with dye and radiocolloid seems to deliver the best results (Kitajima et al. 2005). The preliminary experience in AEG indicates that the method is feasible and yields good results in early tumors. In advanced tumors, the method lacks sensitivity (Burian et al. 2004).

8.4 Summary

Adenocarcinomas of the esophagogastric junction are currently best classified according to the Siewert classification. For AEG type I cancers, we perform a transthoracic en bloc resection with a two-field LAD and a high intrathoracic anastomosis with complete resection of Barrett's mucosa. If necessary, the extent of the LAD will be increased according to the staging results. For AEG type II and III cancers, the standard resection technique in our institution is a total gastrectomy with a transhiatal resection of the distal esophagus (so-called transhiatal extended gastrectomy), lymphadenectomy of the lower mediastinum, and of the abdominal D2 compartment (plus lymph node station 16). A limited resection for early type I-III cancers seems to be a valuable alternative in selected cases and we do perform it using a dual (dye and radiocolloid) sentinel node technique within a prospective trial.

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9 Current Status of Sentinel Lymph Node Biopsy in Adenocarcinoma of the Distal Esophagus, Gastric Cardia, and Proximal Stomach

Stephan Gretschel and Peter M. Schlag

Abstract The resection of the adenocarcinoma of the esophagogastric junction should be considered to the extent of the lymphatic drainage. This, on the other hand, depends on the possible lymphatic metastasizing. As an adenocarcinoma of the esophagogastric junction is located along the borderline between two visceral cavities (mediastinal/abdonimal), it can, in principle, metastasize in both cavities. There is not, however, an imaging (CT, MRI, PET) that can adequately assure the detection of a beginning lymph node metastasis in particular. The sentinel lymph node biopsy could provide the beginning of a solution in this case. The initial results, with all of the necessary accompanying technical work, have been encouraging. The paper presented here provides an introduction to the challenge of the SLNB and the background of a specialized surgical therapy of the AEG. If a lymph nodal metastasis can be definitely confirmed or ruled out, many patients could be spared an unnecessary lymphadenectomy. This is especially important at the AEG because minimizing the evasiveness of the surgery with adequate radical oncological resection (e.g., without thoracotomy) would mean a substantial reduction of postoperative mortality.

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9.1 Introduction

Adenocarcinoma of the esophagogastric junction (AEG) is an emerging distinct entity and shows increasing incidence (Blot et al. 1991; Powell and McConkey 1992). Surgical approach and extent of resection of AEG remain areas of controversy and pose specific challenges because of its critical anatomic location between the thoracic and abdominal cavity.

9.2 Pattern of Lymph Node Metastases

Lymph node metastases occur either in the mediastinum or in the abdominal drainage pathway of the stomach. Dresener et al. (2001) showed that 77% of type I (Siewert) junctional tumors have lymph node metastases in both mediastinal and abdominal cavity. Confirmed by Feith et al., a group from Netherlands found that 22% of patients with adenocarcinoma of

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the cardia (Siewert III) have lymph node metastases in the proximal station of the chest (Lagarde et al. 2005; Feith et al. 2003). Further assessment of the cranial extent of junctional tumors' preoperative staging endoscopy is crucial, but it is essential to decide between transabdominal/transhiatal or transthoracic approach. Although the incidence of lymphatic metastases of AEG is relatively high, it remains limited to regional lymph nodes. Feith also showed that the initial lymphatic spread of type I follows the regional nodes in the lower posterior mediastinum, the left and right pericardial region, and along the lesser gastric curvature following the left gastric artery (Feith et al. 2003). Lymphographic studies from Aikkou detected that main lymphatic pathways originating in type II and III AEG-tumors preferentially make their way to the celiac axis, the splenic hilum, and the para-aortic lymph nodes (Aikou et al. 1987). Skipping the regional lymph node stations remains uncommon, but partly occurs (Li et al. 2008; Moenig et al. 2005). Distant lymph nodes (second step) appeared to be only involved in patients with advanced tumors after tumor dissemination in regional lymph nodes (first step). This stepwise lymphatic spread is in contrast to squamous cell carcinoma of the esophagus, in which skipping of regional lymph node stations appears as common (Saito et al. 2007; Matsubara et al. 2000).

9.3 Extension of Resection

According to Siewert, extension of resection (type I: esophagectomy with resection of proximal stomach, type II: total gastrectomy with thoracal esophagectomy, type III: total gastrectomy with distal transhiatal esophageal resection) is often associated with high morbidity (Siewert and Stein 1998). In a randomized prospective study, Hulscher et al. showed that transthoracic esophagectomy with extended en bloc lymphadenectomy was associated with significant higher morbidity than transmediastinal esophagectomy, but the median overall-, disease free-, and quality-adjusted survival did not show significant differences between the two groups (Hulscher et al. 2002). Pulmonary complications, rising ventilation time, and prolonged hospital stay are the main problems. Especially, there is a high risk for the elderly people and patients having high ASA-classification (Sauvanet et al. 2005). Siewert et al. published their experienced results of a local resection with regional lymphadenectomy and jejunal interposition (Merendino procedure) in patients with Type I and II early AEG and precancerous lesions. It was shown to be an attractive alternative to radical esophagectomy with less complications, tending to have better survival (Stein et al. 2000a; Merendino and Dillard 1955). If nodal spread was ruled out, the resection often is performed less invasive or even minimal-invasive for all these patients, presumably with a lower morbidity. Nevertheless, the use of perioperative imaging (CT, MRI, PET) currently is not determining the existence and location of lymph node metastases prior to resection (mediastinal/abdominal). sentinel lymph node biopsy (SLNB) is a useful diagnostic tool in completing preoperative strategies.

9.4 The Techniques of Sentinel Node Biopsy

The concept of the SLNB is based on the finding that lymphatic drainage does not occur at random, but rather to a designated, e.g., the sentinel lymph node. Therefore, the spread of metastases via the lymphatic pathways is supposed to be evident in the sentinel node first.

Both techniques, the dye technique (DT) and the radiocolloid technique (RCT), were described in detail elsewhere (Gretschel et al. 2003, 2004, 2007). The essential steps are the followings:

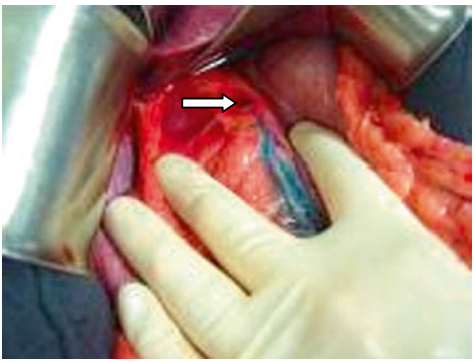

Fig. 9.1 Dye method: 3 min after endoscopic peritumoral injection of blue dye in AEG type III, a blue lymph channel and the SLN in perigastric lymph node station number 1 are identified

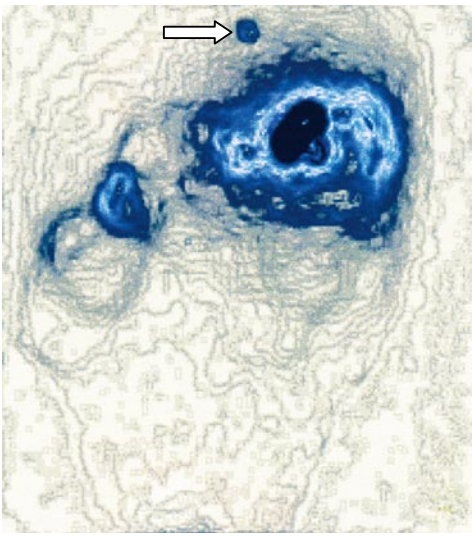

Fig. 9.2 Radiocolloid technique 15 h after endoscopic peritumoral injection of Technetium 99 in AEG type I, one radionuclide enriched SLN (*arrow*) is detected in the neighborhood of tumor

The *(DT)* (Fig. 9.1) is a strictly intraoperative technique that uses several substances for gastric-cancer patients: Indiocyanine-green, Isosulfan blue (Lymphazurin©), and Patent Blue Dye V. The method includes the following steps:

- Subserosal or submucosal (endoscopic) peritumoral injection of the dye.
- Clip-marking or excision of the first stained lymph nodes.
- Postoperative selective histopathological examination of the marked lymph nodes in accordance with a specific protocol.

The *RCT* (Fig. 9.2) usually is a two-step technique with preoperative tracer injection and intraoperative SLN identification:

- Preoperative injection of a radiocolloid (4–17 h prior to surgery), in Europe mostly Tc^{99m}-Nanocoll© with a dosage of 180 MBq.
- Optional preoperative lymphscintigraphy.
- Intraoperative detection of the nuclide enriched lymph node(s).
- Clip-marking or excision of the nuclide enriched lymph nodes.
- Scanning of the situs for residual activity after specimen resection.
- Optional excision of iuxtaregional nuclide enriched lymph nodes.
- Optional scanning of the specimen for further nuclide enriched nodes.
- Selective histopathological examination of the marked lymph nodes in accordance with a specific protocol.

The disadvantage of the RCT becomes clear in the scattering effect of the radionuclide-injection site, if the first draining lymph nodes are close to the tumor. Thus, SLN identification sometimes becomes difficult or impossible. High body mass index (BMI) was associated with a low detection rate in DM. In AEG the lymph drainage is even more difficult to determine because of the varying anatomical location in the abdomen or in the thorax.

Recently, there has been a consideration of the combination of both the blue dye technique and the radiocolloid-method *(dual technique)* in AEG as complementary techniques.

9.5 Upstaging

The use of SLNB in AEG requires preparation of SLN according to a certain protocol. If there is a request to perform serial sections and immunohistochemistry for the SLN as location with the highest probability of metastatic involvement, a procedure that requires too much technical and financial effort should be performed routinely for all resected nodes. Moreover, various markers such as CEA, c-MET, CK20, MAGE-A3, and GalNAc-T are used for immunohistochemistry. Biopsy of the sentinel lymph node also requires surgical skill and experience. Therefore, it is to be expected that a significant percentage of additional micro metastases (0.2–2 mm) or isolated tumor cells (<0.2 mm) will be detected by serial sections with immunohistochemistry or PCR (Fig. 9.3). As stated above, the clinical implication of minimal residual disease (MRD) is not yet defined, but micrometastases have shown high proliferate activity (Yanagita et al. 2008; Yonemura et al. 2007) and prognostic significance (Doekhie et al. 2005; Heeren et al. 2005; Horstmann et al. 2004). In tumor genesis, macrometastases are the result of highly proliferate micrometastases. Therefore, the existence of MRD is of (yet undetermined) prognostic significance.

9.6 Using the SLN as Frozen Section During Surgery

A reliable histological evaluation of the sentinel node during surgery will enable the surgeon to adapt the extent of resection of lymphatic stations. Currently, sensitivity and specificity of potential methods that are fast enough to be applied like Imprint-cytology or frozen section vary between 30 and 96% (Ajisaka and Miwa 2003; Levine et al. 2003; Matsumoto et al. 2003). PCR methods are evaluated to increase sensitivity and specificity (Matsuda et al. 2004). Further development of fast histological detection techniques will be as important as the improvement of sentinel node detection and biopsy.

9.7 Current Status of Sentinel Lymph Node Biopsy in Gastric Cancer

The current evidence concerning the reliability of SLNB to detect lymph node metastases in gastric cancer indicates that detection rate is generally high (90–100%), whereas sensitivity

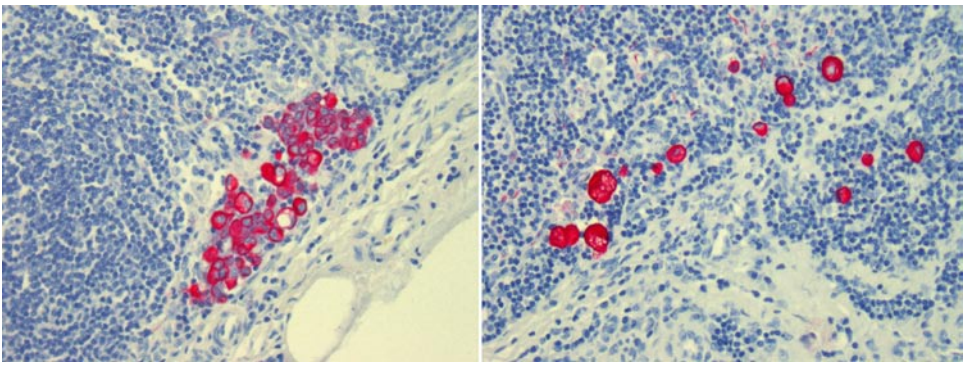

Fig. 9.3 Micrometastasis (*left*, ×200) and isolated tumor cells (*right*, ×400) in SLN, which were detected by intense histological examination by the use of immunohistochemistry with cytokeratin-antibody (MNF-116)

ranges between 80 and 95%. Experience is still limited to a small number of centers. Thus, the still limited experience of most of the centers is considered (Ishizaki et al. 2006; Isozaki et al. 2004; Kitagawa et al. 2002; Miwa 2001; Park et al. 2006; Uenosono et al. 2005). Evaluation of lymph node metastases in early cancers also showed that positive nonsentinel nodes mostly were located in the same region as the sentinel node. A regional lymph node resection can improve the sensitivity of SLNB (Miwa et al. 2003). Based on these findings, a resection of the peritumoral sentinel node basin with intraoperative histopathologic evaluation is under evaluation. If no lymph node metastases are found, the chance for additional lymph node metastases is low (Lee et al. 2008a, b). In perspective, the next step is the clinical application of the laparoscopic SLNB with intraoperative SLN-detection. Nevertheless, initial first studies on laparoscopic SLNB did not achieve sensitivity comparable to the open approach (Kitagawa et al. 2001; Kitagawa and Kitajima 2005; Saikawa et al. 2006; Tonouchi et al. 2003, 2005). However, technical improvements show promising results. As a consequence, many Asian centers started with limited laparoscopic-assisted resection of early gastric cancer after SLNB (Ishikawa et al. 2007; Orsenigo et al. 2008; Tonouchi et al. 2007; Wang et al. 2008; Ishigami et al. 2007).

9.8 Sentinel Lymph Node Concept in AEG

Applying the sentinel lymph node technique in AEG might have increased clinical significance similar or higher than in gastric cancer because of the outstanding anatomical tumor location between two cavities and varying lymphatic drainage. However, the clinical impact of SLNB on AEG is currently open to interpretation. Most of the trials, according to degree of resection in AEG, included many patients with advanced AEG. But early AEG due to Barrett metaplasia is diagnosed more frequently and the surgical approach is not well defined, but should be treated with a less inva sive approach (Ell et al. 2000) (Fig. 9.4). A study from UK showed that 80% of T1 AEG and 60% of T2 AEG did not show metastatic lymph node involvement (Dresner et al. 2001). Another characteristic finding was a close proximity of sentinel nodes to the primary AEG (Feith et al. 2003; Li et al. 2008; Moenig et al. 2005; Stein et al. 2000b). Therefore, SLNB of AEG from abdominal cavity is a feasible technique. Accordingly, the initial step is to determine all the patients without lymph node metastases. Certainly, if nodal spread is ruled out, the resection could be performed less invasive or even minimal-invasive,

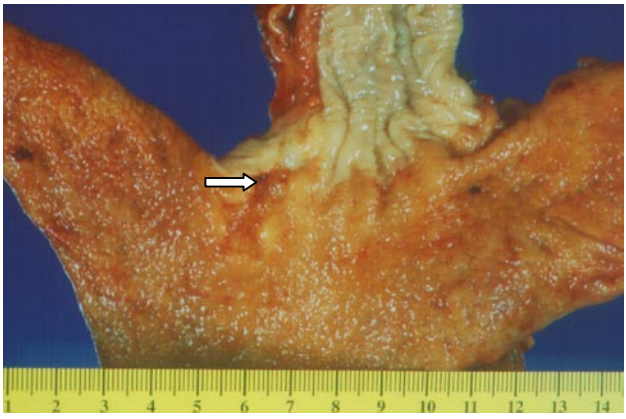

Fig. 9.4 Early cancer of the esophagogastric junction directly on the dental line (Type Siewert II)

presumably with a lower morbidity. Thus, a limited resection without transthoracal esophagus resection (Type I) or without complete gastrectomy (Type II and III) is possible.

Unfortunately, results of sentinel node biopsy in AEG are limited. In 2004, Burian et al. from Munich reported their first results of SLNB in Barrett's and cardia cancer (Burian et al. 2004a, b). The preliminary experience indicated that the AEG for SLNB is feasible, despite the anatomic complexity of this area. However, the overall sensitivity of 85% was reported in the study and yield good results, especially in early tumors (90%). Burian et al. preferred a combination of both radio colloid and dye technique because in AEG the lymphatic drainage was easier to follow after radioactive labeling. Mostly the SLN was in close relation to the primary tumor. Regarding SLNB in Barrett's cancer, the area of malignant transformation is difficult to be detected by endoscopy in any case and further technical advances are required. We also have to consider the possibility of multicentric locations, which makes lymphatic mapping more difficult. However, only the establishment of SLNB in AEG leads to development of individual therapeutic concepts.

In summary, we must aim to confirm recent studies of Burian et al. for clinical implementation. Nodal-negative tumors can be approached in a more limited resection with less morbidity. Furthermore, this might limit postoperative complications of AEG resections, such as reflux or dumping syndrome.

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10 Current Diagnosis and Future Impact of Micrometastases for Therapeutic Strategies in Adenocarcinoma of the Esophagus, Gastric Cardia, and Upper Gastric Third

Asad Kutup, Emre F. Yekebas, and Jakob R. Izbicki

Abstract Esophageal and gastric cancers are aggressive neoplasms with a poor prognosis. Although postoperative mortality has declined and rates of complete resection have improved considerably, 5 year survival rates are still very low. Early metastatic relapse after complete resection of an apparently localized primary lesion indicates that disseminated tumor cells, undetectable by current methods, may already have been present at the time of surgery, even in patients with seemingly early tumor stages. Occult residual tumor disease is suggested when either bone marrow or lymph nodes from which tumor relapse may originate are affected by micrometastatic lesions undetectable by conventional histopathology. The presence of single tumor cells detected by immunohistological methods is increasingly regarded as a clinically relevant prognostic factor. The use of antibodies against tumor-associated targets enables detection of individual epithelial tumor cells in lymph nodes and in bone marrow in various tumor entities. The potential role and benefit of an antibody-based treatment as a therapeutic target would be of particular interest in tumors with a notoriously poor prognosis such as esophageal cancer and cardia cancer.

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10.1 Introduction

In recent decades, the incidence of esophageal adenocarcinoma in the United States and Western Europe has risen at a more rapid rate than any other malignant neoplasm (Blot et al. 1991; Devesa et al. 1998; Bytzer et al. 1999; Vizcaino et al. 2002; Botterweck et al. 2000; Blot and McLaughlin 1999; Trivers et al. 2008).

Gastric cancer is the second most common malignancy worldwide (Parkin et al. 2001; Parkin 2004), and surgical treatment remains the only curative management option (Sano et al. 2004).

The incidence of gastric cardia cancer has increased recently in the West, and this trend is in contrast with a decrease in more distal cancer (Jeon et al. 2006; Orengo et al. 2006; Walther et al. 2001).

According to the prevailing classification, three types of esophagogastric cancer are differentiated: type I is defined as adenocarcinoma in Barrett's esophagus as long as it develops

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within 1–5 cm proximal to the Z-Line. Type II is the "true" carcinoma of the cardia originating from the cardial mucosa. Type III is the subcardial or fundic carcinoma of the stomach infiltrating into the mucosa or submucosa of the distal esophagus (Siewert et al. 1987).

Barrett's dysplasia of the distal esophagus may be causative particularly in type I but may also exist concomitantly in the other types. The term "wanderer between two worlds" reflects the topographic pattern of cardia cancer between the thoracic and abdominal cavity.

Surgical treatment is controversial and varies widely as to the extent of esophageal and gastric resection. Treatment options therefore encompass esophagectomy, limited resection of the esophagogastric junction, esophagogastrectomy, and extended gastrectomy, hereby resulting in different levels of lymphatic clearance.

The importance of lymph node yield and ratio of afflicted lymph nodes with its prognostic relevance and stage migration of the tumors influenced by the surgical approach (transhiatal vs. thoracoabdominal) has been previously described by our own group (Bogoevski et al. 2008). The operative procedure depends on stage, exact localization of the primary tumor, and the patient's general condition.

Although surgical techniques have improved, the overall prognosis for patients remains poor primarily due to local recurrence and the development of distant metastases.

Stage, grade, and status of resection margins are currently accepted as the most accurate pathologic variables predicting survival.

However, even in patients with seemingly early tumors (T1, N0), tumor relapse may occur. This reflects the shortcomings of the current pathologic staging system to sufficiently discriminate patients with a high risk to develop tumor recurrence from those who carry a lower risk. Thus, effort continues to identify new prognosticators of tumor relapse that indicate the need for adjuvant therapy.

Occult residual tumor disease is suggested when either bone marrow or lymph nodes from which tumor relapse may originate are affected by micrometastatic lesions undetectable by conventional histopathology (Pantel and Brakenhoff 2004).

The use of antibodies against tumor-associated targets enables detection of individual epithelial tumor cells both in lymph nodes (Byrne et al. 1987; Passlick et al. 1994; Raymond and Leong 1989) and in bone marrow in various tumor entities (pancreas, breast etc) (Latza et al. 1990).

These immunohistochemical analyses have been accepted as an addendum in the last UICC classification for pancreatic, nonsmall lung, and esophageal cancer (Hermanek et al. 1999).

