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T.K. Chattopadhyay *Editor in Chief*
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Series editor

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Department of HPB Surgery
Institute of Liver and Biliary Sciences
New Delhi
India

This compendium of reviews in gastrointestinal surgery covers topics that are of contemporary interest to surgeons reflecting the popular trends in this field. Started by the *Indian Association of Surgical Gastroenterology* (IASG), the GI Surgery Annual has covered a journey of over 2 decades which speaks for its relevance and popularity among general and gastrointestinal surgeons. The reviews contain up-to-date scientific content of enduring academic interest with each new volume covering 10-12 topics. From 2016 onwards, this Annual turns a new page in its academic journey by publishing the forthcoming titles with Springer. The editorial control continues to remain with the IASG and the current editorial board. The idea of *GI Surgery Annual* was first conceived during the annual conference *of Indian Association of Surgical Gastroenterology* in 1991 and the First Volume came into existence in the year 1994, through the efforts of Professor T.K. Chattopadhyay and his team of co-editors. Professor T.K. Chattopadhyay continues to head the editorial board in his current capacity as Professor Emeritus, AIIMS, New Delhi. This Annual is an essential resource for postgraduate and postdoctoral trainees in surgery and gastrointestinal surgery, for practising surgeons who wish to keep up-to-date with developments in the field and for established academic surgeons as well.

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Preface

It gives me pleasure to present the twenty-third edition of the *GI Surgery Annual*. Over the past 22 years, the Indian Association of Surgical Gastroenterology has rendered support in more ways than one to fulfil its commitment to disseminate knowledge among various categories of its members—students, teachers and practising surgeons of surgical gastroenterology. During these years, the Annual has become a popular ready source of knowledge in various aspects of GI surgery, often not covered in standard texts. To make this happen we readily acknowledge the contributions made by various authors.

All these years we have produced the book on our own against all odds. This edition has found an able global publisher, Springer Nature and with this we expect to have an increased global readership. Hopefully, we will have an increased number of contributors from all over the world in the future.

As in previous years, we are thankful to the people who have contributed to bring out this edition including the editorial team, and the residents and staff of the Department of GI Surgery, All India Institute of Medical Sciences, New Delhi. Lastly, we thank the team from Springer Nature who have coordinated the project at various stages. I hope our efforts will be appreciated by our readers.

New Delhi, India — T.K. Chattopadhyay

About the Editors

T.K. Chattopadhyay is Professor Emeritus, Department of Gastrointestinal Surgery and Liver Transplantation, All India Institute of Medical Sciences, New Delhi. He initiated this series 22 years ago and has been the editor of this series since its inception. Presently, he is Professor and Head, Department of HPB Surgery, Institute of Liver and Biliary Sciences, New Delhi.

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Chapter 1
Lymphadenectomy in Oesophageal Carcinoma

Rajneesh Kumar Singh and Selvakumar Balakrishnan

1.1 Introduction

Cancer is constituted by mutated cells that have escaped the normal checks and balances of regulated cell growth. It is initially localized to the organ of origin and thereafter spreads through the body, and ultimately becomes the cause of unnatural death of the patient. In the natural history of any cancer three distinct phases can be described: (i) limited to the organ of origin (localized phase); (ii) limited to the region of origin (regional phase); and (iii) spread to distant organs (metastatic phase) [1]. Regional phase/stage is usually described as spread limited to the regional lymph node basin. The philosophy of surgical lymphadenectomy, along with extirpation of the primary tumour, is meant to treat the regional stage of the disease.

It will be obvious to those familiar with this field, that high quality evidence to evaluate lymphadenectomy in oesophageal carcinoma is difficult to come by, else there would be no need for reviews like this. To the GI Surgery fellows taking their final examinations this represents a treacherous minefield due to the varying practices followed by surgeons across the world. In this review we attempt to introduce the reader to the concept, guidelines, evidence and practice of lymphadenectomy in the surgical treatment of oesophageal carcinoma.

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1.2 Basic Model of Cancer Spread

William Halstead's work on breast cancer at the turn of the 20th century laid the foundation of the 'Halstedian' philosophy of growth of cancer. This was founded on the concept that cancer sequentially grows outward from the primary lesion to involve the lymph nodes, and then from the lymph nodes, the metastatic cells enter the bloodstream and lead to distant metastases. Based on this principle radical mastectomy was espoused to cure breast cancer in the 'lymph nodal' stage of the disease. About a century later, data from other cancers seems to agree with this philosophy. Gastric cancer data from the National Cancer Centre, Tokyo (Table 1.1), shows the sequential early, intermediate and late stage of the disease [2]. This table shows that lymph nodal spread increases in the intermediate stages and distant spread increases in the late stages.

In the 1960s and 1970s this paradigm was challenged by Bernard Fisher who headed the National Surgical Adjuvant Breast and Bowel Project (NSABP) to test adjuvant chemotherapy in breast and colon cancers [3]. The 'Fisher' hypothesis was that cancer was to be considered a systemic disease right from the beginning. Cancer cells were shed into systemic circulation quite early and no amount of radical surgery could treat this systemic disease. With regard to the nodal metastasis, he believed, 'lymph node metastasis is an indicator, not a governor of prognosis' [3].

Another important hypothesis in this regard was the Paget's 'seed and soil hypotheses' in late 19th century [1]. This proposed that shed cancer cells (seed) needed a fertile environment (soil) to establish metastasis. Thereby meaning that shed cancer cells were only able (programmed) to establish metastasis in specific organs or nodes. In fact, systemic seeding of metastasis was realized to be a terribly inefficient process and only a miniscule percentage of the circulating tumour cells could establish as metastasis [3].

A summation of the above leads us to realize that all these hypotheses were probably true in that they defined the 'spectrum' of cancer behaviour. In this 'spectrum'

Table 1.1 Gastric cancer data to illustrate the sequential spread of the tumour

Tumour depth	N	Node metastasis (%)	Liver metastasis (%)	Peritoneum metastasis (%)	Haematogenous metastasis (%)	5 year survival (%)
pT1 (m)	1063	3	0	0	0.2	93
pT1 (sm)	881	17	0.1	0	1	89
pT2 (mp)	436	47	1	0.5	6	81
pT2 (ss)	325	64	3	2	9	66
pT3	1232	80	6	18	12	35
pT4	724	90	15	42	15	10
Total	4683	48	5	12	7	60

Adapted from Sasako [2]

there exists a stage of regional disease wherein the cancer is confined to regional lymph nodes and lymphadenectomy would be able to 'potentially' cure the disease. The scientific evidence for this comes from the fact that long term survival is possible even in the presence of lymph node positive oesophageal cancer. This tells us that there exists a regional lymph nodal stage of oesophageal cancer in which lymphadenectomy would be potentially useful in curing the patient.

1.3 Rationale of Lymphadenectomy

The aim of extended lymphadenectomy for oesophageal carcinoma is two-fold: first to accurately stage the disease, and second to potentially cure the patient.

Even the staunchest of critics will agree that accurate staging is the most consistent result of extended lymphadenectomy. Accurate staging depends on the pathological determination of the T and N stages. While T stage is reasonably easy to determine from the resection of the primary tumour, the accuracy of N staging depends on the retrieval of a large sample of regional lymph nodes. The Dutch randomized trial (RCT) on this subject showed us that the mean lymph node yield almost doubled between transhiatal oesophagectomy (THE) and transthoracic *en bloc* oesophagectomy groups (16 and 31 lymph nodes, respectively) [4].

The oncological benefit of lymphadenectomy in the regional stage of the disease is undeniable, at least in a subgroup of patients. Several groups have demonstrated that there are long term survivors among patients with lymph node positive oesophageal carcinoma who undergo extended lymphadenectomy procedures. This is in contradiction to the 'Fisher' hypothesis referred to earlier. However, it seems that this benefit is restricted to early lymph nodal spread and is absent in bulky and extensive lymph node positive disease. It seems that extensive lymph nodal burden is a marker of systemic spread of the disease in which radical local surgery will have no oncological benefit.

1.4 Anatomy of Lymphatic Spread

Anatomically and embryologically, the oesophagus is an unique organ traversing three regions of the body, viz. neck, thorax and abdomen. Consequently, the arterial supply and venous drainage of the oesophagus are segmental. However, the same does not apply to lymphatic drainage of the oesophagus, which is said to be longitudinal.

The submucosa of the oesophagus is richly supplied with a network of lymphatic channels [5]. These communicate longitudinally and allow lymphatic drainage up and down far away from the site of the disease. As opposed to veins in the oesophagus, the lymphatic vessels possess numerous valves that direct the lymph flow.

Therefore, lymph flows in the submucosal channels more readily in a longitudinal manner than transversely. This matches the clinical observation that initial tumour spread follows the longitudinal axis of the oesophagus within the submucosa rather than extending in a transverse manner. A tumour-free margin at the resection line, as confirmed from the anatomical point of view, does not guarantee radical tumour removal. Thus subtotal oesophagectomy is recommended to include satellite nodules in the submucosa far away from the primary tumour. This submucosal spread of the tumour is also an explanation for the frequent 'skip' lymph node metastasis that are seen in oesophageal carcinoma. Some researchers, in cadaver studies, have found specific submucosal lymphatic channels leading to recurrent laryngeal nerve lymph nodes as an explanation for the frequent involvement of these lymph nodes in upper and middle third carcinomas [6, 7]. Thus a specific search for faraway nodes should be made even in superficial carcinoma of the oesophagus involving the submucosa.

Another interesting concept proposed by some authors was that of the 'watershed' zone of lymphatic drainage of the oesophagus at the level of the carina [8]. This has some embryological basis and is supported to a certain extent by clinical studies. It states that lymphatic drainage from tumours above the carina flows cranially towards the thoracic duct or subclavian lymphatic trunks, whereas lymphatic drainage from tumours below the carina flows mainly towards the cisterna chyli via lower mediastinal, left gastric and coeliac lymph nodes. The tumours straddling the carina tend to drain in both directions. Flow may, however, change under pathological conditions. When lymph vessels become blocked and dilated because of tumour invasion, the valves become incompetent and the flow reverses. This explains the retrograde and unexpected spread of some malignant tumours but limits the value of establishing pathways of normal flow.

1.5 Definitions

1.5.1 Extent of Lymphadenectomy

The three fields of lymphadenectomy comprise of lymph nodes in the upper abdomen, thorax and the lower cervical regions [9]. The definitions of no formal lymphadenectomy and three-field lymphadenectomy are fairly easily agreed upon. When no formal lymphadenectomy is done, as during a transhiatal oesophagectomy (THE), then only the peri-oesophageal lymph nodes are taken with the specimen. However, some surgeons add the formal abdominal phase of the lymphadenectomy during a THE. Three-field lymphadenectomy is performed by formally dissecting all three fields during oesophagectomy.

The controversy lies mainly with the definition of the two-field lymphadenectomy. In the West, with predominant gastro-oesophageal junction adenocarcinoma, a two-field lymphadenectomy was generally defined to mean dissection of the lower thoracic lymph nodes up to the carina, along with upper abdominal lymph nodes.

For some western surgeons, the third field is taken to mean the upper mediastinal lymph nodes along the recurrent laryngeal nerves in continuity with the cervical nodes along the nerves [10]. In the Japanese terminology, two-field was taken to mean complete thoracic lymphadenectomy, along with upper abdominal lymphadenectomy. Therefore the data of two-field lymphadenectomy between the western and Japanese literature was often not comparable.

During the 1994 Munich meeting of the International Society of Diseases of the Esophagus (ISDE) a consensus definition of lymphadenectomy was reached. Three-field lymphadenectomy comprised of formal dissection of the abdominal, thoracic and cervical fields [11]. Two-field lymphadenectomy was divided into three types (Fig. 1.1):

1. Standard lymphadenectomy (thoracic field including para-oesophageal lymph nodes, subcarinal lymph nodes, and right and left bronchial lymph nodes below the tracheal bifurcation).
2. Extended lymphadenectomy (thoracic field including standard lymphadenectomy plus the right apical, right recurrent laryngeal nerve and right paratracheal lymph nodes)
3. Total lymphadenectomy (thoracic field including extended mediastinal lymphadenectomy plus the left recurrent laryngeal nerve and paratracheal lymph nodes).

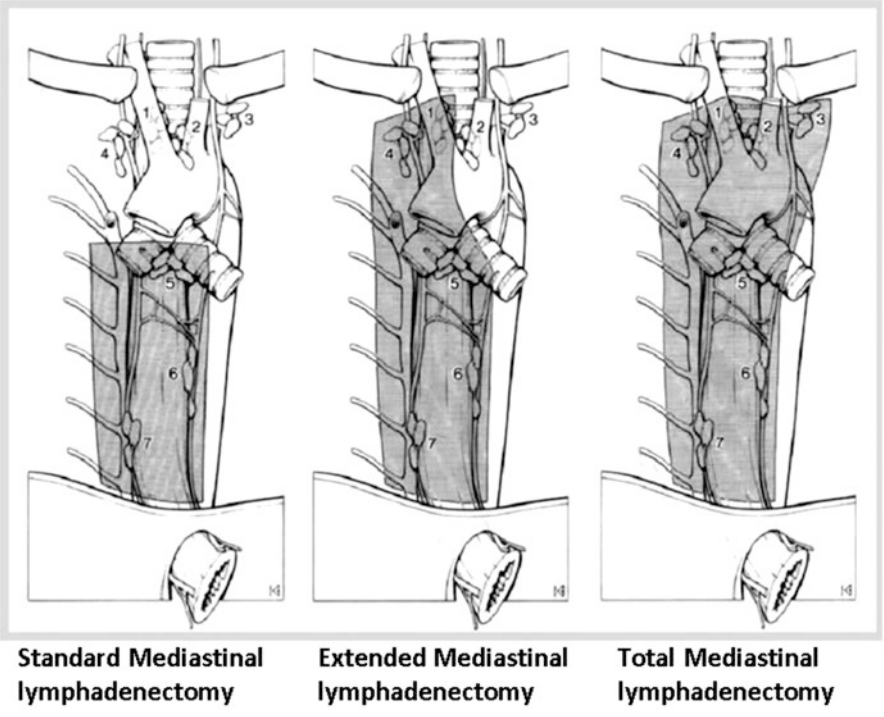

Fig. 1.1 Classification of two-field lymphadenectomy, as per ISDE consensus meeting, Munich, 1994. Extent of lymphadenectomy is represented in each type (Adapted and modified from [11])

In all these, it was agreed that the abdominal field would include lymph nodes around the three major branches of the coeliac artery.

En bloc oesophagectomy was proposed by Logan and furthered by the work of Skinner and colleagues [12, 13]. This refers to radical surgery for lower third oesophageal adenocarcinoma (and Siewert types 1 and 2 gastro-oesophageal junction carcinoma). En bloc resection entails resection of the thoracic oesophagus along with surrounding tissues completely enclosing the tumour-bearing part of the oesophagus with its related lymphatics. It includes the primary tumour and the pericardium, thoracic duct, azygous vein, intercostal vessels, and bilateral pleurae overlying the primary tumour and a surrounding cuff of crura (where the primary tumour is abutting). This original description was modified by others with the sparing of intercostal vessels, pericardium and azygous vein. Lymphadenectomy during this surgery is part of the wide clearance, the primary emphasis being on the wide lateral margins of resection. According to DeMeester, the en bloc dissection provided systematic removal of lymph nodes in the following areas: low paratracheal, subcarinal, perihilar, para-oesophageal, parahiatal, costal-vertebral space, porta hepatis, superior retropancreatic, and around the portal vein and the hepatic, coeliac and splenic arteries [14]. In the Dutch RCT on this subject, the extended en bloc lymphadenectomy included the thoracic duct, azygos vein, ipsilateral pleura, and all peri-oesophageal tissue in the mediastinum [4]. The specimen included the lower and middle mediastinal, subcarinal, and right-sided paratracheal lymph nodes (dissected en bloc). The aortopulmonary window lymph nodes were dissected separately in this trial. Hence, in most cases the extent of lymphadenectomy accompanying an en bloc oesophagectomy approximates either the standard or extended two-field lymphadenectomy described by the ISDE consensus conference.

1.5.2 AJCC TNM Staging and Nodal Nomenclature (7th Edition) [15]

Major data-based changes were done in the American Joint Cancer Committee (AJCC) 7th edition as compared to the 6th edition. Changes relevant to the lymph nodal staging are as follows. Lymph nodal staging was not based on the location of the lymph nodes. Instead, data showed that the number of involved lymph nodes was a strong predictive factor for survival. Hence, the number of regional lymph nodes positive for tumour were stratified as N1=1–2, N2=3–6, and N3=7 or more positive lymph nodes. The regional nodes were defined as in Table 1.2. Any positive non-regional lymph nodes were taken as metastatic disease (Fig. 1.2).

Table 1.2 Regional lymph nodes for oesophageal carcinoma (AJCC TNM 7th edition)

1	Supraclavicular, low cervical, and suprasternal notch
2R	Right upper paratracheal
2 L	Left upper paratracheal
3P	Posterior mediastinal (upper para-oesophageal above tracheal bifurcation)
4R	Right lower paratracheal
4 L	Left lower paratracheal
5	Aorto-pulmonary
6	Anterior mediastinal
7	Subcarinal
8	Lower para-oesophageal (below carina)
9	Inferior pulmonary ligament
10R	Right tracheobronchial
10 L	Left tracheobronchial
15	Diaphragmatic (adjacent to dome or retrocrural)
16	Paracardial (adjacent to gastro-oesopheageal junction)
17	Left gastric artery
18	Common hepatic artery
19	Splenic artery
20	Coeliac artery

Adapted from [15]

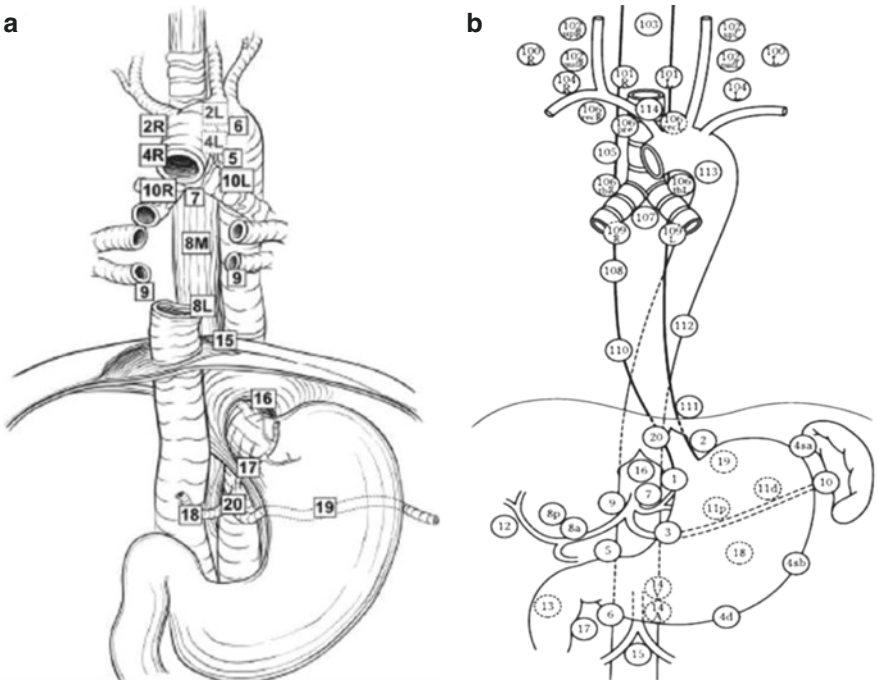

Fig. 1.2 Nomenclature and distribution of lymph nodes for esophageal cancer. A-AJCC 7th edition; B-Japanese classification 10th edition (Adapted from [15, 16])

1.5.3 *Japanese Classification of Oesophageal Cancer (10th Edition) [16]*

This is the most recent version of the classification proposed by the Japanese Esophageal Society (Table 1.3 and Fig. 1.2). The nodal classification is much more extensive and is quite different from the current AJCC nomenclature (Table 1.5). Another fundamental difference is that while the AJCC lumps together different tumour locations for lymph nodal staging (only the total number of positive lymph nodes matter for N staging), the Japanese staging of lymph nodal stations is different for various tumour locations (Table 1.4). This was based on the 'lymph node compartments' proposed by Kakegawa, Fujita and colleagues in their work on the importance of each lymph node station with regard to tumour location [17]. In brief the lymph nodal compartments were proposed based on the possibility of lymph nodal metastasis at that station and the impact on survival on removal of this lymph nodal station. The lymph nodal stations were grouped as in Table 1.4 (different for each tumour location). The extent of lymphadenectomy (as per the location of the tumour) was grouped as follows: D0 if no formal lymphadenectomy has been done, D1 for group 1 lymph nodal dissection, D2 for group 2 lymph nodal dissection and D3 for group 3 lymph nodal dissection (similar to gastric cancer). It is important not

Table 1.3 Japanese classification (10th edition): Number and naming of lymph nodal stations

Cervical lymph nodes		Abdominal lymph nodes	
100	Superficial neck (including those along spinal accessory nerve)	1	Right cardiac
101	Cervical para-oesophageal	2	Left cardiac
102	Deep cervical (lateral to IJV)	3	Lesser curvature
103	Peri-pharyngeal	4	Greater curvature
104	Supraclavicular	5	Suprapyloric
Thoracic lymph nodes		6	Infrapyloric
105	Upper thoracic para-oesophageal	7	Left gastric artery
106	Thoracic para-tracheal *106rec L – Left recurrent laryngeal* *106rec R – Right recurrent laryngeal* *106pre – Pretracheal* *106tb – Tracheobronchial (right and left)*	8	Common hepatic artery
		9	Coeliac artery
		10	Splenic hilum
		11	Splenic artery
		12	Hepato-duodenal
107	Subcarinal	13	Posterior superior pancreatic head
108	Middle thoracic para-oesophageal	14	Superior mesenteric vessel
109	Main bronchus (right and left)	15	Middle colic artery
110	Lower thoracic para-oesophageal	16	Para-aortic
111	Supradiaphragmatic	17	Anterior pancreatic head
112	Posterior mediastinal (paraortic and pulmonary ligament)	18	Along inferior pancreatic margin
113	Ligamentum arteriosum (Botallo)	19	Infradiaphragmatic
114	Anterior mediastinum	20	In oesophageal hiatus of diaphragm

Adapted from [16]

Table 1.4 Japanese classification (10th edition): Lymph node groups according to tumour location

Tumour location	Group 1 (N1)	Group 2 (N2)	Group 3 (N3)
Cervical	101, 106rec	102, 104, 105	100
Upper thoracic	105, 101, 106rec	104, 106tbL, 107, 108, 109	102mid, 106pre, 106tbR, 110, 111, 112, 1, 2, 3, 7
Middle thoracic	108, 106rec	101,105, 106tbL, 107,109, 110, 1, 2, 3, 7	104, 111,112,20
Lower thoracic	110, 1, 2	106rec, 107, 108, 109, 111, 112, 3, 7, 20	101, 105, 106tbL. 9, 19
Abdominal	110, 1, 2, 3, 7, 20	108, 110, 111, 8a, 9, 11p, 19	106rec, 107, 109, 112, 4sa, 4sb, 4d, 5, 6, 11d
Oesophago-gastric junction (EG type)	110, 1, 2, 3, 7, 20	108, 110, 111, 8a, 9, 11p, 19	106rec, 107, 109, 112, 4sa, 4sb, 4d, 5, 6, 11d
Oesophago-gastric junction (GE type)	1, 2, 3, 7, 20	4sa, 4sb, 8a, 9, 11p, 19	108, 110, 111, 112, 4d, 5, 6, 8p, 10, 11d, 16

Adapted from [16]

Table 1.5 Comparison of Japanese and AJCC nodal stations

Node zone	Station number (JES)	Name of node station (JES)	Station number (AJCC)	Name of node station (AJCC)
Supraclavicular	104R	Right supraclavicular	1	Supraclavicular
	104 L	Right supraclavicular	1	Supraclavicular
	101R	Right cervical para-oesophageal		(Cervical para-oesophageal)
	101 L	Right cervical para-oesophageal		(Cervical para-oesophageal)
Upper mediastinal	105	Upper para-oesophageal	3p	Posterior mediastinal
	106pre	Pretracheal	2R	Right upper paratracheal
	106recR	Right recurrent nerve	2R	Right upper paratracheal
	106recL	Right recurrent nerve	2 L	Left upper paratracheal
	106tbR	Right tracheobronchial	4R	Right lower paratracheal
	106tbL	Right tracheobronchial	4 L	Left lower paratracheal
Middle mediastinal	107	Subcarinal	7	Subcarinal
	108	Middle para-oesophageal	8 m	Middle para-oesophageal
	109R	Right main bronchus	10R	Right tracheobronchial
	109 L	Left main bronchus	10 L	Left tracheobronchial
Lower mediastinal	110	Lower para-oesophageal	8I	Lower para-oesophageal
	111	Supradiaphragmatic	15	Diaphragmatic
	112	Posterior mediastinum	9	Pulmonary ligament

continued

Table 1.5 (continued)

Node zone	Station number (JES)	Name of node station (JES)	Station number (AJCC)	Name of node station (AJCC)
Perigastric	1	Right cardiac	16	Paracardial
	2	Left cardiac	16	Paracardial
	3	Lesser curvature		
	7	Left gastric artery	17	Left gastric artery
Coeliac	9	Coeliac	20	Coeliac
	8	Common hepatic artery	18	Common hepatic
	11	Splenic artery	19	Splenic
	19	Infradiaphragmatic		

to confuse the fields of lymphadenectomy (two or three-fields) with the extent of lymphadenectomy (D0, D1, D2 and D3) as per the Japanese classification. The fields of lymphadenectomy are not related to the location of the tumour, while extent of lymphadenectomy (D0, D1, D2 and D3) is related to the location of the tumour in the oesophagus. Udagawa recently corroborated the Japanese lymph nodal stations with a similar concept, the Efficacy index (EI) [18]. The EI of each lymph nodal station was calculated from the raw data of 3-field dissection and follow-up 5-year survival (EI = percentage of lymph nodal positivity for that station X percentage of 5-year survival if this station was positive). The EI referred to the potential survival benefit that would be accrued if the concerned lymph node station was dissected during lymphadenectomy.