Nonetheless, the clinical significance of immunohistochemical assessment of nodal micrometastases (Izbicki et al. 1997; Hosch et al. 2001; Komukai et al. 2002; Waterman et al. 2004) is still controversial (Momburg et al. 1987; Pantel et al. 1994; Z'Graggen et al. 2001; Kasper et al. 1987; Bogoevski et al. 2004), e.g., due to putative sampling errors (Hermanek et al. 1999).

10.2 Incidence of Nodal Micrometastases

Results of current studies have shown that in patients with adenocarcinoma of the esophagus and esophagogastric junction, tumor cells can be detected by immunohistochemistry at a relatively high frequency in regional lymph nodes that have been judged to be "tumor-free" by routine histopathological methods.

Mueller et al. (2000) have shown that 42% of the patients with pN0 staged type II/III-tumors had detectable tumor cells in the regional lymph nodes by immunohistochemistry. Similar studies have been done in patients with gastric carcinoma, with rates from 23.5% in early gastric carcinoma to over 90% in more advanced stages (Maehara et al. 1996; Siewert et al. 1996).

Our group showed a 49% incidence of nodal microinvolvement in lymph nodes classified to

be "tumor-free" in conventional histopathology in patients with an adenocarcinoma of the esophagogastric junction (Schurr et al. 2006).

According to histopathology, lower mediastinal lymph node metastases were found in 24% of type I tumors and 10% of type II tumors. When positive disseminated tumor cells were additionally considered, mediastinal lymph node involvement increased to 40% in type I patients and 33% in type II patients. Similarly, in the paracardial and upper abdominal lymph node compartment a higher frequency of lymph node involvement was found by immunohistochemical staining.

The prevalence of nodal microinvolvement in esophageal cancer was first evaluated in both squamous cell carcinoma and adenocarcinoma by our group (Izbicki et al. 1997).

A total of 399 lymph nodes obtained from 68 patients were found to be free of tumor by routine histopathological analysis and were studied further for isolated tumor cells by immunohistochemical analysis with the monoclonal antiepithelial-cell antibody Ber-EP4. Of the 399 "tumor free" lymph nodes, 67 (17%), obtained from 42 of the 68 patients, contained Ber-EP4–positive tumor cells.

The incidence of nodal microinvolvement in patients with adenocarcinoma of the esophagus was higher in later (pT2/3 = 36%) than in earlier tumor stages (pT1 = 11%) (Koenig et al. 2009).

An important counter-argument challenging the reliability of immunohistochemical assays is that of sampling error.

Factors which might influence this are the number of lymph nodes dissected during the course of resection, the number of lymph nodes assessed by immunohistochemistry, the number of lymph node sections, and the level of these sections within the lymph nodes. Previously, several authors have suggested that the ratio of positive lymph nodes detected by conventional histopathology should be used for a refined pN staging in esophageal and gastric cancer (Koenig et al. 2009).

Apart from staging accuracy, the surgical impetus of radical lymphadenectomy is to remove the surrounding loco-regional soft and lymphatic tissue in the vicinity of the tumor. The importance of lymph node yield and ratio and its influence on stage migration, and therefore as a strong independent prognostic factor on survival, was previously described by our group (Bogoevski et al. 2008). It is not only that the global presence or absence of nodal involvement may serve as a tool for the differentiation of "high-risk" from "low-risk" patients, but also the ratio of immunohistochemically affected lymph nodes to the total number of lymph nodes seems to enable improved risk stratification of cancer patients.

However, extensive removal of the lymphatic tissue carries the ability to uncover the correct pN-status, and immunohistochemistry is a helpful tool to refine the risk stratification in these solid pathologies.

Neoadjuvant treatment modalities were developed to improve local tumor control as well as to reduce lymph node metastases and distant metastases. Prenzel et al. (2007) previously evaluated the influence of neoadjuvant chemoradiation on nodal microinvolvement. A total of 1,186 lymph nodes of 52 patients of both adenocarcinoma and squamous cell carcinoma were diagnosed as negative for metastases in routine histopathology. A major histopathologic response (<10% vital residual tumor cells) was shown by 42.3%, whereas in 30 tumors, only a minor response (>10% vital residual cells) was present. Major response was shown by 19 of 32 patients (59.4%) with pN0-status. Of these, only four patients had a nodal microinvolvement which was significantly reduced compared to those with minor response (9 of 13 patients). Due to the small number of patients in this setting, future studies will show whether this can be further confirmed.

10.3 Mode of Spread

Schurr et al. investigated the role of the mediastinal lymphadenectomy in carcinomas of the

Table 10.1 Positive Lymph Nodes in Histopathology (Hematoxylin and Eosin staining) and immunohistochemistry (Ber-Ep4þ cells) in the Mediastinal, Paracardial, and Upper Abdominal Lymph Nodes

pN0/pN1	No. of patients (%) (n=45 for Type I and n=40 for Type II)	
	Type I	Type II
	Mediastinal	
Histopathology	11 (24%)	4 (10%)
Histopathology and Ber-Ep4þ cells	18 (40%)	13 (33%)
	Paracardial	
Histopathology	15 (33%)	21 (53%)
Histopathology and Ber-Ep4þ cells	17 (38%)	35 (88%)
	Upper abdominal	
Histopathology	8 (17%)	16 (40%)
Histopathology and Ber-Ep4þ cells	13 (29%)	17 (43%)

esophagogastric junction. Frequency, location, and prognostic significance of lymph node metastases detected both histopathologically and immunohistochemically were analyzed in patients with an adenocarcinoma of the esophagogastric junction. The differences of histopathological lymph node involvement between type I and II cancer are shown in Table 10.1.

Immunostaining showed that in type I carcinoma, nodal microinvolvement occurred to mediastinal in 40%, to paracardial in 38%, and to upper abdominal nodes in 29%, whereas in type II carcinoma, nodal microinvolvement corresponded to 33% to the mediastinal, 88% to the paracardial, and 43% to the upper abdominal compartment. Combined assessment of lymph nodes by histopathology and immunohistochemistry raised the numbers of positive patients in the three compartments. Remarkably, in type II carcinoma, an overlap of nodal involvement was detected by conventional histopathology and immunostaining in the mediastinal lymph node compartment. This resulted in nodal involvement detected either by conventional histopathology or immunohistochemistry in a total of 33% of patients with type II carcinoma.

Potential metastatic spread to the lymph nodes of the abdominal and mediastinal compartments indicate that cardia carcinoma behaves like a “wanderer between two worlds” (Schurr et al. 2006).

In esophageal carcinoma, the frequency of metastasis in certain lymph node groups is influenced by the location of the primary tumor. Akiyama published data on 236 patients about this aspect of metastatic spread (Akiyama et al. 1994).

Patients with carcinoma of the upper esophagus had metastases in the neck lymph nodes in 44.1%, upper mediastinum in 50.0%, middle mediastinum in 20.6%, and lower mediastinum in 5.9%. Remarkably, 14.7% of the cases presented with metastases in the upper gastric area.

Carcinoma of the mid-esophagus was associated with metastasis in the neck in 32.9%, the upper mediastinum in 38.1%, the mid-mediastinum 41.0%, the lower mediastinum 20.2%, and in the upper gastric region in 42.5%. Carcinoma of the lower esophagus was associated with 29.4% positive lymph nodes in the neck and 30.9% in the upper mediastinum, 48.5% had metastases in the middle mediastinum, 35.3% in the lower mediastinum, and 69.1% in the upper gastric area.

In summary, the incidence of metastases in the superior mediastinum is high, even in patients with primary tumors located in the lower esophagus. These data underline the importance of extensive lymph node sampling for correct staging.

10.4 Effect of Nodal Microinvolvement on Survival

Immunohistochemistry neither is a clinical routine nor is its use universal because the results of previous studies have been inconclusive. In esophageal carcinoma and cardia carcinoma, previous studies that evaluated the value of nodal microinvolvement with respect to improved risk stratification provide inconsistent data (Siewert and Stein 1998; Casson et al. 1994).

Mueller et al. showed that micrometastases in "tumor-free" lymph nodes have a prognostic impact. In this study, the presence of micrometastases in the lymph nodes of the tumors of the esophagogastric junction (type I, II, III) has shown different rates of tumor cell detection by immunohistochemistry according to the location of the tumor. In comparison, the rate of micrometastases was significantly higher in type II/III tumors compared with type I tumors. Patients with pN0 status and no micrometastases had a mean survival time of 85.8 months, whereas pN0-patients with immunohistochemically detected micrometastases 45.5 months, which was similar to patients with a pN1-status (45.2 months).

Schurr et al. described that after a median observation time of 27 months, the presence of nodal microinvolvement was associated with significantly reduced disease-specific survival. The Kaplan-Meyer-Analysis showed a significant survival benefit for patients negative in immunohistochemistry (Fig. 10.1).

The median disease-specific survival was 87 months for patients without nodal microinvolvement, and 16.8 months for patients with microinvolvement. The estimated 2 and 5-year survival rates were 77 and 39% for patients without and 62 and 21% for those with nodal microinvolvement.

Additionally, micrometastases to mediastinal lymph nodes for type II carcinoma and abdominal micrometastases for type I carcinoma strongly predicted the outcome, thus elucidating

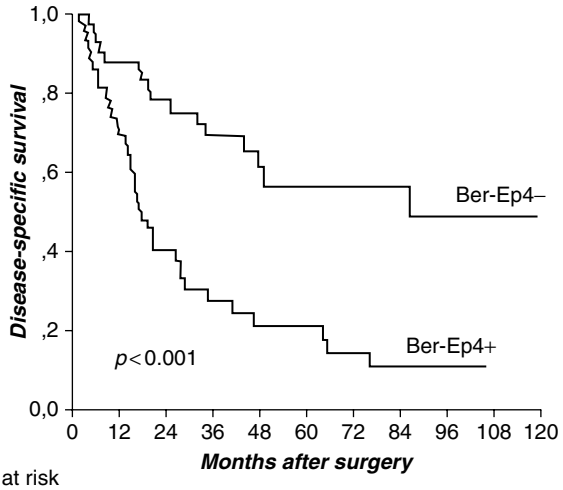

Fig. 10.1 Effect of nodal microinvolvement on disease-specific survival (all patients)

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the role of micrometastases "crossing" the diaphragmatic border. These results show that "proximal" cardia carcinoma located mainly in the distal esophagus may spread "downwards" to the upper abdominal lymph node compartment as may "true" junctional cardia carcinoma, located mainly in the Z-line, metastasize "upwards" to the lower mediastinal lymph nodes. The presence of nodal microinvolvement both in type I and type II carcinoma had a highly significant, independent impact on survival regardless of pT-stage and grading. Patients who had, apart from overt lymph node metastases, additional, occult tumor cells in lymph nodes classified to be "tumor-free" by conventional histopathology, showed significantly shorter disease-specific survival as compared with pN1-patients without such cells. On the other hand, pN0 patients who had Ber-Ep4+ cells in their lymph nodes showed impaired survival (Fig. 10.2).

The median survival was 65 months (95%-CI: 2–113) vs. a median not reached for the presence/absence of the Ber-Ep4+ cells. The prognostic effect of Ber-Ep4+ cells was confirmed by the finding that disease-specific survival of pN0 Ber-Ep4+ patients was similar to pN1-patients (Fig. 10.3).

Disease-specific survival revealed a 2.77 higher independent risk for patients who had nodal microinvolvement (Schurr et al. 2006).

The conclusion of these results is that it is highly suggestive that even single, occult tumor cells in lymph nodes of patients with cardia carcinoma have a strong malignant potential and may contribute to metastatic relapse whether or not overt lymph nodes metastases are assessed by conventional histopathology.

Therefore, transdiaphragmatic removal of both lymph node compartments seems to be mandatory with respect to oncological requirements. Moreover, these results indicate that complementary immunohistochemical analysis of lymph nodes in addition to conventional histopathology yields a distinct increase of staging accuracy, thereby providing a potential tool to identify "at risk" patients who will not be cured by surgery alone.

In patients with esophageal carcinoma, isolated tumor cells in lymph nodes by immunohistochemical analysis are strong prognostic-ators. Izbicki et al. had shown that Ber-EP4–positive cells found in "tumor free" nodes were independently predictive of significantly reduced relapse-free survival and overall survival. They

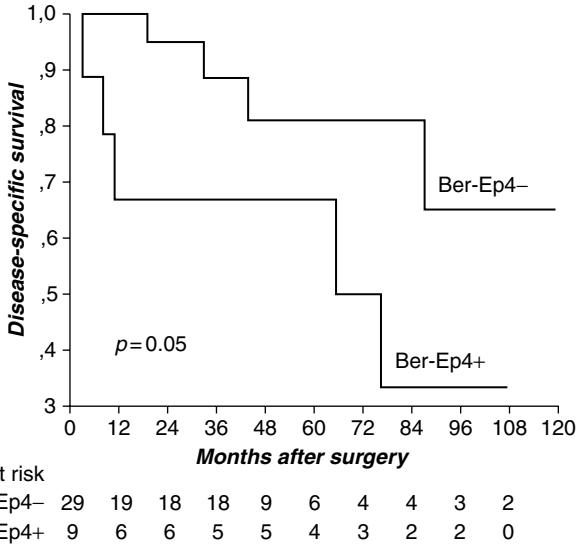

Fig. 10.2 Effect of nodal microinvolvement on disease-specific survival (type I and II carcinomas)

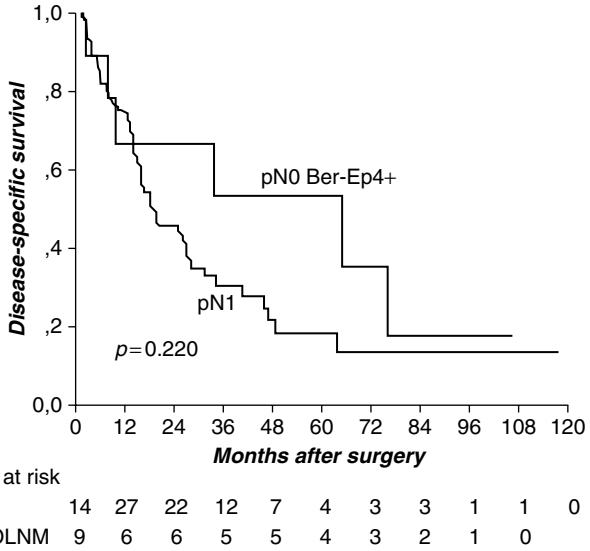

Fig. 10.3 Effect of nodal microinvolvement on disease-specific survival (pN0 with nodal microinvolvement vs. pN1-patients)

predicted relapse both in patients without nodal metastases and in those with regional lymphnode involvement (Izbicki et al. 1997).

Koenig et al. (2009) described that in patients with adenocarcinoma survival was associated with a worse median overall survival (20 months vs. 28 months; $p=0.029$). The 5 year survival probability accounted for 65% in patients without nodal microinvolvement, whereas that in patients with immunohistochemically detectable tumor cells was 0%.

Furthermore, in this study, multivariate analysis showed that micrometastatic lymph node ratio was the most powerful predictive variable for overall survival in patients with esophageal carcinoma irrespective of histopathological tumor type, followed by pT-stage and substratification of patients according to conventional nodal staging (pN0 vs. pN1).

10.5 Current and Future Perspectives

The potential role of an antibody-based treatment as a therapeutic target has been intensely evaluated in numerous types of human cancer. HER-2 gene amplification and protein overexpression occurs in about 20% of breast cancers (Zhang et al. 2003) and is routinely used as the target of an antibody-based therapy (trastuzumab) in metastatic HER-2-positive breast cancer (Baselga et al. 1999; Leyland-Jones 2002; Tripathy et al. 2004).

More recently, adjuvant trastuzumab application was also shown to be dramatically effective in *HER-2*-positive breast cancer patients (Tuma 2005).

The potential benefit of trastuzumab in other tumor entities is largely unknown. HER-2 positivity has been described in most human tumor types but with a highly variable frequency (Ross and McKenna 2001; Allgayer et al. 2000; Safran et al. 2001).

This especially applies for immunohistochemical studies where different reagents and definitions of positivity resulted in an extremely wide range of HER-2 positivity in almost all tumor types.

Despite this, there is evidence for a possible response of HER-2-positive nonbreast cancers to trastuzumab (Langer et al. 2004; Kollmannsberger et al. 1999; Locati et al. 2005).

Applying trastuzumab as additional treatment option would be of particular interest in

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tumors with a notoriously poor prognosis such as esophageal cancer and cardia cancer.

Several studies indeed suggested that HER-2 amplification/overexpression may be relevant for these tumor entities. HER-2 overexpression was reported in 0–83% of esophageal cancer, with a tendency towards higher rates of positivity in adenocarcinoma (10–83%) (al-Kasspooles et al. 1993; Geddert et al. 2002; Walch et al. 2001; Jankowski et al. 1992; Flejou et al. 1994; Nakamura et al. 1994; Hardwick et al. 1995, 1997; Kim et al. 1997; Polkowski et al. 1999; Sauter et al. 1993; Duhaylongsod et al. 1995; Friess et al. 1999; Trudgill et al. 2003; Safran et al. 2004) compared to squamous cell carcinomas (0–56%) (Friess et al. 1999; Hardwick et al. 1997; Mimura et al. 2005; Akamatsu et al. 2003; Lam et al. 1998; Suo et al. 1992, 1995; Suwanagool et al. 1993). A similar variability was observed in amplification analyses. Different methods for analysis (Southern blot or FISH) and definitions of amplification have resulted in amplification frequencies ranging from 15 to 100% in adenocarcinomas (al-Kasspooles et al. 1993; Geddert et al. 2002; Walch et al. 2000a, b, 2001; Jankowski et al. 1992; Persons et al. 1998; Brien et al. 2000) and from 0 to 25% in squamous cell carcinomas of the esophagus (Friess et al. 1999; Mimura et al. 2005; Suo et al. 1995; Ikeda et al. 1996; Tanaka et al. 1997). In a phase I/II study by Safran et al. (2007), trastuzumab was weekly used in combination with paclitaxel, cisplatin, and radiation for advanced esophagogastric junction adenocarcinoma. This combination was well tolerated without an increased incidence of cardiotoxicity or esophagitis when the full dose of trastuzumab was used. HER-2 was overexpressed in 33% (similar to the rates in breast cancer) of the patients. But only those patients with advanced loco-regional and distant adenopathy were included, and therefore, these cases did not receive surgical resection after chemoradiotherapy. Hence, endoscopic responses were used to assess. Five of ten patients in the trastuzumab arm and 10 of 13 patients in the control arm had no tumor on postchemoradiation endoscopic biopsy. However, it should be noted that the negative predictive value of a postchemoradiotherapy endoscopic biopsy is low. A randomized study of patients receiving chemoradiation with and without trastuzumab is needed.

Considering the encouraging results of clinical trials in breast cancer, it could be speculated that trastuzumab might also represent a possible option for HER-2 amplified esophageal adenocarcinomas or cardiacacinoma of the esophagogastric junction after resection of the primary tumor.

Clinical trials investigating the response of HER-2 amplified in these cancer types to trastuzumab are needed.

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11 Quality Indicators of Surgery for Adenocarcinoma of the Esophagus and Gastroesophageal Junction

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Abstract Surgical treatment of adenocarcinoma of the esophagus and gastroesophageal junction is complex and challenging.

Huge variation exist in the immediate and long term outcomes of such interventions and it is generally accepted that this is a direct consequence of the experience of the surgical team.

However beside surgical quality many other indicators of quality management may influence outcome. Definition of the gastroesophageal junction remains controversial and the performance of staging procedures i.e. CT scan, endoscopy and fine needle aspiration, PET scan still suboptimal.

As a result there is disagreement on the selection of patients for surgery, type of surgical approach in particular in relation to the extent of lymph node dissection as well as the extent of esophageal and/or gastric resection. In the design of randomized controlled trials comparing primary surgery versus multimodality treatment surgical quality criteria are notoriously lacking. It therefore remains a matter of debate which patients eventually will benefit from primary surgery versus those who will benefit from induction therapy.

A lack of surgical quality indicators is also very prominent when assessing the value of new surgical technologies such as minimally invasive surgery or robotic surgery.

Improvements in this wide spectrum of aspects is mandatory and will certainly be of great value to further improve both short and long term outcome after surgery for these complex cancers.

11.1 Introduction

> *Physicians tend to see Quality in terms of the excellence of the services they provide (...). The changing nature of medical services is forcing to pay increasing attention to the process of care (...). This is a challenge for which few physicians are prepared.*
>
> (Blumenthal 1996)

The incidence of adenocarcinoma of the esophagus and gastroesophageal junction (GEJ) has been rising over the last decades to become a major health concern in the Western world (Pera et al. 2005). Surgery is the main form of curative treatment for tumors that have spread beyond the most superficial epithelial layers,

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but not extending beyond loco-regional lymph nodes (Lerut et al. 2001; Vrouenraets and van Lanschot 2006). However, the precise indications for surgery, type of surgery, and place/optimal use of other treatment modalities such as chemotherapy and/or radiotherapy remain controversial and vary hugely among centers and countries.

Similarly, huge variations exist in the outcome of surgery for the cancer of the esophagus and GEJ. Expert centers report large series of radically operated patients with 5-year survivals usually exceeding 35–40% (Lerut et al. 2001; Vrouenraets and van Lanschot 2006; Birkmeyer et al. 2007). Conversely, nationwide databases and review papers still assume that transhiatal and transthoracic resections achieve similar poor oncological outcome with overall survival as low as 15–20% (Chang et al. 2008; Rindani et al. 1999; Enzinger and Mayer 2003). Such differences in outcome suggest differences in the quality of surgical management of esophageal cancer from one center to another.

Indeed, it appears that few other oncological operations are as heavily influenced by experience than esophagectomy. Experienced centers not only achieve lower mortality and morbidity rates, but also much higher cure rates than low-volume centers (Birkmeyer et al. 2002, 2007). This suggests differences in the quality of surgical management, depending on the type of center where a given patient is operated on. Although such volume-relations reflect that good quality is strongly linked to experience in the management of these cancers, volume itself, most likely, is only a surrogate indicator for good quality.