1.6 Oncological Outcomes of Lymphadenectomy

1.6.1 Recurrence

Although the literature on recurrence is riddled with problems of data comparability, THE without formal lymphadenectomy is known to have a high locoregional recurrence rate. The recurrence rate for a series of 149 patients from Netherlands who underwent THE was as follows: locoregional only (23.4 %), systemic only (15.3 %) and combined (13.9 %) [19]. Therefore, the total locoregional recurrence rate was nearly 40 % in this series. Of these the majority (49 %) occurred in the thoracic field where no lymph nodal dissection had taken place and multivariate analysis showed that lymph node-positive stage was an independent risk factor for recurrence. En bloc oesophagectomy data from DeMeester's group has shown an isolated locoregional recurrence rate of 8 % as compared with 23.4 % in the preceding THE series [20]. In most published literature, the locoregional recurrence after THE is much higher (23–47 %) as compared to en bloc oesophagectomy (1–10 %) [14, 19–27]. Three-field lymphadenectomy series have reported quite a low incidence of locoregional

recurrence. Altorki *et al*. reported a locoregional recurrence rate of 9.7 % and Lerut's group reported an isolated locoregional lymph nodal recurrence rate of 5.2 % in their series of 80 patients and 174 patients, respectively undergoing a three-field lymphadenectomy [28, 29]. Osugi *et al*. reported a mediastinal lymph nodal recurrence rate of 5.7 % in 140 patients who underwent a video-assisted thoracoscopic surgery (VATS)-assisted three-field lymphadenectomy [30]. In a rather underpowered RCT comparing three-field with two-field lymphadenectomy for squamous cell carcinoma (SCC), Nishihira and colleagues reported a reduced recurrence rate of 12.9 % versus 24 %, respectively (statistically not significant) [31]. However, the Dutch RCT (mostly adenocarcinoma) reported a statistically equivalent locoregional recurrence rate of 19 % and 23 % for en bloc oesophagectomy and THE, respectively [4].

The cervical field of dissection during three-field lymphadenectomy for SCC has shown a metastasis rate of 23.4–49.5 % in different series [9, 32–34]. In Fujita's series of 176 patients (of three-field lymphadenectomy) the cervical lymph node positivity was 24 % but the cervical local recurrence rate was only 14 % [9]. Fujita argued that the cervical node dissection field may have prevented some cervical recurrences.

1.7 Long Term Survival

One needs to look no further than Akiyama's landmark paper to see what three-field lymphadenectomy can do for long term survival in oesophageal cancer [32]. In this paper 717 patients who underwent R0 resection were analysed (393 two-field and 324 three-field lymphadenectomy patients). The overall 5-year survival was 37.1 % and 52.2 %, respectively. Altorki reported their results after three-field lymphadenectomy for adenocarcinoma oesophagus [28]. He reported an overall 46 % 5-year survival for adenocarcinoma. These results may be difficult to interpret due to the retrospective nature of these series and the phenomenon of stage migration. However, the mere fact that in Akiyama's series, three-field lymphadenectomy led to a 25 % 5-year survival in the sub-group of patients with positive cervical nodes, says a lot about the radical procedure [32]. In Altorki's series, the incidence of cervico-thoracic node metastasis for adenocarcinoma was 37 % and in this group, the 5-year survival was a remarkable 15 % [28].

However, the beneficial effect of three-field lymphadenectomy seems to be restricted to patients with a low burden of metastatic lymph nodes. The effect of improved survival disappears as soon as the number of positive lymph nodes increases beyond a threshold. Unfortunately, this threshold has been defined differently by different authors. Akiyama found that of patients with SCC and N+ stage, after three-field lymphadenectomy, those with more than 7 positive lymph nodes have a low survival despite a radical procedure (9 % versus 51 % 5-year survival) [32]. DeMeester's group found that among patients with adenocarcinoma and T3 N1 stage, more than 8 positive lymph nodes had a lower survival (statistically significant). Another series of three-field lymphadenectomy for SCC from Japan showed that the 5-year survival was significantly different for N+ stage 1–4 and >4 lymph nodes: 37 % versus 14 %, respectively [35].

Prospective controlled studies however are not so conclusive on the issue of long term survival. An older Japanese prospective controlled study (? randomized) of two-field versus three-field in SCC showed a 5-year survival difference of 33.7 % versus 48.7 %, respectively [36]. However, the study was criticized for having several methodological flaws. Another RCT from Japan (two-field versus three-field) with a rather small sample size could not demonstrate a significant 5-year survival difference (48 % and 66 %, respectively) [31]. The most recent Dutch RCT in adenocarcinoma (THE versus extended en bloc oesophagectomy) could not demonstrate a survival difference even after complete 5-year follow-up (34 % versus 36 %, respectively) [37]. The authors themselves conceded that the sample size was small for the difference they had intended to prove.

There could be several reasons why these trials could not prove the difference in survival between 'smaller' and 'greater' lymphadenectomy groups. The short answer could be that there is no difference and that lymphadenectomy is useless. However, there are other facts that need consideration. It may be that the difference is actually small and needs a much larger sample size to be demonstrated. Another fact that comes forth from retrospective data is that only a subgroup of patients with limited lymph nodal metastasis benefits from the extended lymphadenectomy. Subgroup analysis of the Dutch RCT, showed that patients with Siewert type 1 carcinoma and 1–8 positive lymph nodes derive the maximum survival benefit with extended en bloc oesophagectomy as compared to those with >8 positive lymph nodes [37]. One would need to do a RCT on such a subgroup to prove a benefit. It would be next to impossible to accurately identify such a subgroup preoperatively to conduct a trial given the imperfect nature of the currently used staging investigations.

1.7.1 Azygous Resection

Enbloc oesophagectomy and three-field esophagectomy were traditionally carried out by open thoracotomy with resection of the azygous vein with the specimen. However, it required meticulous technique to ligate all the intercostal veins and the hemi-azygous veins, with potential for bleeding complications in case of errors. With the advent of minimal access oesophagectomy questions were raised about the oncological necessity for resection of the azygous vein as it added considerable time and effort to the minimal access oesophagectomy. There is only limited published literature directly pertaining to this issue. One study on human cadavers indicated that only a few lymph nodes lay along the azygous vein, therefore there was no real benefit in terms of lymph node yield during the oesophagectomy [38]. Another retrospective clinical study evaluated en bloc oesophagectomy specimens in 92 patients [39]. The azygous vein was dissected from the specimen and the lymph nodes along it were separated out. The authors concluded that a significant number of lymph nodes lay along the azygous vein and it should be resected during oesophagectomy to increase the lymph node yield. This study was however criticized for the amount of tissue that was removed from the specimen with the azygous vein and

that this did not reflect the technique of minimal access oesophagectomy very well [40]. During minimal access oesophagectomy, most surgeons would bare the azygous vein and leave hardly any tissue along it. Hence there didn't seem any real oncological benefit to resecting the azygous vein during an oesophagectomy, minimal access or open. The other reason for leaving the azygous arch intact was the protection it offered to the preserved right bronchial artery that runs alongside it. It has been suggested by some authors that taping the two together would be a good way of ensuring against accidental avulsion of the thin bronchial artery [41].

1.7.2 Thoracic Duct Resection

The thoracic duct enters the thorax through the aortic hiatus, runs in the small space between the azygous vein and the descending thoracic aorta and moves from right to left in the upper mediastinum, eventually joining the venous confluence of the left subclavian and left internal jugular veins. The thoracic duct is routinely removed during an en bloc or three-field oesophagectomy, with the rationale of improved oncological clearance. The oncological benefit of thoracic duct excision has not been studied in great detail. Udagawa published a study on the lymph nodes along the thoracic duct [42]. Their group distinguished these lymph nodes from the station 112 (posterior mediastinum lymph nodes) and noted a 10 % incidence of metastasis in these nodes in T3/T4 tumours. They recommended thoracic duct excision for oncological benefit inT3/T4 tumours. However, another study from Japan could not distinguish thoracic duct lymph nodes from the posterior mediastinum (112) and left recurrent laryngeal lymph nodes (106recL) [43]. The authors noted that if the thoracic duct was excised there was a significant increased yield in other lymph nodal stations as well. Thus it seemed that a change of technique to a more radical dissection is the more likely explanation for the improved lymph nodal harvest rather than resection of the thoracic duct. Thoracic duct excision should be balanced against the risks of the resection. The potential risks include chylothorax, postoperative fluid retention in the abdomen, increased pulmonary morbidity and increased risk of endotoxaemia [43]. A systematic review concluded that prophylactic thoracic duct resection in fact reduces the chances of chylothorax (OR 0.47, 95 % CI 0.27–0.80); though the authors noted significant heterogeneity in the included studies [44]. Imamura, in a study of 24 patients undergoing en bloc oesophagectomy, demonstrated significant retroperitoneal oedema, fluid retention and intravascular hypovolaemia that needed large volume colloid infusion [45]. Aiko, in a study of early enteral nutrition, recommended early enteral nutrition following oesophagectomy but could not demonstrate any benefit for patients with ligated thoracic duct [46]. They did not recommend early enteral nutrition for this group of patients. On the whole, it seems that thoracic duct may be excised in locally advanced tumours for oncological benefit but these patients require careful management of fluid balance in the immediate postoperative period.

1.8 Morbidity and Mortality of Lymphadenectomy

A high mortality and morbidity has been the Achilles heel of radical lymphadenectomy for oesophageal carcinoma. For three-field lymphadenectomy the operative mortality ranges from 0 to 10 % and the overall morbidity ranges from 46 to 80 % [28, 29, 35, 47–49]. In a nationwide survey from Japan 1791 patients underwent three-field lymphadenectomy and the total morbidity was 54 % [50]. The major complications included pulmonary complications (22 %) and recurrent laryngeal nerve palsy (20.3 %). It is clear that there is a learning curve associated with lymphadenectomy. In two reports of en bloc oesophagectomy from DeMeester's group (37 patients in 1999 and 119 patients in 2006), the operative mortality improved from 5.4 to 2.5 % [51, 52].

The major morbidity specific to lymphadenectomy are pulmonary complications and the major contributing factors are the recurrent laryngeal nerve injury, tracheobronchial ischaemia, pulmonary vagal denervation and poor pulmonary lymphatic drainage.

Recurrent laryngeal nerve injury (usually left side) during lymphadenectomy results from handling and taping of the nerve, thermal injury from energy devices and ischaemia due to dissection around the nerve. The reported incidence varies widely (15–70 %) not only due to the differences in surgical technique but also in the method used to diagnose the palsy and rigorousness of follow-up [48, 53–57]. However, it seems clear that cervical anastomosis and three-field lymphadenectomy are associated with a higher incidence of recurrent laryngeal nerve palsy [53]. In a Japanese series of lymphadenectomy, the incidence of recurrent laryngeal nerve palsy was similar in the three-field and the two-field groups wherein left recurrent laryngeal nerve lymph node dissection was done (14.2 % versus 20.5 %, respectively); thereby implying that the dissection around the nerve in the upper mediastinum is most likely responsible for the injury [36]. Most of the palsy is transient and improves with time. In a Dutch series, recurrent laryngeal nerve palsy was 22 %; but most improved over 3–6 months and only 4 % had permanent palsy [53]. The more extensive the dissection, the higher is the incidence of permanent palsy. In two Japanese series of three-field dissection with recurrent laryngeal nerve palsy rates of 36 % and 36.2 %, permanent palsy was seen in 12 % and 21.2 %, respectively [56, 58]. Patients with recurrent laryngeal nerve palsy are also more likely to have pulmonary complications, need for re-intubation, tracheostomy, recurrent aspiration and swallowing problems. Quality of life studies have found persistent recurrent laryngeal nerve palsy to be associated with poor quality of life, poor pulmonary function, repeated aspirations and pneumonia in the long term [48, 59].

Tracheo-bronchial ischaemia and ulceration is typically associated with three-field lymphadenectomy. Experiments in dogs by Fujita demonstrated these to be a result of right bronchial artery ligation and preserving this artery had a protective influence on the tracheal blood supply [60]. The right bronchial artery is closely related to the azygous arch and further on, to the pulmonary branches of the right vagus. Ischaemia is also caused by damage to the vascular sheath of the airways

during skeletonizing dissection. Tracheo-bronchial ischaemia leads to bronchorrhoea (excessive bronchial secretions), pneumonia, respiratory failure and need for tracheostomy.

Fujita modified the mediastinal dissection in light of the understanding of factors associated with pulmonary morbidity [61]. He advocated 'functional' mediastinal dissection to preserve the right bronchial artery, pulmonary branches of the vagus nerve, the azygous vein and the thoracic duct [62].

There is paucity of good quality controlled data on the issue of morbidity of lymphadenectomy. The Dutch RCT on this issue reported a significantly increased incidence of pulmonary complications (57 % versus 27 %) in en bloc oesophagectomy group versus the THE group [4]. In addition, the en bloc oesophagectomy group had a significantly increased ventilation time, and stay in the intensive care unit and hospital. A recent meta-analysis of three-field versus two-field lymphadenectomy (including 2 RCTs and 18 observational studies) reported that three-field lymphadenectomy was associated with a higher incidence of postoperative complications: recurrent laryngeal nerve palsy (p=0.02) and anastomosis leak (p=0.09) [63]. In contrast, there was no significant difference for pulmonary complications (p=0.27) or chylothorax (p=0.69). However, the results of this meta-analysis should be interpreted with caution because of the inherent problems of the included studies such as significant heterogeneity of data, lack of standard definitions and a variety of surgical techniques.

1.9 Arguments For and Against Lymphadenectomy

1.9.1 Arguments for Lymphadenectomy

- *Oncological benefit:* The reader is advised to go through the earlier detailed sections on this issue. It is clear that THE has a high rate of local recurrence and that formal lymphadenectomy reduces the rate of locoregional recurrences. There is paucity of data on the issue of long term survival benefit of lymphadenectomy. From the only recent RCT and several large retrospective series from expert centres, it seems that lymphadenectomy benefits a subgroup of patients with limited nodal burden. However, it has proven difficult to identify this subgroup accurately given the fallacies of the current preoperative staging investigations for oesophageal carcinoma.

  Coeliac and supraclavicular lymph nodes were earlier taken as distant lymph nodes for thoracic oesophageal carcinoma, by the traditional school of thought. Seto *et al*. analysed their cohort of 805 patients who had undergone two- or three-field lymphadenectomy [64]. The incidence of coeliac lymph node positivity was 7.7 % and 17.4 %, respectively for middle and lower third carcinoma. They compared the outcome of only coeliac lymph node positive patients with only left gastric lymph node positive patients and found no significant difference in long term survival. The

prognosis of coeliac lymph nodes was similar to that of left gastric lymph nodes in patients undergoing extended lymphadenectomy. Thus, these nodes are included in regional lymph nodes by the 7th edition of the AJCC TNM classification and should be given a chance at a potentially curative resection.

- *Number of removed lymph nodes and lymph node ratio:* A number of publications have shown that a larger number of removed lymph nodes is associated with long term survival. In various studies different optimal thresholds for lymph nodal resection (varying from 18 to 30 nodes) have been proposed, based on an analysis of their institutional databases [65–69]. However, none of these studies stratified the number of lymph nodes with regard to the T stage. The World Wide Esophageal Collaboration (WECC) is a group of experienced oesophageal teams across the world that has collated their data to produce important information about lymph node staging of oesophageal carcinoma [70, 71]. Of 7884 oesophagectomies for oesophageal cancer done at these 13 participating institutions, 4725 were neither preceded nor followed by adjuvant chemotherapy or radiotherapy (oesophagectomy alone) [70, 71]. Using the endpoint of all-cause mortality and advanced statistical methods the optimal number of lymph nodes to be resected was defined for each stage. The authors recommended that to maximize 5-year survival, a minimum of lymph nodes to be resected were 10 for T1, 20 for T2, and 30 or more for T3/T4 cancers [70, 71]. The WECC data was used to establish the changes in the N staging proposed in the 7th edition of AJCC TNM staging for oesophageal carcinoma.

  The lymph node ratio (LNR) is the ratio of metastatic to total lymph nodes and has been shown to be a prognostic factor in oesophageal cancer but the value that is most predictive of survival is not clear. Though the most commonly quoted figure is 0.2 to define the adequacy of lymphadenectomy, various ratios from 0.1 to 0.3 have been proposed by different series [72–74]. LNR has been shown to be more accurate for inadequately staged patients (<15 lymph nodes resected), whereas the number of lymph node metastasis is pertinent for adequately staged patients (>15 lymph nodes resected) [75].

- *Improved staging:* It is quite clear that lymphadenectomy leads to improved staging of patients. In a prospective series from Netherlands, the authors found that extended en bloc oesophagectomy changed the tumour stage in 23 % of their patients [75]. The WECC data suggests that for each T stage, a minimum number of lymph nodes are to be resected to enable accurate staging [70]. In the 7th edition of AJCC TNM staging, the lymph nodal stage is based on the number of lymph nodes involved by tumour. Hence, a formal lymphadenectomy is important to enable accurate pathological assessment of lymph nodes in the drainage area and improved staging.

- *Lymphadenectomy according to location/histology of tumour:* Most experts agree that three-field lymphadenectomy is the procedure of choice for upper third thoracic oesophageal carcinoma. This was the consensus of experts in a panel during the 1995 ISDE Milan meeting and has also been recommended by

the Japanese Esophageal Society guidelines of 2012 [76, 77]. However, there is disagreement on the issue of three-field lymphadenectomy for middle and lower third oesophageal carcinoma. Japanese guidelines suggest that cervical lymphadenectomy may be omitted in selected patients with middle or lower third oesophageal carcinoma. They further suggest that, for these groups of tumours, a total mediastinal (two-field) lymphadenectomy should be done. These recommendations apply mostly to location of the tumour and do not take into account the histology of the tumour. Most data of three-field lymphadenectomy has been taken from patients with SCC in Japan and there are major differences in the way it is applied to patients with adenocarcinoma in the western world. Apart from a few groups, most surgeons in the West limit the dissection to a two-field lymphadenectomy (usually below the carina).

- *Early carcinoma:* Lymph node spread occurs early in oesophageal carcinoma. As the oesophageal carcinoma invades deeper into the mucosa and submucosa, it gains access to the extensive submucosal lymphatics and the incidence of lymph nodal spread increases proportionately. Hence, lymphadenectomy should be considered even for early oesophageal carcinoma (beyond T1b SM1). A large national survey of superficial carcinoma (2418 patients from 143 institutions) from Japan noted the T stage versus lymph nodal involvement as follows: T1aEP Nil; T1aLPM 3 %; T1aMM 12 %; T1bSM1 26 %; T1bSM2 36 %; T1bSM3 46 % [78]. The recent Japanese guidelines recommend that endoscopic resection can be done for early T1a tumours (T1aEP: limited to epithelium; and T1aLPM: limited to lamina propria) as the incidence of lymph nodal spread is very low. For tumours deep in the submucosa (T1b SM2 and T1b SM3), in view of the high incidence of lymph nodal spread, these should be treated as advanced tumours with formal lymphadenectomy. For the in-between tumours (T1aMM and T1bSM1), a selective approach to endoscopic resection can be taken if endoscopic ultrasound does not suggest lymph nodal disease.

  However, some authors from the West have contended that early adenocarcinoma has a better prognosis than early SCC. Stein *et al*. in a study on superficial oesophageal carcinoma found a lower incidence of lymph nodal metastasis in early adenocarcinoma as compared to early SCC (T1a 0 % versus 8 %, T1b 20.7%versus 36.4 %, respectively) [79]. These authors have made a case for limited resection and limited lymphadenectomy for early adenocarcinoma involving the submucosa only.

- *Skip metastasis:* Though the term has not been conclusively defined, it is loosely taken to mean lymph nodal metastasis to distant lymph nodal stations beyond the immediately adjoining lymph nodes, wherein the lymph nodes at the same level as the primary tumour are negative for metastasis. The incidence varies from 20 to 73 % in various studies [80–83]. In one study the incidence rose from 34 to 66 % once immunohistochemistry was used to detect micrometastasis [83]. The importance of skip metastasis lies in missing out lymph nodal metastasis and understaging the tumour if formal lymphadenectomy of all possible draining lymph nodal stations is not done.

- *Micrometastasis:* Quite a few patients with pN0 nodal stage after resection have been shown to have clusters of tumour cells that were missed by conventional histopathology examination. These clusters of tumour cells (0.2–2 mm in size) are called micrometastasis. Immunohistochemical studies have shown that 14–85 % of patients have nodal micrometastasis [84–87]. The prognosis of these patients has been shown to be similar to pN1 stage [86, 87]. Hence, a formal lymphadenectomy can upstage patients with N0 disease as well as add to survival.

- *Selective application of three-field lymphadenectomy:* It is clear that the increased morbidity of three-field oesophagectomy takes the sheen off the long term oncological benefits of the procedure. Several authors have tried selective application of three-field lymphadenectomy by identifying groups of patients who would benefit most by this approach. A few approaches to select patients for cervical lymph node dissection are as follows:

  1. *Tumour location*: Most surgeons agree that upper and, possibly, middle thoracic tumours should undergo cervical dissection in view of the high incidence of cervical lymph nodal metastasis (13–47 % for upper third and 14–59 % for middle third carcinoma) [28, 88, 89].
  2. *Upper mediastinal lymph nodes*: Lymph node metastasis of the upper mediastinum, in particular along the recurrent laryngeal nerve, may be an indication for cervical lymph node dissection in thoracic oesophageal cancer. Some studies have concluded that cervical dissection can be omitted if the recurrent laryngeal nerve lymph nodes are negative, with similar survival [90, 91].
  3. *Ultrasound imaging of neck lymph nodes*: Ultrasound has been used in breast, and head and neck tumours to stage the neck lymph nodes. Some studies have used ultrasound of the neck to select patients for cervical field of dissection with reasonable results [92, 93]. However, cervical dissection is not recommended for palpably enlarged lymph nodes because of a lack of survival benefit.

- *Transhiatal lymphadenectomy:* Siewert and colleagues have proposed a radical transhiatal en bloc oesophagectomy using special retractors and a mediastinoscope for tumours at the GE junction [94]. A mean of 26 lymph nodes could be resected and the survival was better than THE in the N+ group. However, this procedure has not found much favour with surgeons across the world. Most surgeons believe that this approach provides only limited access to subcarinal and paratracheal lymph nodes and is oncologically incomplete [95].

1.9.2 Arguments Against Lymphadenectomy

- *Oncological benefit?*: There is no level 1 evidence to prove the benefit of lymphadenectomy. The few randomized trials (one from Netherlands and one from Japan) on this issue do not show any conclusive benefit of extended lymphadenectomy. Data from subgroup analysis of these trials and retrospective series need to be proven in high quality trials for clear benefit.

Any suggested therapeutic effect of lymphadenectomy may be explained by stage migration. A larger number of nodes dissected would migrate some patients to a higher N-stage, called 'stage migration'. Thus, the prognosis of the group left behind after extended lymphadenectomy with a lower N-stage, would be better than the group with no formal lymphadenectomy and lower N-stage. This is because the second group would have some patients of the higher N-stage who are hitherto undiagnosed in the absence of formal lymphadenectomy. Stage migration thus would lead to a biased stage-by-stage comparison of survival.

With the possible exception of randomization, there is no fool-proof way of negating the effect of stage migration on survival of groups of patients.

- *High mortality and morbidity*: With experience, refinement of technique and improvement of perioperative care, the mortality of three-field lymphadenectomy has been brought down to acceptable levels. However, the morbidity of the procedure continues to be high as shown in both retrospective as well as prospective studies. The main morbidity includes recurrent laryngeal nerve palsy, pulmonary complications and anastomotic leakage.

- *Quality of life (QOL)*: QOL studies after oesophagectomy have suggested that patients with postoperative complications have a lower QOL on follow-up [96, 97]. It would be difficult to pin point what component of this reduced QOL is because of lymphadenectomy. However, since lymphadenectomy is associated with increased morbidity, it is to be expected that the long term QOL would also deteriorate. Nishihira *et al*. in a 1998 RCT of two-versus three-field lymphadenectomy found a non-significant increase in recurrent laryngeal nerve palsy (30 % versus 56 %) and a significant increase in the need for tracheostomy (10 % versus 53 %) [31]. Baba *et al*. found that permanent recurrent laryngeal nerve palsy led to lesser QOL; and specifically lower performance status, reduced ability to go upstairs and poor swallowing function at 1 year follow-up and a low body weight, poor pulmonary function and recurrent aspiration pneumonia after 3 years of follow-up [56].

- *Regional or systemic disease?*: Several surgeons continue to believe that lymph nodal deposits in the mediastinum and cervical region constitute systemic disease and extensive locoregional surgery will not have much benefit [98–100]. The low survival of patients with multiple lymph nodes in the mediastinum/cervical region seems to support this contention.

- *Is cervical dissection necessary?*: Several series of three-field lymphadenectomy have shown cervical lymph nodal metastasis from lower third or GE junction tumours in 15–30 % of patients [9, 32, 35]. However, others have found that the cervical recurrence rates after two-field lymphadenectomy in patients with lower third carcinoma, were quite low (3–11 %) [101, 102]. Mariette *et al*. in their series of 439 patients undergoing en bloc oesophagectomy found locoregional recurrence rate of 20.5 % and of these only 3.6 % had cervical recurrence [101]. Their group questioned the need for three-field dissection and proposed that two-field lymphadenectomy was enough.

- *Learning curve of three-field lymphadenectomy*: The learning curve of oesophagectomy has been variably defined to be from 6 to 20 procedures [103–106]. However,

no attempt has been made to define learning curve separately for lymphadenectomy. Osugi *et al*. tried to define the learning curve for minimally invasive oesophagectomy with three-field lymphadenectomy and concluded that 34 such procedures are needed to reach a plateau in technique [107]. An interesting recent study from Sweden found that although operative mortality plateaus after 15 cases of oesophagectomy, the lymph node yield showed no plateau and continued to increase with experience [108]. Three-field lymphadenectomy is a demanding surgical procedure and it is likely that a poorly regulated diffusion of three-field lymphadenectomy worldwide, especially in western countries, would lead to an increase in morbidity and mortality, counterbalancing the potential survival benefit of the technique.

Although experts and high volume institutions wax eloquent about the need for lymphadenectomy, its acceptance and penetration among surgeons dealing with oesophageal cancer is woefully inadequate. In a study on the variation in lymphadenectomy across the USA, 13,995 patients from 639 institutions were studied [109]. Taking the National Comprehensive Cancer Network (NCCN) recommendation to resect at least 15 lymph nodes during oesophagectomy, it was found that at least 15 nodes were examined in 28.7 % patients and at only 45 centres (7 %) [109]. This makes apparent the huge gap between teaching and practice of lymphadenectomy in oesophageal cancer.

- *Autopsy and cadaver studies*: The surgical lymph node yield of three-field lymphadenectomy should be viewed in light of cadaver studies of lymph node yield. In an Indian study 10 cadavers were dissected and the authors found 183 (118–234) lymph nodes in stations relevant to lymphadenectomy in oesophageal cancer. To put things in perspective several series of three-field lymphadenectomy have reported a range of 59–85 mean lymph nodes removed, though it may not be fair to compare cadaveric to clinical studies [31, 48, 110, 111]. An autopsy study on recurrence after oesophagectomy has shown that though the local and lymph nodal recurrence after three- or two-field lymphadenectomy is lower than standard oesophagectomy it is still quite high (19 % and 38 %, respectively for oesophagectomy with lymphadenectomy versus 66 % and 66 %, respectively for standard oesophagectomy) [112]. Anatomical difficulty of ‘complete’ removal of lymph nodes by surgical procedures was suggested by the authors.

1.10 Special Situations

1.10.1 Relevance of Lymphadenectomy in the Era of Neoadjuvant Therapy

Several articles have made note of the effect of neoadjuvant chemoradiotherapy on lymph nodes. Radiotherapy is responsible for lymphocyte depletion at lower doses and atrophy and fibrosis of the lymph nodal stroma at higher doses [113]. Both the number and size of the lymph nodes is reduced after neoadjuvant chemoradiotherapy. Bollschweiler *et al*. in a study with matched pair analysis of surgery with or without

neoadjuvant chemoradiotherapy reported that the frequency of lymph nodal metastasis was least in major responders versus minor responders/no chemoradiation (20 % versus 65 %, respectively) [114]. The size of metastatic lymph nodes was also significantly smaller (median 5 mm versus 7 mm). There are several reports of reduced lymph node harvest after neoadjuvant chemoradiotherapy. Post hoc analysis of a French RCT (FFCD9901) on neoadjuvant chemoradiation and surgery versus surgery alone showed that the median lymph node harvest was significantly lower in the former group (16 versus 22) [115]. Similar analysis of the CROSS trial data gave number of median lymph nodes harvested to be 14 versus 18 in the respective groups [116]. Thus it is clear that neoadjuvant chemoradiation before surgery has a negative impact on the number of lymph nodes harvested at surgery. Whether only neoadjuvant chemotherapy can have the same effect on lymph nodal metastasis was answered by the JCOG9907 Japanese RCT of preoperative chemotherapy versus postoperative chemotherapy [117]. The preoperative chemotherapy arm had a pN0 rate of 35 % versus 24 % in the postoperative chemotherapy arm.

Some authors have questioned the need for formal lymphadenectomy after neoadjuvant chemotherapy citing lack of impact of lymphadenectomy, in this scenario, on long term survival [116, 118]. On the other hand, groups such as the WECC have found a significant survival benefit and said that the WECC recommendations for lymphadenectomy (refer to earlier sections) are equally applicable to patients undergoing surgery following neoadjuvant chemoradiation [119, 120]. Chao *et al*. showed that in a subgroup of patients who did not experience complete pathological response, the mean survival was better in those who underwent complete lymphadenectomy versus those who underwent incomplete lymphadenectomy (mean 32 versus 15.9 months) [121].

Although there is a lack of high quality studies on this issue, from the existing studies it seems that lymphadenectomy in this scenario (surgery after neoadjuvant chemoradiation) is associated with survival benefit in certain subgroups of patients, i.e. those who are not down-staged by pathological tumour depth (T) classification and those with persistent lymph nodal metastases after chemoradiation [119]. However, this needs to be ratified in higher quality studies on this issue. Meanwhile, in patients who undergo surgery after neoadjuvant chemoradiation, there is currently no justification for the modification of surgical lymphadenectomy based on tumour response to chemoradiation [120]. It should be kept in mind that tumour response is a postoperative pathological diagnosis and currently there is no accurate means of predicting the same before surgery. In addition, inadequate lymphadenectomy may lead to positive lymph nodes being missed and patients being erroneously classified as ypN0.

1.10.2 Minimally Invasive Oesophagectomy (MIE) and Lymphadenectomy

Oesophagectomy and lymphadenectomy is a technically challenging operation to be performed through the minimally invasive route. The TIME trial is the only RCT comparing minimally invasive oesophagectomy to open thoracotomy and

oesophagectomy [122]. Surgery included standard two-field lymphadenectomy in both arms, up to the carina. The lymph node count was similar in the two arms (20 versus 21, respectively), while the pulmonary morbidity was lower (pulmonary infection was 9 % versus 29 %, respectively) [122]. The low lymph node count in both arms is probably reflective of the fact that more than 90 % patients in the study received neoadjuvant chemoradiotherapy. However, it does prove that MIE can be carried out with comparable lymphadenectomy to open surgery with the added advantage of lower morbidity.

A meta-analysis comparing open to MIE included 16 case-control studies with 1212 patients [123]. The median (range) number of lymph nodes found in the MIE and open groups were 16 (5.7–33.9) and 10 (3.0–32.8), respectively, with a significant difference favouring MIE (p=0.04). A much larger number of lymph nodes were retrieved in the Japanese series of MIE (median lymph node range 24–34) than in the MIE series' from the West (median lymph node range 7–22) [124–130]. This is to be expected as the Japanese centres have a strong tradition of two or three-field lymphadenectomy. Interestingly, all the Japanese centres reported an equivalent yield in both arms (open and MIE), while at least some of the western centres reported an increase in lymph node yield with MIE.

1.11 Guidelines (Specifically Relevant to Lymphadenectomy)

1.11.1 NCCN, USA, Guidelines, 2016, Version 1 [131]

- Principles of Surgery
  - T1a: To be considered for EMR + ablation or oesophagectomy
  - T1b: Oesophagectomy
  - T1–T3: Resectable even with regional lymph nodal metastasis, although multi-station lymph node involvement is a relative contraindication to surgery.
- Acceptable operative approaches for resectable oesophageal carcinoma
  - Ivor Lewis oesophago-gastrectomy
  - McKeown oesophago-gastrectomy
  - Minimally invasive Ivor Lewis oesophago-gastrectomy
  - Minimally invasive McKeown oesophago-gastrectomy
  - Transhiatal oesophago-gastrectomy
  - Robotic minimally invasive oesophago-gastrectomy
  - Left transthoracic or thoracoabdominal approaches
- Acceptable lymph node dissections
  - Standard
  - Extended (en bloc)

- Lymph node numbers
  - Without preoperative chemoradiation: at least 15 lymph nodes should be removed to achieve adequate staging
  - With preoperative chemoradiation: the optimal number of lymph nodes is unknown, although similar lymph node dissection is recommended as above.

1.11.2 UK guidelines, 2011 [132] (on behalf of Association of Upper Gastrointestinal Surgeons of Great Britain and Ireland, the British Society of Gastroenterology and the British Association of Surgical Oncology)

- Oesophageal and gastric cancer surgery should be performed by surgeons who work in a specialist multi-disciplinary team (MDT) in a designated cancer centre with outcomes audited regularly (grade B).
- Surgeons should perform at least 20 oesophageal and gastric resections annually either individually or operating with another consultant both of whom are core members of the MDT. There is no evidence favouring one method of oesophageal resection over another (grade A), and evidence for minimal access techniques is limited (grade C).
- The operative strategy should ensure that adequate longitudinal and radial resection margins are achieved with lymphadenectomy appropriate to the histological tumour type and its location (grade B).
  - In an era of increasing use of neoadjuvant therapies where specific treatments are increasingly stage dependent, the surgeon should avoid carrying out an operation that is likely to underestimate the extent of disease or leave disease behind.
  - For squamous carcinoma, adequate lymphadenectomy in the mediastinum and abdomen seems logical as most western patients have middle or upper third tumours. For this reason two- and three-phase operations are generally advocated. Transhiatal surgery seems illogical on the grounds that mediastinal lymphadenectomy is likely to be compromised. This latter operation seems most suited to patients with early stage tumours thought to be lymph node negative.
  - For adenocarcinomas, most surgeons accept the need for an adequate abdominal lymphadenectomy as the predominant route of lymphatic spread in lower third tumours is in a caudal direction. The extent of mediastinal lymphadenectomy, particularly in the upper half of the mediastinum, remains unclear. The most widely practised operation is the two-phase Ivor Lewis operation with a laparotomy followed by a right thoracic approach with the anastomosis high in the chest. Some surgeons favour a third stage

with a cervical incision to create the anastomosis at this level. This may be an important consideration to gain adequate clearance in proximal tumours. Transhiatal surgery again seems best suited to early stage disease including multifocal high grade dysplasia in patients with very long Barrett's segments. A small group of patients who would not withstand thoracotomy may tolerate a transhiatal approach.

1.11.3 Japan Esophageal Society Guidelines, 2012 [77]

- *Endoscopic resection*
  - Endoscopic resection should be carried out in T1a–EP (limited to the mucosal epithelium) or T1a–LPM (limited to the lamina propria mucosae) as these only rarely are associated with lymph node metastasis.
  - Endoscopic resection can be done (relative indication) for T1a–MM (reaching the muscularis mucosae) or T1b–SM1 (slightly infiltrating the submucosa-up to 200 μm), but may have a risk of lymph node metastasis.
  - Lesions that are T1b–SM2 (lesions invading deeper than 200 μm into the submucosa) and beyond, have a 50 % chance of lymph node metastasis. Thus these should be treated as advanced carcinomas with radical surgery.
- *Upper thoracic oesophageal carcinoma (Ut)*
  - Dissection should ordinarily cover all the three regions, i.e. cervical, thoracic and abdominal regions, including the left gastric artery lymph nodes. Addition of median sternotomy or manubriotomy has also been suggested to allow a better field of view of the cervicothoracic junction region.
- *Middle thoracic oesophageal carcinoma (Mt)*
  - In general, dissection should cover all three fields as metastatic lymph nodes in cases of Mt are relatively evenly distributed over the cervical to upper, middle, and lower mediastinal and abdominal regions. Some have proposed lymph node dissection via the intrathoracic approach instead of the cervical approach, because the involvement of cervical lymph nodes other than the cervical paraoesophageal lymph nodes (101) is relatively rare. When the thoracic approach is judged to be inadequate based on the preoperative diagnosis of metastasis, it is important to add a cervical approach to dissect the lymph nodes surrounding the bilateral recurrent laryngeal nerve up to the inferior pole of the thyroid.
- *Lower thoracic oesophageal carcinoma (Lt)*
  - The optimal approach for lymph node dissection remains under discussion. In cases of Lt, while lymph node metastasis mainly occurs in the mediastinal and abdominal regions, metastasis to the cervical lymph nodes may also occur, albeit at a lower frequency. While some propose adding the cervical approach, similar to the case for Mt, others regard the thoracic approach as being

superior. Because metastasis to the upper mediastinal lymph nodes is less frequent in cases of superficial carcinoma of the lower thoracic oesophagus, there is a view that the extent of lymph node dissection could be minimized and that cervical lymph node dissection could be omitted altogether in some cases.

- *Carcinoma of the oesophagogastric junction*
  - In cases of oesophagogastric junction carcinoma extending more to the oesophageal side than to the gastric side (E, EG), right thoracotomy with dissection including the upper mediastinal lymph nodes and reconstruction using a gastric tube are frequently performed in the same manner as for cases of thoracic oesophageal carcinoma. In cases of oesophagogastric junction carcinoma extending more to the gastric side than to the oesophageal side (G, GE), metastasis to the mediastinal lymph nodes is less frequent; thus dissection of these lymph nodes is of lesser consequence.

1.12 Pragmatic Point of View for the Surgeon

After taking into account all the controversies that are associated with lymphadenectomy for oesophageal cancer there are a few facts that stand out. It is clear that it is a complex surgery that needs to be carried out in high volume centres with protocols of management in place, in a multidisciplinary environment. Stated simply, one needs to have technical expertise, some experience and a good team for perioperative management.

It cannot be denied that some patients, possibly those with limited lymph nodal metastasis, would certainly derive benefit from lymphadenectomy. With the present inaccuracies in the staging investigations and the relative rarity of the disease, it is difficult if not impossible, to generate level 1 evidence for identifying this group of patients. Therefore, all patients who are fit to withstand the procedure should undergo lymphadenectomy along with oesophagectomy. The exact extent of lymphadenectomy is presently a matter of experience and belief, but a minimum standard two-field lymphadenectomy should be carried out.

Last but not the least is the morbidity of the procedure. Along with gaining experience in the procedure the team needs to be ready to manage the increased morbidity and minimize the operative mortality. With the present state of medical education in India, the need of the hour is of inter-institutional collaboration and mentorship in specific areas to overcome these challenges, or else the treatment of oesophageal carcinoma is going to be riddled forever with empiricism and bias.

Editorial Comments

Please see the section on Oesophageal cancer in the chapter ‘Advances in Gastrointestinal Surgery’ on page 202

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Chapter 2
Short Bowel Syndrome

Gautham Krishnamurthy and Rajesh Gupta

2.1 Introduction

Short bowel syndrome (SBS) is characterized by inadequate length of intestine following surgical resection, and intestinal failure means need of specialized medical and nutritional support because of inadequate digestion or absorption of nutrients or both [1]. The term 'ultra short bowel syndrome' is used in children when the remnant bowel is less than 10 % (with ileocaecal valve) or 20 % (without ileocaecal valve) of predicted short bowel length for that age [2].

The incidence varies between adults and children. In the neonatal age group, the incidence is 24.5 per 100,000 live births and 22.1 per 1000 admissions in neonatal intensive care units [3]. Though the exact incidence in adults is difficult to ascertain, nearly 15 % of adults who undergo intestinal resection develop SBS. It could result from a single time massive resection or multiple sequential resections which account for 75 % and 25 % of cases, respectively [4].

2.2 Aetiology

The aetiology is age-specific. SBS in neonates can be secondary to necrotising enterocolitis, intestinal anomalies and gastroschisis. In adults, major vascular insufficiency, malignancy, Crohn's disease and radiation enteritis might result in massive intestinal resection causing SBS. The aetiology of SBS has a bearing on the management. For instance, in children, necrotising enterocolitis is more favourable in achieving enteral autonomy than intestinal atresia. In adults with

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Crohn's disease, since the remaining bowel is likely to be affected, therefore a longer remnant segment of bowel is required for enteral autonomy compared to non-malabsorptive aetiology.

The manifestations of SBS are due to both anatomical and physiological reasons. Anatomical considerations include loss of absorptive surface area and loss of site-specific transport processes whereas physiological reasons include loss of site-specific endocrine cells, gastrointestinal hormones and loss of ileocaecal valve [5].

2.3 Post-resection Anatomical and Physiological Considerations

The site-specific absorption along the gastrointestinal system predicts the probable nutrient deficiencies that can manifest if a particular anatomical site is removed surgically. Duodenum is the major site for iron and folate absorption; whereas jejunum is the primary site for macromolecules such as carbohydrate and protein while the terminal ileum plays a vital role in the enterohepatic circulation of bile acids and absorption of vitamin B12. Disturbance of enterohepatic circulation can in turn affect the absorption of fat soluble vitamins [6]. Thus the loss of multiple bowel segments has a synergistic effect on malnutrition. The malabsorption can further be accentuated by bacterial overgrowth and impaired motility.

Ileocaecal valve resection predisposes to small bowel contamination with colonic bacteria. This can result in bacterial overgrowth and anastomotic ulcers. In addition, the resultant rapid transit predisposes to malabsorption [7]. Generally, jejunal resection is better tolerated than ileal, because of the better adaptive ability of the remnant ileum.

The natural course of these patients starts from optimization of fluids and electrolytes, followed by supportive medical and nutritional therapy during the period of intestinal adaptation. This may be followed by enteral autonomy or requirement of surgical management such as autologous reconstructive surgery or transplantation.

2.4 Natural Course of Adaptation and Rehabilitation

Like any other part of the body, the gastrointestinal system tries to adapt to loss of one of its components as effectively as possible. These adaptive changes can occur as early as 24 h and can continue up to 2 years or more [8]. These changes increase the absorptive capacity of the remnant gut compensating for the loss of the absorptive area which otherwise would have devastating effects. The adaptation occurs at molecular and cellular levels through structural and functional changes.

In rats, following intestinal resection, there is rapid proliferation of crypt cells resulting in increased crypt depth and villous height [9]. Increased tissue oxygenation and blood flow derived from angiogenesis sustain this mucosal growth [10]. Similar

results have been shown in humans. At 2 years following jejunoileal bypass, Doldi et al. showed enterocyte hyperplasia with 70–75 % increase in small bowel villus height [11].

Actually, functional changes may have more role in intestinal adaptation than morphological changes [12]. These include increased expression of transporter proteins involved in nutrient absorption. Ziegler et al. showed increased expression of PepT1, a protein responsible for increased dipeptide and tripeptide absorption, in the colon after massive intestinal resection [12]. Exchangers involved in fluid and electrolyte absorption such as sodium glucose cotransporter, Na+/H+ exchangers and Na+/K+ adenosine triphosphatases are also expressed at a higher quantity in these individuals [13–15]. Motility of the small bowel is also decreased resulting in increased contact time of the nutrients with the mucosa. Quigley et al. were able to show increased small bowel transit time of approximately 35 % between 4 and 12 weeks following resection in dogs [16]. Apart from these, the increased secretion of peptide YY, a gastrointestinal hormone, is also implicated in the delayed gastric and increased intestinal transit time [17]. All these adaptive changes result in decreased stool output.

Anatomy of the remnant bowel, enteral nutrition and growth factor have a bearing on the extent of intestinal adaptation. The ileum shows greater adaptation than the jejunum. Thus, proximal resections are better tolerated than distal resections [18]. Though parenteral nutrition may provide the required calories and proteins, enteral nutrition is known to maintain intestinal mucosal integrity, improve adaptation and also reverse parenteral nutrition induced mucosal atrophy [19–21]. Fats, especially short chain fatty acids and long chain fatty acids, are known to have a positive effect on mucosal growth [22–24]. The action and therapeutic role of various growth factors is described later.

2.5 Nutrition and Rehabilitation

Nutrition is the primary component of the multidisciplinary approach that has vastly improved the outcome in SBS. This includes understanding the altered physiology of enteral nutrition and improvement in parenteral nutrition.

The easiest practical way of assessing intestine failure is to measure 24-h urine output volumes plus sodium content, when the patient is only on enteral fluid and nutrition. Intestine failure is not considered if the 24-h urine volume is greater than 1 litre and urinary sodium is greater than 20 mEq/day. These measurements are also very useful in gauging intravenous fluid and electrolyte requirements in patients requiring TPN or home parenteral nutrition (HPN).

Patients are also predisposed to lactose intolerance due to decreased absorptive surface area and subsequent osmotic diarrhoea [25]. Complex carbohydrates are preferred to refined ones in the feeding of such patients. They carry less risk of osmotic diarrhoea. In addition, they help formation of short chain fatty acids due to bacterial fermentation in the colon, and this process can provide up to 1000 calories [26]. This

is supported by the fact that by adding pectin to the diet, there was increased fluid absorption and increased excretion of faecal short chain fatty acids [27].

Fat is an important constituent in the diet with tremendous effect on improving adaptation and prevention of intestine failure associated liver disease. Medium chain triglycerides (MCT) can directly get absorbed across the intestinal epithelium into the portal circulation without the need for bile salts. Theoretically, small peptides also have better absorption but this has not been proven in clinical studies.

Metabolic complications specific for enteral nutrition in SBS include oxalate nephropathy and D-lactic acidosis. Normally oxalate combines with calcium to produce insoluble, non-absorbable calcium oxalate. Malabsorbed fatty acids bind to the calcium leaving free oxalate to be absorbed in the colon. Colonic absorption of free oxalate results in oxalate nephropathy [28]. Mechanism of D-lactic acidosis includes action of colonic bacteria on unabsorbed carbohydrates which acts as a substrate for colonic bacteria. This results in formation of D-lactic acid among other organic acids. Absorption of large quantities of D-lactic acid leads to D-lactic acidosis resulting in neurological complications such as delirium and ataxia [29].

Studies have been done to predict enteral autonomy. One large multicentre trial by Khan et al. [30] involving 272 infants showed that enteral autonomy was achieved in 118 patients (43 %) in their study. They defined enteral autonomy as discontinuation of parenteral nutrition for more than 3 consecutive months with maintenance of acceptable growth variables. The authors observed that diagnosis of necrotizing enterocolitis, care at an intestinal failure unit without an associated intestinal transplantation programme and an intact ileocaecal valve were independent predictors of enteral autonomy.

The prognosis of SBS has improved secondary to better understanding of the nutritional management. Parenteral nutrition, total or supplemental, is required in all patients till the intestinal adaptation is complete. Institution of parenteral nutrition can be as early as the second postoperative day after cardiovascular stability is achieved [31]. Daily electrolyte monitoring is required until the patient is clinically stable, when the frequency of electrolye monitoring may be decreased [32].

Customized parenteral nutrition has been shown to have better outcome than standard bag parenteral nutrition. The European Society for Clinical Nutrition and Metabolism (ESPEN) guidelines recommend the composition of parenteral nutrition [33]. The calorie supplementation should include 20–35 kcal/kg/day [34]. For every gram of nitrogen, 100–150 kcal of non-protein energy has to be provided. In view of long term fatty acid supplementation being responsible for intestinal failure associated liver disease, the recommendation is not to exceed 1 g/kg per day of fatty acids. The content of essential fatty acid in the parenteral nutrition should be 7–10 g per day [35].

Vascular access for the purpose of parenteral nutrition forms an important component in the short as well as long term management of chronic intestinal failure. The ESPEN guidelines published in 2009 laid specific emphasis on venous access for parenteral nutrition [36]. Peripheral access can be used to infuse a low osmolarity solution in an hospital setting for a short duration. However, a peripheral line is not recommended for HPN due to the high risk of dislodgement and thrombophlebitis. Based on the duration of parenteral nutrition requirement, the guideline has recom-

mended non-tunnelled central venous catheters and peripherally inserted catheter for short term; and tunnelled central venous access and Hohn catheter for medium term. Tunnelled catheter is recommended for long term HPN [36].

HPN is recommended in patients who have not achieved enteral autonomy but do not require acute care [33]. The incidence of HPN has gradually risen over the years [37]. The prognosis of HPN primarily depends on the underlying disease and catheter-related complications. The initiation of HPN should be preceded by proper training of the patient and the caregiver, and followed by strict monitoring of anthropometry and biochemical parameters at regular intervals [38]. Measurement of trace elements and DEXA scan is recommended every 6 months and 1 year, respectively [33, 37].

Though parenteral nutrition has been instrumental in improving outcomes, long term supplementation is associated with adverse effects. Catheter-related blood stream infection accounts for 60 % of hospital admissions in patients on HPN. These in turn can lead to venous thrombosis, loss of venous access and bacterial endocarditis.

Long term parenteral nutrition can lead to intestinal failure associated liver disease (IFALD) presenting as jaundice and portal hypertension. Among the various factors, excessive lipids and glucose, high content of omega-6 fatty acids and presence of phytosterols in the parenteral fluid are known to cause IFALD [39]. Studies have shown that lowering lipid component can partially reverse IFALD [39].

2.6 Pharmacotherapy

Drugs are directed at specific problems arising during the phases of intestinal recovery, adaptation and rehabilitation. The initial phase of recovery following massive resection involves management of diarrhoea resulting in fluid and electrolyte imbalances. This phase can last up to a few months and is followed by intestinal adaptation. After 2–5 years, the intestinal adaptation reaches a plateau and stabilization is achieved. This phase constitutes the rehabilitative phase.

Antimotility and antisecretory agents constitute the mainstay of treatment during the recovery phase. These agents can be used alone or in combination. After control of sepsis and institution of parenteral nutrition, opiod agonists are the first line antimotility agents to decrease stool output. In increasing order of potency, loperamide, diphenoxylate and codeine are the agents used. Loperamide is the preferred drug due to its low side-effect profile. It utilises the enterohepatic circulation for absorption. Impaired enterohepatic circulation necessitates increased dosing of loperamide to achieve an adequate clinical response. An additive effect has been shown with the use of loperamide and codeine simultaneously [40].

The loss of negative feedback mechanism after massive intestinal resection leads to hypergastrinaemia mediated by neurohumoral mechanisms. This results in fluid loss and peptic ulcer disease which can last up to 1 year [41]. In a randomized controlled study, omeprazole (40 mg twice daily) was found to be more efficacious than ranitidine (150 mg twice daily) in reducing water loss [42].

Somatostatin as an antisecretory is highly potent and can be used after maximal opiod therapy. A trial administration for 48 h can be used to assess response after maximal dosage of opiods. An additional benefit is unlikely if the drug is not effective during this period [43]. Loss of bile acids and subsequent fat malabsorption due to ileal resection can be overcome by administering cholestyramine. However, steatorrhoea can also result from pancreatic enzyme inactivation by gastric acid hypersecretion. Thus, bile acid sequesterant, cholestyramine, is administered after optimization of acid suppressive and antimotility drugs [44, 45]. Other adjuncts used during the adaptation phase include antibiotics to treat bacterial overgrowth. Given the possibility of repeated requirement of antibiotics, care has to be taken to avoid development of antibiotic resistance and *Clostridium difficile*-associated diarrhoea [46].

Growth factors are recommended after maximal medical and nutritional therapy fails to achieve enteral autonomy. Recombinant human growth hormone (r-hGH) and GLP-2 analog are proven drugs in these selected group of patients. Somatropin (r-hGH analog), used along with glutamine for a 4-week period, has shown greater reduction in the requirement of parenteral nutrition compared to parenteral nutrition alone or glutamine alone. Byrne et al. also showed that the response was sustained for 3 months [47].

GLP-2 is an enteric hormone secreted in the terminal ileum. It has an effect on proliferation of enterocytes and structural changes at the cellular level to increase absorption of nutrients. Thus GLP-2 analog has targeted intestinotrophic effects. In patients with the terminal ileum resected and no increase in postprandial GLP-2 levels, administration of GLP-2 analog (Teduglutide) has shown significant increase in intestinal absorption and body weight [48]. Microscopic examination has confirmed an increase in villus height and crypt depth after administration of teduglutide [49]. Jeppessen et al. did a randomized controlled study involving 86 patients with 43 receiving 24 weeks of teduglutide. The teduglutide group showed reduction in the requirement of parenteral nutrition as assessed by urine output. The study group also showed an increase in plasma citrulline levels indicating increased mucosal mass [50]. Table 2.1 summarises the drugs used in the management of SBS.

2.7 Surgical Management

Advances in the medical and nutritional management of patients suffering from SBS have made a remarkable impact on the quality of life, achievement of enteral autonomy and overall survival. Despite this, 19–26 % of patients continue to be permanently dependent on parenteral nutrition with mortality rates of 13–38 % by 2–5 years resulting from development or management of intestinal failure [59, 60].