From a quality management point of view, it would be more interesting to analyze the complex quality issues of classification, staging, and therapy for esophageal and GEJ cancer in a given setting, rather than simply a rough measurement of the most obvious end-points, such as mortality, morbidity, and long-term survival (Blumenthal 1996). Identifying the real indicators of quality management of these cancers may help further improve the outcome of this currently dreadful disease and allow comparison between surgical vs. nonsurgical therapeutic modalities with curative intent (Bedenne et al. 2007; Stahl et al. 2005). This paper will discuss quality issues based on the available literature on various aspects of the surgical management of adenocarcinoma of the esophagus and GEJ.

11.2 Quality Issues in the Definition of Cancer of the Gastroesophageal Junction (GEJ)

Adenocarcinoma may be located entirely in the tubular esophagus, but often the clinician is confronted with adenocarcinomas that straddle the gastroesophageal junction (GEJ). Various criteria have been used to categorize tumors situated at the GEJ. In most of these classification systems, the anatomic location of the epicenter or predominant mass of the tumor is used to determine whether the neoplasm is esophageal or gastric (cardia) in origin.

Siewert and Stein (1998) proposed a topographic classification for the cardia carcinomas. According to the authors, epidemiologic, clinical, and pathologic data support that adenocarcinomas arising into the vicinity (i.e., that have their center within 5 cm proximal and distal of the anatomical cardia) of the GEJ can be subclassified into (a) adenocarcinoma of the distal esophagus, which usually arises from an area with specialized intestinal metaplasia (i.e., Barrett esophagus) and may infiltrate the GEJ from above (type I); (b) true carcinoma of the cardia arising immediately at the GEJ (type II); and (c) subcardial carcinoma that infiltrates the GEJ and distal esophagus from below (type III). In contrast to previously described classification systems, Siewert and Stein attempt to solve the problem of splitting up GEJ tumors into esophageal and gastric tumors by creating a third entity. This third entity is lumping a large

group of tumors (i.e., with the center of the tumor within an area of 5 cm proximal and distal of the anatomical cardia). This third entity is called cardiacarcinoma in which the true GEJ tumors are squeezed between the type I and type II tumors. Their effort seems rather adding to the confusion than helping to solve the true problem, i.e., that of the true GEJ tumors. Moreover, this classification is entirely based on identifying the "anatomical" cardia and measuring the center of the tumor in relation to this anatomical cardia on the resected specimen, i.e., the pathological staging. Especially measuring the center of the tumor is impractical, if not impossible, for clinical staging purposes (e.g., in presence of a hiatal hernia). Not surprisingly, Omloo et al. recently reported a substantial discrepancy between the clinical staging and the pathological staging using this classification (Omloo et al. 2007). It is obvious to stress the need of an, as accurate as possible, clinical staging required for therapeutic decision-making.

In 2000, the World Health Organization Classification of Tumors published *Pathology and Genetics of Tumours of the Digestive System* (Spechler et al. 2000). This book includes a chapter on adenocarcinoma of the GEJ. The authors formulate diagnostic criteria based on the following definition of the GEJ: the GEJ is the anatomical region at which the tubular esophagus joins the stomach. The guidelines specify the following: Adenocarcinomas that cross the GEJ are called adenocarcinomas of the GEJ, regardless of where the bulk of the tumor lies. Adenocarcinomas located entirely above the GEJ, as defined above, are considered esophageal carcinomas. Adenocarcinomas located entirely below the GEJ are considered gastric in origin. The use of the ambiguous and often misleading term *carcinoma of the gastric cardia* is discouraged. These tumors should instead be referred to as carcinoma of the body of the stomach.

In the recommendations of the International Union Against Cancer (*TNM*, 6th ed., 2002) (Sobin and Wittekind 2002) according to the advice formulated in the TNM supplement (Wittekind et al. 2003), adenocarcinomas situated at the gastroesophageal junction are to be classified into esophageal, esophagogastric junction, or cardiac (site C 16.0) adenocarcinomas according to a single major criterion (i.e., the localization of the bulk of the tumor). If more than 50% of the mass of the tumor is situated in the cardia (ICD-10 classification site C16.0), the tumor should be considered to be of cardiac origin (site: C16.0) and classified as a gastric tumor; if the mass of the tumor is predominantly found in the esophagus, it is to be classified as an esophageal tumor. Furthermore, it is specified that a tumor situated on the gastroesophageal junction is likely to be of esophageal origin when the neoplastic lesion was associated with a Barrett esophagus of the specialized or intestinal type. Unfortunately, the description of how to handle these tumors in the 2002 AJCC Cancer Staging Manual appeared not always be compatible, thereby again creating confusion (Greene et al. 2002). The chapter on stomach (Chap. 10) refers to the 50% rule, whereas the chapter on esophagus (Chap. 9) indicates that "tumors arising within the EG junction and gastric cardia that have minimal (2 cm or less) involvement of the esophagus are considered primary gastric cancers."

A continuing increase in the incidence of cardia cancer has been reported since the mid 1970s. The output of scientific publications on cardia and cardiac cancer has internationally evolved in parallel. Unfortunately today, the vast majority of data available on the cardia and cardiac cancer are not comparable because of lack/variability of diagnostic criteria. This has resulted in therapeutic approaches based on loose (nonscientific?) grounds, e.g., treating adenocarcinoma of the esophagus and gastric carcinomas as a single same entity using identical chemo ± radiotherapy and/or surgical regimens. And if not so, the difference in classification of the true cardia cancers and the subsequent different definitions of loco-regional vs. nonregional lymph nodes,

i.e., classifying celiac nodes as gastric N1 nodes vs. esophageal M1a nodes has caused confusion as to the subsequent therapeutic implications (e.g., therapy with curative option in case of N1 vs. therapy with palliative intention in case of M1a). In our experience however, it would appear that the similarities between adenocarcinoma of the GEJ or cardia and Barrett adenocarcinoma outnumber the dissimilarities and are to be differentiated from gastric (including "subcardia") cancer (Driessen et al. 2003, 2004).

In the latest 2009 edition of the AJCC/TNM classification (Edge et al. 2009), an agreement has been reached on how to classify the adenocarcinoma of the GEJ. Cancers whose epicenter is in the lower thoracic esophagus, GEJ, or within the proximal 5 cm of the stomach (cardia) but which extend into the GEJ or esophagus are stage-grouped similar to adenocarcinoma of the esophagus. All other cancers with an epicenter in the stomach greater than 5cm distal to the GEJ or those within 5cm of the GEJ but not extending into the GEJ or esophagus are stage-grouped using the gastric cancer systems. As to the lymph node involvement, regional lymph nodes are now defined as extending from peri-esophageal nodes to celiac nodes (discarding the M1a definition). In classifying N, the data support grouping of the number of positive nodes: N1 (1–2 positive nodes), N2 (3–6 positive nodes), and N3 (7 or more positive nodes).

It is hoped that this simplification of both definitions of GEJ tumors and regional lymph nodes will provide a better basis for therapeutic decision making.

11.3 Quality Control and Quality Issues in the Staging of Esophageal Cancer

A discussion on how to stage an esophageal cancer may seem odd considering that various guidelines clearly describe which examinations should be performed (www.kce.fgov.be; NCCN). However, the mere performance of these examinations does not suffice to assure good quality of the work-up. Similarly to surgical procedures, staging procedures such as EUS and even CT-scan are also heavily influenced by experience (Lightdale and Kulkarni 2005; Van Vliet et al. 2006, 2008). Learning curves and annual volumes may play an important role in the quality of staging of cancers of the esophagus and GEJ.

The performance of a conventional CT-scan examination has been shown to be highly dependent on both the quality of the examination (generation of the CT-scan, systematic use of contrast media, slice thickness, etc.) and the experience of the radiologist with esophageal cancer (Van Vliet et al. 2008). However, this study also showed that even in the more expert hands, a newest-generation CT-scan still has a relatively low accuracy of detecting either lymph node or systemic metastases (<75%).

EUS seems even more operator-dependent with a learning curve for EUS exceeding 100 procedures (Lightdale and Kulkarni 2005; Van Vliet et al. 2006). Van Vliet et al. found centers performing annually more than 50 EUS staging procedures for esophageal cancer to be more accurate than centers with a lower volume (Van Vliet et al. 2006).

In general, EUS aims at determining tumor depth (T factor) and identifying lymph node involvement (N factor).

In early tumors, the distinction of tumors limited to the mucosal layers (T1m or T1a) vs. invasion of the submucosa (T1sm or T1b) is very important as lack of lymph node involvement characterizes T1m tumors, making those patients candidates for nonsurgical endoscopic treatment such as endoscopic mucosal resection (EMR). Tumors invading the submucosal layers (T1sm tumors) are accompanied by positive lymph nodes in 30–35% of cases, and therefore, usually require radical surgical resection for cure (Pera et al. 2005; Lerut et al. 2001). High-resolution

endosonography (HR-EUS) using 20 MHz or even 30 MHz miniprobes have to be used for this purpose. May et al. reported accuracy rates of 80% in a group of 100 patients with early carcinoma (27% T1sm and 73% T1m) (May et al. 2004). Sensitivity for T1m detection was 91.6%, but specificity was only 48%. Even in such very experienced hands, HR-EUS combined with HR-EUS still understaged 40% of all T1sm tumors (May et al. 2004).

In a similar population with 106 early lesions (prevalence of T1sm of 30%), Chemaly et al. reported accuracy, sensitivity, and specificity rates in differentiating T1sm from T1m of 73.5, 62, and 76.5%, respectively (Chemaly et al. 2008). The technique for HR-EUS also seemed to be very important as results were incorrect in 57% of cases when a balloon-sheated catheter was used compared to 31% incorrect assessments when a lumen filled technique was used ($p=0.015$). As in other previous studies, HR-EUS performed particularly poorly in tumors located in the distal esophagus (52% incorrect T1 m/sm staging) (May et al. 2004; Chemaly et al. 2008; De Manzoni et al. 1999; Kelly et al. 2001). These reports are all from expert authors. Results in less experienced hands are unknown or unreported.

Much attention today is given on EMR as a staging procedure in early (T1) carcinoma. Such EMR allows, indeed, for discrimination between T1a and T1b tumors. However, again this technique requires sufficient expertise. In particular, piecemeal resections of such lesions and coagulation artifacts may jeopardize the correct interpretation of deep section margin, putting at risk some of these patients for a suboptimal treatment (Peters et al. 2008).

For the determination of lymph node involvement, standard EUS currently is unsatisfactory and cannot sufficiently reliably select patients for induction chemoradiotherapy treatments: False assessment by EUS can not only result from poor experience, but also depend on aspects such as the need for dilation of a stenotic tumor or the use of fine needle aspiration (FNA) histology in lymph nodes close to the tumor when the biopsy needle may be contaminated by passage through the primary tumor. Undoubtedly, poor quality use of EUS can impair the quality of the overall treatment plan by inducing poor patient selection for various treatment modalities.

In a population of 214 operated patients with a prevalence of 60% lymph node involvement, Kutup et al showed that the specificity for N1 detection by usual criteria (5 mm size, round borders, smooth shape, and hypoechogenic center) was only 20%, and as a result, 80% of pN0 were overstaged as uN1 (Kutup et al. 2007). In their hypothetical setting of a therapeutic strategy that would submit to chemoradiotherapy any patient with uN1 while sending for primary surgery only those with uN0, based on EUS alone, 36% of all uN1 patients would have received unnecessary induction treatment, while 32% of all uN0 patients would have been primarily operated although they might have required an induction treatment. This study clearly highlights that therapeutic decision-making should not be based solely on EUS features and that histological confirmation, by FNA or mini-invasive surgical staging procedures, is mandatory before taking any therapeutic decision. This study also showed that the need for dilation of stenotic tumors frequently leads to overstaging in T1–2 tumors and that EUS performance was particularly poor in early-stage tumors with poor tumor grading (25% correct diagnosis in G3 tumors vs. 94% in G1–2 lesions) (Kutup et al. 2007).

Furthermore, there are only very limited data available on the additional value of routine lymph node biopsies by EUS-FNA. The few available studies used FNA in very selected patients where FNA was used to confirm invasion of nodes that appeared highly suspicious on CT-scan, PET, or EUS. The few available studies did almost not include any N0 patients, and thus, the value of the use of routine FNA in normal looking nodes is unknown. It, thus, remains to be proven if systematic use of FNA really can improve the precision of staging.

The use of *PET-scan* for the primary staging of esophageal cancer also remains controversial. Recently, the Z0060 trial demonstrated that in patients without evidence of metastasis after a conventional work-up, FDG-PET identified unsuspected distant metastasis in 4.8% (95% CI: 2.2–8.9%) of cases (Meyers et al. 2007). An additional 3.7% (95% CI: 1.5–7.5%) had unconfirmed evidence of M1b disease and were treated non-surgically, at least in part owing to the PET findings. However, such PET-detected metastases should always, if possible, be confirmed by histology before excluding a patient from surgical consideration, since apparent M1 findings by PET in at least 3.7% (95% CI: 1.5–7.5%) were false positives. Conversely, an additional 5% of patients can be expected to harbor metastatic disease that escapes detection by both CT and PET (Meyers et al. 2007).

The quality of staging, thus, can be improved, although to a rather limited extent, by adding a PET to a conventional work-up. The modest potential gain in staging precision may, however, be lost if the performance of a PET implies loss of time on a waiting list or if positive PET findings excluding patients from a potentially curative surgery would be accepted without any tissue confirmation. Performing or not performing a PET-scan by itself may, thus, not be a quality indicator. Quality should rather be determined by the way in which use is made of any additional information gathered through adding a PET to a conventional staging procedure.

Altogether, conventional staging strategies hitherto have not been focused on the real determinants of good surgical outcome: T-staging should aim at distinguishing T1m (potential candidates for endoscopic treatment) from T1sm or more and to distinguish surgically resectable T3 or T4 (i.e., pleura, lung, or pericardium) from unresectable T4 disease (i.e., tumors without adequate lateral tumor clearance (R1) because of microscopic invasion into the trachea or aorta).

For lymph node staging, available studies have merely tried to distinguish N+ from N0 patients. Better quality of staging would imply better information on the number and location of the involved nodes, rather than just identifying N1. Indeed, better quantitative assessment of lymph node involvement could allow a better patient selection for induction chemoradiotherapy. In our experience the prognosis of T3 patients with limited (i.e., less than seven positive nodes) LN involvement in the vicinity of the primary tumor is similar to patients without node involvement. In our experience, such subsets of patients do not gain from adding induction therapies and can best be treated by aggressive surgical resection (Lerut et al. 2008). Other strong prognostic predictors of survival such as the presence or absence of capsular lymph node rupture can currently not be reliably predicted by EUS (Lagarde et al. 2006; Lerut et al. 2003).

Good quality of the staging work-up, thus, is necessary in order to allow a good patient selection for therapy, and hence, is a prerequisite for a high quality surgery.

11.4 Quality Issues in the Use and Indications for Induction Chemo- and Chemoradiotherapy

Despite all efforts in refining indications for surgery and the resulting improved long-term outcome, still a majority of patients die from general and/or loco-regional metastasis. This has resulted in an interest in combined therapeutic modalities. Over the last decade, neoadjuvant (induction) protocols aiming at downstaging of the disease have been widely used.

11.4.1 Chemotherapy

Several randomized trials comparing chemotherapy plus surgery vs. primary surgery have been published. The two largest of these trials revealed

conflicting results. The US trial published by Kelsen did not show any difference in the various parameters that were analyzed (Kelsen et al. 1998).

In contrast, the UK-based MRC trial did show a small but significant 5-year survival benefit favoring the combined arm (Medical Research Council Oesophageal Cancer Working Group 2002).

A Cochrane metaanalysis (Malthaner and Fenlon 2003) including eight trials on the use of neoadjuvant chemotherapy detected no statistical difference between the combined arm over surgery alone. Based on these data, primary surgery is recommended for patients with resectable thoracic esophageal cancer for whom surgery was considered appropriate. Another metaanalysis by Gebski indicated, however, a small benefit in favor of the combined arm (Gebski et al. 2007).

11.4.2 Chemoradiotherapy

As to the use of chemoradiotherapy as mode of induction, there are now eight published randomized controlled trials (Gebski et al. 2007). Only one trial, the Irish trial, has been able to show a statistically significant difference in overall survival in favor of the multimodality arm (Walsh et al. 1996; Malthaner et al. 2004). But this trial was heavily criticized because of the very poor outcome in the surgery alone arm, 6% after 3 years, most likely due to selection bias. Also in the five published metaanalyses (Gebski et al. 2007; Urschel and Vasan 2003; Greer et al. 2005; Fiorica et al. 2004; Geh et al. 2006), the conclusions are not unequivocal. Three metaanalyses indicate improved 2–3-year survival, R0 resection, and lower recurrence after induction chemoradiotherapy (Gebski et al. 2007; Urschel and Vasan 2003; Greer et al. 2005). Another metaanalysis indicates a small but nonsignificant improvement in overall survival (Fiorica et al. 2004), while the fifth metaanalysis (Geh et al. 2006) favors surgery alone because of the impact on postoperative mortality in the multimodality arm.

Several criticisms are to be made on these different trials and metaanalysis:

The first trial bringing under attention the potential value of induction therapy published by Walsh et al. is a clear illustration of the quality issue, particularly in the surgical arm (Walsh et al. 1996). Indeed, in the surgery alone arm 3-year survival was only 6%, well below any standard. This low survival most likely resulted from a selection bias induced by a lack of accurate clinical staging.

In fact, in all the trials the results of surgery are suboptimal with 3-year overall survival figures varying between 6 and 36% (Gebski et al. 2007). Obviously, these poor surgical results are the consequence of a lack of quality criteria related to the surgical technique as indeed neither surgery, even when it might be possible, has been standardized or optimized nor have instruments for quality control been used.

Of concern is that there are considerable variations in the different aspects of the trials, i.e., location of the tumor, different histological types, clinical stage, and variation in chemotherapy and radiotherapy (e.g., drug, dose, volume, schedules, number of cycles etc.). This may cause differences in outcome (Geh et al. 2006).

Also most of the trials have insufficient power to indicate significant differences. Not surprisingly, the mean Jadad quality score of the different prospective randomized trials is rather low (2.1 on the scale of 5 points) (Jadad et al. 1996). Consequently, the results of the metaanalysis may suffer from bias based on poor individual data (Egger et al. 2002). It therefore may be concluded that today there is still no proof of a clear benefit of routine multimodality treatment vs. radical surgery only because of a lack of a sufficiently large prospective randomized trial comparing multimodality treatment vs. such radical surgery including extensive, i.e., at least two-field lymphadenectomy. The latter now frequently results in overall 5-year survival rates exceeding 40% and for advanced stage III disease exceeding 25% (Lerut et al. 2008).

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This lack of convincing evidence as to the value of induction chemo ± radiotherapy may also be a consequence of absence/presence of clear selection criteria based on which patients should be candidates for such induction therapy.

Historically, the indications were based rather on the T factor (Van Raemdonck et al. 1997). Indeed, the discrimination between T3 and T4 tumors may be very difficult at clinical staging. This is particularly true in middle and proximal third carcinoma as a fat plane between the pars membranacea of the trachea/stem bronchus is absent. The guarantee to obtain a R0 resection, i.e., negative lateral margins, is therefore at risk. These patients are obvious candidates for an induction therapy regimen.

In subsequent trials, induction therapy also includes the N factor extending the indication for induction therapy to T1-3N0-1 disease. This extension therefore brings up the issue of quality of clinical staging. Despite all technological improvements, it must be acknowledged that there is still a problem of considerable both under and overstaging of both T and N in up to 26% of the patients even in the era of PET-scan and refinement of EUS (Zuccaro et al. 2005).

A recent analysis performed on a series of 296 de novo cancers of the esophagus and GEJ at our institution revealed both an understaging of node involvement, and more importantly, overstaging, i.e., false positive nodes, in 21.6% of the cases. Node negative patients after radical primary surgery have a good prognosis with a 5-year survival in pT3N0 patients reaching 60% in our experience. As a result, one can hypothesize that clinical trials on induction therapies including patients clinically staged as cN+ but being in fact false positive will result in an artificial upgrading of survival at 5 years by at least 5% by giving induction therapy to patients who in reality were N0.

Moreover, it is well known that an estimated 50% of patients will not respond to this induction treatment (Ancona et al. 2001). While the complete responders (approximately 20–25% after induction chemoradiotherapy), and to a certain extent, major responders are generally accepted to benefit from induction therapy, the nonresponders may well pay the price for the responders.

Indeed, Ancona et al. (2001) showed in their study on the value of induction chemoradiotherapy that the nonresponders had a dismal 12% 5-year survival after surgery. One reason among others why nonresponders have a survival below the expected is thought to be related to the loss of precious time during the course of the start of induction therapy and the time point at which surgery is performed, i.e., usually 3–4 months after initiation of induction therapy. Another reason for these low figures in the nonresponders may be the development of resistance against induction therapy. Unfortunately, there are no markers allowing to detect those patients who will respond (the winners) vs. those who will not respond (the losers).

From such data, it becomes clear that the selection of candidates for primary surgery vs. combined treatment modality should be carefully performed on the basis of the pros and cons of both primary surgery and induction therapy. A first prerogative is that all physicians involved in the selection process, and this in contrast to the actual perception (Enzinger and Mayer 2003), should be aware of today's golden standard of primary surgery, i.e., an overall 5-year survival of over 35% in most high volume centers being over 40% in some of them and a 25% or more 5-year survival in locally advanced staged III cancer of the esophagus and GEJ.