Surgical management of SBS starts from the incident surgery. All precautions should be taken towards preservation of maximal bowel length and the ileocaecal valve. This includes early diagnosis of preventable massive bowel gangrene entities such as malrotation as well as the judicious use of second-look surgery in other surgical emergencies including trauma.

Table 2.1. Pharmacotherapy in short bowel syndrome

Class of agent (mechanism of action)	Drug	Route	Dosage	Adverse effects	Remarks
Antimotility agents					
Decrease motility and increase contact time Loperamide: decrease pancreatic and gastric acid secretions	Diphenoxylate	PO	2.5–7.5 mg QID (20–25 mg/day)	Confusion, dry mouth, lethargy, dizziness, drug dependence	Second line after maximal dosage of loperamide [51]
	Loperamide	PO	2–6 mg QID; 16 mg/day (32 mg/day in SBS)	Nausea, toxic megacolon, angioedema	First line of drug due to low adverse effect profile [51]
	Codiene	PO	15–60 mg/day	Subsequent bowel adaptation can result in small bowel obstruction if dose not reduced	After loperamide and diphenoxylate. Have synergistic effect [52]
	Morphine	PO	2–20 mg/day	Drug dependency	
	Opium tincture	PO	0.3–1 ml	Dizziness, seizure, painful urination, nausea	
Proton pump inhibitors					
Decrease hypergastrinaemia and gastric hypersecretion	Pantoprazole	PO or IV	20–40 mg BD	Possible micronutrient deficiencies. Drug interaction	Particularly first 6–12 postoperative months [41]
	Esmoprazole	PO or IV	20–40 mg BD		
Histamine blockers					
Decrease hypergastrinaemia and gastric hypersecretion	Ranitidine	PO or IV	150–300 mg BD		

(continued)

Table 2.1. (continued)

Class of agent (mechanism of action)	Drug	Route	Dosage	Adverse effects	Remarks
Alpha receptor agonist					
Alpha-2 mediated absorption of fluid and electrolyte by enterocytes [53]	Clonidine	PO or transdermal	0.1–0.3 mg TDS	Orthostatic hypotension, arrhythmias, angioedema, syncope and bradycardia [54]	Available as transdermal patch. Limited by side-effect profile [54]
Somatostatin analog					
Inhibition of secretion of gastrointestinal hormones Decreased faecal output Prolonged transit time	Octreotide	SC	50–250 μg TDS/QID	Malabsorption, exocrine insufficiency, cholelithiasis and intestinal obstruction [55]	Limited by cost [55]. Some studies have shown decreased intestinal adaptation [56].
Bile acid binding resin					
Lipid and fat soluble vitamin absorption	Cholestyramine	PO	2–4 g QID	Binds to several medications	Patients with more than 100 cm of ileum may have worsening of fat-soluble vitamin deficiency
Antibiotics					
For small bowel bacterial overgrowth	Ciprofloxacin	PO	500 mg BD for 7–14 days	Broad-spectrum antibiotics predispose to *Clostridium difficile* infection	Rotating antibiotics decreases development of resistant bacteria
	Metronidazole	PO	250 mg TDS for 7–14 days		
	Tetracycline	PO	250–500 mg QID for 7–14 days		
	Rifaximin	PO	250–500 mg TDS for 7–14 days		

Recombinant human growth hormone					
Increased small bowel length, mucosal height, jejunal villus height	Somatropin	SC	0.1 mg/kg OD for 4 weeks	Carpal tunnel syndrome, glucose intolerance, acute pancreatitis, intracranial hypertension [57]	Contraindicated in active malignancy, newly diagnosed SBS, active proliferative or severe non-proliferative diabetic retinopathy, and sepsis. Approved for 4 week treatment regimen in adults [57]
Glucagon like peptide-2 analog					
Increased small bowel weight, small bowel surface area, villus height, microvillus height, crypt cell proliferation, nutrient transporter expression, and nutrient absorption	Teduglutide	SC	0.05 mg/kg OD	Abdominal distension, peripheral oedema, stomal complications [58]	Approved for clinical use in adults with parenteral nutrition dependency after adaptation

The long time required for intestinal adaptation through functional and morphological changes of the remnant bowel mandates purposeful supportive therapy during this period. Nearly three-fourth of patients with SBS may not require surgical management [61]. Infants with necrotizing enterocolitis may achieve enteral autonomy even with a very short bowel remnant [62]. During the adaptive phase, constant monitoring for complications of parenteral nutrition and IFALD is required. Intestinal transplantation remains the only option once the patient develops parenteral nutrition-induced advanced liver disease in the form of portal hypertension [63].

Surgical management is indicated in patients who have reached a plateau in weaning parenteral nutrition after maximal intestinal adaptation. Thus patients are subjected to autologous reconstruction when further weaning of parenteral nutrition fails [2]. The only exception in which surgery is considered earlier is in ultrashort bowel syndrome.

Antiperistaltic bowel loops have been attempted in individuals with sufficient bowel length (>25 cm) with the sole purpose of increasing transit time in undilated bowel without liver disease [64]. However, the technique has not been widely practised due to the potential risk of intestinal obstruction. Autologous gastrointestinal reconstruction is based on the principles of improving motility of dilated bowel after adaptation and increasing the absorption. The common procedures include tapering enteroplasty, Bianchi's longitudinal intestinal lengthening and tailoring (LILT), and the serial transverse enteroplasty (STEP). These techniques can be performed in isolation or in succession to achieve enteral autonomy [65].

2.7.1 Bianchi Procedure (LILT: Longitudinal Intestinal Lengthening and Tailoring)

The dilated bowel with decreased motility was initially addressed by surgical excision of the redundant bowel or with plication. However, these were associated with loss of absorptive surface and poor long term results. Bianchi, in 1980, described a technique where the dilated short length of bowel is rearranged as longer and narrower bowel [66]. In this technique, longitudinal intestinal lengthening and tailoring is based on the principle that the mesenteric arteries are arranged in an alternate manner and supply the bowel on one side or the other (Fig. 2.1). This distinctive feature can be used to dissect the mesenteric arteries and veins and separate these to either side of the bowel wall. This will enable longitudinal division of the bowel, and subsequently anatomosing these segments results in bowel with double the length and half the luminal size. King et al. [67] in their review in 2013 reported that 82.5 % of patients improved after the procedure in terms of requirement of parenteral nutrition, symptomatic improvement or resolution of liver abnormality. More than half the patients (54.9 %) did not require parenteral nutrition postoperatively. Complications of the procedure include stenosis, inter-loop fistula, loss of bowel segment due to vascular compromise and redilatation [68].

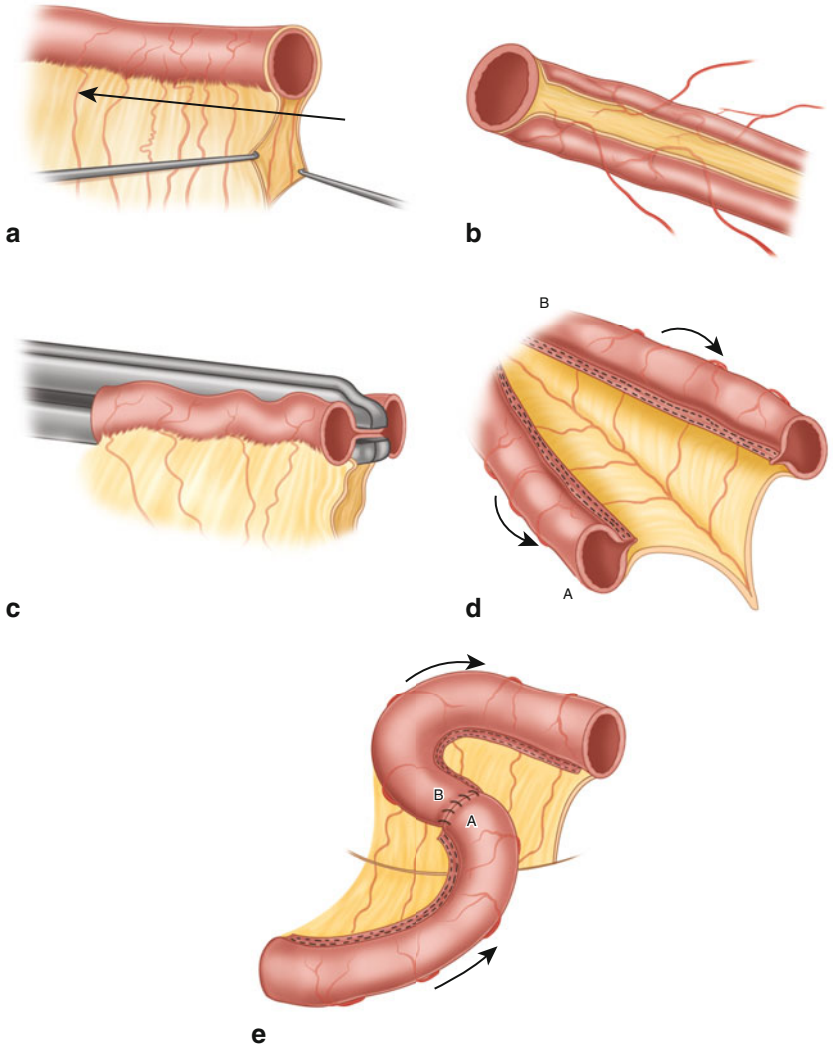

Fig. 2.1. Longitudinal intestinal lengthening and tailoring (LILT). (**a**, **b**) Mesentery being separated and the mesenteric vessels supplying alternate sides dissected. (**c**, **d**) Bowel divided longitudinally with stapler. (**e**) End to end anastomosis of divided intestinal loops

2.7.2 Serial Transverse Enteroplasty (STEP)

Given the complexity of the Bianchi procedure, Kim et al. devised a simpler technique to taper the dilated bowel in piglets, which later has been successfully reproduced in humans [69]. This technique is called STEP. The procedure involves applying serial linear staplers at 90 and 270 degrees, with mesentery being

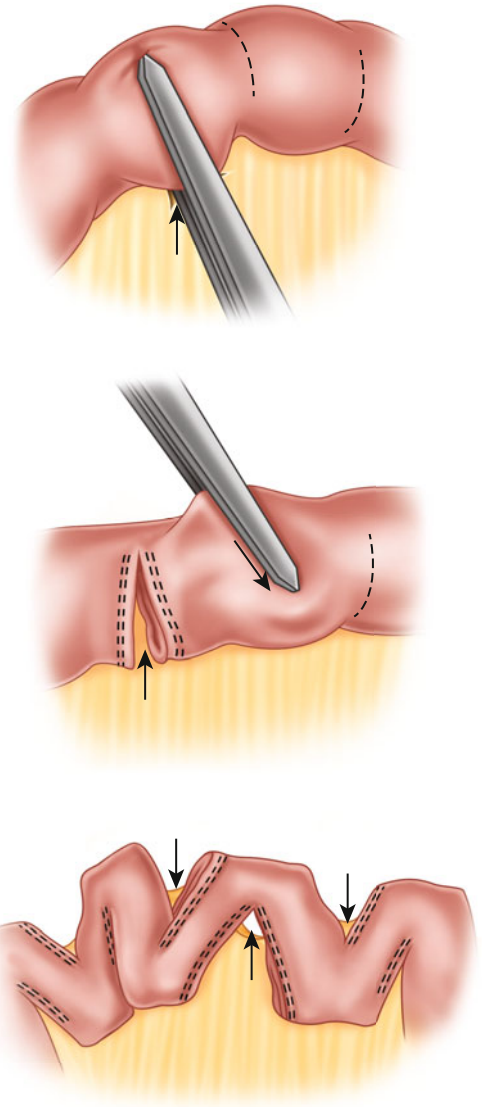

Fig. 2.2. Serial transverse enteroplasty. Applying linear stapler at regular intervals at alternate side of the bowel

considered at 0 degrees in a flattened bowel (Fig. 2.2). This results in a zig zag partial division of the dilated bowel, thereby increasing the effective bowel length. One major physiological drawback of the procedure is that concentric fibres become longitudinal and vice versa. This predisposes to dilatation due to unpredictable peristalsis [70]. The complications are similar to that of Bianchi procedure with slightly higher incidence [67]. Though the success of weaning is lower when compared to the Bianchi procedure, the survival rate is comparable [67].

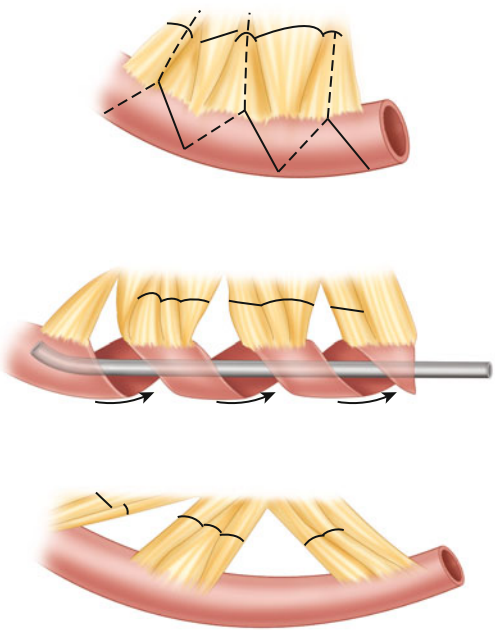

Fig. 2.3. Spiral intestinal lengthening and tailoring. The first two figures show bowel divided at 60° and tubularized. The bottom figure shows the final outcome

2.7.3 Spiral Intestinal Lengthening and Tailoring (SILT)

To overcome the derangement of the muscle fibres, Cserni et al. described SILT where the bowel is divided at 45 degrees to the long axis and then sutured after tubularization (Fig. 2.3) [70]. Adequate mesentery cuts are made to enable the lengthening. Though the procedure has been applied in humans, long term and large volume data is still awaited [71, 72].

The choice of surgery is dictated by the feasibility of the procedure. Bianchi procedure is preferred given the good outcome and long term data available. One important factor that determines the choice is the status of the mesentery. The Bianchi procedure is technically not possible in foreshortened mesentery or prior surgeries, including Bianchi, wherein the leaflets of the mesentery have been handled. Hence one probable sequence could be an initial Bianchi followed by STEP if recurrent dilatation occurs. STEP is preferred in patients with bowel segment less than 20 cm, since Bianchi is associated with higher failure and mortality in shorter remnant intestinal segments [73].

In situations of undilated bowel with minimal chance of spontaneous adaptation, controlled obstruction to produce dilatation is being attempted. The resultant dilated bowel can then be subjected to the above mentioned reconstructive procedures [74].

2.7.4 Intestinal Transplantation

There has been improvement in the outcome of SBS in recent years secondary to specialized multidisciplinary centres managing these patients. However, with tissue engineering still at the foetal stage, intestinal transplantation remains the only effective choice in managing irreversible intestinal insufficiency to avoid the morbidity and mortality of long term parenteral nutrition. This accounts for 10–15 % of patients with irreversible intestinal failure [75]. Apart from intestinal failure, transplantation or autotransplantation is done for indolent abdominal malignancies such as neuroendocrine or desmoid tumours [76].

Evolution in immunosuppression has paved the way for improved outcomes after intestinal transplant. The presence of abundant immunologically active lymphoid tissue in the intestinal graft poses unique problems in intestinal transplantation. The fine balance of intestinal innate immunity against harmful pathogens with immunotolerance of other antigens ensures effective immunity [77]. Disturbance of this equilibrium leads to activation of the immune system through the Toll-like receptor pathway [78]. The resultant cytokine and chemokine cascade activation leads to acute rejection. The evolution of intestinal transplantation from an experimental procedure to a reality was facilitated by the advent of potent immunosuppressants. From the path breaking results of tacrolimus in the 1990s, effective immunosuppression is now achieved in isolation or combination with steroid, anti-thymocyte antibody, thymoglobulin, alemtuzumab (anti-CD52), basiliximab (anti-IL-2 receptor), mycophenol mofetil and rituximab (anti-CD20) [79]. Various regimens have been attempted to achieve compromise between acute rejection and infection rate. Trevizol et al. found a combination of thymoglobulin, rituximab and tacrolimus to be the most effective immunosuppressive regimen (3-year patient survival of 78 %) with the least infection rate (7.4 %) [80].

The American Society of Transplantation has listed the indications for intestinal transplantation in SBS [81]. These include irreversible intestinal and nutritional failure along with

1. Significant hepatic injury due to parenteral nutrition;
2. Loss of central venous access (in children loss of 2 of the 4 access sites, i.e. bilateral subclavian and internal jugular veins; in adults loss of 3 of the 6 access sites, i.e. bilateral femoral veins in addition);
3. Catheter-related infection, single episode of fungal infection or requirement of hospitalization more than twice in any year.

The contraindications for transplant include:

1. Poor psychosocial support
2. Life-threatening and other incurable illnesses not directly related to the digestive system
3. Hereditary or acquired immune deficiencies
4. Non-resectable malignancies
5. Insufficient vascular patency to guarantee easy central venous access for up to 6 months following transplantation.

The most common aetiology of SBS in patients who undergo transplantation is gastroschisis in children and mesenteric ischaemia in adults. These account for 21 and 23 % of patients in the respective age groups. Though early referral for transplantation is associated with better outcome in terms of success rate and quality of life, transplantation is considered as a rescue therapy after maximal medical, surgical and nutritional management [82]. With early intestinal transplant, potential parenteral nutrition-associated liver failure can be avoided thus precluding the need for multivisceral transplant. Cost analysis has shown that transplantation becomes cost-effective when compared with HPN on the long run despite the exorbitant initial cost. The break-even point occurs between 1 and 3 years after transplantation [83]. Table 2.2 summarizes the various techniques of intestinal transplantation.

2.7.5 Complications of Intestinal Transplantation

Acute cellular rejection (ACR) is the leading cause of graft loss despite effective immunosuppression reducing the incidence from 70 % to 30 % [90, 91]. It typically occurs within 90 days [84]. The pathophysiology involves cytotoxic T-cell mediated inflammation by the recipient to the donor antigens [92]. The clinical features of ACR include fever, nausea, vomiting, abdominal pain and distension, increased ileostomy output and haemorrhagic effluent. Mild rejection is treated with steroids while moderate and severe rejection require antithymocyte globulin.

Chronic rejection results from *de novo* production of donor-specific antibodies. The presence of these antibodies has a profound implication on the graft survival with 5-year graft survival of 30 and 80 % in patients with or without antibodies, respectively [93]. These antibodies causes mesenteric arteriopathy which results in mucosal atrophy and ulceration, mesenteric lymphoid depletion and mesenteric shortening from fibrosis and sclerosis. Chronic rejection manifests as persistent diarrhoea, weight loss and nutritional deficiencies. Plasmapheresis, intravenous immunoglobulin and rituximab are used in the initial treatment of chronic rejection with re-transplant being the last resort [79].

Large lymphocytic mass in the intestinal graft predisposes to graft-versus-host disease. Multivisceral transplant recipients are more affected than recipients of isolated small bowel transplant [94]. The clinical manifestations include rash, fever and diarrhoea and the diagnosis is made upon tissue biopsy. Treatment is difficult with no standard guidelines.

2.7.6 Nutritional Monitoring Post Transplant

Recipients of small bowel transplantation are monitored for body mass index in adults, gain in height and weight in children, monitoring serum albumin concentrations and micronutrient deficiencies. These serve as a guide for weaning from parenteral nutrition. The average time taken for adults to start oral diet is 6 months.

Table 2.2. Techniques in Intestinal transplant

Type of transplant (paediatric graft survival rate)	Indications	Technique	Remarks
Isolated small bowel transplant [84] (73.1 % at 1 year and 62.3 % at 5 years) [85]	Preserved liver function	Graft: Intestine +/− pancreas; Inflow: Donor superior mesenteric artery to infrarenal aorta; Outflow: Donor portal vein to inferior vena cava.	Reverses mild to moderate liver fibrosis [86].
Liver–intestine transplant (71 % at 1 year, 50 % at 5 years, and 41 % at 10 years) [87]	Intestine failure associated liver disease; Thrombosis of the porto-mesenteric venous axis	Graft: Liver and intestine +/− intact allograft pancreaticoduodeno-biliary axis; Inflow: Infrarenal aorta to a donor aortic conduit; Outflow: Piggy back or caval replacement to the native inferior vena cava [79].	Separate liver and bowel graft permits removal of bowel in the event of bowel allograft rejection with preservation of liver allograft [79]
Multivisceral transplant [88]	Additional organ involvement apart from intestinal and liver failure; pancreatico-duodenal trauma; indolent tumours like desmoids or neuroendocrine	Graft: Intestine + Liver + Stomach + Duodenum + Pancreas +/− Spleen Native pancreaticoduodenal complex preserved	Loss of domain is a unique challenge for this transplant [88]
Living donor intestinal transplant [89]	Alternative to cadaver small bowel transplant on waiting list (weight >8 kg)	Graft: Intestine +/− left lateral liver segment [79]	Reduction in waitlist mortality [89]

2.8 Conclusion

Despite advances in the medical field, SBS continues to be a difficult entity to manage. Multidisciplinary teams specializing in the management of intestinal failure have shown promising results. Effective utilization of these facilities is still to be achieved given the demanding initial treatment. Early coordination between primary care clinicians and these centres cannot be over emphasized. Nutritional management and surgical interventions have shown good outcome with early intestinal transplantation having a great potential in becoming the first line of treatment for those who fail weaning from parenteral nutrition.

Editorial Comments

Short bowel syndrome is one of the most difficult problems to treat in clinical medicine. The physiological abnormalities seen in this condition are enormous and its management is a test of knowledge of these. I will therefore dwell on these in some detail to help understand the problem and its management.

From the ligament of Treitz to the ileocaecal valve, the small intestine is approximately 480 cm long. Any resection which leaves less than 200 cm of small intestine is regarded as short bowel [95].

In adults, various conditions requiring small bowel resection that cause SBS include mesenteric ischaemia (resulting from primary vascular disease, embolism, coagulopathies, etc.), radiation enteritis, surgical diseases of the small bowel including both benign and malignant mesenteric tumours, extensive trauma to the mesenteric vasculature, Crohn's disease, midgut volvulus leading to gangrene, etc. In children, the common causes include gastrochisis, intestinal atresia, malrotation, aganglionosis and necrotizing enterocolitis.

Resection of up to 50 % of the small bowel is generally well tolerated. Up to 75 % of resection by and large needs dietary adjustment with oral supplementation along with measures promoting intestinal adaptation. More than 75 % resection cannot sustain life on oral feeds alone and hence needs parenteral nutrition. This is required if 120 cm of the small intestine is available but the colon is not present or 60 cm of the small intestine is present with an intact colon [96, 97]. The factors associated with a poor prognosis of massive small bowel resection include old age, very short segment of remaining small bowel, distal resection, absence of the ileocaecal valve and inability of the intestine to adapt adequately [98, 99].

Segmental resection of the jejunum or ileum has a direct bearing on the outcome and needs a little discussion. Length for length, the jejunum has several times higher absorptive power than the ileum. This is because its villi are taller and crypts deeper. The majority of digestion and absorption occurs in the first 150 cm of the small bowel including the duodenum [100, 101]. Thus, any patient who has 100 cm of the proximal small bowel (jejunum) remaining can successfully manage with oral feeding. At the same time it has

to be stressed that the ileum has better adaptability and hence patients with jejunal resection do better [102]. After resection, the small intestinal transit time is decreased (allowing for quicker passage of intestinal contents). This does not allow maximum contact of nutrients with the enterocytes. The presence of the ileum tends to negate this (so-called 'ileal brake' effect) [103]. The maximum transit time is seen in the ileum, when the ileocaecal valve along with the colon is preserved.

The ileocaecal valve maintains the balance between the ileal and colonic bacteria. Its resection allows migration of colonic bacteria into the ileum and its resultant overgrowth. This has a detrimental effect because these bacteria now deconjugate the bile salts. As a result, dietary fat cannot be emulsified and hence vitamin B12 cannot be absorbed. This further reduces the enteric transit time [104].

Enteric absorption of various nutrients is site-specific. The proximal intestine including the duodenum is the region from which iron, phosphorus and water soluble vitamins are absorbed. Therefore, in most small bowel resections no abnormality of these nutrients is seen because the duodenum and the proximal jejunum are intact. However, both calcium and magnesium deficiency can occur (these are discussed later). Vitamin B12 and bile salts, as has been mentioned earlier, are absorbed from the terminal ileum. Apart from these micronutrients, absorption of water and electrolytes is also affected in patients with SBS due to which patients present with explosive diarrhoea. Patients lose so much water that they become hypovolaemic. Quite frequently, they also are hyponatraemic and hypokalaemic. The release of gastrointestinal hormones is also site-specific and has implications for patients with SBS. While gastrin, cholecystokinin, secretin, gastric inhibitory polypeptide (GIP) and motilin are secreted in the proximal small bowel [105], glucagon-like peptide (GLP)-1 and 2, neurotensin and peptide Y-Y are secreted in the ileum and colon [106]. Hence, in most massive small bowel resections, where the proximal bowel is preserved, secretion of these hormones remains unaffected, but the latter ones are depleted. As a result rapid gastric emptying occurs with decreased small intestinal transit time (rapid transit) [106]. Hypergastrinaemia is another problem seen in 50 % of patients with SBS. This is possibly due to deficient inhibitory effects of GLP-1 and 2, neurotensin and peptide Y-Y on gastrin (related to distal small intestinal resection). The hypersecretion of gastric acid has further deleterious effects—low pH inactivates pancreatic enzymes and bile salts which affects adequate mixing of chyme with pancreaticobiliary juices. The hypersecretion of acid may also cause ulcerations in the small intestine [107].

Vitamin B12 in association with intrinsic factor liberated from parietal cells of the stomach is absorbed from the distal 100 cm of the ileum and its deficiency occurs following resection of more than 60 cm of this segment. Its digestion and absorption is facilitated by pancreatic proteases [108].

Bile salts (conjugated) are extremely important for digestion and absorption of fats and fat soluble vitamins. The normal bile acid pool is maintained by the enterohepatic circulation. This has two components: cyclical secretion by the liver and absorption by specific receptors located in the distal 100 cm of the ileum [109]. In ileal resection of less than 100 cm, bile salt malabsorption is only mild or moderate because it is compensated by increased secretion by the liver. Severe bile salt malabsorption occurs when more than 100 cm of the ileum is resected. This is because the deficit is so much that even its hypersecretion by the liver cannot cope with the loss. In these patients fat malabsorption occurs along with deficiency of fat soluble vitamins. The net result is steatorrhoea, secretory diarrhoea and deficiency of fat soluble vitamins. It is important to note that hepatic bile in impaired enterohepatic circulation is grossly lithogenic (supersaturated with cholesterol) and thus patients with SBS tend to develop cholesterol gallstones [110]. Another consequence of the deficiency of bile salts is formation of oxalate stones in the kidney [111]. Normally, long chain fatty acids are conjugated with bile salts. In the absence of bile salts (lost through the colon) these fatty acids are bound to calcium. As a result very little calcium is available to bind with oxalates (calcium bound oxalate is not absorbable and is cleared in the faeces). Free oxalates on the other hand get absorbed from the colon and excreted in the urine in excess (crystaluria) resulting in stone formation.

Absorption of water, electrolytes and minerals is another issue that needs careful consideration. To tackle the problems of water absorption associated with SBS, one has to consider the physiological aspects of normal water absorption. Normally, about 9 litres of water enters the intestine daily; mostly from endogenous sources (saliva, gastric juice, succus entericus, bile and pancreatic juices). The exogenous source of water is through oral intake and is about 2 litres per day. Eighty per cent of this water entering the small bowel is absorbed by the small intestine, delivering 1.5–2 litres into the colon which absorbs 90 % and only about 100 ml is passed out in the faeces. Following massive small bowel resection, such large volume of water and electrolytes cannot be reabsorbed from the residual small intestine (if any remains). As a result patients develop large volume watery diarrhoea, hyponatraemia and hypokalaemia [112]. However, following such resection, absorption from the colon increases to 2–6 litres per day. A minimum of 100 cm of jejunum is required to maintain the water and electrolyte equilibrium. The colon is also capable of preserving nearly 1000 calories per day from unabsorbed carbohydrates and soluble dietary fibres. These are fermented by anaerobes to form short chain fatty acids to be transported to the liver for metabolic purposes. These fatty acids have a role to play in the adaptation of the bowel in SBS [113, 114].

Sodium absorption too needs to be understood. Sodium is absorbed from enterocytes through a sodium pump. The electrochemical gradient created by

this allows water to enter the enterocytes passively; the efficiency of this is dependent on the leakiness of the intracellular tight junction of the enterocytes. If they are more 'leaky' it is better as it allows more back diffusion of water into the lumen. Once inside the lumen the contents become isotonic and this helps digestion. The tight junctions are really tight in the ileum and colon and as a result water cannot enter the colonic lumen. This renders the content hyperosmolar which in a way preserves water [115]. As mentioned earlier, calcium, magnesium, phosphorus, iron, water and fat soluble vitamins are exclusively absorbed from the duodenum and proximal jejunum. Patients with SBS and an intact duodenum and proximal jejunum are therefore not likely to develop malabsorption of these except calcium and magnesium. These may be deficient because of their binding with unabsorbed long chain fatty acids. Low fat diet has been shown to improve their absorption.

One of the rarest complications of massive small bowel resection is D-lactic acidosis. This occurs only when the colon is preserved. Fermentation of residual unabsorbed carbohydrates by acid-resistant Gram-positive anaerobes produces D-lactate. The enzyme(s) needed to detoxify these acids are absent in the human colon. This leads to metabolic acidosis manifested by nystagmus, ophthalmoplegia, ataxia, confusion and behavioural abnormalities. The condition is confirmed by estimating the pH of the blood and demonstrating an anion gap. The condition is managed by administration of sodium bicarbonate, a low carbohydrate diet and non-absorbable antibiotics [5].

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Chapter 3
Postoperative Liver Failure

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3.1 Introduction

Technical innovations in surgical techniques, anaesthesia, critical care and a spatial understanding of the intra-hepatic anatomy of the liver, have led to an increasing number of liver resections being performed all over the world. However, the number of complications directly attributed to the procedure and leading to inadequate or poor hepatic functional status in the postoperative period remains a matter of concern. There has always been a problem of arriving at a consensus in the definition of the term: postoperative liver failure (PLF). The burgeoning rate of living donor liver transplants, with lives of perfectly healthy donors involved, has mandated a consensual definition, uniform diagnosis and protocol for management of PLF. The absence of a uniform definition has led to poor comparison among various trials. PLF remains a dreaded complication in resection of the liver, with a reported incidence of up to 8 % [1], and mortality rates of up to 30–70 % have been quoted [2]. Several studies have quoted a lower incidence of PLF in eastern countries, but when it occurs the mortality is as high as in the West [3].

The pathophysiology of PLF remains unclear with most authors presenting clinical conditions which are an overlap of acute liver failure (ALF) and small for size syndrome (SFSS), seen after an inadequate sized liver graft in transplantation. Prevention and treatment strategies also parallel the management of ALF for want of a better understanding of PLF, belying the fact that the former is caused by a toxin or virus and not surgery. The 30-day mortality of PLF is about 25 %, stressing the importance of evaluation of long-term mortality when comparing studies [4].

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In 2005, Balzan et al. [5] published their results of 775 elective liver resections over a span of 5 years. They focussed on serum bilirubin (SB) and prothrombin time (PT) as important prognostic markers of postoperative liver functional status and proposed the '50–50' criteria for the definition of PLF, i.e. the combination of PT >50 % of baseline normal and SB >50 μmol/L on postoperative day (POD) 5 (the '50–50' criteria) was found to be strongly predictive of mortality. The fact that this 'criteria' was a precursor of clinical complications 3–8 days before they appeared lent it a strong base for life-saving interventions. The criticism of this simple calculation has been that it relies only on two laboratory tests and does not factor in the existing clinical status of the patient. The '50–50' rule is limited by the fact that it cannot be applied before POD 5, does not stratify patients and though it predicts death in up to 70 % of patients, it is not based on the clinical severity of the patient.

In 2010, Rahbari et al. [2], of the International Study Group of Liver Surgery (ISGLS) defined PLF as 'a postoperative acquired deterioration' in the functions of the liver: synthetic, excretory and detoxifying. This deterioration is evident by an increase in international normalized ratio (INR) (There may be a need of clotting factors for abnormal INR) and SB, on or after POD 5 (compared with the values of the preceding day). Biliary obstruction needs to be ruled out as a cause for the deranged SB. They also stratified PLF into three grades: A, B and C, depending on up-scaling of the required level of care.

Traditionally, surgeons have resorted to keeping an eye on deteriorating liver function by charting rising INR (coagulopathy), rising SB (hyperbilirubinaemia) and the advent of hepatic encephalopathy (failure of detoxification) as surrogate markers for the functions of the liver. Other scores such as the Child–Pugh score (CTP) and the Model for end stage liver disease (MELD) have also been used by various authors for defining PLF, but a uniform consensus has evaded clinicians due to the multifactorial and diverse aetiology and pathogenesis of PLF.

3.2 Pathophysiology

Following liver resection the patient has multiple pathophysiological mechanisms at work. There is the trauma of surgery, the anaesthetic and haemodynamic changes, the metabolic demands of wound healing and especially in case of the liver: the pathophysiology of ischaemia–reperfusion injury (IRI), liver regeneration and the small for size syndrome (SFSS). Not only do the number of hepatocytes have to be adequate for body homeostasis, they should be functioning optimally and retain their capacity for regeneration. The liver cells suffer mainly from a combination of IRI, hepatic venous congestion and sepsis.

The 'hyperfusion theory' is widely accepted and postulates that the relative spike in sinusoidal perfusion of the decreased cell mass precipitates a vicious cycle. A cascade mechanism of which is a combination of congestion, inflammation, cholestasis and cell death taking place, preventing the normal function of a hepatocyte: uptake, secretion and excretion [6]. In addition cell proliferation and regeneration

are impeded. A standard liver resection for a liver tumour has to deal with IRI, congestion, portal hypertension and sepsis, while, in transplantation denervation and immunosuppression are added as precipitating factors.

IRI persists even after parenchymal damage during liver resection. After a period of ischaemia the inflammatory response in the form of the complement cascade is activated. Activated Kupffer cells generate reactive oxygen species (ROS) which cause endothelial cell damage [7]. Later in the reperfusion phase, these metabolites are swept around leading to a cycle of microvascular injury and microcirculatory changes resulting in apoptosis and cell necrosis with resultant hepatocyte death.

Sepsis may intervene in as high as 50 % of patients after liver resections and may be related to loss of Kupffer cell volume with impaired immune function. The relationship between infection and PLF has not been fully explained [8]. Patients with ALF are particularly prone to developing sepsis. It has been shown that 73 % of patients with PLF develop postoperative sepsis compared with 18 % of patients without [9]. Sepsis has a triad of detrimental effects on liver synthetic function, hepatocyte regeneration and apoptosis by inducing a relative hepatic ischaemia due to systemic hypotension. It induces Kupffer cell dysfunction, releases proinflammatory cytokines, and diminishes detoxification of liver endotoxins thereby leading to diminished hepatocyte proliferation and regeneration [10]. Liver surgery by itself may increase the incidence of infection [8] as major resections are associated with enteric bacterial translocation, which is enhanced by the prolonged inflow clamping and duration of surgery. A major liver resection involving multiple segments significantly impedes the function of the reticuloendothelial system, which is crucial in immune defence against sepsis.

3.3 Precipitating Factors

The precipitating factors for development of PLF can be broadly divided into patient factors, surgery-related factors and postoperative complications and their management (Table 3.1).

Patients with diabetes have a significantly poorer outcome after elective liver resections compared to those who do not have diabetes [11]. Apart from being at higher risk for infections due to decreased immune tolerance, patients with diabetes may also have a higher incidence of fatty liver with insulin resistance and concomitant poorer functional reserve. Preoperative diabetes mellitus is also an independent predictor of 90-day mortality [12].

Patients with cholangitis and active viral hepatitis also do poorly after surgery. In a study, mortality was significantly higher in patients who had resection of hepatocellular carcinoma (HCC) in cirrhosis associated with active hepatitis (8.7 versus 1.5 %; $p < 0.05$) [13]. However, increased risk of PLF with raised SB has been controversial [14]. Cherqui et al. showed that patients with a raised SB level had a morbidity rate of 50 % compared to 15 % in patients with normal SB ($p < 0.01$). However, the incidence of PLF or mortality did not rise when compared with matched controls [14].

Table 3.1 Precipitating factors for postoperative liver failure

Patient factors	Surgery related factors	Postoperative factors
Diabetes mellitus Obesity Chemotherapy-associated steatohepatitis Hepatitis B, C Malnutrition Renal insufficiency Hyperbilirubinaemia Thrombocytopenia Lung disease Cirrhosis Age >65 years	Estimated blood loss >1200 ml Intraoperative transfusions Need for vascular resection Multisegment resection or major hepatectomy including right lobectomy Prolonged surgery with denervation of liver <25 % of liver mass remaining Surgical experience Ischaemia–reperfusion injury Hepatic parenchymal congestion	Postoperative haemorrhage Intra-abdominal infection

Most patients being planned for liver resections have colorectal liver metastasis and receive chemotherapy with 5-fluorouracil, oxaliplatin and irinotecan, and newer monoclonal antibodies cituximab and bevacizumab [7]. Chemotherapy induces marked histopathological changes in the liver parenchyma including fatty liver, chemotherapy-associated steatohepatitis (CASH), or sinusoidal injury (sinusoidal obstruction syndrome, SOS). CASH is pathognomonic of patients treated with irinotecan and is characterized by 'steatosis, lobular inflammation and ballooning of hepatocytes': also called the 'grey liver syndrome'. SOS is caused by the use of oxaliplatin and the syndrome is called 'blue liver syndrome' because of the characteristic bluish-red hue of the firm liver [15, 16]. Irinotecan-induced CASH has been shown to be an independent risk factor for postoperative mortality and PLF. Oxaliplatin induced SOS develops after more than 6 cycles and is a risk factor for increased hospital stay and postoperative complications [17, 18].

Hepatic steatosis is a major determinant of postoperative outcomes. Over 20 % of patients undergoing a major liver resection have some degree of steatosis, significant enough to alter postoperative recovery [19]. Patients with biopsy-proven hepatic steatosis have a higher incidence of PLF (14 %) than patients with healthy livers (4 %) [20] even though the steatosis was of moderate grade. Belghiti et al. [21], reported a series of 478 patients who underwent liver resections, of which 37 patients had steatosis. Steatosis was an independent risk factor for postoperative complications (8 % of patients with steatosis), while only 2 % of patients with a normal histology developed complications. The increasing incidence of CASH, NASH and SOS has sparked interest in the use of preoperative liver biopsy as an assessment of the liver function and structure. Screening of high-risk patients (obese, high body mass index or those on chemotherapy) has been proposed. If a moderate degree of steatosis is established, these patients could benefit from manipulation of the volume, or surgery could be deferred till the acute changes subside either by treating the underlying aetiology or withdrawing the inciting agent.

Hepatitis B and hepatitis C virus infection-associated HCC develops along with the presence of fibrosis in the liver parenchyma. There is no correlation with fibrosis and liver resection, but when cirrhosis is established by a biopsy, it remains an

independent predictor of poor outcomes in terms of overall and tumour-free recurrence. Shen et al. used markers of liver fibrosis preoperatively to predict PLF in patients with HCC undergoing liver resection [22]. They evaluated preoperative hepatitis B virus (HBV) DNA levels, serum prealbumin (PA), hyaluronic acid (HA) and laminin (LN) levels and correlated these with PLF. A prospective model was used with these four laboratory results and validated in 89 HCC patients with a sensitivity and specificity of 62 % and 91 %, respectively.

Malnutrition is commonly prevalent among cirrhotics and leads to increased morbidity and mortality [23]. Malnutrition causes 'disordered mitochondrial function' which alters the immune response and thus reduces the hepatocyte regenerative capacity when exposed to ischaemia [24]. It is thus essential to objectively evaluate the nutritional status of all patients with liver disease, and to intervene with supplements as indicated.

PLF and postoperative renal dysfunction are independent predictors of 90-day mortality following liver resection but the predictive value for mortality is significantly higher when both systems fail simultaneously. Renal dysfunction following liver surgery may occur because of liver failure and hepatorenal syndrome but also due to hypovolaemia and release of free radicals and pro-inflammatory mediators during surgery [25].

Advanced age is no longer a deterrent to hepatic resections, which is now increasingly performed in elderly people with an acceptable morbidity and mortality [26]. Advancing age reduces the capacity of the liver to regenerate. The American Society of Anaesthesiology (ASA) and Acute Physiology and Chronic Health Evaluation (APACHE) scores have proved useful in anticipating complications following major liver surgery [27].

Assessment of the true functional status of the liver is fraught with complexities and routine blood tests have proved unreliable predictors of PLF. Notwithstanding this, all patients planned for major liver resections should have complete liver biochemistry, a complete blood count and a prothrombin time as baseline investigations [10].

Experience in liver surgery/high volume centres show an inverse relationship with outcomes. It has been suggested that patients needing liver resections be referred to centres that perform 10–17 liver resections per year [28]. Massive estimated blood loss (EBL) remains a key prognostic factor for a safe resection. EBL correlates with the extent of resection and the number of segments resected [29] and this correlates with the incidence of PLF. Massive EBL during a major liver resection should be anticipated in tumours abutting the inferior vena cava or major hepatic veins, or if there is injury to the middle hepatic vein during resection, and not by patient age, tumour size alone, or type of hepatectomy. Cirrhosis creates a hyperdynamic milieu with increased cardiac output and decreased systemic vascular resistance. The hepatic buffer response of the cirrhotic liver is altered: portal blood flow is reduced/shunted as a result of collaterals in portal hypertension, and arterial blood flow is impeded because of hepatic fibrosis and sinusoidal resistance. This altered flow renders the cirrhotic liver relatively anoxic and less tolerant to hypotension and hypoxia.

An intraoperative blood loss greater than 1000 ml increases the risk of PLF [30]. This effect may be caused by a massive fluid shift secondary to EBL causing global

inflammation because of bacterial endotoxins, peripheral vasodilation and pooling in third spaces. Coagulopathy following blood loss with the inability of the liver to catch up, seems to increase the potential for intra-abdominal collections and bacterial infections. Avoiding prolonged hypotension and hypothermia by using judicious and timely transfusion, rapid infusion devices and safe surgical techniques is the key to salvage these patients. In fact, even major blood loss may be tolerated, if adequate efforts have been made to maintain euthermia, perfusion, avoid metabolic acidosis and provide an adequate and timely buffer against the dangerous triad of acidosis, hypothermia and coagulopathy resulting from EBL [30]. Prolonged operating time also leads to a poorer outcome and is extended in patients with EBL, vascular reconstructions and difficult surgery due to adhesions and tumour extensions into unsafe areas.

The functioning liver remnant (FLR) in patients has become a topic of much debate especially with the popularity of living donor liver transplantation. In a liver with normal parenchyma <25 % FLR is associated with a poor outcome, compared to that of patients with ≥25 % FLR [31]. The risk of PLF is 3 times greater. The FLR and the method of calculating it are even more important in livers with steatosis and fibrosis as in these livers functional reserve is markedly reduced. Patients with histologically proven parenchymal changes of steatosis, fibrosis or cirrhosis, mandate a FLR of up to 40 % [32].

Postoperative management has an important bearing on outcome. The first 48 h after a major hepatic surgery are crucial for a successful outcome. Metabolic, functional and haemodynamic alterations after hepatic resection are unique to each patient and demand specific management protocols. A multidisciplinary team approach is required with goal-directed therapeutic options. It is mandatory to have invasive haemodynamic monitoring, mechanical ventilation, critical parameter monitoring, strict antisepsis measures, metabolic control and optimal nutritional support.

Some degree of coagulopathy is the expected norm after a major hepatic resection and can be assessed by markers such as PT/INR, platelet counts and partial thromboplastin time (PTT). Postoperative coagulopathy peaks 48–96 h postoperatively and can be best monitored by a thromboelastograph (TEG) [33]. The underlying coagulopathy leads to postoperative haemorrhage and blood collecting in the abdomen, leading to postoperative infection.

Postoperative antibiotic prophylaxis does not control infections [34] and no effort should be spared in obtaining meticulous haemostasis and following strict infection control protocols.

3.4 Preoperative Risk Assessment

Preoperative risk assessment involves a thorough evaluation of all the factors mentioned above. A physical examination followed by appropriate clinical tests will identify patients at risk of developing PLF. The patient's liver status, hepatic reserve potential and functional aspect need to be investigated along with the metabolic and haematological derangements, which may lead to PLF.

Pre-existing liver disease can be determined by a thorough clinical history, recording previous blood transfusions, hidden illicit drug use, excessive ethanol use, history of jaundice, family history of familial cholestasis as well as history of adverse drug reactions. In India, it is important to take a history of use of complementary and alternative medicines (CAM) as many of them maybe hepatotoxic [35]. Physical examination should be able to pick up subtle signs of incipient liver failure and decompensation such as proximal muscle wasting, spider naevi, ascites and other signs.

Though routine liver tests have a low yield, they are of value in liver resections as the major indications for hepatectomy in eastern countries are HCC and in the West metastatic disease arising in either normal or cirrhotic livers. HCCs are usually sequelae of HBV/HCV disease and it is prudent to evaluate for active disease as well as cirrhosis. Though colorectal metastasis can occur in a liver with normal parenchyma, the widespread use of preoperative chemotherapy, as mentioned earlier, mandates a more thorough evaluation of steatohepatitis and fibrosis. In patients with HCC, cirrhosis is present in 64–74 %, but conversely in patients with cirrhosis there is only an 11 % incidence of HCC [36]. The rest would be divided equally between alcohol-related disease and HBV/HCV, with about 5 % due to metabolic factors. In a cirrhotic patient with HCC, it is the underlying liver parenchymal disease which precludes a safe liver resection and this needs to be addressed. A cirrhotic liver is much less rarely involved with metastasis in comparison to normal livers.

Liver tests may be labelled as

1. Screening tests to indicate the presence of liver disease
2. Diagnostic tests to discern aetiology
3. Quantitative tests to measure functional reserve.

3.4.1 Screening Tests

1. Serum bilirubin evaluates conjugation and excretion functions. Total bilirubin is a poorly sensitive and specific test for liver disease. Direct bilirubin does not differentiate between extra- and intrahepatic cholestasis. However, it is an important factor of scores such as CTP and MELD for prognostication. Miyagawa et al. [37] found no significant differences in morbidity and mortality after major hepatectomies in spite of a raised SB. Postoperatively, SB is often increased; however this does not always indicate impending PLF.
2. Serum bile acids evaluate excretion and shunting. Elevated bile acids are a good marker for portosystemic shunting with a sensitivity of over 90 % in detecting cirrhosis in patients with normal transaminases [38].
3. Alkaline phosphatise (ALP) evaluates cholestasis. It is also synthesized in the bone and placenta and is elevated in metastasis and thus is not a specific hepatic marker. ALP also has a lag curve in acute obstruction. High preoperative alkaline phosphatase level is indicative of metastatic disease and may be associated with increased

mortality after major resections [39]. Concomitant with a raised carcinoembryonic antigen (CEA) level, it should raise a strong suspicion of liver metastasis.

4. Gamma glutamyl transpeptidase (GGT) evaluates cholestasis, enzyme induction, alcohol abuse, renal failure, myocardial infarction, diabetes and pancreatic diseases, and intake of enzyme inducing agents. Elevation of both GGT and ALP indicates a hepatic origin for ALP elevation.
5. Transaminases evaluate necrosis and parenchymal damage. Raised serum levels do not correlate with the extent of parenchymal necrosis and have no prognostic value. Both enzymes are evaluated together as ALT is more liver specific and AST more sensitive to changes. After full course chemotherapy, transaminases can be elevated up to 2.5 times of normal. Partial hepatectomy induces only a mild-to-moderate increase in serum enzymes [40].
6. Coagulation factors and PT evaluate synthetic functions. PT is a routine investigation and is used in prognostic scores. As its half-life is shorter, it is a better index of the synthetic function than serum albumin, which has a half-life of 20 days. Fibrinogen levels in mild liver disease are normal/slightly elevated but markedly decreased in massive hepatocellular damage. If the prothrombin time is prolonged, a detailed evaluation of the coagulation system is warranted. Massive hepatectomy invariable leads to a fall in platelet counts and a depression of coagulation factors such as factors I, II, V, VII, X and plasminogen [40] with resultant disseminated intravascular coagulation (DIC).
7. Albumin evaluates synthesis. It is not only a part of the CTP score but is associated with many non-hepatic diseases such as renal disease, and nutritional entities such as protein malnutrition, protein-losing enteropathy and burns. Patients with preoperative albumin <3.0 g/dl are at risk of increased operative morbidity [41].

The serum concentrations of the above tests may not be truly reflective of liver function alone as many extrahepatic causes may also alter the results, e.g. transfusion associated haemolysis, resorption of haematomas, extrahepatic loss of albumin in bowel-related diseases, or altered PT due to a lack of absorption of vitamin K in either resected small bowel or due to absence of bile in the gut, i.e. obstructive jaundice. Moreover the production, excretion and absorption of these factors are varied and laboratory techniques also result in variances.

3.4.2 Diagnostic Tests

1. Acute hepatitis A: Hepatitis A IgM
2. Hepatitis B: Hepatitis B surface antigen, anti-HBs, anti-HBc, HBV DNA
3. Hepatitis C: Anti-HCV, HCV RNA
4. Primary biliary cirrhosis: Antimitochondrial antibodies
5. Primary sclerosing cholangitis: Antineutrophil antibodies
6. Haemochromatosis: Iron, iron-binding capacity, ferritin

Quantitative analysis of viral markers gives an idea of replicating viral activity and response to antiviral therapy.

3.4.3 Quantitative Tests

1. Aminopyrine breath test (ABT) evaluates microsomal function. Cytochrome P450-mediated N-demethylation of a ^{14}C- or ^{13}C-labelled methyl group of aminopyrine is measured. The formed $^{14}CO_2$ or $^{13}CO_2$ are trapped and measured. Merkel et al. [42] studied ABT and CTP scores and reported that both reliably predict death from liver failure in patients with cirrhosis. ABT had 94 % sensitivity and 88 % specificity and this was independent of the Child's classification. Though the test is easy to do, it has not become popular due to the need for expensive equipment.
2. Organic anionic dyes assess hepatic perfusion and excretory function. Normal liver cells take up sulphobromophthalein (BSP), conjugate it with glutathione and excrete into the bile. BSP clearance differentiates cirrhotic from non-cirrhotic livers and provides the status of hepatic uptake and biliary excretion. However, BSP is metabolized in the liver and has been reported to cause anaphylaxis, which has restricted its use. In contrast ICG is not metabolized in the liver.

The 15-min retention rate for indocyanine green (ICG15) is the most common preoperative test for evaluating hepatic reserve [43]. When a hepatectomy is done in a patient with a high ICG15 retention, the volume of non-tumorous liver resected must be minimized. Hepatic function is estimated by ICG15 or of its maximal removal rate (ICG-Rmax). The ICG15 should be approximately 10 % in normal persons. The threshold value for a safe major hepatectomy is set at 14 %, although the cut-off of ICG clearance has shown significant reduction in cirrhotic patients who underwent resection and died subsequently. This was most accurate on day 3 following surgery. When ICGR15 exceeds 20 %, a major hepatectomy should be deferred [43]. Patients with ICGR15 between 14 and 20 % benefit from volume manipulation to achieve a viable FLR.

Preoperative ICG clearance may predict 30-day hospital mortality in patients with cirrhosis [44]. With an accuracy of 100 % for prediction of long-term prognosis in both retrospectively and prospectively evaluated cases, Noguchi et al. [45] reported a ratio of ICG-Rmax relative to the FLR after hepatectomy, which could reliably predict outcome. Mainly researched by Japanese surgeons, ICG clearance has not been popular with other centres. An ICGR15 value of 14 % has been proposed as a cut-off for identifying patients who will have high postoperative morbidity following a major hepatic resection [45].

Recently, ICG has been investigated again. Fung et al. [46] studied liver stiffness (fibrosis) using a fibrosis measuring impedance elastograph. Although ICG extraction is unique to the liver with minimal extrahepatic elimination, the clearance rate is dependent on local and systemic haemodynamics. Any change in hepatic flow or systemic perfusion causes variances in ICG rates. Therefore, they correlated liver stiffness with ICGR15 and liver biochemistry, to determine its reliability in predicting postoperative outcomes. Liver stiffness correlated well with ICGR15 in liver resection patients, and predicted early postoperative complications and was recommended, to provide 'better prognostic information for patients undergoing resection.'