Moreover, it appears now clearly that provided a limited number of involved lymph nodes and located within the peritumoral area, primary surgery can offer 5-year survival figures exceeding 35%. In our own experience, patients with cT3N0-1 staging with less than six involved nodes located in the peritumoral area on final pathological examination had a 5-year survival of 38% after primary radical surgery (Lerut et al. 2008). This subset of patients is a substantial group, i.e., 35% of all cT3N0-1 patients analyzed in our study. It is unlikely that these results will

be improved by induction chemo±radiotherapy since almost none of the trials showed overall figures exceeding 35% 5-year survival.

However, drawing the line at a limited number of peritumoral involved nodes as the discriminator between yes or no for induction therapy raises again a quality issue in clinical staging. At this point, there seems to be no method, including EUS to correctly diagnose the number of involved nodes. The latter yet become incorporated in the expected 2009 new edition of the UICC-AJCC TNM classification and thus confirms the prognostic importance in relation to the number of involved nodes.

11.5 Type of Surgical Approach, Extent of Esophageal/Gastric Resection, and Extent of Lymph Node Dissection

Huge technical variability exists throughout the world in the performance of an esophagectomy for cancer. A long tradition of radical esophageal surgery exists in the East, while currently only a minority of Western centers perform resections that would seem radical by Eastern standards (Nishimaki 2006). Not all of these differences can be explained by differences in the incidence of squamous carcinoma vs. adenocarcinoma. Even within the Eastern and Western countries (although much less in the former), huge differences exist in the use of various surgical approaches and in the extent of esophageal resection. Oral tumor margins obviously differ with the routine use of cervical vs. intrathoracic anastomosis, and aboral margins, i.e., variations in the distal extent of the gastric resection (total gastrectomy, polar proximal gastrectomy, resection of the lesser curve), certainly exist for tumors of the GEJ. These are reflected by the type of reconstructions using a gastroplasty or coloplasty rather than a jejunoplasty. Additionally, the lateral resection margin obviously decreases when moving from en bloc to non en bloc, to transhiatal resections, certainly for resections performed for tumors of the middle or upper third.

Concerning the extent of lymph node dissection (LND), the problem is even greater. A recent multivariate analysis on a large patient population found that the absolute number of removed lymph nodes during an esophagectomy was a strong independent predictor of survival (Peyre et al. 2008). An optimal survival benefit required resection of at least 23 lymph nodes. This was not due to stage migration as within every tumor stage (I to III), patients with more than 23 resected lymph nodes had better survival than patients with less than 23 resected nodes, thereby strongly underlining the importance of performing an adequate LND.

Within every compartment of a two-field dissection (thoracic and superior abdominal compartment), the extent of LND can vary, e.g., celiac, hepatic, and splenic artery nodes should routinely be removed during the abdominal stage of any en bloc resection. This, however, is often omitted in recent series, even when dealing with lower third adenocarcinomas and is almost never done in centers performing minimally invasive esophagectomies (MIE) (Decker et al. 2009). Those nodes can also be removed during a transhiatal resection, but the literature reviews on this topic suggest that they often are not (Rindani et al. 1999).

In the chest, the variability of LND is even more problematic. Since 1994, thoracic LND has been standardized as standard (lower periesophageal and subcarinal nodes), extended (including some upper mediastinal nodes, i.e., right paratracheal nodes), and total thoracic LND (including the uppermost mediastinal, i.e., left and right paratracheal and aorto–pulmonary window nodes) (Fumagalli 1996). Nevertheless, many Western publications do not specify the type of LND they perform, and the requirements by the TNM handbook to remove only 12 lymph nodes in no way encourage performance of an adequate LND (Sobin and Wittekind 2002). Additionally, the indications

for LND in the cervical field (so-called third field seems well established in the eastern world, but is highly controversial in the rest of the World (Altorki 2005; Lerut et al. 2004).

Throughout most of the literature, there is currently a huge confusion in terminology. Approach is often confused with radicality, favoring belief that a transthoracic resection is a radical resection while a transhiatal resection would be nonradical in terms of LND. However, large thoracic incisions do not necessarily mean radicality of the resection, while a transhiatal resection is not necessarily a mere palliative stripping of the esophagus. This is nicely illustrated by the Dutch study comparing transhiatal vs. transthoracic esophagectomy for esophageal and GEJ adenocarcinoma (Omloo et al. 2007). The transhiatal resections had been performed including an abdominal LND of the peritruncal nodes up to the subcarinal nodes whenever possible. This leads to a lymph node yield of 16 nodes (median ±9) in the transhiatal arm. This has lead to a better 5-year survival than what had been expected based on previous literature reports on transhiatal esophagectomy (Hulscher et al. 2001). Although the transthoracic route was able to achieve a much higher lymph node yield, both arms performed well in terms of lymph nodes leading to an obvious but statistically nonsignificant survival difference in favor of the transthoracic approach (Omloo et al. 2007). For tumors of the GEJ (where the majority of involved nodes lay in the lymph node stations within the scope of removal by both approaches), there was no difference in survival. This was interpreted by some as an argument to apply the transhiatal approach for any tumor location. Conversely, the fact that some literature reviews did not find any survival differences after transhiatal compared to transthoracic resections is most likely due to the fact that numerous centers may perform nonradical LNDs through thoracotomy, while some other may perform a more adequate abdominal LND by transhiatal approach, thereby leading to a lack of difference in LN numbers and survival, at least when speaking about adenocarcinoma of the GEJ and distal third adenocarcinoma.

When looking at the literature on minimally invasive esophagectomy (MIE), this confusion is even more pronounced (Decker et al. 2009). Laparoscopy, thoracoscopy, videoassisted thoracic surgery (VATS), or hybrid variations can be combined in various fashions to perform an esophagectomy. Numerous technical approaches have been reported, but none of them seemed correlated with a higher number of removed lymph nodes. While some (again mostly eastern) publications on MIE reported very high numbers of removed lymph nodes (Yamamoto et al. 2005), the majority of MIE studies do not. Consequently, the hitherto reported median lymph node numbers of ten nodes (range 5–15) for transhiatal and 17 (range 7–62) for transthoracic MIE are both unacceptably low throughout the MIE literature (Decker et al. 2009).

Considering such enormous differences in the quality of the performance and reporting of surgical radicality, it is not surprising that the nonsurgical literature ignores this problem. No randomized trial on preoperative therapies organized by medical oncologists has bothered to analyze the quality of surgery performed within the trial. Most studies consider surgery as a uniform therapeutic intervention such as a given dose of chemotherapy or radiation. Unaware of the underlying technical complexity, most medical oncologists rather consider poor results of a surgical study arm a failure of surgery itself rather than poor performance by a given surgical team or center. In other words, how could a prospective randomized trial (PRT) on induction chemoradiotherapy potentially be comparable with another similar trial if the surgery performed varies as much as between radical en bloc resection with extensive LND in one study to another study using merely a transhiatal resection without any LND. Most hitherto reported trials on induction chemotherapy or

chemoradiation did hardly report the used surgical criteria and none of these trials reported on potential markers of surgical quality, e.g., the extent of LND, the site, or the numbers of lymph nodes resected. Therefore, any effort to draw conclusions from metaanalysis based on studies of such uncertain and unequal surgical quality becomes meaningless.

Since possible quality variations in an esophagectomy may interfere with the results of both control and investigational treatment modalities, from a quality perspective, the standardization of surgical approaches, extent of resection, extent of LND, definition of an R0 resection, etc. seems crucial before any additional RCT on esophagectomy after induction treatment could allow any meaningful conclusions.

11.6 Use (and Misuse?) of Minimally Invasive Esophagectomy Techniques

Since the first report in 1992 of an esophageal cancer resection using "minimally invasive techniques," i.e., laparoscopy and/or thoracoscopy, this approach has gained a wide acceptance during recent years (Cushieri et al. 1992). In the nineties, the reported complication rates were very high and enthusiasm initially remained low (Decker et al. 2009; Law 2006). Later reports did not really show a spectacular improvement in morbidity, but the terminology of "Minimally invasive esophagectomy" (MIE) suggesting less morbidity seemed to be evidence enough to some that MIE was really less invasive than conventional esophagectomy.

Currently, MIE, without any restriction to a particular technical approach, has been accepted by many cancer organizations and guidelines (NICE, NCCN, etc.) as a valid approach for esophageal cancer resection, despite the fact that not a single comparative trial has been performed and that, up to the end of 2008, not a single retrospective series has ever reported full 5-year survival figures for transhiatal MIE. The few available oncological outcome data stem from Asian and Australasian studies reporting on hybrid techniques using thoracoscopy or minithoracotomy-VATS, together with more or less minilaparotomies for the abdominal stage. In these very experienced hands, the outcome neither seemed to be inferior, nor was there an obvious advantage over open esophagectomy (Yamamoto et al. 2005; Smithers et al. 2007).

For most nonexperts in this field, the large variety of different currently available techniques for MIE, respectively various combinations of available endoscopic techniques (VATS and laparoscopy) with hybrid techniques (minilaparotomy and/or minithoracotomy combined with either laparoscopy or VATS or robotic surgery) has made it very difficult to keep an overview.

Moreover, MIE requires a long learning curve that can only be overcome in centers with huge annual patient volumes (Decker et al. 2009).

Considering this and the fact that today, mortality and morbidity rates of radical transthoracic esophagectomy in experienced centers are not higher than the best currently reported results of MIE, it may not seem wise for most surgeons performing esophageal cancer resections to embrace MIE before any comparative trial has shown its oncological validity.

The most recent literature review on MIE has clearly shown that there is a selection bias favoring early cancers to be submitted to MIE. Favorable case-mix, thus, seems responsible for the apparently similar oncological results of transhiatal and transthoracic MIE series.

Striking is also the fact that the quality of reporting oncological outcome is very poor in most MIE papers (Decker et al. 2009; Law 2006). Only very few centers have reported complete data including 5-year survival results (Yamamoto et al. 2005; Smithers et al. 2007). It may seem characteristic of the poor quality of most papers in this field that some "expert

centers of MIE" have published dozens of scientific papers on MIE, but lacked to ever report mature 5-year survival figures for any of these techniques (Luketich et al. 2003).

Awaiting more data on MIE, these techniques have still to be considered investigative and one has to stay aware of the fact that apparently similar oncological outcome after both approaches may be an effect of patient selection favoring much earlier stage tumors as an indication for MIE. Valid comparisons could only be made by future studies including similar tumor stages for both MIE and conventional esophagectomy.

11.7 Quality of Perioperative Management

Esophagectomy is generally considered a formidable intervention, lengthy with lots of blood loss and a difficult painful postoperative recovery for the patients and a substantial postoperative mortality.

In so far, this perception has among a number of other factors stimulated the development of nonsurgical therapeutic modalities.

However, results published by high volume centers have shown that today postoperative mortality should be below 5% (van Lanschot et al. 2001) and near zero mortality in large series is increasingly reported not to speak about the development of fast track strategies after esophagectomy (Cerfolio et al. 2004).

The introduction of prolonged thoracic epidural analgesia during the eighties has revolutionized substantially postoperative thoracic pain and postoperative pain management resulting in a substantial decrease of pain-related respiratory failure.

But of equal importance are the issues of immediate extubation in the operating room, meticulous attention to immediate pain control, and pulmonary toilet possibly with the help of a minitracheotomy placed at the end of the operation (Low 2007).

Of utmost importance is the management of preoperative fluid administration. Traditionally, fluid administration has been calculated by anesthesiologists on the basis of blood loss, insensible fluid losses, and urine output. This results invariably in patients receiving large intraoperative fluid volumes including blood transfusions, which are now recognized as being a potential cause of cardiopulmonary complications (Holte and Kehlet 2006).

However, several publications have clearly demonstrated that fluid restriction reduces complication rates particularly in pulmonary infection and respiratory failure, the latter resulting in a potentially increased postoperative mortality. Furthermore, surgeons, challenged by the results of videoscopic surgery usually accompanied with minimal blood loss, have adapted their surgical techniques accordingly. Today, esophagectomy is mostly performed with blood loss less than 500 mL, and thus also without a need for transfusion but without compromising the oncologic principles of radical resection and extensive lymphadenectomy. Thanks to modern refined surgical techniques, unexpected episodes of hemodynamic instability can be avoided decreasing the need for large volume of fluid administration. But obviously, in many centers standard fluid therapy is not at all evidence-based (Brandstrup et al. 2003).

Such standardization requires a mutual agreement between surgeons and anesthesiologists (Joshi 2005).

Standardizing clinical care pathways will favorably affect outcome after esophagectomy both in terms of postoperative mortality and morbidity, but possibly also reduce cost (Zehr 1998) and more importantly, even have a beneficial effect on oncologic outcome by less compromising immunoresponse.

11.8 Conclusion

Quality indicators urgently need to be identified or refined by future studies to allow an improvement of the management not only in those centers with suboptimal results, but also in those with good results. Improved quality is needed not only for the surgical procedures, but also for every other aspect of the management of esophageal cancer, starting with the very definition of the cardia and GEJ, the use and interpretation of staging procedures, the patient selection for surgical and nonsurgical treatment options, and finally the performance of the esophageal cancer resection and its perioperative management. Improvements in all of these aspects are possible and could certainly help to further improve the overall outcome of this disease.

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12 Peri-Operative and Complication Management for Adenocarcinoma of the Oesophagus and Oesophagigastric Junction

K. Tobias E. Beckurts

Abstract Surgical resection of oesophageal cancer still offers the only chance of cure for this disease. Nevertheless, oesophageal surgery may be accompanied by relevant mortality and morbidity, the causes of which can be both directly related to surgical technique as well as a large spectrum of non-surgical complications.

In the last few years, improvements in patient selection and technical advances, as well as elaborated peri- and post-operative management, have helped to reduce these threats.The following article adresses important aspects of patient selection and evaluation, pre-operative preparation, anaesthesia, operative prohylaxis of complications, immediate post-operative care and complication management. All these factors are important contribiutions to improve the outcome in this challenging medical condition.

Nowadays, experienced centres report operative mortality rates of around 5% for radical transthoracic resections (Low et al. 2007; Orringer et al. 2007; Ando et al. 2000; Karl et al. 2000; Whooley et al. 2003), down from rates of up to 30 or 40% in previous decades (Earlam and Cunha-Melo 1980). Many factors have contributed to these improvements; some authors claim large volume centres have a tendency to improve results, mostly due to more aggressive management of post-operative complications (Forshaw et al. 2006; van Lanschot et al. 2001; Smith et al. 2008). The following article summarizes the factors that have been identified in the past decades to influence the outcome of major surgery for the resection of adenocarcinoma of the oesophagus.

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12.1 Patient Selection and Evaluation

Patient factors related to peri- and post-operative complications are mainly age and underlying diseases. The later are – among others – chronic pulmonary diseases, vascular disease, hepatic and/or renal dysfunction, psychiatric disorders and metabolic dysfunction.

Many groups have tried to quantify the individual contribution of factors to post-operative outcome, and in some institutions, a standardized evaluation has proven useful to identify and categorize the individual risk factors (Steyerberg et al. 2006; Schröder et al. 2006; Liu et al. 2000; Ra et al. 2008).

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Besides complete oncological staging procedures to rule out distant metastases or locally advanced stage of disease, leaving no chance for curative (R0-)resection, the vital organ functions that may limit the patient's ability to cope with the operative and peri-operative demands have to be evaluated. This includes pulmonary function (minimal requirements: FeV1, vital capacity, O_2-saturation and O_2 partial pressure in the capillary blood), a stress-ECG, serum urea and creatinine values and 24 h-creatinine-clearance, bilirubin, quick-value, albumin, ASAT/ALAT for a rough estimate of kidney and liver function (Saito et al. 1993). If any of these tests reveals pathological findings, further evaluation may be necessary. This is especially important for the hepatic function, as it has been shown that diminished liver function (i.e., cirrhosis) is an independent factor for post-operative morbidity and mortality (Ferri et al. 2006). In patients with suspected liver cirrhosis, even a diagnostic laparoscopy may be justified to confirm this suspected disorder before including such patients in protocols with neo-adjuvant therapy and radical resections. If results of pulmonary evaluation show obstructive disease, brochiodilating medications should be optimized and pulmonary training programmes should be initiated well before the onset of surgery. Arterial hypertension and cardiac arrhythmias should also be addressed prior to surgery, and care should be taken not to discontinue β-blocking medications during the peri-operative period.

12.2 Pre-Operative Preparation

Apart from thorough evaluation and patient selection, the immediate pre-operative patient preparation is not much different from that in any large surgical procedure. If a reconstruction of the alimentary tract is to be performed with the use of large bowel, i.e., colonic interposition, the colon should be prepared by anterograde lavage. The patients' nutritional status should be normal, and in patients with severe weight loss due to dysphagia, an access for pre-operative enteral nutrition should be discussed (transnasal tube or even jejunal catheter) well before surgery. A percutaneous gastric catheter is also a possible option, but great care must be taken during placement to prevent injury of the gastroepiploic arcade along the greater curvature; this could make the later use of the stomach for reconstruction of intestinal passage impossible. The patient should not enter the OR in a status of dehydration to avoid serious hypotension with the need for vasoconstricting medications and massive intraoperative fluid replacement, both of which have negative effect on the outcome of surgery. Electrolyte status should be balanced with special attention to potassium values; a low serum potassium may be a trigger for peri-operative and post-operative cardiac arrhytmias. In some recent publications, a selective bowel decontamination has been used successfully to reduce bacterial contamination of the pulmonary tract (Riedl et al. 2001; Liberati et al. 2004).

12.3 Anaesthesia

A multitude of studies have shown the beneficial effect of peridural thoracic anaesthesia (PDA) for oesophageal surgery, and the use of this method is most likely one of the most important advances in oesophageal surgery in the past decades. The use of PDA has shown to reduce time to extubation, pulmonary complications, time in intensive care unit (ICU), total hospital stay, hospital mortality and total cost of the procedure (Chandrashekar et al. 2003; Rudin et al. 2005; Cense et al. 2006a; Lázár et al. 2003). Post-operative mobilisation and restoration of intestinal function are enhanced in comparison to conventional methods of anaesthesia

and pain relief. The use of systemic opioids has been shown to be reduced in patients with PDA. In addition, the use of PDA has shown to enhance perfusion of the gastric tube in experimental studies, thereby offering potential for a reduction of anastomotic leakage of the oesophago-gastrostomy in the intrathoracic or cervical position (Lázár et al. 2003).

If PDA cannot be realized in a patient, the surgeon should at least support post-operative analgesia by administrating a long-lasting local anaesthetic agent in the pericostal spaces neighbouring the anterolateral thoracotomy. Fluid overload during oesophageal surgery should be avoided in order to reduce pulmonary complications, especially pneumonia (Pennefather 2007; Takashi et al. 2002).

12.4 Operative Prophylaxis of Complications

Of greatest importance for a smooth peri-operative course is the operative procedure itself. The direct operative trauma can be reduced by the use of minimally invasive operation techniques, such as the laparoscopic preparation of the stomach for oesophageal replacement (Benzoni et al. 2007; Aoki et al. 2001; Márton et al. 2005; Luketich et al. 2003; Cense et al. 2006b). If this (laparoscopic) gastrolysis is performed 4–5 days prior to transthoracic oesophageal resection, the operative trauma of the later is reduced to a single-cavity procedure and, in addition, the stomach may benefit from a degree of ischemic preconditioning and collateral perfusion (Schröder et al. 2004; Hoelscher et al. 2007). If the perfusion of the stomach is insufficient for the use as gastric tube, this can be identified with greater certainty due to obvious demarcation after the interval of 4–5 days with reduced gastric perfusion, mainly due to the dissection of the left gastric artery and vein. Another method to reduce the risk of oesophagectomy in high-risk patients may be to perform resection without immediate reconstruction; in this case, the cervical oesophagus is formed into a temporary terminal cervical stoma. After complete clinical reconstitution >10 days after resection, the reconstruction will be performed as a retrosternal transhiatal gastric or colonic pull-up procedure with a cervical anastomosis (Stein et al. 2001).

During radical oesophagectomy, great care has to be taken to avoid a number of "typical" operative mistakes that invariably lead to complicated and possibly fatal post-operative courses (Iannettoni et al. 1995). Examples are the inadvertent severation of the thoracic duct, leading to chylothorax; lesions of the tracheal bifurcation or the thoracic trachea, leading to airway fistulas; dissection of the recurrent laryngeal nerve during lymphadenectomy in the upper mediastinum, leading to uni- or bilateral vocal cord palsy with corresponding pulmonary complications (Leon et al. 2003; Hulscher et al. 1999); vagal denervation of the bronchus and heart, which can be avoided despite radical resections at least in patients with distally located tumours; lesions of visceral pleura and lung parenchyma, leading to post-operative air fistular and pneumothorax and inaccurate reposition of lung lobes, possibly leading to post-operative torsion and pulmonary gangrene. The tracheobronchial system has to be treated with great care to avoid immediate or secondary lesions, which are extremely difficult to manage and are in many cases fatal complications. In adenocarcinoma, the tracheobronchial system is usually not involved by the tumour itself, but care must be taken during the lymphadenectomy on the tracheal bifurcation. When performing an intrathoracic anastomosis, the pre-conditions of anastomotic healing must be kept in mind, i.e., sufficient perfusion and a tension-free anastomotic line (Hoelscher et al. 2003). The use of modern endoluminal stapling devices can also help reduce the rate of anastomotic leakage. During the entire operative procedure, meticulous haemostasis has to be maintained in order to prevent excessive blood loss and post-operative haemorrhage (Law et al. 2004).