3. MEGX test: evaluates microsomal function and is a measure of the formation of the metabolite monoethylglycinexylidide (MEGX) after injection of a bolus of lidocaine and is evidence of the conversion rate of lidocaine by hepatic cytochrome P450. A value ≤25 μg/L is related to PLF in patients with cirrhosis [47].
4. Technetium-99m galactosyl human serum albumin (99m Tc-GSA): GSA scintigraphy studies [48] have been reported to be useful for predicting the functional reserve of the liver and superior to ICG. 99m Tc-GSA is a scintigraphy agent that binds specific hepatic receptors, and can be used to assess the functional hepatocyte mass and thus the hepatic functional reserve in various physiological and pathological states. Unlike ICG it is not affected by the haemodynamic status.

3.5 Scoring Systems

Various scoring systems are in vogue to assess the suitability and risk stratification of hepatic resections in patients with cirrhosis. The CTP and MELD score were initially designed for other prognostications, and their validity in predicting PLF has been the objective of many trials. The results are inconsistent [1, 2, 5, 49]. In general, it is well accepted that a CTP class C patient is not suitable for any liver resection and those in class B are suitable for only minor liver resections [49].

Schroeder et al. [50] reported the superiority of CTP over the MELD score in predicting 30-day morbidity and mortality after hepatic resections. However, other studies validate the MELD score as a reliable predictor. A MELD score above 11 in patients with cirrhosis could predict PLF accurately [51].

3.6 Imaging

3D CT reconstructions or magnetic resonance imaging (MRI) reconstructions are now used exclusively for volumetric analysis and predicting FLR [52]. Calculation of FLR however remains a cause of disagreement and various techniques and calculations are in vogue. 3D reconstructions allow delineation of the hepatic veins, congestion volumes, exact tumour localization and facilitates virtual resection planning. However, imaging at present over estimates the FLR, and different formulae are in use, in an attempt to account for this error. The crux of any imaging or formula used is to ensure that the FLR is compatible with a smooth recovery and it is vital to assess the functional status of the FLR. Addition of preoperative hepatobiliary scintigraphy and CT volumetric measurement were performed by Dinant et al. in preoperative patients [48] to assess the accuracy of risk assessment for postoperative morbidity, liver failure and mortality. They concluded that using hepatobiliary scintigraphy with preoperative measurement of 99mTc-mebrofenin uptake in the FLR, proved more valuable than measurement of the FLR on CT alone in assessing the risk of PLF.

3.7 Prevention

Keeping the pathophysiology in mind, PLF can be prevented by a two-pronged strategy: Protect the parenchyma against damage and increase the parenchymal volume.

3.7.1 Hepatoprotective Strategies

1. Ischaemic preconditioning: After a brief period of inflow clamping, reperfusion is allowed, prior to the prolonged inflow clamping ischaemic insult (10 min of ischaemia and 10 min of reperfusion). It increases tolerance to the subsequent prolonged ischaemia and adenosine 5-triphosphate (ATP) depletion by exposing the parenchyma to brief intervals of anoxia and reperfusion before the final resection. It acts by presumably controlling IRI and retards the complement cascade. This reduces reperfusion injury particularly in steatotic patients. Clavien et al. [53, 54] did the initial trials and demonstrated a two-fold reduction in the postoperative serum transaminase levels. A reduced mass of apoptotic cells was noted on histopathology. A randomized trial by Chouker et al. [55] comparing ischaemic preconditioning and continuous clamping, showed stable cardiovascular haemodynamics, lowering the need for adrenaline/noradrenaline after liver reperfusion. Additionally, a recent Cochrane analysis observed no statistically significant difference in the mortality, liver failure, blood loss or haemodynamic changes [56]. However, length of hospital stay was significantly lower in the ischaemic preconditioning group.
2. Intermittent vascular clamping: consists of repeated periods of 15 min of inflow clamping followed by 5-min reperfusion phases. Belghiti et al. [57] reported that in contrast to the presumption, blood loss was significantly more in the intermittent clamping group. Acute phase liver enzymes and transaminase levels were significantly higher in the continuous portal triad clamping group than in the intermittent portal inflow clamping group when livers with chronic liver disease were included. Postoperative SB levels in cirrhotics were also significantly higher in the continuous inflow clamping group compared to the intermittent portal inflow cohort. They concluded that livers with chronic disease do not tolerate continuous vascular clamping as well as normal livers.
3. Avoiding inflow clamping: The Cochrane meta-analysis published in 2009 [56], based on three randomized trials, revealed statistically insignificant decreased blood loss with vascular clamping, when compared with no clamping. Total vascular occlusion is to be avoided unless resection is required at the cavohepatic junction when it cannot be avoided.
4. Hypothermic liver preservation: Interest in decreasing warm ischaemia of transported livers has spawned experiments into isolating the inflow and perfusing cold preservative into the future liver remnant, which is immersed in crushed ice to maintain the core temperature of the liver at 4 °C. Hypothermic liver preservation

when combined with total vascular exclusion attenuates IRI. In situ cold isolation techniques are still in their infancy and remain isolated case reports used in special situations with total vascular exclusion/cardiopulmonary bypass [58].

5. Pharmacological preconditioning: It has been reported in a clinical study that the use of isoflurane before clamping the inflow protected the liver from IRI [59]. Preconditioning with sevoflurane also significantly reduced postoperative transaminase levels and the overall incidence of postoperative complications was reduced especially in patients with fatty livers. Inhaled nitric oxide has also been cited to 'significantly decreasing the length of hospital stay, improving serum transaminase levels and coagulation times, and reducing the number of apoptotic hepatocytes.' A similar effect has been demonstrated with preoperative administration of 500 mg of methylprednisolone [59]. During major resections, intraoperative preconditioning with 600 mg of alpha-lipoic acid also reduced markers of hepatic damage by inflow occlusion.

3.7.2 Recommendations

Lesurtel et al. [60] have made the following recommendations: with better understanding of intrahepatic anatomy, newer energy devices and maintenance of a low central venous pressure during parenchymal transection, vascular clamping cannot be systematically recommended (level A). Portal inflow clamping reduces blood loss and use of blood products but does not influence morbidity (level A). Among various methods of inflow exclusion, they support intermittent clamping as better tolerated especially in patients with chronic liver disease (level A). Ischaemic preconditioning has been recommended for steatotic patients (level A). Intermittent clamping is preferred over ischaemic preconditioning in major liver resections and prolonged surgery (level A). Currently no evidence supports or refutes the use of ischaemic preconditioning in donor liver retrievals during living donor transplants.

3.7.3 Parenchymal Volume Management

Portal vein ligation (PVL/PVE) by ligation/embolization: PVL is usually performed by surgical ligation or percutaneously by transhepatic portal vein embolization (PVE). PVE induces apoptosis in the ipsilateral lobe, and hypertrophy and hyperplasia of the contralateral lobe. This increases the functional volume of the FLR, thus obviating hyperperfusion in a SFSS scenario. It is also a precursor phenomenon and predicts the regenerative response in the future remnant. PVE can increase contralateral lobe mass by up to 20 %, with the peak in growth occurring within 2–4 weeks of the procedure [61, 62]. The failure of the liver to enlarge after PVE is indicative of patients with impaired regenerative capacity in whom major resection should be avoided [62]. To prevent a surge in tumour growth due to enhanced differential hepatic artery flow to the tumour, local control by ablation/chemotherapy are also added as well as biliary drainage.

3.7.4 Splenic/Portal Inflow Modulation

Hyperperfusion of a small for size graft is often modulated by splenic inflow control by ligation/embolization or shunting. PLF is determined by haemodynamic parameters of the hepatic circulation and, specifically, by a portal blood flow that, when excessive for the volume of the liver parenchyma leads to an inflow/outflow mismatch causing pressure build up in sinusoids with a leaking capillary bed in the liver. Perisinusoidal and periportal haemorrhage occurs within a few minutes in a major hepatic resection as well as after the reperfusion of a SFSS graft. Late effects occur due to hepatic arterial and biliary epithelial hypoxia [6].

3.7.5 Staged Resections

ALPPS—the 'associating liver partition and portal vein ligation in staged hepatectomy' (ALPPS) strategy is one of the surgical innovations used to manage FLR volumes [63]. The ALPPS approach is proposed to induce rapid hypertrophy of the FLR in patients with HCC and whose preoperative volume does not allow a safe resection. The procedure entails the combination of in situ splitting of the liver along the Cantlie's line and ligating the portal vein on the side of the tumour. Subsequently the second stage hepatectomy is done. The median FLR volume increase was 18.7 % within 1 week after the first phase and 38.6 % after the second [64, 65]. Recently, a number of trials comparing ALLPS and post-PVE liver resections have been published [66–68]. ALPPS has shown higher hypertrophy rates compared to PVE/PVL (40–80 % within a week compared to 8–27 %). However, ALPPS has higher sepsis rates (16–64 % of patients) and mortality rates (12–23 %).

ALPPS facilitates an early removal of tumours whilst waiting for an adequate FLR. Due to the high morbidity rates there has to be a strict criteria for selecting a patient for ALPPS as PVE has shown comparable FLR hypertrophy rates.

3.7.6 Different Tumour Strategies

Downsizing tumours with chemotherapy, local ablative techniques and embolization is yet another strategy to gain functional reserve volume when planning resections in livers, which are likely to have a low FLR.

3.8 Management of PLF

The typical clinical features of PLF parallel the clinical picture of ALF: coagulopathy, raised SB and encephalopathy. In addition renal failure, respiratory compromise, hypotension and features of sepsis may be present. This clinical presentation

parallels the presentation of ALF, but is closer to that of subacute liver failure than to that of hyperacute liver failure [69]. With deteriorating liver function the patient will develop hyperbilirubinaemia and coagulopathy which in particular is a poor prognostic marker [70].

If PLF is detected in a patient, it should be scored by the ISGLS system [2].

PLF grade A: should be monitored well, but may not require specific treatment.
PLF grade B: it has to be evaluated if the patient should be placed in an intensive care unit (ICU)
PLF grade C: need ICU care

Rahman et al. [71] have cited a daily measurement of serum C-reactive protein (CRP) as an early warning indicator of patients likely to develop PLF. Patients prone to developing PLF had a lower CRP level on POD 1 than patients who did not develop PLF. A prognostic utility of postoperative CRP was a serum CRP <32 g/dl, which was an independent predictor of PLF. Initial treatment of PLF is supportive: ventilatory support, vasopressors, renal replacement therapy and anti-sepsis protocols. Controlling coagulopathy and supporting nutrition are the other mainstays.

Patients of liver resections are normally monitored closely in the intensive care or high dependency units. It is normal for SB levels and the INR to rise in the first 2–3 days postoperatively. SB concentration above 50 μmol/l (3 mg/dl) or INR greater than 1.7 on or beyond 5 days suggests liver dysfunction. Sepsis is indicated by raised serum lactate. The use of antibiotics in patients suffering from ALF is associated with a significant decrease in sepsis and this may also be of benefit in patients suffering from PLF [72]. Overall the management of PLF is along the lines for ALF. Identifying and controlling sepsis is the key to managing PLF [73].

Trials have shown that prophylactic antibiotics after liver resection do not lead to a reduction in PLF or sepsis [74]. ALF management guidelines propose that broad-spectrum antibiotics should be administered empirically to patients who progress to grade 3 or 4 hepatic encephalopathy, renal failure and/or worsening systemic inflammatory response syndrome (SIRS) [73, 75].

Many clinicians strive to provide heptoprotection with N-acetylcysteine (NAC) [76]. However, no evidence exists that it has any benefit in ALF. NAC is advocated in the management of paracetamol-induced ALF and its use in non-paracetamol hepatic failure remains controversial. Sporadic papers do mention a benefit for NAC and it is used empirically for its anti-oxidant role. Early stage non-acetaminophen patients with ALF benefit from intravenous NAC. Patients with encephalopathy grades 3 or 4 do not benefit from NAC and will require emergency liver transplantation. NAC is commenced in a loading dose of 150 mg per kg per hour for 1 h followed by 12.5 mg per kg per hour for 4 h and 6.25 mg per kg per hour for the remaining 67 h.

The rest of the management is along supportive care protocols as shown in Table 3.2.

Hepatocyte transplantation has been used in trials as an effort to rejuvenate existing liver function. Intrahepatic hepatocyte infusion [77] has been used successfully to treat patients with certain metabolic disorders of the liver. Results in liver failure (ALF and PLF) have been poor due to insufficient delivery of viable and sustainable functional hepatocytes.

Table 3.2 Supportive care protocols

Support	Investigation	Intervention
Nutrition	Check serum albumin	Enteral preferred over parenteral Euglycaemia to be maintained
Respiratory	Acid–base gas analysis Chest X-ray Sputum culture	Control acid–base imbalance Chest physiotherapy Pulmonary toilet Early recognition of ARDS, ventilator support and weaning Avoid fluid overload
Renal	Urea, creatinine, electrolytes	Modify nephrotoxic drug dose/ avoid volume overload/ electrolyte imbalance Renal replacement therapy
Coagulopathy	INR, platelets, factors, TEG	Vitamin K and fresh frozen plasma if INR >1.5 or manifest bleeding Correct profound thrombocytopaenia Recombinant factor VIIa (rFVIIa)(uncertain role)
Sepsis	Wound, ascites, drain, urine, sputum cultures CT adbomen for collections	Antibiotics to be started if encephalopathy worsens, worsening renal failure or SIRS parameters
Encepahalopathy	CT head if worsening ICP monitoring	Lactulose
Others Stress ulcer prophylaxis Ascites Vascular events	Ultrasound Doppler	Proton pump inhibitors Large volume paracentesis Interventions

ARDS acute respiratory distress syndrome, *INR* international normalized ratio,*TEG* thromboelastograph, *SIRS* systemic inflammatory response syndrome, *ICP* intracranial pressure

Though, liver support systems have been available for some years now, their high operational cost and sepsis rates have not improved. These include:

1. Molecular absorbent recirculating system (MARS)
2. Modified fractionated plasma separation and adsorption (Prometheus)
3. Bioartificial liver (BAL) and extracorporeal liver assist device (ELAD).

Extracorporeal systems are predominantly sustained on albumin dialysis, and bioartificial devices are bioreactors with permeable membranes containing hepatocytes, either synthetic or natural. Very few trials exist in the setting of PLF, with the exception of one case series which showed no significant benefit [78, 79]. They are not currently recommended in the medical management of ALF. Because their actual place in the global field of acute or acute on chronic liver failure remains to be determined, their role in PLF is undefined. However, because outcomes in PLF are morbid, it is worthwhile to continue to investigate the beneficial roles of these devices [80–82].

3.9 Surgery

The use of a rescue hepatectomy (removal of necrotic portions or segments) in patients suffering from PLF may be of value when faced with a very sick patient. It is based on the concept that the 'necrotic liver' is the source of unknown humoral substances that contribute to SIRS [83].

The efficacy of orthotopic liver transplantation (OLT) for PLF has recently been reported [84]. In this paper, Otsuka et al. did a retrospective review of 435 patients who had a liver resection between 1990 and 2004. Nine of them (2 %) developed PLF of which seven were offered OLT at a mean of 25 days post resection. Indications for resection included malignancies and benign disease. Patients developing PLF had significantly altered biochemical and coagulation parameters manifesting on POD 2 and had the classical triad of coagulopathy, hyperbilirubinaemia and encephalopathy. There was no mortality following OLT, though one patient required a retransplant. The mean survival with and without OLT was 42.2 and 1.4 months, respectively ($p = 0.03$).

They concluded that all patients ($n = 4$) who suffered from PLF but were not considered suitable for liver transplantation, died, while all those undergoing OLT survived ($n = 7$). OLT allows salvage of an otherwise fatal condition. However, no definitive criteria are available for emergency liver transplantation for PLF.

OLT as a rescue for PLF has been gaining in popularity, governed only by the availability of organs or suitable donors in an emergency. The principles of transplantation should however be adhered to: in most instances the indications for OLT after PLF should be limited to patients who fulfill the primary indication for HCC—pre-resection tumour burden within the Milan criteria [85]. Patients with metastatic disease, beyond Milan criteria, advanced medical and anaesthetic comorbid conditions, and poor functional status, should not be candidates for OLT.

OLT is the only radical surgical remedy that improves survival in patients with end-stage liver disease. However, patients suffering from PLF are rarely eligible for liver transplantation because of tumour characteristics or comorbid conditions.

3.10 Conclusion

The incidence of PLF after a major hepatic resection averages 8 %. An abnormal FLR is the main cause for the pathogenesis of PLF. Other reasons, which worsen PLF, are hepatic parenchymal congestion, IRI and postoperative sepsis. These can exist singly or in combination.

Risk factors for the development of PLF are small FLR, blood loss, malnutrition, diabetes mellitus and active liver disease. A comprehensive preoperative assessment includes evaluation of liver volume, anatomy and function. A physical examination followed by appropriate clinical tests will identify patients at risk of developing PLF. The patient's liver status, hepatic reserve potential and functional aspect need to be investigated along with the metabolic and haematological derangements, which may lead to postoperative liver failure. Corrective measures should be applied when-

ever possible, as curative treatment options are limited. The risk of PLF is high when FLR is below 25–30 % in livers without cirrhosis and below 40 % in livers with pre-existing liver disease. PVE and/or two-stage hepatectomy are options when surgery cannot be deferred. Additional liver damage may be prevented by intermittent clamping techniques, though used with caution in steatotic livers. Management principles are on the lines of management of ALF with support of liver, cardiorespiratory and renal support function. Control of sepsis is an important aspect. Emergency liver transplantation has shown promise as a remedy for PLF.

Editorial Comments

Postoperative liver failure after hepatectomy is a potentially life-threatening complication. Fortunately, even though the rates of liver resection are increasing, the mortality from the procedure is decreasing. The operative mortality at specialized centres varies from 0 to 6 % [86]. However, the morbidity continues to be high. The definition of post-hepatectomy liver failure has not been standardized. Three definitions are currently being followed. Two of these (the 50–50 criteria and the International Study Group of Liver Surgery [ISGLS] criteria) have been mentioned by the authors [2, 5]. The latter not only diagnoses the condition, it stratifies the severity into 3 categories. Grade A does not need any change in management strategy, Grade B may be managed without any invasive intervention while Grade C needs alteration in management including invasive intervention. The ISGLS criteria have been validated by one study [87]. The study detected post-hepatectomy liver failure using this criteria in 11 % of patients–8 % had Grade A, 72 % Grade B and 20 % Grade C. The mortality in these patients was 0 % in grade A, 12 % in grade B and 54 % in grade C. Thus, the grading has been shown to correlate with mortality. However, in 2 separate reports, 41 and 67 % of patients fulfilling the ISGLS criteria recovered completely highlighting the importance of adequate management rather than just using the definition [4, 5].

The third definition described by Jarnagin et al. is simple. They define post-hepatectomy liver failure as high bilirubin in the absence of biliary obstruction or leak occurring with ascites and coagulopathy with or without encephalopathy [88].

The authors have discussed the possible pathophysiological factors in detail. To this I may add the possibility of hepatic venous outflow tract obstruction as described by Lhuaire et al. [89] The authors documented outflow obstruction with contrast enhanced CT, Doppler ultrasound, cavography and assessment of pressure gradient between the hepatic vein and inferior vena cava. They managed the patient successfully with placement of a metallic stent in the left hepatic vein and documented reduction in the hepatic vein–inferior vena cava pressure gradient. The patient improved thereafter and was discharged. Hepatic venous outflow obstruction following hepatectomy has been reported in experimental studies in rats [90].

Various risk factors have been indentified and have been discussed elaborately by the authors. This should allow surgeons to select proper patients for extensive resection to avoid post-hepatectomy liver failure. The main issue is the adequacy of the residual liver volume and presence of cirrhosis. While 30 % of residual volume is adequate for extended resections in a normal liver, it is grossly inadequate for a cirrhotic patient in whom at least 40 % of liver volume is required. This brings us to the question of increasing future liver remnant by various strategies. Both portal vein embolization (PVE) and liver partition with portal vein ligation are effective. However, the simplicity of PVE makes it the most used approach. It has the advantage of the tumour biology being assessed during the waiting period of 4–6 weeks. If the tumour progresses especially with chemotherapy the patient should not undergo liver resection. On the question of properly selecting patients for major resection in cirrhosis the prevailing guidelines should be followed. These are Child's A status, platelet count above 100,000/cm, absence of clinically significant portal hypertension, a future liver remnant of 40 %, and the 15 min indocyanine green (ICG) clearance of no more than 15 %. A number of tests are available to assess various functional aspects of the liver but they are cumbersome, not available at most centres and more importantly are not accurate with the exception of 15 min ICG clearance. Even this is not done routinely in the West.

Patients with features of postoperative liver failure by either the '50–50' criteria or the ISGLS criteria have circulatory changes as seen in septic shock such as vasodilatation, increased vascular permeability resulting in accumulation of fluid in the third space, tachycardia and increased cardiac output leading eventually to hypotension. Coagulapathy too is seen commonly. Altered kidney function usually occurs due to hepatorenal syndrome or acute tubular necrosis because of sustained hypotension causing compromised renal perfusion. With worsening renal function, fluid accumulates in the periphery or pulmonary bed. This often necessitates renal replacement therapy. With improvement in renal function the liver function also improves. Hepatic encephalopathy is seen more commonly in patients with renal failure because serum ammonia cannot be cleared by either the kidney or the liver. The presence of sepsis is another problem. Hypotension resulting from sepsis is detrimental to liver regeneration essentially due to ischaemia. Endotoxins produced in sepsis interfere with Kupffer cell activation and its function. One should not forget that following hepatic resection there is a depletion of Kupffer cells in the liver. Thus following hepatectomy there is a higher incidence of sepsis, and sepsis interferes with hepatic regeneration [91]. Therefore, every attempt must be made to avoid sepsis. Execution of the surgical procedure with utmost care avoiding excess blood loss, tissue necrosis, haematoma formation, prolonged ischaemia, etc. should minimize infection.

Management of post-hepatectomy liver failure has been duly addressed. I will emphasize on the fluid and nutrition therapy. Following hepatectomy the

urine output may be low but it is expected. It is not necessary to give bolus fluid therapy in these patients unless they are grossly oliguric. Cirrhotic patients should probably be given parenteral nutrition in place of dextrose solutions because parenteral preparations have branch chain amino acids, dextrose, medium chain triglycerides, phosphates and vitamins. Usually up to 2 l of such fluid is necessary. If volume deficit exists, it should be managed with additional fluids. Parenteral nutrition in post-hepatectomy liver failure helps liver regeneration and decreases septic complications. The addition of phosphate is extremely important because it is necessary for both energy production and liver regeneration. Moreover the phosphate level goes down considerably after major liver resection [92]. Since the available phosphate solutions contain potassium, these may need to be stopped if the serum potassium level is high. The phosphate will then need to be replaced orally and the oral forms have sodium. Hence, the serum sodium would need to be monitored.

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Chapter 4
Xanthogranulomatous Cholecystitis

Asit Arora and Shyam Sunder Mahensaria

4.1 Introduction

Xanthogranulomatosis is a rare, idiopathic, inflammatory disorder that may involve various organs such as the skin, gastrointestinal tract, genitourinary tract and the gall bladder. It is characterized by deposition of fat laden histiocytes in the involved organ and intense peri-lesional inflammation. Xanthogranulomatous cholecystitis (XGC) was first described by McCoy in 1976 [1]. Bile in the gall bladder wall results in severe inflammation and fibrosis that culminates in dense adhesions with the adjacent organs such as the duodenum, bile duct and colon. This leads to two of the hallmark presentations of XGC, i.e. an inflammatory mass mimicking gall bladder cancer (GBC) and a variant of chronic cholecystitis that by virtue of its inflammation and tendency to form fistulae with the surrounding viscera is a nightmare for a surgeon.

4.2 Aetiopathogenesis

Though not very well elicited the most widely accepted theory for the genesis of XGC is rupture of the Rokitansky Aschoff sinuses and extravasation of bile into the gall bladder wall. This incites a foreign body reaction with accumulation of foamy histiocytes and foreign body giant cells [2]. Blockade of the gall bladder neck by a stone and rarely a tumour resulting in increased intraluminal pressure is the triggering factor for the rupture of sinuses in most cases. Another proposed mechanism is

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recurrent inflammation due to stone disease resulting in degeneration of the gall bladder wall and abscess formation [3]. The end product of this inflammation is fibrosis resulting in gall bladder wall thickening, mass formation and fistulization.

4.3 Relationship of XGC with GBC

There is no conclusive evidence to suggest XGC is a premalignant lesion even though there are reports of co-existence of XGC with GBC [4]. The association of XGC and GBC can be better explained by the fact that both stem from a common aetiology, i.e. gallstones resulting in chronic inflammation. Thus, it should not be surprising to find both entities in the same specimen. Another explanation for this association is GBC as an initiator of the xanthogranulomatous reaction. The mucosal ulceration and resulting discontinuity allows easy egress of bile into gall bladder wall leading to XGC [5]. There has also been a suggestion that GBC of the neck causing obstruction of cystic duct can also lead to XGC [4]. In an effort to address the issue of premalignant nature of XGC, a study was conducted to assess the expression of p53, proliferating cell nuclear antigen (PCNA) and beta catenin in XGC vis-a-vis GBC. It failed to show any premalignant potential of XGC [6].

Nevertheless it is important to realize that not only XGC mimics GBC, but both these conditions may co-exist. The implication of this finding is that on one hand every effort should be made to differentiate XGC from GBC preoperatively so that a more aggressive approach can be avoided for a benign disease, on the other hand a small focus of malignancy amidst XGC should not be missed as it may lead to loosing the chance for a potentially curative surgery.

4.4 Clinical Presentation

The usual clinical presentation is similar to symptomatic gallstone disease. It affects people in the fifth and sixth decade with a female preponderance. Pain is the most common symptom, being present in almost all patients. A history of pain of several weeks and months can be elicited in a majority of patients but it is not rare to encounter a patient with a short history of less than 4 weeks and at times less than 7 days. The presence of jaundice due to concomitant choledocholithiasis or Mirrizi's syndrome is reported in 6.5–36 % of patients. The presence of constitutional symptoms such as anorexia and weight loss is rare in XGC and, if present, it should alert a clinician to the possibility of GBC. However, fever is uncommon with XGC. Clinical examination may reveal a tender palpable lump in the right hypochondrium in fewer than half the patients [7].

There is a significant overlap of symptoms between XGC and GBC and at time it becomes impossible to differentiate the two on the basis of the history and clinical examination.

4.5 Radiological Assessment

The onus to detect XGC preoperatively lies largely on the radiological assessment, of which contrast enhanced CT scan is the corner stone. However, XGC as a pathological surprise is not uncommon in patients suspected to have GBC, despite a complete and detailed radiological assessment.