12.5 Immediate Post-Operative Care

Post-operatively, patients should be referred to an intensive care unit (ICU) to optimize monitoring and therapy. The beneficial effects of early extubation have been stressed before. A ventilator therapy of more than 3 days is associated with prolonged weaning (Marini 1991). Pain therapy, preferably by PDA and augmented by systemic doses of pain medication as necessary, should allow for early mobilisation and early onset of respiratory training of the patient. Fluid balance should avoid accesses of 500–1,000 mL in the first days following the operation to prevent pulmonary oedema and development of pneumonia. If possible, a bronchoscopy with asservation of a microbiological specimen should be performed immediately after the operation to prevent atelectasis due to secretion retention following single-lung respiration, where the left lung is typically at risk for such retentions. Immediately after the operation and daily for the first 2–3 days following the operative procedure, chest-X-rays are mandatory to rule out dystelectasis, thoracic fluid retention and pneumonia. While there is no place for a general antibiotic prophylaxis (with the exception of a peri-operative single- or dual dose scheme), a broad spectrum antibiotic therapy should be initiated, when pneumonia is suspected (Stippel and Beckurts 2004). If the post-operative weaning period is prolonged, or if a secondary post-operative respiratory failure requires reintubation, the indication for tracheotomy should be discussed timely. Percutaneous dilatation tracheotomy offers a safe and rapid method to create a reliable airway access with optimal conditions for weaning and evacuation of endobronchial secretions (Stippel and Beckurts 2004). The patient's torso should be positioned in a slightly elevated position to prevent reflux and aspiration of gastric content. In case of delayed gastric emptying, the cause of which can be reduced propulsion and/or post-gastric obstruction (pylorospasm due to vagal denervation!), a gastric tube may be necessary to evacuate secretion and allow for tonisation of the gastric remnant. Pylorospasm can be successfully overcome by endoscopic balloon dilatation in the majority of cases a technique that has previously proven usefull in the treatment of dysphagia following antireflux surgery. (Balondilatation pylorus) Gaudric et al (1999). Special attention has to be attributed to post-operative cardiac arrhythmias, the majority of which will present as supraventricular tachyarrhythmia. The incidence of this complication has been reported as high as 50–60% of patients and is often an indicator of technical or septic complications (Murthy et al. 2003; Stippel et al. 2005). Symptomatic tachyarrhytmias can lead to severe impairment of tissue perfusion, and thus, may have a negative effect on anastomotic healing, renal and hepatic function and cerebral perfusion. For the prevention and therapy of this condition, electrolytes have to be optimized (potassium and magnesium), and in many cases additional antiarrhytmic therapy may be warranted. If the application of β-blockers or calcium channel blockers is unsuccessful or contraindicated, amidaron has proven to be a very effective agent to control heart rate and eventually convert patients to a stable sinus rhythm (Stippel et al. 2005; Clemo et al. 1998; Butler et al. 1993; Della Karth et al. 2001). An algorithm for the management of post-operative tachyarrhythmias is outlined in Fig. 12.1.

In the patient population with oesophageal cancer, post-operative cerebral and neurological function may be impaired due to withdrawal symptoms (Spies et al 1996). In cases of post-operative agitation and vegetative decompensation, the continuous application of Clonidine as a central nerve blocker can be beneficial, sometimes in combination with short-acting benzodiazepines (Stippel and Beckurts 2004; Della Karth et al. 2001).

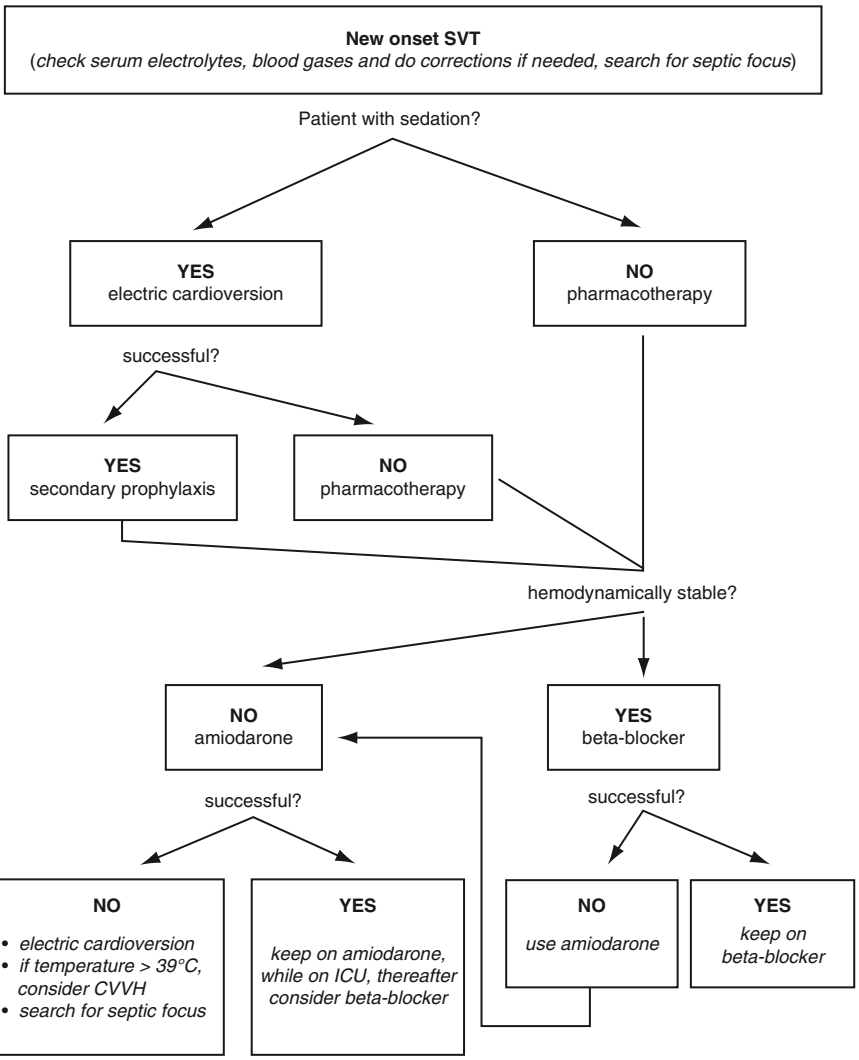

Fig. 12.1 Algorithm for the management of post-operative supraventricular arrhythmias following oesophagectomy

12.6 Surgical Complications

The spectrum of possible surgical complications following oesophagectomy is broad due to the nature of the procedure. One of the most frequent and possibly fatal complications is anastomotic leakage (Siewert et al. 2004; Martin et al. 2005). This is especially threatening in patients with intrathoracic anastomosis, as an untreated early anastomotic leakage will invariably lead to pleuritis and mediastinitis. Thus, every sign of an impaired post-operative recovery should raise doubts in the anastomotic patency and willingly lead to effective diagnostic

measures. If the intrathoracic drain yields intestinal secretions, the diagnosis is usually clear. In less evident cases, an early post-operative endoscopy may be necessary to inspect the anastomotic region and the vitality of the gastric tube or colonic interponate. If the endoscopy is performed carefully and with skill, the diagnostic value far outweighs the potential risk involved concerning the patency of the anastomosis in the early post-operative period (Griffin et al. 2001). If this complication occurs early, i.e., within the first 3–5 days after the operation, and the leak is large or combined with partial necrosis of the interponate, the author strongly suggests immediate operative reintervention by rethoracotomy to achieve control. In favourable cases with early recognition, debridement and drainage of the mediastinum and pleura can be achieved and reanastomosis may be possible and lead to recovery. If the vitality of the interponate is dubious or the local infection far progressed, a discontinuation operation with a cervical oesophagostomy and removal of the gastric tube may be the only way to achieve control of this septic focus (Siewert et al. 2004). If the symptoms of anastomotic insufficiency occur late and the signs of general sepsis and inflammation are controlled, an anastomotic leakage may, in selective cases, be treated by the application of an endoluminal stent; this interventional therapy has gained significant attention in the past years and has helped to reduce the morbidity and mortality of anastomotic complications (Roy-Choudhury et al. 2001; Alanezi and Urschel 2004; Johnsson et al. 2005; Kauer et al. 2008; Tuebergen et al. 2008). In patients with cervical anastomosis, anastomotic leakage is generally less catastrophic if diagnosed and treated timely and can usually be managed by local measures such as wound opening and drainage; in some cases results can be improved with the use of T-drains or local vacuum techniques (VAC). Unfortunately, late anastomotic strictures will frequently follow anastomotic leakages which have been managed by secondary healing alone (Hünerbein et al. 2004).

Consistently active secretion of thoracic drains with volumes of greater 500–1,000 mL/day may be an indicator of a leakage of the thoracic duct. In some cases, conservative treatment with total parenteral nutrition and prolonged drainage of the pleural cavity may lead to success. If the secretion persists, an operative reintervention with identification of the leak can be advocated. In such cases, it has proven useful to administer a small volume (100 mL) of full cream to the patient's intestinal tract to induce chylomicrons, which will lead to an increased flow of easily identifiable chylos from the leak and thus allow for a precise ligature of the structure.

The post-operative development of a pneumothorax and/or tissue emphysema can be diagnostic of a parenchymal lesion of the lung, or worse, a defect of the tracheobronchial system. While a parenchymal fistula of the lung can usually be managed by sufficient drainage of the chest (including the application of suction, if needed to fully expand the lung), the treatment of a defect in the tracheobronchial wall is much more difficult. Possible treatment methods include operative reintervention with suture of the defect followed by the application of a muscle flap, or in some case an omental flap; nevertheless, chance of healing is minimal, if the patient requires continuous positive pressure ventilation. In some cases, an endoluminal stent (Y-stent, if the lesion is located near or in the bifurcation) may offer a chance to seal the defect. Until today, this complication has a high overall mortality, and hence, great care must be taken to avoid aggressive operative manipulation of the tracheobronchial system during tumour removal.

12.7 Management of Pulmonary Complications

A number of factors put patients with transthoracic oesophageal resections at high risk for the development of pulmonary complications.

These are, among others, pre-existing pulmonary disease and nicotine abuse, prolonged single-lung ventilation during the operative procedure, potential damage to lung parenchyma during the operation, reduced mucociliar clearance, compromised immunocompetence due to the operative trauma, in many cases aggravated by alcohol abuse and neoadjuvant chemotherapy. In addition, delayed emptying of the gastric tube and temporary or permanent damage to the vagus/recurrent laryngeal nerves may lead to aspiration pneumonia. Pleural fluid collections can induce compression atelectasis (Nishi et al. 1988; Mao et al. 2005). One-lung ventilation leads to microbarotrauma of the ventilated dependant lung, in addition to the negative effects of elevated intraoperative oxygen concentrations (Tandon et al. 2001; Lodato 1994). The measures to overcome pulmonary complications include peri-operative fluid restriction and early extubation, which has proven to be beneficial in the majority of published results (Caldwell et al. 1993; Lanuti et al. 2006). After extensive operative trauma, i.e., one-stage abdominothoracic oesophagectomy, a post-operative ventilatory support may be of benefit at least for subgroups with increased risk of secondary pulmonary decompensation (Bartels et al. 1998). If prolonged ventilation is necessary, care should be taken to avoid baratrauma by the use of pressure-controlled low tidal volume respiration (Anon 2000). Pulmonary recruitment can be achieved by intermittent high-PEEP ventilation or Lachman manoeuvres. In cases with hypostatic dorsal atelectasis, temporary prone positioning of the patient can help to improve pulmonary gas exchange (Gattinoni et al. 2001). In cases of prolonged weaning >8 days or other factors prohibiting safe early extubation, the decision to perform a temporary tracheostomy should be discussed liberally. The technique of percutaneous dilatational tracheotomy offers a quick and safe way to achieve a secure airway access.

The use of low-dose corticosteroids has been shown to reduce the rate of pulmonary complications in a recent study (Nakamura et al. 2008). Other groups have tried to improve the patients' immunocompetency by the peri-operative application of GCSF. Even though granulocyte counts were significantly enhanced by this medication, a beneficial effect on the incidence and outcome of pulmonary complications could not be demonstrated (Schäfer et al. 2004).

12.8 Postoperative Nutrition

In general, oral food intake should be postponed for 6–8 days following esophageal resection to allow for anastromotic healing. During this period, balanced parenteral nutrition should be provided. In patiens with severe malnutrition or in cases of prolonged recovery phases, early enteral nutrition administered via a jejunal feeding tube has proven beneficial (Aiko et al 2001, Baigrie et al 1996, Page et al. 2002,Watters et al. 1997). The operative placement of feeding catheters has been previously advocated (Wakefield et al. 1995), but serious complications of this procedure have been reported (Han-Geurts et al 2004). In our institution, we favour the use of transnasal feeding tubes placed into the proximal Jejunum under endoscopic guidance. These tubes are usually well tolerated and can be used for supplementary nutrition even after the active oral food intake has commenced.

12.9 Summary

In conclusion, oesophagectomy remains a challenging procedure both for the patient and the surgeon. Patient selection and evaluation aim at preventing individuals unfit for surgery or without chance of cure from this operation. The use of modern operative techniques and, in some

cases, sequential strategies help reduce the operative trauma. Regional anaesthesia, such as PDA, and an individualized concept of peri-operative pain treatment, early extubation, fluid restriction, mobilisation and physiotherapeutic assistance aim at the prevention of pulmonary complications, one of the dominant threats to this patient population. Rapid recognition and aggressive diagnostic work-up of any complication, especially anastomotic leaks, in the post-operative period are essential to prevent an uncontrolled progression of pathophysiologic cascades. A close multidisciplinary cooperation of surgeons, anaesthetists, endoscopists, radiologists and other associated disciplines is essential to further reduce the peri-operative morbidity and mortality in this demanding surgical procedure.

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13 Multimodality Therapy for Adenocarcinoma of the Esophagus, Gastric Cardia, and Upper Gastric Third

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Abstract There is considerable controversy over the level of recommendations from randomized trials underpinning management decisions for patients presenting with localized adenocarcinoma of the esophagus and esophagogastric junction. Despite a paucity of Level 1 recommendations compared with other gastrointestinal sites, in particular rectal cancer, there is an emerging consensus in practice to consider multimodal approaches in all cases that present with T3 or node-positive disease. There is also an optimism that new approaches, including response prediction based on sequential ^{18}FDG-PET scanning following induction chemotherapy, and novel drugs targeted at EGF, EGFR, VEGF, and tyrosine kinase inhibition may improve treatment pathways and outcomes. In this review, we assess the level of recommendations from the major published trials and discuss new trials and approaches.

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13.1 Introduction

Adenocarcinoma of the lower esophagus and esophagastric junction (EGJ) has markedly increased in the West over 20–30 years, with a corresponding reduction in squamous cell carcinoma (Daly 2000; Blot et al. 1991). Esophageal and junctional tumors are often advanced at presentation. The 5-year survival overall is between 10–20 and 35–50% for resectable localized disease (Portale et al. 2006). The classification of tumors at this site has been greatly enhanced by the topographical classification advanced by Siewert and colleagues (Siewert and Stein 1998; Siewert et al. 2000), with adenocarcinoma of the esophagogastric junction (AEG) divided into true esophageal, arising from Barrett esophagus (AEG 1), true cardia (AEG II), and subcardia (AEG III), with cardia and subcardiac tumors being predominantly of gastric histiogenesis. Several advances in standards of care have emerged in recent years that have improved management. First, comprehensive staging with CT, endoscopic ultrasound (EUS), and ^{18}FDG-PET imaging and the judicious use of laparoscopy permit improved selection of patients for curative approaches and avoid surgery for purely palliative intent. Second, unassailable evidence supports the case

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for esophagectomy to be performed in high-volume hospitals by high-volume surgeons, and policies underpinning reform have taken place in many countries through action from third-party payers, government, and the profession itself (Enzinger and Mayer 2003; Birkmeyer et al. 2002). Third, palliation of esophageal cancer has been simplified and made safer with the advent of self-expandable metal endoprostheses. Finally, neoadjuvant and adjuvant therapies are considered in most centers for patients with localized esophageal adenocarcinoma and, although controversial, subgroups of patients may benefit from this approach (Enzinger and Mayer 2003; Fiorica et al. 2004). The broad principles underpinning achieving optimum outcomes in adenocarcinoma at these sites are developed in other chapters in this book, and this article focuses exclusively on the evidence and controversies relating to neoadjuvant and adjuvant multimodality protocols, and the promise of novel approaches.

13.2 Multimodal Therapy

In a review of esophageal cancer published in the New England Journal of Medicine in 2003, the authors conclude that "despite the widespread use of preoperative chemotherapy and radiotherapy, there remains no proof of principle that this strategy is effective in patients with esophageal cancer" (Enzinger and Mayer 2003). From a rigorous academic assessment of existing trials, this interpretation cannot be criticized, and no trial has been published since 2003 that would alter this conclusion. In fact, no randomized trial has been conducted in patients with adenocarcinoma of the esophagus and junction that is adequately powered exclusive to this pathology or tumor site. Notwithstanding this analysis, the reality is that mutimodality approaches have steadily supplanted surgery-alone as the standard approach to adenocarcinoma at these sites. This relates to several factors, including a strong theoretical rationale due to high relapse rates following surgical resection alone Wayman et al. 2002), the evidence from the similar management paradigm of rectal cancer where multimodal approaches are the established standard of care for locally advanced disease, the evidence-base support from a few key randomized trials and meta-analysis, and the outcomes achieved with patients who have an excellent clinical, metabolic, or histomorphologic response to neoadjuvant therapy.

13.3 The Evidence-Base for Neoadjuvant and Adjuvant Approaches

13.3.1 Neoadjuvant Chemotherapy

There are three key studies (Table 13.1). An appropriately powered Phase III randomized study of 467 North American patients (US Intergroup 0113) with esophageal adenocarcinoma ($n=236$ esophageal or junctional) or squamous cell cancer showed no benefit from pre and postoperative combination 5-FU and cisplatin, with a 2-year survival of 35% in the combination group compared with 37% in the surgery-alone group, and a median survival of 15 and 16 months, respectively (Kelsen et al. 1998). A complete pathological response was observed in 2.5% of cases. A similar study of 802 patients conducted by the Medical Research Council (OEO2), which randomized patients to 2 cycles of preoperative ciplatin and 5-FU vs. surgery-alone, was powered to detect a 10% increase in 2-year survival from 20 to 30%. This trial reported a significantly improved survival at 2 years (43 vs. 34%) in the combined modality group, and a median survival of 16.8 vs. 13.3 months (MRC Group 2002). The principal

Table 13.1 Randomized trials of neoadjuvant chemotherapy vs. surgery

References	Chemotherapy regimen	Tumor type	Sample size	Primary outcome
Cunningham et al. (2006)	3 Cycles: cisplatin, 5-fluorouracil (5-FU), epirubicin	Adenocarcinoma	503[a]	Prolonged survival in chemotherapy arm at 5 years
Kelsen et al. (1998)	3 Cycles: cisplatin, 5-fluorouracil	SCC and adenocarcinoma	467	No difference in overall survival
MRC (2002)	2 Cycles: cisplatin, 5-fluorouracil	SCC and adenocarcinoma	802	Prolonged survival in chemotherapy arm at 2 years

[a]Fourteen percent of 503 had tumors of the lower oesophagus

differences between the Intergroup and MRC study was that the total preoperative chemotherapy administered was greater in the Intergroup trial, there was a longer delay to surgery (median 93 vs. 63 days), and the median survival in the surgery-alone arm was improved (16 vs. 13 months). Notwithstanding the different outcomes in both studies, in the U.K. neoadjuvant chemotherapy is accepted as standard of care. In the U.K., the OEO5 study following on from the OEO2 study has been activated; it has a target accrual of 1,300 patients in a patient cohort of resectable adenocarcinoma of the esophagus and junction (AEG I and AEG II), and compares preoperative cisplatin and fluorouracil (2 cycles) with epirubicin, cisplatin, and capecitabine (ECX; 4 cycles).

The recent findings of the Medical Research Council Adjuvant Gastric Infusional Chemotherapy (MAGIC) trial provide further support for proponents of neoadjuvant chemotherapy (Cunningham et al. 2006). This phase III trial randomly assigned patients with resectable adenocarcinoma of the stomach, esophagogastric junction, or lower esophagus to either perioperative chemotherapy and surgery (250 patients) or surgery-alone (253 patients). Chemotherapy consisted of three preoperative and three postoperative cycles of intravenous epirubicin and cisplatin and a continuous intravenous infusion of 5-FU (ECF). Postoperative morbidity and 30-day mortality did not differ between the two arms (46 vs. 45% and 5.6 vs. 5.9%, respectively). Compared with patients receiving surgery-alone, the patients on the trial regimen had significantly improved overall ($p=0.009$) and progression-free survivals ($p<0.001$). The 5-year survival rate was 36% for combined modality therapy compared with 23% for patients with surgery-alone ($p=0.008$ log-rank test), a hazards ratio of 0.75 corresponding to a 25% relative reduction in the risk of death. The toxicity profile was acceptable, and less than 12% of patients had Grade 3 or 4 toxicity. In the MAGIC trial approximately 75% of patients had gastric tumors, 14% had tumors of the lower esophagus, and 11% had junctional tumors. The effect was consistent for each site, with a hazards ratio of 0.81, 0.44, and 0.75 for gastric, junction, and esophageal, respectively. The principle of neoadjuvant therapy is supported by MAGIC, but the trial was not powered to address junctional and esophageal adenocarcinoma, and therefore, no Level 1 evidence is provided for tumors at these sites. Nonetheless, the MAGIC trial is a high quality study and does provide a compelling rationale for considering neoadjuvant chemotherapy for gastric adenocarcinoma including junctional tumors of gastric origin (AEG II and AEG III). In the U.K, the MAGIC B trial is currently recruiting and compares 6 cycles (3 pre and 3-postoperative), cycles of

ECX with ECX combined with bevacizumab in patients with operable gastric and junctional (AEG III) tumors. Of note, the oral fluoropyrimidine capecitabine (X) and oxaloplatin are increasingly replacing fluorouracil and cisplatin, respectively, in new clinical trials, and recently Cunningham and colleagues in the National Cancer Research Institute of the United Kingdom proved in a random assignment study of over a thousand patients with advanced esophagogastic cancer that this new combination was not inferior to the previous standard, and that the toxicity of oxaloplatin was less than cisplatin (Cunningham et al. 2008).

The use of ^{18}FDG-PET as a marker of tumor responsiveness to induction chemotherapy is a novel approach developed principally by Siewert and colleagues in Munich. In preliminary studies a decrease in the standardized uptake value of ^{18}FDG after 2 weeks of chemotherapy was evident in patients who went on to achieve a significant histomorphologic response (Weber et al. 2001; Ott et al. 2006). These studies paved the way for the MUNICON (metabolic response evaluation for individualization of neoadjuvant chemotherapy in esophageal and esophagogastric adenocarcinoma) phase II study (Lordick et al. 2007). In this prospective single-centre trial, 119 patients with locally advanced adenocarcinoma of the distal esophagus and junction were assigned to 2 weeks of cisplatin and 5-FU and a second PET scan was performed. Those with decreases in ^{18}FDG avidity, predefined as decreases of 35% or more at the end of the evaluation period, were defined as metabolic responders. Responders continued to receive neoadjuvant chemotherapy for 12 weeks and then proceeded to surgery. Metabolic nonresponders discontinued chemotherapy after the 2-week evaluation period and proceeded to surgery. One hundred and ten patients were evaluable, of whom 49% were classified as metabolic responders. One hundred and four patients had tumor resection (50 in the responder group and 54 in the nonresponder group). After a median follow-up of 2.3 years, the median overall survival was not reached in metabolic responders, whereas median overall survival was 25.8 months in nonresponders ($p=0.015$). The median event-free survival was 29.7 months in metabolic responders and 14.1 months in nonresponders ($p=0.002$). A major histopathological response defined as less than 10% residual tumor cells in the resected specimen was noted in 58% of the metabolic responders, but no histopathological response was seen in metabolic nonresponders. This is an important study as it is the first clinical trial to incorporate early response evaluation to neoadjuvant chemotherapy as measured by ^{18}FDG-PET into a treatment algorithm.

13.3.2 Neoadjuvant Chemoradiotherapy (Table 13.2)

The interpretation of trials of combination chemotherapy and radiation therapy prior to surgery and meta-analysis is more difficult compared with trials using chemotherapy alone for several reasons. Only one trial, a negative study, appears adequately powered with over 200 patients (Burmeister et al. 2005); there is a mix of pathologic types, adenocarcinoma, and squamous cell cancer in most studies, and the total dose of radiation therapy administered, and treatment fractions, is different across trials.

There are two positive studies. The Dublin trial, performed at this center between 1990 and 1995 in patients with adenocarcinoma of the esophagus ($n=75$) and cardia ($n=39$), randomized to preoperative cisplatin and fluorouracil in combination with 40 Gy (15 fractions) prior to surgery or surgery-alone (Walsh et al. 1996). Median survival was 16 vs. 11 months ($p=0.01$), the 3-year survival was 32 vs. 6% ($p=-0.01$), and 42% compared with 82% had pathological nodal involvement ($p<0.0001$) in multimodality compared with surgery-only cohorts, respectively ($p=0.01$). The interpretation of the trial may be

Table 13.2 Randomized trials of neoadjuvant chemoradiotherapy vs. surgery

References	Chemotherapy regimen	Radiotherapy regimen	Concurrent or sequential	Tumor type	Sample size	Outcome
Burmeister et al. (2005)	1 Cycle: cisplatin, 5-FU	35, 2.3 Gy/fraction	Concurrent	SCC and adenocarcinoma	256	ns
Tepper et al. (2008)	2 Cycles: cisplatin, 5-FU	50.4, 1.8 Gy/fraction	Concurrent	SCC and adenocarcinoma	56	$p<0.05$
Urba et al. (2001)	2 Cycles: cisplatin, 5-FU, vinblastine	45, 1.5 Gy/fraction	Concurrent	SCC and adenocarcinoma	100	ns
Walsh et al. (1996)*	2 Cycles: cisplatin, 5-FU	40, 2.7 Gy/fraction	Concurrent	Adenocarcinoma	113	$p<0.05$

compromised by relatively small numbers, limited cross-sectional imaging in pretreatment staging, and an outcome in the surgery-alone arm (6% 3-year survival) below standard benchmarks (Walsh et al. 1996). The lack of T or N staging prerandomization in combination with an absence of strict pathologic quality assurance with respect to R classification suggests that the poor outcomes in the surgery-only arm relate to the inclusion of many patients in the trial who had palliative resection, cohorts that would now be excluded from the design of randomized trials for localized disease. The second positive Phase III study (CALBG 9781) recruited 56 patients of a planned 475 before closing due to poor accrual. Patients were randomized to surgery-only or cisplatin, fluorouracil, and radiation therapy (50.4 Gy; 1.8 Gy/fraction). The intent to treat analysis showed a median survival of 4.48 vs. 1.79 years favoring the treated group, with a 5-year survival of 39 vs. 16% (Tepper et al. 2008).

Notwithstanding the relatively tenuous data from which it is drawn, these trials as well as meta-analysis (Fiorica et al. 2004) have resulted in widespread adoption of combination chemotherapy and radiation therapy, particularly in the United States. The Patterns of Care studies from the United States showed that multimodal therapy increased from 10.4% during 1992–1994, to 26.6% in 1996–1999 (Suntharalingam et al. 1999). Apart from the above phase III trials, some outcome indicators from negative trials provide proxy support for this approach. In an adequately powered Australasian, both the R0 resection rate (80 vs. 59%) and node negativity (67 vs. 43%) were significantly better in the multimodal vs. surgery-alone group (Burmeister et al. 2005). In the University of Michigan trial of 100 patients (Urba et al. 2001), which was powered to detect a large increase in median survival, the overall survival was 30% at 3 years in the treated (CF and vinblastine; 45 Gy/1.5 Gy fractions) arm compared with the surgery-alone (16%) cohort ($p = 0.15$).

The surrogate target of a complete or major pathological response is achieved by neoadjuvant chemoradiation in approximately 20–30% of traditional regimens. Where major tumor regression is achieved, this translated into an approximate 50% chance of cure (Geh et al. 2001; Reynolds et al. 2007; Gebski et al. 2007), and the attainment of such a response, as well as high R0 resection rates, is undoubtedly a factor in the increasing use of multimodal regimens. In this latter regard,

new approaches to increase the complete pathological response rate would appear to have a sound rationale. The addition of paclitaxel to cisplatin and fluorouracil-based regimens have increased pCR rates, but may result in significant toxicity. A recent study using a paclitaxel, carboplatin, and fluorouracil chemoradiotherapy regimen in patients with stage II and III disease but with a reduced paclitaxel dose demonstrated acceptable toxicity along with a complete pathological response rate of 38% and R0 resection rate of 96% (van de Schoot et al. 2008).

Finally, the increasing use of chemoradiotherapy prior to surgery is also supported by the increasing acceptance of a multimodal approach for other cancers, in particular rectal cancer (Sauer et al. 2004; Habr-Gama et al. 2004). Surgical and pathological quality assurance, as well as uniform definition, have been applied in the major rectal cancer trials and convincing conclusions reached from large studies, and it can be argued that the improvement in local control in the best rectal trials from preoperative therapy provides a logic to applying the same principle in the similar paradigm of locally advanced esophageal cancer.

A caveat with respect to the multimodal approach relates to the potential for increased operative risks. A large randomized trial in patient with esophageal squamous cell cancer was stopped because of increased postoperative mortality in the multimodal arm (Bosset et al. 1997). Meta-analysis of phase III trials has also confirmed increased postoperative mortality (Fiorica et al. 2004), and this unit and others have reported increased major postoperative respiratory morbidity in patients on multimodal protocols compared with case-matched controls undergoing surgery-only (Reynolds et al. 2006; Lee et al. 2003).

13.3.3 Postoperative Combination Therapy

The Intergroup Study 0116 (INT 0116; Macdonald et al. 2001) enrolled 556 patients with pathological stage IB through IV M0 and R0 resection gastric and junctional adenocarcinoma, and randomly assigned to surgery-alone or postoperative chemoradiation (fluorouracil and leucovorin plus external beam radiation (45 Gy/1.8 Gy/days × 5 weeks) delivered to the site of the gastric resection and the areas of draining lymph nodes). These patients were at significant risk of relapse as 85% had lymph node metastases and 65% had stage T3 or T4 tumors. Approximately 20% of patients had proximal gastric tumors. Median survival in the surgery-only and chemoradiation groups was 27 and 36 months, respectively ($p = 0.005$ by the log-rank tests; the corresponding figures for disease-free survival were 19 and 30 months ($p < 0.001$). Although a positive trial, with a hazards ratio of 0.75 for improvement with the combination regimens, equivalent to what was observed in the MAGIC trial, a number of cautionary messages emerge from this trial that merit emphasis. First, 64% of randomized patients completed the post-operative regimen, 17% stopped due to toxicity, and Grade 3 or greater hematological toxicity occurred in 54% of patients. Overall Grade 3 toxicity occurred in 41% of patients and Grade 4 in 32%, with 3 deaths from toxicity (1%). Second, although an extensive lymphadenectomy (D2) was recommended, this was performed in only 10% of patients, with a D1 dissection in 36% and an D0 lymphadenectomy in 54% of patients. Finally, akin to the MAGIC trial, the study was not powered to address the question with respect to junctional tumors. Nonetheless, it does provide support for this approach in patients who have had initial surgery and are shown to have node-positive disease or adverse pathologic features such as poor differentiation and vascular or lymphatic invasion in the primary tumor.

13.4 New Combinations and Novel Agents

Recent advances in molecular biology have led to a better understanding of the molecular pathways involved in the development and progression

of esophageal and junctional adenocarcinoma. Elucidation of these pathways has led to the development of targeted therapies that can potentially inhibit or reverse the progression of disease, and this has resulted in the design of novel clinical trials (Peters and Fitzgerald 2007). The epidermal growth factor receptor (ErbB1 or EGFR) and the ErbB2 (HER2/neu) receptor represent the two main members of the tyrosine kinase type ErbB-receptor family. EGFR overexpression occurs in esophageal adenocarcinoma and is associated with a poor prognosis. Cetuximab is an anti-EGFR monoclonal antibody, which has been approved for the treatment of metastatic colorectal cancer and advanced squamous cell cancer of the head and neck (Cunningham et al. 2004). A phase II study to determine the feasibility and toxicity of the addition of cetuximab with paclitaxel, carboplatin, and radiation for locally advanced esophageal cancer demonstrated that cetuximab can be safely administered with concurrent chemoradiation with a complete clinical response rate of 70% (Safran et al. 2008). While dermatologic toxicity and hypersensitivity reactions were associated with the addition of cetuximab, there was no increase in radiation-enhanced toxicity.

Erlotinib (Tarceva) and Gefitinib (Iressa) are orally active selective reversible inhibitors of EGFR tyrosine kinase. A recent phase II study of gefitinib monotherapy in advanced esophageal adenocarcinoma demonstrated an overall clinical response rate of 11% and associated toxicities were mild (Ferry et al. 2007).

Vascular endothelial growth factor (VEGF) is the most potent of the endothelial growth factors and is central to angiogenesis. Direct VEGF stimulation of cancer cells results in tumor cell proliferation, increased survival, and migration. VEGF is overexpressed in 30–60% of esophageal cancer specimens, and overexpression of VEGF is associated with poor outcomes in patients undergoing curative resections (Kleespies et al. 2004). Bevacizumab (Avastin) is a recombinant humanized monoclonal antibody that binds to all isoforms of human VEGF, thereby neutralizing VEGF and inhibiting its angiogenic activity (Presta et al. 1997). The multicentre phase II trial of bevacizumab, irinotecan, and cisplatin in metastatic gastric and GEJ adenocarcinoma patients demonstrated an overall response rate of 65% and that the median time to disease progression was improved over historical controls by 75% (Shah et al. 2006). As mentioned previously, Bevacizumab in combination with ECX is being compared with ECX alone in the MAGIC B trial of patients with gastric and AEG III adenocarcinoma.

Most targeted studies to date have been in patients with advanced or metastatic disease. For adjuvant studies, the incorporation of anti-EGFR and anti-VEGF monoclonal antibody therapies (Table 13.3) and EGFR tyrosine kinase inhibitors (Table 13.4) into multimodal therapies for resectable esophageal and junctional cancer is ongoing and results from these phase II trials are eagerly awaited and will form the basis for phase III studies.

13.5 Conclusions

The specific title of this article relates to multimodal management of adenocarcinoma of the esophagus, junction, and proximal stomach, and it is unassailable from the literature that the evidence-base is not underpinned by Grade A recommendations for this pathologic type and these locations. Moreover, the lack of standardization in surgery and radiation therapy and the relative rarity of the tumor make it difficult to conduct definitive trials that may require over a thousand patients, akin to rectal cancer trials. Outside clinical trials, a pragmatic approach is therefore adopted in most specialist units that is based on risk assessment, accurate staging, an adherence to the fundamental principles of cancer surgery, and a reasonable interpretation of the evidence-base from neoadjuvant and adjuvant studies.

In this unit, a multimodal approach is offered to patients who have locally advanced

Table 13.3 Ongoing and planned trials of cetuximab and bevacizumab in resectable esophageal cancer

Trial identifier	Phase	Intervention	Planned sample size	Trial eligibility	Trial start date	Scheduled follow-up (years)	Trial close	Primary outcome
NCT00165490	II	Cetuximab plus chemoradiotherapy and surgery	39	Resectable esophageal cancer	June 2004	3	2009	Response to the combination of cetuximab, cisplatin, irinotecan, and radiation therapy
NCT00551759	II	Cetuximab plus chemoradiotherapy and surgery	42	resectable adenocarcinoma of esophagus or junction	October 2007	3–5	2009	Complete pathological response rate
NCT00445861	I/II	Cetuximab plus chemoradiotherapy and surgery	27	Resectable locally advanced esophageal cancer	January 2007	3	2009	Limiting toxicity of radiotherapy in combination with chemoimmunotherapy
NCT00544362	II	Cetuximab plus chemoradiotherapy and surgery	45	Resectable carcinoma of thoracic oesophagus	July 2007	2		Complete pathological response rate
NCT00354679	II	Bevacizumab plus chemoradiotherapy and surgery	33	Locally advanced esophageal adenocarcinoma	April 2006	3	April 2009	Safety and toxicity
NCT00450203	II/III	Bevacizumab plus chemotherapy vs. chemotherapy alone	1100	Operable adenocarcinoma of stomach and GEJ	Not yet recruiting			Safety, efficacy, and overall survival

Table 13.4 Ongoing trials of EGFR tyrosine kinase inhibitors in resectable esophageal and junction cancer

Trial identifier	Phase	Intervention	Planned sample size	Trial eligibility	Trial start date	Scheduled follow-up (years)	Trial close	Primary outcome
NCT00499564	II	Erlotinib plus chemoradiotherapy and surgery	64	T2-4, N1, Squamous or adenocarcinoma of esophagus	April 2007	2	April 2009	Pathological complete response
NCT00493025	II	Gefitinib plus chemoradiotherapy and surgery	36	Operable adenocarcinoma of the esophagus	April 2005	5	June 2008	Pathological complete response
NCT00258323	II	Gefitinib plus chemoradiotherapy before and after surgery	80	Advanced esophageal or GEJ cancer	October 2005	5		Survival at 1 year; distant metastatic control at 1 year
NCT00290719	I/II	Gefitinib plus chemoradiotherapy before surgery	20	Resectable esophageal cancer	November 2005		July 2008	Complete and partial pathological response
NCT00100945	II	Gefitinib posttherapy with curative intent	72	Locally advanced esophageal cancer	July 2005	5		1-Year overall survival rate

adenocarcinoma of the esophagus or AEG 1 junctional tumors. Patients must have excellent physiological reserve and are advised of the increased operative risks that we and others have observed (Reynolds et al. 2006; Bosset et al. 1997). In our experience, and in contrast to the experience with induction chemotherapy and the MUNICON trial, sequential ^{18}FDG-PET scanning is not helpful to identify early responders after induction chemoradiation, possibly because of the early inflammatory response to radiation therapy (Gillham et al. 2006).

For adenocarcinoma of the cardia (AEG II) or subcardia (AEG III), our view, consistent with that of the Munich group, is that the majority of these are of gastric origin. Since the publication of the MAGIC trial, this regimen is now considered in all patients except predicted T1-2 N0 cases. We had previously used the Macdonald regimen of combination chemoradiation postoperatively in this scenario, but now this is preserved for patients who have had surgery initially, and pathology reveals node positively or adverse features. The surgical preference is increasingly a radical total gastrectomy, D2 lymphadenectomy, and distal esophagectomy, rather than a proximal gastrectomy. Preoperative radiation has not been considered previously because of the risk of radiation damage to the gastric conduit, but the shift in surgical preference makes this potentially feasible to study within future trials.

In the next decade, the results of several clinical trials may clarify some matters and hopefully improved outcomes. A collaborative group in the Netherlands is comparing neoadjuvant chemoradiation and surgery-alone in esophageal adenocarcinoma in an adequately powered study. In the U.K., the OEO5 study and the MAGIC B trial will be of interest, and the evaluation of targeted therapy in phase II and III trials may uncover effective strategies that may increase complete or major pathological response rates. Finally, we should be cautiously optimistic that the explosion of knowledge in genomics, proteomics, and transciptiomics, along with the use of functional imaging, may allow pretreatment or early posttreatment response prediction of response to induction therapy, so that new trials and treatments may be developed based on a better understanding of the biological behavior of the tumor.

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14 Metabolic Response Evaluation by PET During Neoadjuvant Treatment for Adenocarcinoma of the Esophagus and Esophagogastric Junction

A. Sendler

Abstract Following several randomized trials, neoadjuvant therapy in adenocarcinoma of esophagus and the esophagogastric junction can be seen as an international standard. However, in a large proportion of patients the objective response achieved is unsatisfactory. These patients do not benefit from neoadjuvant therapy, but do suffer from toxic side effects; sometimes progressive and appropriate surgical therapy is delayed. For this reason, a diagnostic test that can accurately assess tumor response to neoadjuvant therapy might be of crucial importance. Response evaluation using CT scan, endoluminal ultrasound, or rebiopsy is not reliable. In recent times, response evaluation using 18FGD PET after and during neoadjuvant treatment is in the focus of clinical and scientific interest. Most studies have evaluated the diagnostic modalities for response to neoadjuvant treatment after completion of the treatment. Following the published data so far, FDG-PET seems to be less accurate after and during chemoradlatlon than after chemotherapy alone. The data of early response evaluation (14 days after the onset of chemotherapy) are very much encouraging; however, they have to be evaluated in an international randomized trial. Standardization of PET technology as well as defining the thresholds used for the estimation of early response is mandatory. So far, FDG-PET does not change treatment In esophageal and gastric cancer.

Despite progress in the operative and perioperative care for patients with adenocarcinoma of the esophagus and esophagogastric junction (so-called Siewert Type I–III tumors), the prognosis of these patients is still dismal. The overall 5-year survival rates in most studies do not exceed 20% (Daly et al. 2000; Stein et al. 2000). Most patients present with advanced disease and are unsuitable for curative resection. The ongoing failure to improve survival by surgery alone has led to increasing interest in the role of neoadjuvant or perioperative treatment in these tumors. In squamous cell carcinoma (SCC) of the esophagus neoadjuvant chemoradiation is mostly used, sometimes preceded by induction chemotherapy (Stahl et al. 2005a, b). In adenocarcinoma of the esophagus and in adenocarcinoma of the esophagogastric junction as well perioperative (neoadjuvant) chemotherapy and neoadjuvant chemoradiation are used in a large variety (Ajani et al. 2001, 2007; Gebski et al. 2007; Lordick et al. 2007b). These various preoperative treatment modalities make the judgment of the value of preoperative positron emission tomography (PET) difficult.

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The rational of the preoperative treatment is to treat potential micrometases while downsizing the primary tumor and to increase the chance of curative resection. Furthermore, this approach offers a kind of an in vivo testing of the chemotherapy regimens used (Sendler and Siewert 2003).

Patients who have a significant histopathological response to neoadjuvant treatment have improved survival when compared to nonresponding patients and to patients having surgery alone (Lowy et al. 1999; Siewert et al. 2007b). Three randomized controlled trials have investigated perioperative chemotherapy in patients with esophageal and gastric cancer; the results demonstrate a 5-year survival benefit of about 14% for the perioperative therapy (Boige et al. 2007; Cunningham et al. 2006; Medical Research Council Oesophageal Cancer Working Party 2002). Following these trials, neoadjuvant therapy in adenocarcinoma of the esophagogastric junction can be seen as an international standard.

However, in a large proportion of patients (about 40–60%) the objective response achieved is unsatisfactory. These patients do not benefit from neoadjuvant therapy but do suffer from toxic side effects, sometimes progressive disease (about 5–8% of patients), and appropriate surgical therapy is delayed. For this reason, a diagnostic test that can accurately assess tumor response to neoadjuvant therapy is of crucial importance (Siewert et al. 2007a). Moreover, a noninvasive test that can predict tumor response early in the course of multimodal therapy may distinguish responders from nonresponders, thereby allowing discontinuation of the ineffective treatment in the latter (Ott et al. 2006a). This may allow a change of the preoperative treatment, e.g., from chemotherapy to chemoradiation, or the possibility of immediate salvage surgery, thus ameliorating the prognosis of even these primarily nonresponding patients.