Transabdominal ultrasound is usually the first investigation, as in most biliary diseases. It may reveal features of chronic cholecystitis, pericholecystic oedema and fluid collections, as well as uniformly thickened gall bladder wall with hypoechoic nodules. The presence of gallstones is common (Fig. 4.1).

Contrast enhanced CT scan is the most extensively studied modality for evaluation of XGC. Various CT findings have been described and the most characteristic is diffuse gall bladder wall thickening with homogenous enhancement, uniform mucosal lining, presence of intramural hypoattenuating nodules and absence of liver infiltration. Even these so-called characteristic findings lack sensitivity and specificity, and have a significant overlap with GBC (Table 4.1) (Fig. 4.2).

Of all the features mentioned above the most reliable ones are diffuse wall thickening, continuous mucosal enhancement, presence of intramural hypoattenuating nodules and absence of liver infiltration. Individually these findings have sensitivity, specificity and accuracy in the range of 61–89 %, 65–82 % and 66–77 %, respectively [8]. However, when at least three of the above four findings are present the sensitivity, specificity and accuracy for diagnosing XGC increases to 83 %, 100 % and 91 %, respectively [8]. In another study Agarwal et al. [10] compared 31 patients with XGC and 167 with GBC and found that continuous mucosal line enhancement and intramural hypodense band had a statistically significant association with XGC as compared to GBC ($p < 0.001$ and $p < 0.025$). Even in their study, the accuracy of these finding to diagnose XGC was a modest 86.4 and 72.4 %. Since the inflammation in XGC involves the wall of the gall bladder leaving the

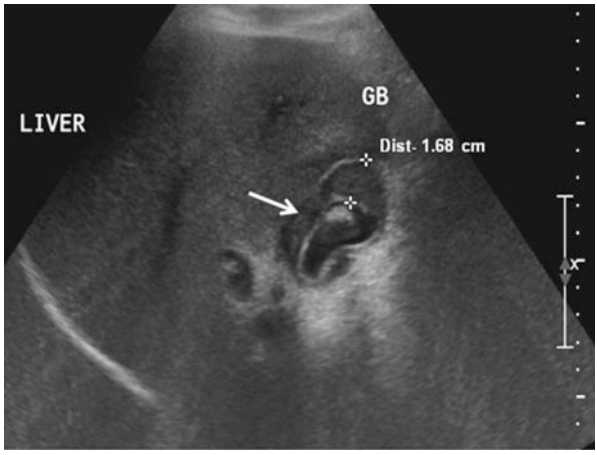

Fig. 4.1 Xanthogranulomatous cholecystitis. Ultrasound image of a 72-year-old man showing marked gall bladder wall thickening with intramural hypoechoic nodules (*arrow*) and an intraluminal calculus

Table 4.1 Comparison of CT findings in xanthogranulomatous cholecystitis and gall bladder cancer [8–13]

Radiological feature	Xanthogranulomatous cholecystitis	Gall bladder cancer
Gall bladder wall thickening		
Diffuse	Very common	Rare
Focal	Rare	Very common
Wall thickness (in mm)	8.3–18.0	12.6–21.0
Mucosal lining		
Continuous	Very common	Rare
Disrupted	Rare	Very common
Intramural hypoattenuating nodules		
Absent	Rare	Very common
<30 %	Very common	Rare
30–60 %	Very common	Rare
>60 %	Very common	Rare
Pericholecystic fat stranding	Common	Common
Liver infiltration		
None	Very common	Common
Indistinct borders	Common	Common
<2 cm	Rare	Very common
>2 cm	Absent	Very common
Lymph nodes	Common	Common
Intrahepatic biliary radical dilatation	Rare	Common
Adjacent organ involvement		
Duodenal	Common	Common
Hepatic flexure	Common	Common
Omental fat stranding	Common	Common

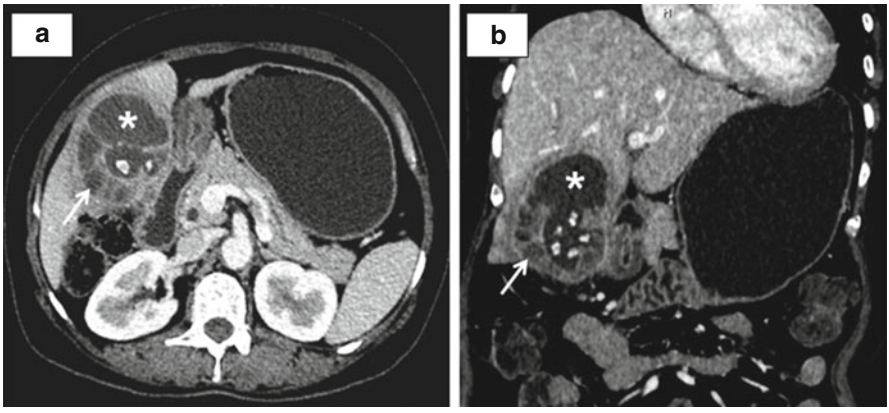

Fig. 4.2 Xanthogranulomatous cholecystitis with contained rupture. Axial contrast enhanced CT image of a 48-year-old lady showing circumferential wall thickening containing multiple hypodense nodules within the wall (*white arrow*) and multiple intraluminal calculi with a mucosal defect and associated intramural collection (*asterisk*)

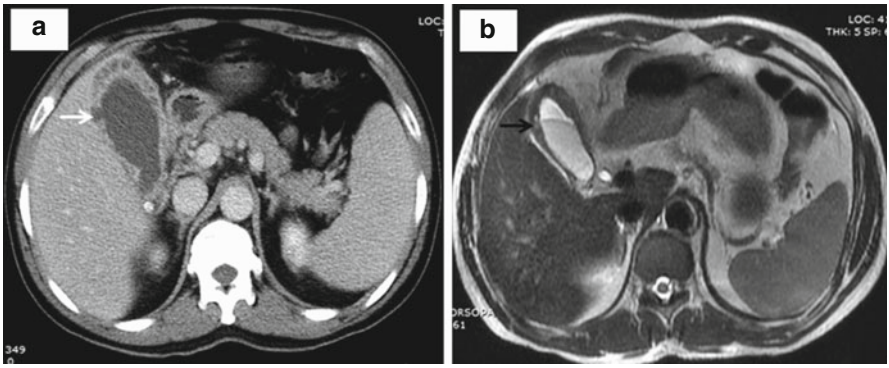

Fig. 4.3 Xanthogranulomatous cholecystitis. Axial contrast enhanced CT image (**a**) and axial T2-weighted MR image (**b**) of a 38-year-old lady showing diffusely thickened gallbladder wall containing nodules within the wall. Nodules are hypodense on contrast enhanced CT (*white arrow*) and T2 weighted hyper-intense on MRI (*black arrow*) with continuous mucosal enhancement

mucosa intact, it results in the CT finding of continuous mucosal line enhancement whereas in GBC mucosal ulceration and breach due to a tumour indicates a disrupted mucosal lining [14]. Similarly the hypoattenuating bands and nodules represent the foamy histiocytes and micro-abscesses in the wall of the gall bladder in XGC [15] (Fig. 4.3).

PET scan has also been used to differentiate XGC from GBC and there have been reports of both false positive and false negative tests resulting in a low sensitivity and specificity rates of 75 % and 87.5 %, respectively [16, 17].

Though MRI does not offer any advantage over CT and is not routinely used in this clinical scenario, there has been a report of a chemical shift gradient ECHO MRI and its ability to differentiate XGC from GBC by virtue of detecting a small amount of fat in the wall of the gall bladder [18].

Ultrasound-guided fine needle aspiration cytology (FNAC) is also used occasionally as a problem-solving tool when conventional and functional imaging fails to differentiate between XGC and GBC. The diagnostic accuracy of FNAC is 97 % [19].

4.6 Surgical Management

As far as surgical management is concerned XGC should be divided into two subsets. The first subset would be a variant of chronic cholecystitis which due to excessive inflammation and fibrosis results in adhesions and fistulization with adjacent organs making a laparoscopic cholecystectomy a formidable procedure with higher conversion rates, more bile duct injuries and necessitating a partial cholecystectomy in a substantial number of patients. The second subset is a mass forming variant which on imaging and even on intraoperative assessment mimics GBC and thus ends with a radical and mutilating surgery. Both of these subsets require a different and individualized management approach.

Table 4.2 Surgical series reporting laparoscopic cholecystectomy (LC) in xanthogranulomatous cholecystitis (XGC)

Author, year	Histologically proven cases of XGC	Patients in whom LC attempted (%)	Successful LC (%)
Jetley et al. (2012) [20]	13	13 (100)	5 (38.5)
Han et al. (2012) [21]	39	7 (17.9)	5 (71.4)
Alvi et al. (2013) [22]	27	17 (63.0)	8 (47.1)
Yabanoglu et al. (2014) [23]	21	15 (71.4)	8 (53.4)
Qasaimeh et al. (2015) [24]	42	35 (83.3)	24 (68.6)

Laparoscopic cholecystectomy is the standard of care for gallstone disease and remains the first choice of treatment for the first subset of XGC as well. In the hands of experts it can be done safely (Table 4.2). A preoperative MRCP helps to provide a road map, the availability of intraoperative cholangiogram can allow for identification of the bile duct and its course, a skillful operator with sufficient dexterity to handle the shrunken and friable gall bladder which is difficult to retract, the ability to do a fundus first and, if necessary, partial cholecystectomy are useful skills. The surgeon should be mentally prepared to deal with the fistulae to adjacent structures such as the duodenum or common bile duct. There should be a low threshold for conversion both for the inability to delineate anatomy and also if there is intraoperative suspicion of malignancy. Examination of the cut section of the resected gall bladder and availability of frozen section is a must while operating on such cases.

XGC poses a challenge not only during laparoscopic cholecystectomy but also during open cholecystectomy. A morbidity of 15–28 % has been reported after open cholecystectomy as well [25]. High conversion rates (up to 80 %) and high morbidity in earlier experiences led some authors to recommend an open cholecystectomy for patients with a preoperative diagnosis of XGC [25]. However, as experience with laparoscopic cholecystectomy increased the conversion and morbidity rates decreased. The laparoscopic approach is now used more frequently in the management of this challenging problem as is evident in Table 4.2.

The mass forming XGC poses a different set of problems altogether. Even with the use of the best imaging modalities it is often impossible to distinguish XGC from GBC. Hence, a clinical algorithm proposed by Agrawal et al. can be useful in this scenario (Fig. 4.4) [10].

If the diagnosis of XGC cannot be made with reasonable confidence on preoperative imaging and intraoperative findings and to achieve R0 status the resection required is up to an extended cholecystectomy it is better to proceed with the radical resection. However, when the resection required for an R0 resection is of a larger magnitude such as an extended right hepatectomy, hepatopancreatoduodenectomy or requiring a vascular resection and reconstruction it is better to confirm malignancy by intraoperative FNAC or trucut biopsy. It is better to avoid doing a procedure with a much higher mortality and morbidity for a benign disease.

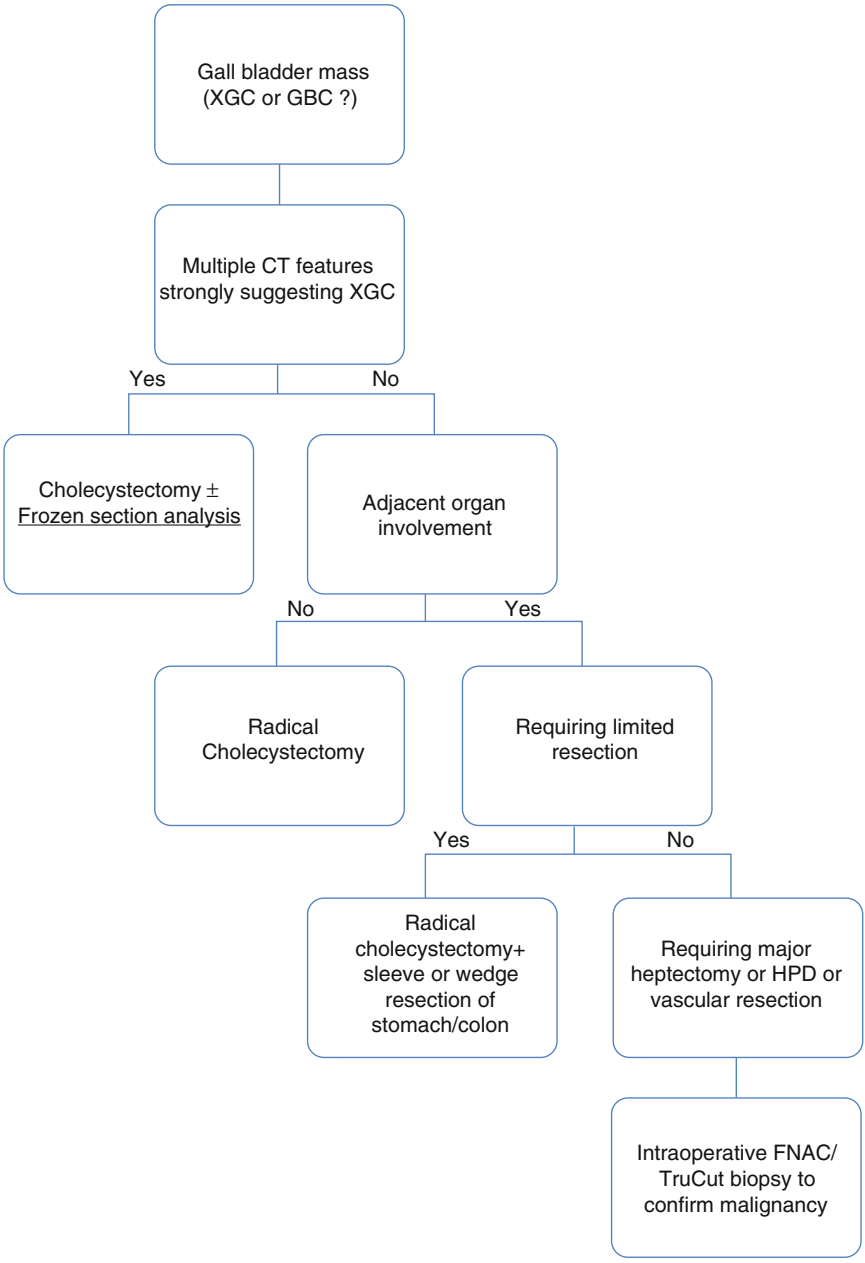

Fig. 4.4 Algorithm for managing a patient presenting with radiological features of a gall bladder mass. *XGC* xanthogranulomatous cholecystitis, *GBC* gall bladder cancer, *HPD* hepatopancreatoduodenectomy, *FNAC* fine needle aspiration cytology

4.7 Histopathology

XGC is a pathological diagnosis than a clinical or radiological diagnosis. It is characterized by foamy histiocytes, xanthoma cells and a lot of inflammatory cells in the early stage and fibroblastic reaction in the late stage [26]. As bile enters the wall of the gall bladder, histiocytes gather and ingest bile lipids and cholesterol to form xanthoma cells. This is followed by micro-abscesses and eventually the formation of xanthogranuloma. As chronicity sets in there is healing by fibrosis and scarring [2] (Fig. 4.5).

4.8 Our Experience

From 2010 to 2015, of the 796 patients who had a cholecystectomy, 72 had histology proven XGC resulting in an overall incidence of 9 %. Of these 7 patients had mass forming XGC with suspicion of GBC and thus underwent open surgery. Three patients had cholecystectomy with wedge resection of the liver and intraoperative frozen section that was negative for malignancy. The other 4 patients underwent radical cholecystectomy with Segment IVb-V resection in 3 and an additional colonic resection in 1 patient. Final histopathology revealed XGC in all with no evidence of malignancy. In the remaining 65 patients laparoscopic cholecystectomy was done in 62 patients with a conversion rate of 25.8 %.Three patients underwent planned open cholecystectomy due to a preoperative diagnosis of cholecystoenteric fistula and Mirrizi's syndrome (type 3). Subtotal cholecystectomy was needed in 16 patients (24.6 %). The overall morbidity rate was 16.9 % with the most common complications being deep surgical site infection in six patients; 4 of these required

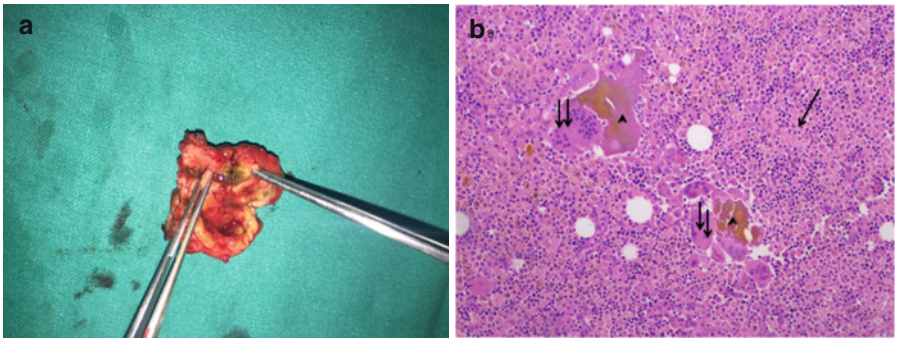

Fig. 4.5 (**a**) A cut open gross specimen of a uniformly thick walled gall bladder, intact mucosa and inspissated bile in the wall suggestive of xanthogranulomatous cholecystitis, (**b**) Photomicrograph showing the characteristic histopathological features of xanthogranulomatous cholecystitis: High power view showing sheets of lymphoid cells and macrophages (*single arrow*) with inspissated bile (*arrow heads*) and foreign body giant cell reaction (*double arrows*), 200×, H and E

percutaneous drainage for collections in the gall bladder fossa. Five patients developed a bile leak due to a cystic duct stump leak detected by bilious drain output. All resolved spontaneously by day 10 and no intervention was required.

Editorial Comments

XGC is an unusual form of cholecystitis. Its pathogenesis continues to be an enigma. This condition is important as it resembles carcinoma of the gall bladder both clinically, radiologically and intraoperatively. Hence, an accurate preoperative diagnosis is useful in avoiding an unnecessary and extensive operation (extended cholecystectomy). However, one should not miss a malignancy. Unfortunately, accurate preoperative diagnosis is often not possible because the so-called characteristic features commonly attributed to XGC——echogenic nodule (on ultrasound) or hypodense nodule on CT with intact mucosal lining can be seen in gall bladder cancer. Thus for diagnostic accuracy, EUS-based cytological evaluation has been advocated so as not to resort to over or under treatment [27]. During surgery one should obtain a frozen section for confirmation of either condition for proper treatment.

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Chapter 5
Pancreatic Trauma

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5.1 Introduction

Unlike 'Liver' and 'Splenic' trauma where rapid strides have been made in understanding, 'Pancreatic trauma' still remains a relative enigma, inspite of advances in diagnostics and surgical techniques. Largely, it is injury to the main pancreatic duct, its timely diagnosis and appropriate management which decides the mortality and morbidity. Most pancreatic trauma scores including the widely followed 'American Association for the Surgery of Trauma (AAST)' focus on injury to the pancreatic duct in grading pancreatic trauma.

Pancreatic trauma causes higher morbidity and mortality than that observed in injuries to other intraperitoneal organs because of three reasons [1].

- First, the pancreas anatomically resides in a relatively protected position high in the retroperitoneum. This results in it being infrequently injured in blunt abdominal trauma (BAT) such as vehicular accidents especially when compared to the spleen and liver and is often ignored. Further, it can be easily missed on clinical

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examination. There are no reliable serum markers. Imaging such as focused assessment by sonography for trauma (FAST), regular ultrasound (USG) and computerized tomography (CT) also may miss or under-diagnose pancreatic trauma.

- Second, as other abdominal organs, the pancreas can be injured in BAT and penetrating abdominal trauma (PAT). While in PAT, emergency exploratory laparotomy is usually done, BAT today is likely to be managed conservatively if the patient is relatively stable. This results in 'missing' or a delay in recognizing pancreatic injuries. Even if a laparotomy is done, unlike other intraperitoneal organs, physical evaluation and examination of the pancreas in the operating room may miss an isolated pancreatic ductal injury. Adjunctive intraoperative tests such as endoscopic retrograde cholangio-pancreatography (ERCP) may be required, the expertise for which may not be available at a particular centre.
- Third, the pancreas shares an intricate relation with the duodenum and biliary system. Severe trauma usually results in complex injuries to these organs as well thus increasing the morbidity and mortality.

5.2 Aetiology

5.2.1 Anatomical Considerations

The pancreas is located in a relatively protected area of the abdominal cavity. It is retroperitoneal and lies across the vertebral column, sheltered by the bony rib cage and the thick dorsal paraspinous muscle groups. Anteriorly, the rectus and abdominal muscles as well as all other solid and hollow organs such as the liver, colon, duodenum, stomach and small bowel, provide physiological padding that protects the pancreas from blunt injury. Severe BAT may result in fracture of the body over the vertebral bodies posteriorly. However, the anatomical position of the pancreas neither protects nor increases the risk from PAT.

In patients with pancreatic trauma, the proximity of vascular structures to the head of the pancreas has a marked effect on the morbidity and mortality rates. The subhepatic inferior vena cava (IVC) and the aorta are related posteriorly and just to the right of the pancreatic head. The superior mesenteric vein joins the splenic vein to form the portal vein immediately behind the neck of the pancreas. Exsanguinating haemorrhage from concurrent injury to these vessels is a frequent cause of death in patients with severe pancreatic trauma. Even if recognized and explored early, the complex and highly vascular anatomy with multiple branches, especially in the region of head and neck, preclude easy repair or control of bleeding.

5.2.2 Mechanical Considerations

A major force is usually required to cause a pancreatic injury in BAT. In most instances it is a sudden localized force to the upper abdomen that compresses the pancreas against the vertebral column with injury most commonly occurring just to the left of the mesenteric vessels at the junction of the neck and body of the pancreas [2].

A tangential force from the left may result in injury to the distal pancreas along with the spleen, left kidney and stomach. Similarly, right sided forces injure the head or uncinate process of the pancreas along with the liver, gall bladder and duodenum [3]. Hence concomitant injuries to adjacent organs are not uncommon in BAT.

5.2.3 Age

Blunt pancreatic injury is more common in children and young adults because they have a thinner or absent mantle of protective fat, which often surrounds the pancreas in older adults. It occurs from direct abdominal blows from malpositioned seat belts, bicycle handle-bar and scooter injuries or intentional child abuse [4]. In adults, sports injuries, direct blows, seat belt injuries and crushing road traffic accidents are the usual causes.

PAT is usually the result of firearms and also almost always associated with concurrent injury to other intra-abdominal organs. As mentioned earlier, the proximity of large vessels (portal vein, splenic vein, abdominal aorta and the inferior vena cava) increases the risk of exsanguinating haemorrhage and this also accounts for the largest number of deaths in patients with pancreatic injury. Similarly complex duodenal and biliary injuries can occur. An isolated pancreatic injury is a rarity and may occur with penetrating trauma to the mid back in the form of stab wounds or impalement. In the majority of instances there is at least one coexistent injury; 60 % are duodenopancreatic lesions, while 90 % involve at least one other abdominal organ [3]. Therefore, multiple organ injuries are a red flag suggesting the possibility of coexistent pancreatic injury. In the Armed Forces, shrapnel injuries from improvised explosive devices (IEDs) are a unique and frequent cause of pancreatic injury. IEDs cause multiple, irregular shrapnel to penetrate the body and unlike a rifled bullet, cause much more damage along its path through the 'yaw and tumbling' effect as well as through ricochet from bony structures.

Pre-existing diseases of the pancreas do not result in a higher risk of injury or mortality rate in pancreatic trauma unlike the spleen where previous enlargement, friability or disease increases chances of rupture. However, the development of pancreatitis or diabetes mellitus after injury is associated with a significant increase in morbidity and overall mortality rates in patients with pancreatic trauma.

5.3 Incidence

The pancreas is estimated to be the 10th most injured organ compared to other organs (e.g. liver, spleen, brain) given its anatomical characteristics and the severity of force required. Specialized trauma and tertiary care centres encounter many more patients with pancreatic trauma than smaller hospitals. PAT accounts for many more cases of pancreatic trauma than BAT. While the incidence is about 0.2 % of patients with blunt trauma abdomen, it is higher in penetrating injuries, ranging from 1 to 12 % in published series [5, 6]. Pancreatic injury is rarely a solitary injury. This is because while in patients with BAT, the blunt force required to injure the pancreas

is very significant; penetrating trauma usually injures multiple organs. Hence, when the pancreas is injured, with the possible exception of a well-placed stab in the back, the physician or surgeon can be confident that other organs are also affected and conversely multiple organ injury is a red flag suggesting the possibility of a pancreatic injury. While the mortality directly attributed to pancreatic injury ranges from 2 to 17 %, morbidity reported is much higher ranging from 45 % where early and correct treatment has been instituted to 60 % where there is a delay [7].

5.4 Clinical Presentation

It is important to suspect pancreatic injury; only then will it be looked for and treated in time. Therein lies the importance of a detailed history and physical examination. Enquiring about the offending object or injuring agent (knife, gunshot, IED, etc.) is important to the clinician not missing the possibility of pancreatic injury.

Depending on the history, a careful search should be made for seat belt marks, flank bruises or ecchymosis. In case of penetrating injuries, the abdomen should be considered to extend from the clavicles to mid-thigh and ricochet injuries should be kept in mind for potential pancreatic injury.

Isolated pancreatic trauma can be worryingly symptom-free early in the post-injury period from hours to even days. In combined injuries with the spleen, kidney or retroperitoneal haematoma, the symptoms of injury to other structures commonly mask the features of pancreatic trauma. Here again a high degree of clinical awareness is necessary to ensure that pancreatic injuries are not overlooked or missed, either early in the course of trauma or later in the intensive care unit (ICU) when the patient is not improving as expected.

5.5 Classification

Most commonly, the AAST grading is followed to assess the severity of pancreatic trauma. It takes into consideration the integrity or injury to the pancreatic duct and the increasing grade correlates well with the morbidity and mortality (Table 5.1).

Advance one grade for multiple injuries up to grade III. Proximal pancreas is to the patients' right of the superior mesenteric vein.