There is currently no universally accepted, reproducible, and reliable means of monitoring the response of adenocarcinoma of the esophagogastric junction to chemotherapy as well as to chemoradiation. Response has been evaluated using morphological imaging such as computed tomography (CT) and endoscopic ultrasonography (EUS). More recently, metabolic imaging using PET with ^{18}F-2-fluoro-2-deoxy-D-glucose (^{18}FDG) has come in the focus of interest, as promising studies were published. Most recently, the MUNICON trial published by Lordick et al. seems to offer the possibility to assess the response to neoadjuvant chemotherapy in adenocarcinoma of the esophagus even after 2 weeks of chemotherapy (Lordick et al. 2007a). At present however, the data are conflicting as will be discussed later.

^{18}FDG-PET represents a nuclear medicine imaging technique that permits visualization and measurement of physiological and biochemical processes within various human organs. Using a unique data acquisition, PET allows quantitative measurements of regional tissue radioactivity; furthermore, compared to conventional scintigraphic procedures, sensitivity and spatial resolution are improved. Depending on the selected radiopharmaceutical, PET imaging can provide quantitative information regarding blood flow, receptor status, and metabolic processes. As only minimal amounts of material are administered, non pharmacologic effect occurs and there is no perturbation of targeted biochemical process (Phelps 2000).

The glucose analog ^{18}FDG is by far the most commonly used radiopharmaceutical of oncological PET studies. Accelerated glycolysis of malignant tumors is since years accepted as a characteristic biochemical marker of malignant cellular transformation. Similar to glucose, cellular FDG uptake is mediated by glucose transporter proteins. Intracellularly, FDG and glucose are phosphorylated by hexokinase. In contrast to glucose, FDG-6-phosphate cannot be further metabolized. Furthermore, the activity of glucose-6-phosphatase, which mediates the dephosphorylation of glucose-6-phosphate to glucose, is low in most human cells except the liver.

Since FDG-6-phophate is a highly polar molecule it cannot diffuse out of the cell and remains trapped intracellularly. Thus, following an intravenous injection of ^{18}FDG, it continuously accumulates in metabolically active cells. At later time points after injection (more than 45 min) the FDG concentration within a tissue is proportional to its glucose utilization. Due to its high image contrast, ^{18}FDG-PET allows a sensitive detection of metastatic lesions in almost all organs except for the brain and the urinary tract (Shreve et al. 1999).

The spatial distribution of the current FDG-PET studies of the chest or the abdomen is about 5–8 mm. As a consequence of this limited spatial distribution, small lesions, like tumor cell residues in the wall of the esophagus or the proximal stomach cannot be fully resolved. If the structures smaller than twice the resolution are imaged, the true traces concentration in such structures will be underestimated (partial volume effect) (Hoekstra et al. 2000; Young et al. 1999).

There are various approaches for analytical methods ranging from visual assessment (qualitative) to (semi)-quantitative indices. The standardized uptake value (SUV) is used most often: a pixilated region of interest (ROI) can be outlined within a region of increased FDG uptake and, after correction for radioactive decay, analyzed semi-quantitatively according to the following formula:

$$\text{SUV} = \text{ROI activity (MBq/mL)/injected dose (MBq/body weight/g)}$$

Adenocarcinoma of the esophagus (Siewert Type I) and adenocarcinoma of the cardia (Siewert Type II) are both characterized by a high FDG uptake (Ott et al. 2006a, Siewert and Stein 1998). In proximal gastric cancer (Siewert Type III), approximately one-third of the tumors, even with locally advanced tumor, initially have insufficient FDG uptake for quantification. FDG-nonavid tumors are associated with diffuse Laurén classification (predominately in Type III tumors), small tumor size, good differentiation, and mucinous content (Ott et al. 2008b). No studies investigating FDG-PET in these tumor entities do address the problem of Type III tumors separately.

14.1 Response Evaluation

It is accepted that patients who respond to induction therapy have a significantly improved survival compared to patients who do not respond. However, no standardized concept of response evaluation has been established so far. Especially, clinical response evaluation has specific limitations in esophagogastric tumors.

According to standard WHO criteria for the assessment of tumor response, esophageal tumors are not measurable (Miller et al. 1981). Therefore, different investigators have used varying definitions of tumor response, which makes it difficult to compare the individual results.

Furthermore, clinical response evaluation in Siewert Type III tumors is more complicated. According to the WHO criteria, gastric cancer is not bidimensionally measurable. The response evaluation criteria in solid tumor (RECIST) ratings, which use one-dimensional measurements, are in principle, applicable for gastric cancer (Therasse et al. 2000). However, the measurement of wall thickness is critically dependent on the distension of the stomach during examination. RECIST criteria have been used on only a few phase II trials with induction therapy so far (Park et al. 2003; Yoshida et al. 2000). Clinical response evaluation using a combination of clinical assessment, CT scan, and EUS used for restaging after one cycle of chemotherapy before surgery might be predictive of histopathologic response and even prognosis (Ott et al. 2003).

Gold standard for response evaluation is the histopathological regression as noted in the resected specimen. Although similar criteria for histopathological regression have been used in several studies, these criteria are not standardized

and are also investigator-dependent. In esophageal cancer, the regression score of Mandard is mostly used, which was inaugurated after chemoradiation (Mandard et al. 1994). This score was modified by Becker et al. for gastric cancer (Becker et al. 2003).

By applying this scoring system, patients with less than 10% residual tumor cells after neoadjuvant treatment are classified as histopathological responders (score 1a, complete response, score 1b, less than 10% residual tumor cells). In other studies, only patients with complete tumor regression are classified as histopathological responders. In contrast, Shah et al. defined patients with less than 50% residual tumor cells as histopathological responders (Shah et al. 2007).

International homogenization of the scoring systems used for clinical as well as histopathological response evaluation is mandatory. Only an internationally accepted response scoring system makes studies of induction therapy comparable with each other.

14.2 Response Evaluation by CT Scan Studies and EUS

Response to therapy is currently evaluated mostly by using morphologic imaging such as CT and endoscopic ultrasound. Westerterp et al. investigated recently in a systematic review the influx of both the methods on the assessment of response to neoadjuvant therapy in esophageal cancer (Westerterp et al. 2005). As in most studies, there is no differentiation between the different histological types in esophageal cancer: SCC and adenocarcinoma. Overall, CT has poor accuracy for the assessment of response in patients with esophageal cancer.

Walker et al. studied 38 patients with esophageal cancer by CT scan after the completion of preoperative chemotherapy wherein different chemotherapy regimens were used (Walker et al. 1991). Pathological response was defined as follows: complete microscopic response (no microscopically visible residual tumor), complete macroscopic response (no visible residual tumor), partial response (unequivocal signs of healing), and no response (no signs of healing). Response to therapy (partial or complete) was found in 92% of the patients, but only 48% showed a response on CT using the criteria of Miller et al. (1981).

Griffith et al. assessed the response to two courses of 5-FU and cisplatin in 45 patients with SCC with spiral CT (Griffith et al. 1999). Radiographic response to therapy was defined as a volume reduction of more than 50% of CT. Pathological response was assessed according to the criteria of Mandard et al. According to Mandard, 24% of the patients were responders. There was no correlation between tumor volume reduction of serial CT and quantitative pathological tumor assessment nor was a correlation found between tumor volume reduction and survival. Wieder et al also reported that in comparison to PET, in tumors of the esophagogastric junction, changes in tumor metabolism are a more sensitive parameter for assessing the effects of chemotherapy than are changes in tumor size (Wieder et al. 2005).

Jones et al. investigated modern serial CT for tumor response assessment in 50 patients who were treated with combined chemoradiation (45 Gy) (Jones et al. 1999). Pathological response was dichotomized: no tumor (42% responders) and tumor (58%, nonresponders) present in the surgical specimen. Radiographic response by CT is defined as a volume reduction of more than 50%. They reported a sensitivity of 33% and a specificity of 66% in the assessment of the pathological response of the tumor to therapy.

EUS has been developed over the past two decades and has proved to be highly accurate in initial T-staging of the primary tumor in the esophagus; however, especially in proximal gastric cancer its lacks sensitivity in actual studies (Bösing et al. 2003). Most studies used restaging after therapy in T-stage as a parameter to assess

therapy response, while some studies used change in volume measurements of the maximum tumor cross sectional dimensions as a parameter. However, most studies regarding restaging using EUS did not describe a test definition, pre and post TNM was described properly, but the definition of responders vs. nonresponders was not described. Accuracy regarding T-staging after the completion of various neoadjuvant therapy protocols (chemotherapy and/or chemoradiation in adenocarcinoma or SCC) varied between 27 and 82% with a median value of only 48%. Shwisher et al. investigated 103 patients with esophageal cancer (90 patients with adenocarcinoma) after the completion of neoadjuvant chemoradiation. He reported a sensitivity of 56%, with a specificity of 74% and an accuracy of 68% for EUS (Swisher et al. 2004b).

In a recent prospective study, Schneider et al. reported the restaging results of 80 patients (39 patients with adenocarcinoma) after neoadjuvant chemoradiation (Schneider et al. 2008). In this study, only the histomorphologic regression was an objective parameter of significant prognostic importance. Neither EUS nor endoscopy, or even rebiopsy after treatment was adequate for objective response evaluation.

Following the studies mentioned above, no classical staging method permits to judge response – or even early response properly in clinical practice.

14.3 Response Evaluation by PET After Neoadjuvant Treatment

As already mentioned, multimodality treatment with chemotherapy, radiation, and surgical resection is increasingly used in patients with locally advanced adenocarcinoma of the esophagus and the esophagogastric junction. The appropriate selection of patients who undergo preoperative chemoradiation followed by surgical resection is important, as this therapy is associated with significant morbidity and mortality. In this regard, a significant improvement in survival has been shown to occur in those patients who respond to preoperative therapy especially with a complete pathologic response. Thus, the clinical importance of correctly differentiating these patients from those who fail to respond to therapy is of high clinical importance. As outlined, assessment of posttreatment TNM status by CT, EUS, or rebiopsy does not correlate with pathologic response.

Although PET after chemotherapy or chemoradiation may be useful in detecting occult metastases (up to 5%), most studies have evaluated FDG-PET in terms of the response of the primary cancer to induction therapy and prediction of prognosis. The results of these studies are varied and conflicting. Some authors report reliable assessment of response to therapy whereas others have found no correlation and limited impact of PET. The studies concerning the histology of the primary neoadjuvant treatment used and different thresholds concerning the SUV to discriminate responders from nonresponders vary significantly. The most relevant studies are summarized in Table 14.1. Figure 14.1 shows the distribution of the decrease of FDG uptake in repeated PET scans.

Smithers et al. reported in a study on 45 patients with adenocarcinoma of the esophagus, who received neoadjuvant chemotherapy ($n=22$) or neoadjuvant chemoradiation ($n=23$) (Smithers et al. 2008). For response evaluation after therapy they used two different methods: the SUV and tumor/liver ratio (TLR). In this study, there was no difference between the two methods of assessment, a less variation with SUV was observed. Furthermore, there was no correlation between FDG-PET response and the histopathological response. The authors state that at the present time FDG-PET should not be used as a marker of the potential results of treatment. Furthermore, the optimal timing of PET remains still unclear (Smithers et al. 2008).

Table 14.1 Sensitivity and specificity following neoadjuvant treatment, selected studies

Study	Histology	*n*	Therapy	Sensitivity (%)	Specificity (%)
(Weber et al. 2001)	AC	40	CTX	89	75
(Flamen et al. 2002)	AC/SCC	29/7	CRT	71	82
(Swisher et al. 2004a)	AC/SCC	90/13	CRT	62	84
(Cerfolio et al. 2005)	AC/SCC	43/5	CRT	87	88
(Levine et al. 2006)	AC/SCC	52/9	CRT	61	60
(Bruzzi et al. 2007)	AC/SCC	75/13	CRT	57	46

AC adenocarcinoma; *SCC* squamous cell carcinoma; *CTX* Chemotherapy; *CRT* chemoradiation

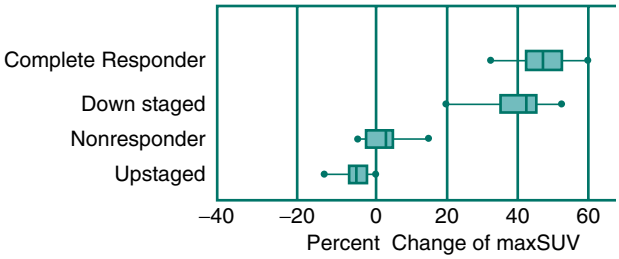

Fig. 14.1 Median percentage decrease in maximum standardized uptake value (maxSUV) of repeat 18FDG-PET after neoadjuvant chemoradiation as reported in the study by Cerlolio et al. (2005). Reprint from Cerfolia et al. (2005), with permission

In a recent study, presented at the ASCO 2008, Vallböhmer et al. reported on the results of posttreatment FDG-PET in 133 patients with SCC and adenocarcinoma after neoadjuvant chemoradiation (Vallböhmer et al. 2008). Although the multimodal treatment led to a significant reduction of intratumoral FDG uptake, in this study no significant correlation between pre and posttherapy FDG-PET and histopathological response was detected. A SUV-threshold with predictive or prognostic value was not observed; only histomorphological regression was reconfirmed as a prognostic parameter.

Following various studies, a negative FDG-PET after preoperative chemoradiation is unable to distinguish small-volume residual disease from a complete pathologic response to therapy (McLoughlin et al. 2008; Munden et al. 2006). The poor sensitivity of PET in differentiating those patients who had residual cancer from those with a complete response to therapy is in large part owing to the small volume of disease below the detectability of FDG-PET imaging. Because patients with an apparent complete response after neoadjuvant treatment can have residual disease, a negative PET should not be used as the sole criterion to obviate esophagectomy. It has been reported that 42% of the patients with a complete response to chemoradiation according to FDG-PET who did not undergo resection subsequently had locoregional recurrence (Nakamura et al. 2002).

In terms of PET, the assessment of the response of esophageal malignancy especially to preoperative chemoradiation, esophagitis, and ulceration are important confounding factors (Bhargava et al. 2003; Hautzel and Muller-Gartner 1997). The high false-positive rate for

persistent tumors after therapy is most likely owing to the presence of metabolically active leucocytes and macrophages associated with inflammatory esophagitis and ulceration that usually follow radiotherapy. Following that, it has to be questioned whether therapy control using PET should be limited to the effect of chemotherapy only.

14.4 PET During Treatment

Most studies have evaluated the diagnostic modalities for response to neoadjuvant treatment after completion. As discussed, when using chemoradiation, there seems to be a limited value for response evaluation using FDG-PET. However, there is an urgent need for a diagnostic noninvasive test that can predict tumor response early in the course of neoadjuvant therapy.

By discriminating responders from nonresponders, the treatment plan may be adjusted; in particular,treatment may be discontinued in nonresponders, switching to a different chemotherapy- or chemoradiation or perform immediate salvage surgery. So far, only limited data about early response assessment are available in adenocarcinoma of the esophagus and esophagogastric junction, mainly from the group from Munich. In contrast to the majority of other studies, they investigated the metabolic changes after chemotherapy only, which does not lead to inflammatory changes in the tissue. Furthermore, an early approach (14 days after the onset of chemotherapy) may be of special value. Figure 14.2 shows an example of a responding tumor 14 days after chemotherapy.

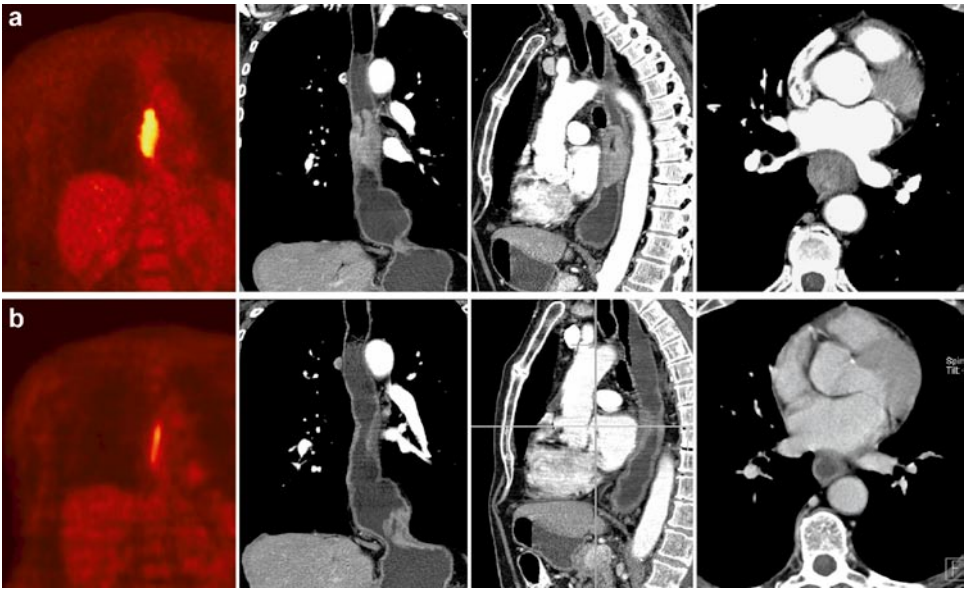

Fig. 14.2 An example of a responding patient with adenocarcinoma of the distal esophagus during neoadjuvant chemotherapy. (**a**) FDG-PET and corresponding CT Scans before therapy. (**b**) FDG-PET and corresponding CT Scans at day 14 during CTX. The SUV is decreased markedly

Weber et al. reported on a series of 40 patients with Siewert Type I and II tumors who received chemotherapy of 72 days duration (Weber et al. 2001). Already after 14 days of therapy, reduction of tumor FDG uptake was significantly different between responders according to Mandard (−54+17%) and nonresponders (−15+21%). An optimal differentiation was achieved by a cut-off value of 35%. This threshold allowed prediction of subsequent clinical response with a sensitivity and specificity of 89 and 75%, respectively. The 2-year survival rate was 49% in the FDG-PET responders vs. 9% in the nonresponders.

In a next step, this concept was evaluated prospectively. Ott et al. reported on 65 patients with Siewert Type I or Type II tumor, in which the threshold of 35% cut-off of FDG uptake was prospectively used (Ott et al. 2006b). After 14 days, the patients were classified according to their cut-off value as responders and nonresponders. Metabolic responders showed a high histomorphologic response rate (44%) with a 3-year survival rate of 70%. In nonresponding patients prognosis was poor, with a 3-year survival rate of 35% and a histomorphologic response rate of only 5%. Furthermore, multivariate analysis demonstrated that metabolic response was the only factor predicting recurrence in the completely resected patients.

This work led the group to the recently published MUNICON trial by Lordick et al., establishing a so-called "PET-controlled" chemotherapy (Lordick et al. 2007b). Metabolic responders (threshold −35% FDG uptake) after 2 weeks of chemotherapy received two complete cycles of preoperative chemotherapy. Metabolic nonresponders after 2 weeks were immediately referred to surgery. Out of the 119 patients investigated, 110 patients were evaluated for metabolic response. Fifty-two percent of these patients had metabolic response and 48% were metabolic nonresponders. There was a statistical difference in the rate of complete resections for responders (90%) compared to nonresponders (61%). There was no difference in postoperative morbidity and mortality. Consequently, after a short median follow-up of 2.3 years, median overall survival was not reached in metabolic responders, whereas median overall survival was 25.8 months in metabolic nonresponders.

In this respect, the problem of Siewert Type III tumors (proximal gastric cancer) is not solved. Data on early metabolic response prediction are more sparse, the timing of early PET is on debate (Munich group day 14, MSKCC group day 35); furthermore, as discussed above, up to 40% of gastric tumors are FGD nonavid (Ott et al. 2008a, Shah et al. 2007). These tumors are so far not properly addressed in the studies. It seems to be doubtful to subsume proximal gastric tumors solely in the group of tumors of the esophogogastric junction in respect of early or late metabolic response assessment.

A problem of these very promising data is that other groups do not confirm them yet. The problem will be solved by the yet initiated multicenter trial by the EORTC in which the concept of FDG-PET guided chemotherapy will be evaluated (imaging in gastroesophageal cancer – IMAGE study). Treatment plan consists of randomization after PET at day 14 in four treatment arms: nonresponder: immediate resection vs. taxane based chemoradiation; responder: chemotherapy vs. chemo-immunotherapy followed by resection.

14.5 Conclusion

Response evaluation in adenocarcinoma of the esophagus and the esophagogastric junction is not possible using serial CT scan, endoscopic ultrasound, or rebiopsy. Although there is a significant decline in FDG uptake using the PET technology, complete pathohistologic response cannot be detected. The data of early response evaluation are very much encouraging; however,

the data has to be evaluated in an international randomized trial. Standardization of PET technology as well as defining the thresholds used for the estimation of early response is mandatory. Following the published data so far, FDG-PET seems to be less accurate after and during chemoradiation than after chemotherapy alone. So far, FDG-PET does not change treatment in esophageal and gastric cancer. This promising method has to be investigated further in randomized trials.

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15 Molecular Response Prediction in Multimodality Treatment for Adenocarcinoma of the Esophagus and Esophagogastric Junction

Georg Lurje and Heinz-Josef Lenz

Abstract Cancers arising from the esophagus are becoming more common in the United States and Europe. In 2009, an estimate of 14,530 new cases will be diagnosed and more than 90% will die of their disease. Esophageal cancer is currently the most rapidly increasing cancer in the western world and is coinciding with a shift in histological type and primary tumor location. Despite recent improvements in the detection, surgical resection, and (radio-) chemotherapy, the overall survival (OS) of esophageal cancer remains relatively poor. It is becoming increasingly apparent that neoadjuvant chemoradiation followed by surgery may be beneficial in terms of increasing resectability and OS compared to surgery alone. Results from clinical trials are encouraging; however, they also demonstrated that only patients with major histopathological response (pCR) will benefit from neoadjuvant therapy. In addition, these therapies are expensive and the prognoses of patients who do not respond to trimodality treatment strategies appear to be inferior to that of patients who had surgery alone. Accordingly, the development of validated predictive molecular markers may not only be helpful in identifying EA patients who are more likely to respond, but they will also be critical in selecting more efficient treatment strategies with the means of a tailored, targeted, and effective therapy to the molecular profile of both the patient and their disease while minimizing and avoiding life-threatening toxicities.

15.1 Introduction

Over the past 30 years, esophageal adenocarcinoma (EA) has become the most rapidly increasing cancer in the western world, and its incidence has surpassed that of esophageal squamous cell carcinoma (Bollschweiler et al. 2001; Pohl and Welch 2005; Blot and McLaughlin 1999; Devesa et al. 1998; Jemal et al. 2008). EA is an aggressive tumor with an overall survival (OS) rate of 15–20% (Enzinger and Mayer 2003). Transthoracic en bloc esophagectomy with gastroplasty and two-field lymphadenectomy has offered significant improvements in local disease control and is currently considered the procedure of choice worldwide for patients with

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resectable middle to lower third EA (Hagen et al. 2001). Despite recent improvements in the detection (Lordick et al. 2007), surgical resection (Hagen et al. 2001; Holscher et al. 2007; Peyre et al. 2007) and neoadjuvant radiochemotherapy (Mariette et al. 2007; Schneider et al. 2005a), the OS of patients with EA remains lower than other solid tumors. In addition, patients with locally advanced EA have a poor prognosis when treated by surgery alone. Therefore, neoadjuvant treatment strategies were applied in an effort to improve survival (Sherman et al. 2002). Interestingly, a recent meta-analysis by Gebski et al. analyzed eight randomized clinical trials consisting of 1,724 patients and compared neoadjuvant radiochemotherapy followed by surgery with surgery alone (Gebski et al. 2007). The authors concluded that trimodality treatment with neoadjuvant radiochemotherapy followed by surgery is beneficial for patients with early and locally advanced esophageal carcinoma (Gebski et al. 2007). Results from clinical trials are encouraging; however, they also demonstrated that only patients with major histopathological response (pCR) will benefit from neoadjuvant therapy (Urba et al. 2001; Walsh et al. 1996). In addition, these therapies are costly and the prognosis of patients who do not respond to trimodality treatment strategies appears to be inferior to that of patients who had surgery alone (Brucher et al. 2004; Zacherl et al. 2003). Despite these recent advancements, selection of the most beneficial treatment strategy in esophageal cancer remains a challenge and is hindered by the lack of predictive and prognostic markers.

Although still in its infancy, research efforts on a global scale have attempted to identify subsets of molecular markers that can predict both response to multimodality treatment strategies and prognostic markers to assess the aggressiveness of the disease and the likelihood of recurrence after surgery. The science of pharmacogenomics is emerging as a useful molecular tool to investigate the disparity in drug efficacy by simultaneous analysis of variables in the patient and their disease such as genetic polymorphisms in drug targets, metabolizing enzymes, transporters, and influential receptors (McLeod and Yu 2003). Accordingly, the development of validated predictive and prognostic markers may not only be helpful in identifying EA patients who are more likely to respond, but they will also be critical in selecting more efficient treatment strategies with the means of a tailored, targeted, and effective therapy to the molecular profile of both the patient and their disease while minimizing and avoiding life-threatening toxicities.

The aim of this review is to provide an update on the most recent data on molecular predictive and prognostic markers in the clinical outcome of localized EA (Table 15.1).

15.2 Molecular Markers; Defining their Role

For the clinician, it is important to distinguish between prognostic and predictive molecular markers. Predictive markers are associated with treatment specific therapy and are mostly evaluated through clinical response, time to progression, or toxicity. In contrast, prognostic markers reflect the nature/aggressiveness of the disease, independently of a specific treatment. They are generally evaluated in terms of OS. In some cases, predictive markers can also carry prognostic weight, and both play important roles in the prospective evaluation for a given treatment regimen. Molecular markers may be protein or gene expression levels or genetic variations in the DNA of the host or the tumor.

Over the last decade, a number of targets have been identified as potential predictive and prognostic markers. These include growth factor receptors (Akamatsu et al. 2003; Gibault et al. 2005; Gibson et al. 2003; Inada et al. 1999;

Table 15.1 Molecular predictive and prognostic markers in esophageal cancer

Type of cellular pathway/factor	Method	Prognostic (OS, PFS)	References	Predictive (pCR)	References
Angiogenic factors					
EGFR	IHC	Local recurrence, tumor invasion, OS	(Gibault et al. 2005; Gibson et al. 2003; Inada et al. 1999)	n/a	–
HER2/neu	RT-PCR	n/a		Response to neoadjuvant radiochemotherapy	(Akamatsu et al. 2003; Miyazono et al. 2004)
COX-2	IHC, RT-PCR	Metastases, Tumor stage, GERD	(Kuo et al. 2003; Lurje et al. 2007)	Response to neoadjuvant radiochemotherapy	(Kulke et al. 2004; Xi et al. 2005)
Apoptotic factors					
p53	Sequencing	Survival	(Ikeda et al. 1999; Ikeguchi et al. 2000)	Response to neoadjuvant radiochemotherapy	(Nakashima et al. 2000; Sohda et al. 2004)
Survivin	IHC, RT-PCR	n/a	–	Response to neoadjuvant radiochemotherapy	(Warnecke-Eberz et al. 2005; Vallbohmer et al. 2008)
DNA repair					
ERCC1	IHC, RT-PCR	Recurrence, survival	(Joshi et al. 2005)	Response to neoadjuvant radiochemotherapy	(Warnecke-Eberz et al. 2004)
CpG island methylator phenotype (CIMP)	MS-PCR	n/a	–	Response to neoadjuvant radiochemotherapy	(Hamilton et al. 2006)

Lurje et al. 2010; Miyazono et al. 2004), enzymes of angiogenesis (Han et al. 2005; Imdahl et al. 2002; Kulke et al. 2004; Kuo et al. 2003; Shimada et al. 2002; Xi et al. 2005), tumor suppressor genes (Ikeda et al. 1999; Ikeguchi et al. 2000; Kitamura et al. 2000; Nakashima et al. 2000; Shimada et al. 2000; Sohda et al. 2004), cell cycle regulators (Nakashima et al. 2000; Sohda et al. 2004; Itami et al. 1999; Kuwahara et al. 1999), enzymes involved in the DNA repair system (Joshi et al. 2005; Terashita et al. 2004; Warnecke-Eberz et al. 2004), and in the degradation of extracellular matrix (Ishibashi et al. 2004; Sharma et al. 2004; Tanioka et al. 2003). The results of these mainly retrospective studies are promising, however, no single marker or panel of markers has emerged as a strong candidate, though several appear promising.

15.2.1 Epidermal Growth Factor Receptors (EGFR, HER2/neu)

The human EGRF 1 (EGFR) and 2 (HER2/neu), members of the type I receptor tyrosine kinase family, are commonly overexpressed in a variety of malignancies, including up to 92% of esophageal cancers (Gibault et al. 2005; Inada et al. 1999; Salomon et al. 1995; Hickey et al. 1994; Schneider et al. 2005b). Activation of the EGF/EGFR axis triggers multiple signaling pathways that result in endothelial cell proliferation, apoptosis, angiogenesis, and metastasis (Herbst and Shin 2002). Conversely, inhibition of the EGFR pathways with anti-EGFR monoclonal antibodies, such as cetuximab, was reported to block cell cycle progression and induce apoptosis in numerous in vitro and xenograft models (Fan et al. 1993; Karnes et al. 1998; Wu et al. 1995). In fact, multiple phase II/III clinical trials have demonstrated that cetuximab has promising efficacy in patients with mCRC and locally advanced head and neck cancers (Cunningham et al. 2004; Saltz et al. 2004; Bonner et al. 2006; Lenz et al. 2006).

Miyazono et al. investigated the predictive value of EGFR and HER2/neu mRNA expression in 36 patients with locally advanced esophageal cancer (SCC $n=23$/EA $n=13$) in an attempt to identify patients who are more likely to show pCR to neoadjuvant radiochemotherapy with cisplatin and 5-fluorouracil (5-FU) followed by transthoracic en bloc esophagectomy (Miyazono et al. 2004). Although, quantitative EGFR mRNA expression was not associated with the degree of histopathological response, low intratumoral expression levels of HER2/neu were significantly associated with pCR to preoperative trimodality treatment, compared to patients whose tumors showed high levels of HER2/neu mRNA expression (Miyazono et al. 2004). In another study of mostly EA patients, EGFR expression was assessed by immunohistochemistry (IHC) using pretreatment biopsies from 54 patients who underwent neoadjuvant radiochemotherapy with cisplatin and 5-FU (Gibson et al. 2003). Even though EGFR protein expression, as assessed by IHC, was not significantly associated with pCR at the $p<0.05$ level, its expression levels were associated with progressive disease and poor OS after adjustment for covariates in the multivariable model (Gibson et al. 2003). However, it should be noted that IHC is a semiquantitative and subjective method and is limited by the sensitivity of the monoclonal antibody and the tissue handling.

15.2.2 Tumor Suppressor Gene *p53*

The tumor suppressor gene *p53* is located on chromosome 17p and is involved in cell cycle regulation, apoptosis, and DNA-repair. Mutations of *p53* occur commonly in esophageal cancers and are present in the progression toward SCC (Bennett et al. 1992) and EA (Paulson and Reid 2004). Due to its central role in the detection of genotoxic stress, *p53* is often referred to as the "guardian of the genome" (Lane 1992). Whereas,

wild-type *p53* exerts a restraining influence on cell growth, mutant *p53* inactivates this restraining capacity. Further, p53 proteins oligomerize in vivo and mutant p53 proteins are thought to inactivate wild-type p53 protein present in cells, hence acting as "dominant negative" mutations when the wild-type allele is still present in the cell (Herskowitz 1987; Kraiss et al. 1988). Thus, p53 protein has been associated with genetic instability (Livingstone et al. 1992; Yin et al. 1992) and poor histopathological response to neoadjuvant radiochemotherapy in vivo, suggesting that p53 status may be an important determinant of tumor response to (radio-) chemotherapy (Lowe et al. 1994). p53 status has been rigorously analyzed as both a prognostic and predictive marker in esophageal cancer. One positive study evaluated *p53* mutational analysis on 42 esophageal cancer specimens (mostly EA) from patients who received preoperative trimodality therapy. The presence of *p53* mutations correlated with lower rates of pCR (6 vs. 32%; 0.01), worse disease-free (14 vs. 28 month; $p=0.0004$) and overall (22 vs. 40 month; $p=0004$) survival (Ribeiro et al. 1998).

Although alterations of p53 have been shown to be a plausible predictive marker for pCR (Kitamura et al. 2000; Ribeiro et al. 1998), other studies did not find a significant relationship between *p53* gene or protein status and response (Gibson et al. 2003; Shimada et al. 2000; Hironaka et al. 2002; Sarbia et al. 1998). In addition, studies of *p53* in EA patients who received trimodality therapy are fewer, similarly inconsistent. Therefore, the role of p53 as a predictive marker for pCR in patients with locally advanced EA treated with neoadjuvant radiochemotherapy is still regarded as controversial.

15.2.3 Survivin

Survivin, a member of the inhibitor of apoptosis protein (IAP) gene family, was first described by Ambrosini et al. over a decade ago (Ambrosini et al. 1997). Besides its central role in the (dys-) regulation of apoptosis, survivin has also been implicated in cell-cycle regulation and tumor angiogenesis. In fact, survivin protein expression is detectable in most human fetal tissues and is further suppressed during fetal development (Ambrosini et al. 1997). While its expression levels are usually undetectable in differentiated normal tissue, overexpression of Survivin mRNA and protein is frequently observed in numerous human malignancies (Hoffmann et al. 2007), including EA (Vallbohmer et al. 2005). Recently, Vallbohmer et al. reported that survivin mRNA levels increase in a stepwise manner during the progression through the Barrett's metaplasia-dysplasia-adenocarcinoma sequence, suggesting that survivin may have a promising role as a biomarker in EA disease progression (Vallbohmer et al. 2005). Finally, two studies (comprising 42% of EAs) from the same group have demonstrated that survivin mRNA (Warnecke-Eberz et al. 2005) and protein (Vallbohmer et al. 2008) expression may be predictive markers for patients with esophageal carcinoma, treated with neoadjuvant radiochemotherapy, followed by transthoracic *en bloc* esophagectomy. Interestingly, survivin protein expression was significantly down-regulated during neoadjuvant treatment and failure in down-regulation of intratumoral survivin expression following neoadjuvant radiochemotherapy was associated with minor histopathological response and prognosis (Vallbohmer et al. 2008). However, prospectively conducted clinical trials are needed, to validate and confirm these preliminary findings that are often generated in relatively small retrospective studies.

15.2.4 Cyclooxygenase-2 (COX-2)

COX is the rate-limiting enzyme in the conversion of arachidonic acid to prostaglandins. The isoform COX-1 is thought to be constitutively

expressed in a variety of tissues, whereas COX-2 is induced by cytokines, growth factors, mitogens, and oncoproteins (Stoehlmacher and Lenz 2003). COX-2 is involved in the regulation of a broad range of cellular processes including tumor onset and progression, metastases, angiogenesis, and resistance to chemotherapy (Dandekar and Lokeshwar 2004; Kishi et al. 2000; Oshima et al. 1996; Tsujii et al. 1997, 1998). In addition, COX-2 mRNA is over-expressed in a variety of malignancies (Stoehlmacher and Lenz 2003) and has been shown to be increased in a stepwise manner during the progression through the Barrett's metaplasia-dysplasia-adenocarcinoma sequence (Lurje et al. 2007), suggesting that COX-2 may be a promising biomarker in addition to its potential role as a therapeutic target in EA disease progression (Lurje et al. 2007; Hamoui et al. 2004; Lurje et al. 2008; Zimmermann et al. 1999).

Recent evidence suggests that high COX-2 expression was associated with increased intratumoral microvessel density and suppression of tumor cell apoptosis in human esophageal carcinomas (Kase et al. 2003). It has been known that cells overexpressing COX-2 tend to be resistant to undergo apoptosis (Tsujii and DuBois 1995). Interestingly, a recent study by Xi et al. suggests that patients (39% EA 61 SCC) with high intratumoral COX-2 mRNA and protein expression showed to be less sensitive to neoadjuvant radiochemotherapy (Xi et al. 2005). Although preliminary in nature, due to a relatively small sample size and mixed study population (39% EA 61 SCC) this phenomenon may be explained by the induction of apoptosis as an important mechanism of resistance to various anticancer agents and radiation therapy (Blank et al. 1997; Kaufmann and Earnshaw 2000).

15.2.5 Excision Repair Cross-Complementing 1 (ERCC1)

Resistance to oxaliplatin chemotherapy has been attributed to several different mechanisms such as decreased drug accumulation, increased drug inactivation, but most importantly to enhanced DNA repair capacity. The nucleotide excision repair (NER) pathway is the only known mechanism in mammalian cells for the removal of bulky helix-distorting DNA adducts produced by platinum agents such as oxaliplatin (Reardon and Sancar 2006). Thus, a more efficient DNA repair system might lead to increased clinical resistance to the chemotherapeutic agent (Reardon and Sancar 2006). The ERCC1 enzyme is an essential member of the NER. ERCC1 gene expression levels in tumors have been shown to be predictive for therapeutic response and survival to oxaliplatin-based chemotherapy. Shirota et al. evaluated ERCC1 gene expression levels in metastatic colorectal cancer (mCRC) refractory to 5-FU and CPT-11. Patients with low gene expression levels of ERCC1 ($<4.9 \times 10^3$) experienced a significantly longer median survival compared to those patients with high gene expression levels for ERCC1 ($>4.9 \times 10^3$) in the tumor tissue (Shirota et al. 2001). Further, numerous studies have reported that increased ERCC1 mRNA expression may be an indicator for nonresponse to neoadjuvant CDDP-based chemotherapy (CDDP, leucovorin, and 5-FU) in a variety of gastrointestinal malignancies (Shirota et al. 2001; Lord et al. 2002; Metzger et al. 1998), including esophageal cancer (Warnecke-Eberz et al. 2004). In fact, Warnecke-Eberz et al. showed that low intratumoral expression of ERCC1 correlated significantly with better response to neoadjuvant radiochemotherapy with cisplatin and 5-FU, even though OS could not be evaluated, due to the relatively short follow-up of the study cohort (Warnecke-Eberz et al. 2004).

15.2.6 Gene Expression Microarray Profiling

Microarray-based gene expression profiling technology provides a strategy to search systematically for molecular markers of cancer classification

and outcome prediction in a combinatorial manner. Recognizing the complexity of disease progression, a simultaneous analysis of a large number of genes may offer a powerful and complementary approach to clinical or pathologic examination. In a recent study by Luthra et al., a genetic signature derived from microarray gene expression analysis and classifications methods has been shown to be potentially valuable in an effort to better discriminate EA patients who are sensitive vs. those who are resistant to trimodality treatment regimens (Luthra et al. 2006). The study included pretreatment tumor biopsies, which were taken from 19 esophageal cancer patients (16 EA, 2 SCC, and 1 adenosquamous carcinoma). Patients were enrolled onto a neoadjuvant radiochemotherapy protocol, comprising of two cycles of induction chemotherapy, followed by intravenous 5-FU/irinotecan and surgical resection. Interestingly, unsupervised hierarchical cluster analysis segregated the cancers into two molecular subtypes, consisting of ten (subtype I) and nine (subtype II) specimens. Five out of six cancers that showed pCR clustered into subtype I, whereas subtype II comprised almost entirely (9/10) of cancers that had less than pCR. Nevertheless, a serious limitation of genome-wide association studies is that gene expression profiling only gives a snapshot of one level in the hierarchy of cell activity. Due to the strong methodological and technological differences between different platforms, concerns about the reproducibility and comparability of experimental results obtained with different platforms appear reasonable. Although intriguing, the study by Luthra et al. included only a small number of specimens; hence, vigorous validation with a larger set of samples is warranted to assess the predictive power of these potential markers.

15.2.7 CpG Island Methylator Phenotype (CIMP)

The CIMP with widespread promoter methylation and tumor suppressor inactivation is a distinct epigenetic phenotype and is thought to be an important mechanism in human carcinogenesis (Issa 2004; Jass 2005; Laird 2005). Among the molecular alterations and epigenetic events described in human neoplasia, changes in DNA methylation are one of the most common (Jones and Baylin 2002). It is increasingly recognized that the CpG islands of a growing number of genes (which are mainly unmethylated in nonneoplastic, normally differentiated cells) are methylated to varying degrees in many types of human cancer, including EA (Brock et al. 2003). In fact, such promoter hypermethylation is regarded as a critical mechanism for tumor suppressor gene silencing and inactivation (Jones and Baylin 2002). In one retrospective study in esophageal cancer patients (EA = 23, SCC = 12) who received trimodality therapy, aberrant CpG island hypermethylation (CIMP-H) was assessed from 11 candidate genes in pretreatment tumor specimens (Hamilton et al. 2006). Interestingly, the number of methylated genes per patient was significantly lower in patients who had experienced pCR than in those who did not (1.2 vs. 2.4 genes per patient; $p = 0.026$).

Since CIMP-high does not occur in nonmalignant, normally differentiated cells, Wallner et al. suggested that methylated DNA released in the circulation could possibly be used as a prognostic indicator and for tumor detection (Wallner et al. 2006). Over the last years, it has become evident that CIMP can be detected in tumor DNA found in the serum and plasma of patients with cancer (Laird 2003; Jen et al. 2000) and its prognostic value has been demonstrated for numerous malignancies (Fiegl et al. 2005; Koyanagi et al. 2006; Lecomte et al. 2002; Leung et al. 2005; Usadel et al. 2002; Widschwendter et al. 2004). However, several issues need to be addressed before these markers can be introduced into routine clinical practice. These include standardization of sample collection, DNA isolation and preparation as well as the usage of standardized assays with an adequate extent of reproducibility.

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15.3 Conclusion

Several biomarkers have been evaluated over the last decades and it is becoming increasingly apparent that disease progression and response to trimodality treatment regimens are largely driven by complex pathways, and analysis of one single marker is unlikely to precisely predict the progression of disease with sufficient resolution and reproducibility. A major problem with some aforementioned studies and the reason for discrepant and sometimes contradictory data in the literature are the following: one can bring in several factors like small study sample number, heterogeneous study populations, lack of standardized methodologies for measuring gene expression or genetic polymorphisms, suboptimal samples consisting of different mixtures of cells, tissue-specific differences, and study populations with different histopathological characteristics. In this regard, it is being increasingly recognized that SCC and EA are separate and distinct disease groups, in terms of molecular biology, comorbidities, and treatment, and therefore need to be considered individually (Metzger et al. 2004; Montesano et al. 1996).

The impact of biomarker-driven treatment decisions is therefore yet to be proven in prospective clinical trials. Unfortunately, biomarker-embedded clinical trials do not receive the same commercial attention as new chemotherapeutic compounds. Lack of financial support, coupled with a traditional conservatism of the medical establishment has been a major problem in the development and validation of new molecular markers. Furthermore, standards need to be agreed upon for what determines the validity of a biomarker before they can be used in biomarker-embedded clinical trials. In a few years, microarray technology with the advent of customizable chips might be the preferred method of genetic and genomic profiling. The introduction of new therapeutic agents and the discovery and validation of predictive and prognostic markers along with new screening tools will enable clinicians to tailor patient specific chemotherapy regimens by maximizing drug efficacy and minimizing adverse and possibly severe side effects. Much work, however, remains to be done. Ongoing and future clinical trials hold promise for further improvements in optimizing and specifying chemotherapy individually, not only in prolonging lives but also in augmenting the quality of life.

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