5.6 Laboratory Studies

Blood investigations including serum amylase and lipase levels may be within reference ranges or show delayed elevation, even in the presence of ductal disruption and pancreatic transection. Hence, these are unreliable in diagnosing blunt or penetrating trauma to the pancreas and do not guarantee or exclude pancreatic injury. Conversely,

Table 5.1 AAST classification of pancreatic trauma

Grade	Injury description
I. Haematoma Laceration	Minor contusion without ductal injury Superficial laceration without ductal injury
II. Haematoma Laceration	Major contusion without ductal injury or tissue loss Major laceration without ductal injury or tissue loss
III. Laceration	Distal transection of pancreatic parenchymal injury with ductal injury
IV. Laceration	Proximal transection of pancreatic parenchymal injury involving ampulla
V. Laceration	Massive disruption of pancreatic head

Adapted from [8]

an elevated amylase level is 'suggestive but not diagnostic' of pancreatic injury or inflammation. A host of sources such as salivary glands, small bowel injury and ovarian injury may result in elevated amylase levels. Similarly lipase levels are not specific for pancreatic injury. Studies have also shown that in concomitant brain injury, serum amylase is not a reliable indicator of pancreatic injury. A significant percentage of patients with 'Central Nervous System' (CNS) trauma have hyperamylasemia in the absence of abdominal trauma, suggesting an independent CNS pathway in the regulation of serum amylase levels [9]. Hence, these markers cannot be used as screening tools for pancreatic trauma in abdominal injuries as once thought.

5.7 Imaging in Pancreatic Trauma

The objectives of imaging are: (i) early detection of pancreatic trauma in order to reduce complications related to delay; (ii) identify ductal injury, i.e. AAST grade 3 and higher injuries since ductal involvement has higher morbidity and mortality; (iii) evaluate associated injuries including duodenum and other organs; (iv) evaluate the evolution of pancreatic trauma; and (v) diagnose complications and facilitate image-guided interventions.

To fulfill these objectives, CECT is the mainstay imaging in pancreatic trauma. MRI with magnetic resonance cholangiopancreatography (MRCP) and ERCP are useful in definitive diagnosis of ductal injury both in early and late cases while a newer modality such as contrast-enhanced ultrasound (CEUS) has also been evaluated in pancreatic trauma.

5.7.1 CECT

As mentioned earlier, the AAST classification for pancreas is based on CECT which is also the modality of choice for evaluating pancreatic injury in patients with polytrauma. It provides the simplest, most comprehensive and least invasive means of diagnosis of pancreatic trauma. CECT has a reportedly variable sensitivity (65–80 %) and specificity for detecting pancreatic trauma [10–12].

Newer multidetector CT (MDCT) scanners allow volumetric data acquisition and isovoxel reconstruction, thereby improving the sensitivity and the standard of diagnosis. Applications such as curved multiplanar reconstruction (MPR) are helpful in evaluating an anatomically curved and obliquely located organ such as the pancreas as well as improved ductal visualization. Teh et al. [13] initially published data regarding evaluation of blunt pancreatic injuries with high resolution CT scanners. In a cohort of 50 patients with pancreatic trauma, operative correlation was available in 33 patients. CT findings corresponded precisely to the operative findings in 18 patients (55 %). In the subset of 13 patients with confirmed pancreatic ductal injury (PDI), CT scan was true positive in 10 patients, false positive in 2, and false negative in 1 patient. Thus, while CT was 55 % sensitive for pancreatic injury, it was 91 % sensitive and 91 % specific for pancreatic ductal injury. In another study by Panda et al. [14], operative correlation was available in 24 patients and MDCT correctly identified the surgical grade in 22 of 24 patients (91.7 %). In the subset of 19 patients with pancreatic ductal injury, CT correctly identified ductal injury in 18 patients (true positives) and correctly ruled out ductal injury in all 5 patients (true negatives) giving a sensitivity, specificity and accuracy of 94.7 %, 100 % and 95.8 %, respectively for pancreatic ductal injury. Regarding the technique and timing, the portal venous phase CT was the most accurate scan to detect pancreatic duct injuries.

CT reveals certain 'hard' and 'soft' signs in pancreatic trauma. While 'hard' signs are definitive and specific for pancreatic injury, 'soft' signs are non-specific, supportive and due to associated pancreatitis.

Hard signs. The characteristics of 'pancreatic contusion' (AAST grade I and II injury) are a focal area of hypo-attenuation against a background of normally enhancing pancreas or diffuse or focal enlargement or a heterogeneously attenuating pancreas. An area of hyper-attenuation within the substance of the gland suggests pancreatic haematoma while active extravasation within the gland, i.e. contrast leak which increases on delayed scans are very specific signs of pancreatic trauma [3].

Pancreatic laceration (AAST grade III and above) usually appears as a low-attenuating line oriented perpendicular to the long-axis of pancreas because the direction of force (steering wheel, seat-belt, handle-bar), tends to split the pancreas over the vertebral column in the region of the neck and body. Tangential injuries may be more complicated. A laceration may be very thin initially and seen on only one or two sections and hence can be missed if not carefully looked for. Pancreatic lacerations should also be differentiated from clefts. Signs of inflammation favour laceration while a cleft is lined by fat with clear surrounding area [15, 16]. Further, lacerations can be superficial (<50 % of the gland thickness) or deep (>50 % of the gland). The importance is that superficial lacerations usually imply non-involvement of the major duct while deep lacerations imply major duct disruption. This is a useful substitute marker for ductal involvement as the duct often cannot be traced on CT. A full thickness laceration involves the whole thickness of the gland and is termed as transection or fracture.

Soft signs. The splenic vein is closely opposed to the posterior aspect of the pancreas or separated from it by a thin layer of fat. Pancreatic trauma should be suspected in a patient with history of abdominal trauma if there is fluid insinuating

between the splenic vein and the pancreas. The fluid represents either blood tracking into peri-pancreatic tissues or a leak from a transected duct and is more commonly seen in distal pancreatic injuries. This sign was first described by Lane et al. [17].

Peri-pancreatic fat stranding and peri-pancreatic fluid collections in the lesser sac, pararenal spaces and transverse mesocolon are seen in 70–90 % of patients with pancreatic injury. These are strongly predictive of pancreatic injury. Similarly inflammatory changes such as thickening of the anterior renal fascia was seen in 44 % of patients with pancreatic trauma [18].

CT signs should be followed strictly in combination with clinical parameters of the patient. If stable, patients with only soft signs on CT may be closely monitored clinically, biochemically and radiologically (Figs. 5.1, 5.2, 5.3, 5.4, and 5.5).

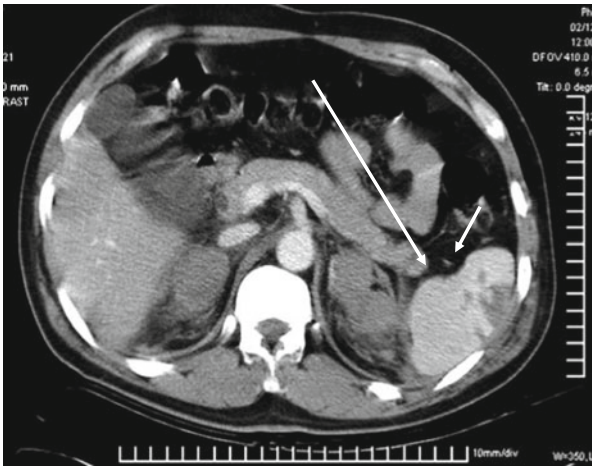

Fig. 5.1 A 50-year-old ex-serviceman sustained a blunt injury in a road traffic accident against the handle-bar of his motorcycle over the left side. While ultrasound detected splenic injury, grade I–II injury involving tail of the pancreas was seen on CECT (*arrows*). Serum amylase was raised. The patient was managed conservatively

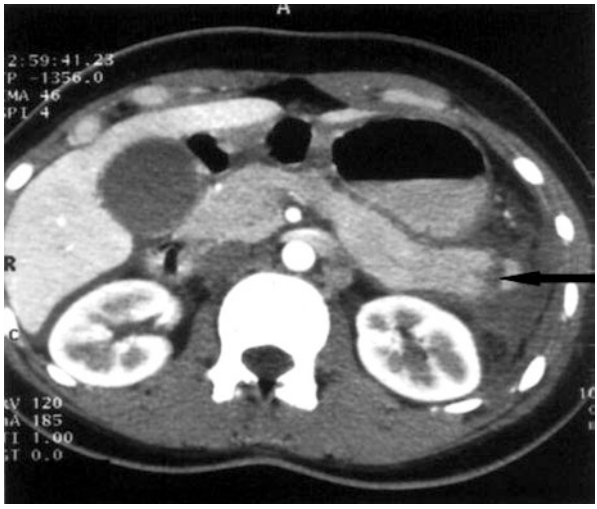

Fig. 5.2 A 46-year-old man sustained tangential injury to the left upper abdomen in a cycle accident. He was stable. Ultrasound missed a pancreatic injury. Based on a significantly raised serum amylase, CECT was done which detected transection of the tail of pancreas (*black arrow*). Distal pancreatectomy and splenectomy was done and the patient recovered well

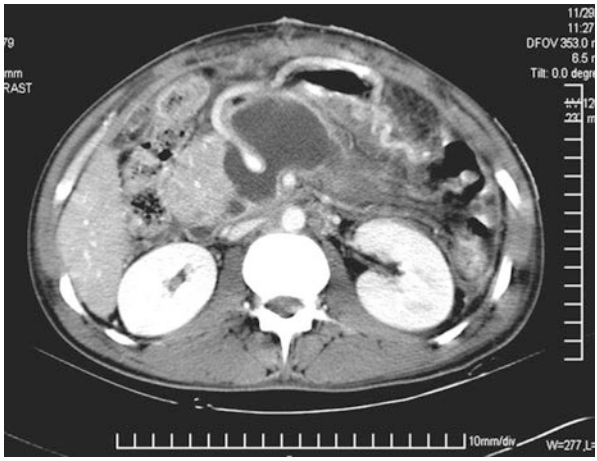

Fig. 5.3 CECT of a 32-year-old man who sustained crush injury to the abdomen when he came between the tailboard of a vehicle and a wall. He presented after 36 hours. CECT shows complete transection at the level of the neck and evidence of early pancreatitis. Distal pancreatectomy with splenectomy was done

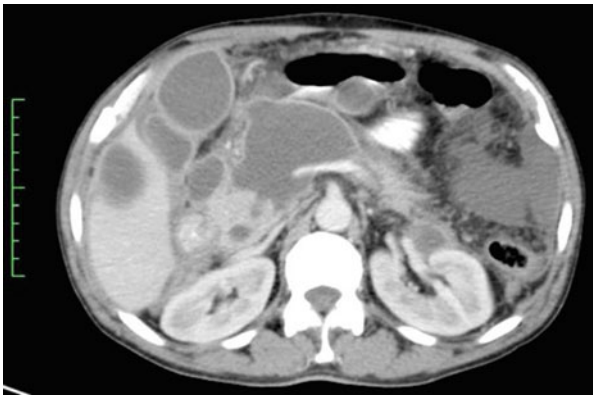

Fig. 5.4 A 56-year-old man presented with history of abdominal trauma following a road traffic accident. He presented to a tertiary care centre 96 h after injury. CECT revealed complete disruption of the pancreatic duct with multiple collections in the head, neck of pancreas and right side of abdomen. At emergency exploration, there was evidence of pancreatitis. Only wide drainage could be performed. He succumbed to his injuries in the postoperative period

5.7.2 Magnetic Resonance Imaging with MRCP

MRI with MRCP may serve as a trouble-shooting tool in pancreatic trauma by throwing more light on the disruption or integrity of the pancreatic duct which is crucial in improving outcomes. Though not dynamic, it is a non-invasive alternative to ERCP to evaluate the pancreatic duct. The other advantages over ERCP being its ability to demonstrate the status of the duct upstream of the laceration, better definition of parenchymal injury and the extent and location of peripancreatic fluid collections. MRI also has good correlation with CT. Pancreatic contusions are seen as focal T2 hyperintense areas while lacerations are seen as linear T2 hyperintense areas within the gland [14]. MRI is also helpful in conservatively managed patients under follow-up to identify sequel of pancreatic trauma

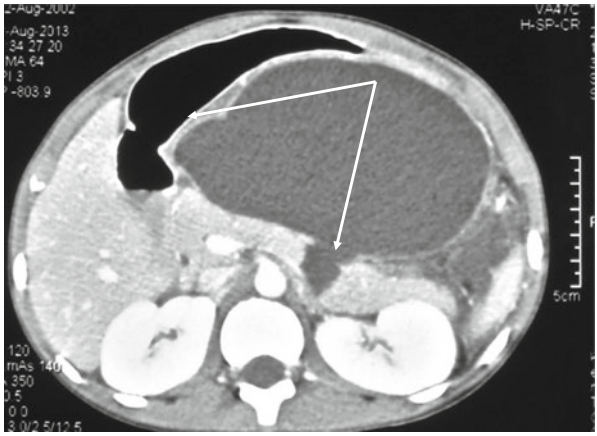

Fig. 5.5 A 21-year-old medical cadet sustained injury during a football match. CECT showed a grade III injury involving the body of pancreas with collection in the lesser sac compressing the stomach (*arrows*). Distal pancreatectomy with splenectomy was done

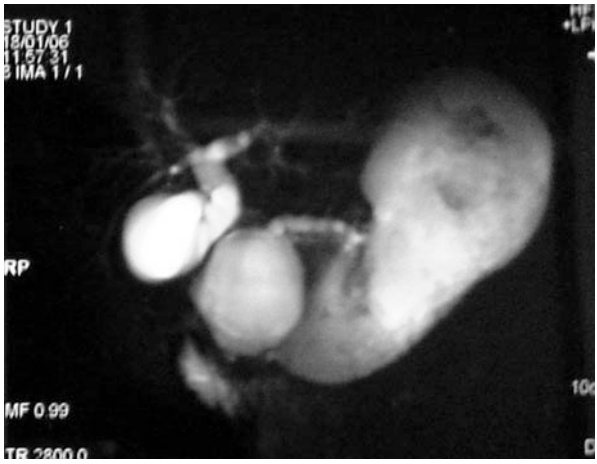

Fig. 5.6 A 34-year-old man presented 4 weeks after sustaining blunt abdominal trauma following a boxing bout. On ultrasound there was a suspicion of injury to the pancreas. MRCP showed a large collection in relation to the tail of pancreas due to an injury to the tail of pancreas. He was stable and was offered surgery after 4 weeks due to pressure effects

such as pseudocysts, pancreatic strictures and chronic pancreatitis [19]. MRI is also useful for initial scan as well as follow-up evaluation in children as it provides a non-radiation alternative to CT (Fig. 5.6).

Secretin-enhanced MRCP (MRCP obtained after i.v. injection of secretin may help further characterize pancreatoduodenal injury). Secretin increases the output of pancreatic secretions and can be used to actively demonstrate leak from the disrupted pancreatic duct [20].

5.7.3 Contrast Enhanced Ultrasound (CEUS)

Unlike conventional US which is not a good tool in detecting pancreatic injuries, CEUS using sulphur hexafluoride provides better contrast between normal and contused pancreas due to differential blood supply. Pancreatic injuries appear as

anechoic or hypoechoic irregular perfusion defects in both arterial and parenchymal phases. In a study by Lv et al. [21], in comparison to CT, CEUS detected pancreatic injuries in 21 of 22 patients (95.5 %). It is also a non-radiation alternative to CT for follow-up in known cases of pancreatic trauma to assess peripancreatic collections and pseudocysts. The disadvantages include cost, learning curve, short window time to obtain useful information and limited information regarding extent of other injuries sustained by the patients compared to CT.

5.7.4 ERCP

ERCP was, traditionally the gold standard for assessing integrity of the pancreatic ductal anatomy or disruption in injury. However, MRCP has superseded ERCP in evaluating acute pancreatic trauma. Theoretically, though ERCP can directly and more accurately visualize ductal injury. Its invasive nature, difficulty in doing it in an emergency situation, and high rate of complications (5–15 %) such as pancreatitis, cholangitis and duodenal perforation beset the advantage and make the treating surgeon wary of performing this procedure in the acute setting. Its role is better defined and acceptable in subacute cases and in chronic follow-up cases where it provides therapeutic options such as pancreatic sphincterotomy for pancreatic fistula and duct stenting for pseudocysts and strictures [22].

Endoscopic transpapillary drainage and ERCP guided stenting can also be done for partial duct disruptions and in isolated grade 3 injuries, respectively [23, 24].

5.7.5 X-Ray

Although a simple investigation and part of the advanced trauma life support (ATLS) protocol, it is mentioned in the end because it may incidentally pick up and give indirect evidence about a metallic body, bullet or shrapnel in the region of the pancreas (Fig. 5.7). Other indirect evidence may be in the form of gas bubbles adjacent to the right psoas muscle, fracture transverse process of lumbar vertebrae, anteriorly displaced stomach and transverse colon and ground glass appearance.

5.8 Evolution of Pancreatic Injury

Imaging soon after blunt pancreatic injury (within 12 hours) and more so in children (due to lack of contrast provided by surrounding adipose tissue to appreciate pancreatic injuries), may result in the pancreas appearing normal in 20–40 % of patients [3]. This is due to the close apposition of the pancreatic fragments which may obscure the fracture plane. Findings become more radiologically apparent over time

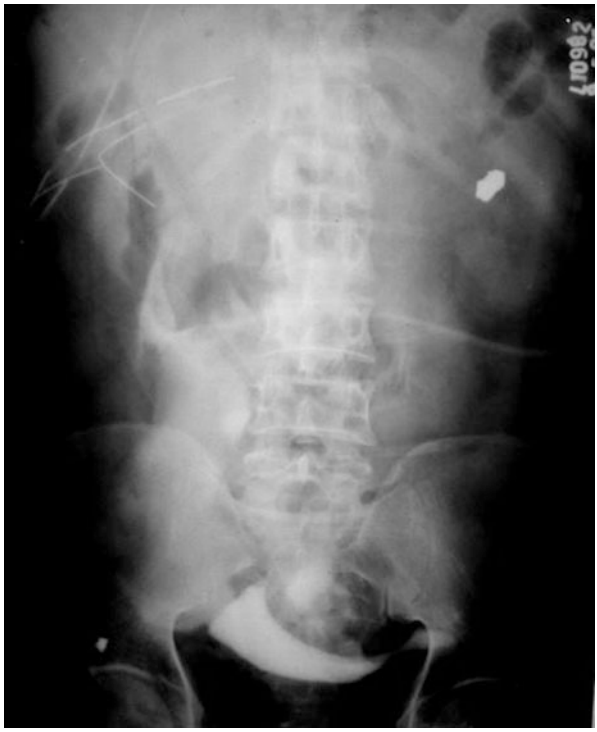

Fig. 5.7 A 46-year-old patient sustained penetrating abdominal injury due to shrapnel from an improved explosive device blast. Though the patient was stable, the pancreas was evaluated with CECT based on the location of the metallic foreign body in the left hypochondrium. He was found to have a Grade 3 laceration of the tail of pancreas requiring a distal pancreatectomy and splenectomy

with the development of post-traumatic pancreatitis, oedema, leakage of pancreatic enzymes, and subsequent auto-digestion of the surrounding parenchyma. An abnormality which was initially ambiguous or subtle becomes more evident. Hence, sequential imaging along with correlation with clinical and laboratory parameters should be done to avoid a missed diagnosis.

5.9 Management

Initial management should be along the lines of the advanced trauma life support (ATLS) protocols. Immediate resuscitation and management of life-threatening injuries such as tension pneumothorax take precedence over all else. Haemodynamically unstable patients are rushed to the operating room after an urgent 'primary survey'. Minimal investigations including blood for cross match and a FAST may be done en route. Pancreatic injuries in such patients are looked for and addressed at laparotomy.

More stable patients with reason to suspect pancreatic injuries should undergo further investigations and imaging since physical examination is usually not reliable in the setting of acute pancreatic trauma [25]. Tell-tale signs suggesting pancreatic trauma should not be missed or ignored.

5.9.1 Conservative Management

Observation of pancreatic injury was noted to have 100 % mortality in the early twentieth century. Then came the era of exploration for all cases. Currently with better imaging and understanding, selected cases of Grades I and II pancreatic injuries who are stable and can be observed closely for a period of time, can be managed conservatively.

Like with splenic and hepatic injuries, literature on non-operative management of pancreatic trauma mostly pertains to children with reported outcomes similar to operative management [26, 27]. However this approach can also be extended to adults [28]. As mentioned, appropriate patient selection (stable patients with low-grade injuries, isolated pancreatic injuries and absence of ductal involvement on MRI or ERCP); availability of continuous reliable patient monitoring and radiological or endoscopic interventions for management of local/pancreatic complications are keystones to successful conservative management [29]. Patients continuing to have pain or developing haemodynamic instability or showing radiological progression should be thoroughly reassessed for pancreatic injury and planned for operative intervention. Laparotomy has shown better outcomes with fewer complications [30].

The standard of care in penetrating injuries is still operative exploration. Very selective cases with peripheral or apparently superficial trajectories, stab injuries in a stable patient with no abdominal signs may be managed conservatively with close monitoring and imaging.

5.9.2 Surgical Management

Surgery is by far the most common therapeutic modality for patients with pancreatic trauma. ATLS standards and protocols should be adhered to. Adequate preparation for emergency surgery and high volume trauma centres have been shown to reduce morbidity and mortality rates. Similarly early surgical intervention with identification of ductal injuries reduces the incidence of early and late complications and death.

The broad parameters dictating surgery are:

1. Grade/severity of injury along with haemodynamic stability of the patient and general condition including co-morbid conditions.
2. Location of the pancreatic injury.
3. Associated abdominal injuries.
4. Time elapsed since injury.

BAT and PAT differ in so far as there are greater chances of minor (AAST grades I and II) injuries in BAT while major (AAST grades III to V) and multi-organ complex injuries are more likely in PAT. Also as mentioned earlier, in PAT, the abdomen

is deemed to extend from the clavicle to the mid-thigh. This is especially true in shrapnel injuries sustained by soldiers due to an IED blast. The innumerable irregular and jagged shrapnel take a crooked course as well as get ricocheted from bony structures and can cause pancreatic injury. Secondary bony pieces can act as missiles and can cause pancreatic trauma. However, after exploration, irrespective of the aetiology, management is based on the factors listed above.

5.9.3 Minor Injuries (Grade I and II)

Most commonly, the damage is minor and findings such as capsular tears, superficial lacerations, small contusions or haematomas should be inspected and documented. They should not be explored unless ductal injury is suspected. Suturing and surgical resection is not only unnecessary in such situations but may be harmful. Soft closed suction drains should be used.

However, occasionally ductal injury may be suspected but not obvious. A delay in exploration may also have resulted in vitiating an otherwise clear picture. In such cases, some authors recommend intra-operative ERCP as discussed in the 'imaging' section earlier. While ERCP certainly increases the rate of identification of ductal injury and more accurately assesses the true grade of injury, doing the same in emergency circumstances in a haemodynamically suboptimal patient on the operation table with a laparotomy is not easy. The availability of a gastroenterologist at odd-hours as well as the risk of causing complications as discussed previously makes this option less attractive. If not done for the above mentioned reasons or not available, thorough lavage, debridement, repair and drainage should be done. In such cases continued drainage with high amylase levels persisting beyond 48–72 hours is highly suggestive of a missed ductal injury. This problem must be treated with work-up for ductal integrity with MRCP/ERCP and may require another operation after the critical period is over. In such a situation, if major ductal transection is ruled out, a trial of total parenteral nutrition (TPN) or elemental diet through a nasojejunal tube/feeding jejunostomy may result in decreased drainage and closure of the leak.

5.9.4 Major Injuries (Grade III to V)

The less commonly encountered situation is a major ductal injury. If the patient has been explored early and features of pancreatitis/significant oedema have not set in, major ductal damage or splitting injuries can be seen directly. Various options are available thereafter:

(i) *Transection of the body or neck of pancreas*: Integrity of the main pancreatic duct is the most important determinant of outcome after injury to the pancreas.

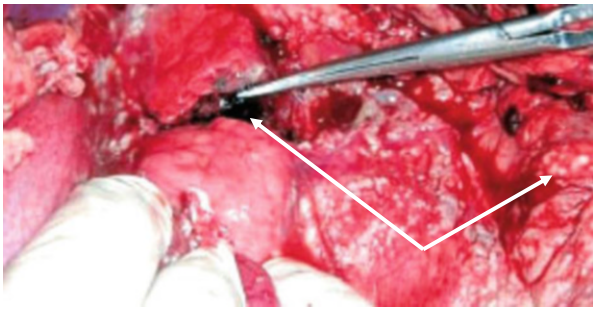

Fig. 5.8 This is an intraoperative photograph of the patient mentioned on pg. 101, Fig. 5.5. Imaging showed complete transection of the pancreas at the neck (*arrow*) with the tear going upto the superior mesenteric vein (SMV). At surgery, the findings were confirmed and the SMV exposed (*Arrows*). There was early saponification. A distal pancreatectomy and splenectomy was done

If the pancreas is otherwise normal, a resection of more than 80 % can be done without endocrine deficiency. The most commonly performed procedure is distal pancreatectomy with splenectomy (Fig. 5.8). Splenic preservation, although ideal if the spleen is not shattered, is frequently not possible with a fracture of the pancreatic body. The same anatomical orientation over the spinal column that created the parenchymal fracture and ductal injury has usually caused a splenic artery or venous injury, which results in thrombosis or aneurysmal formation and eventual splenic loss. Also, splenic preservation takes longer to do and may be harmful in the haemodynamically unstable patient. After a distal pancreatectomy, the cut edge can be hand-sewn or a stapler (white vascular cartridge) fired. Traditionally non-absorbable sutures have been used but recently a few authors have had good results with the newer, long-lasting monofilament absorbable sutures. As mentioned, resection of the pancreas at the vertebral column over the neck or body usually does not cause permanent diabetes and exocrine insufficiency since about 40–50 % of the glandular tissue is preserved. In isolated pancreatic injuries, the procedure is technically straightforward and can be done rapidly (Fig. 5.9).

If a distal pancreatectomy is not done, the laceration can be over-sewn but contused, oedematous pancreatic parenchyma is notoriously difficult to sew. Drainage of the bed may be all that is possible in this situation (Fig. 5.10). A high chance of pancreatic fistula remains. This should be managed initially by giving TPN, octreotide (100 μg 8 hourly i.v.) and keeping the patient nil by mouth. Randomized trials have shown that octreotide can reduce pancreatic secretions but not hasten healing of the fistula.

(ii) *Injuries to the head and neck of the pancreas*: These injuries may require more imaginative and intricate operative procedures. Deep injuries and lacerations, and appearance of bile from the injury site should alert the surgeon to the possibility of a ductal injury. At this juncture a cholangiogram or ductogram is extremely

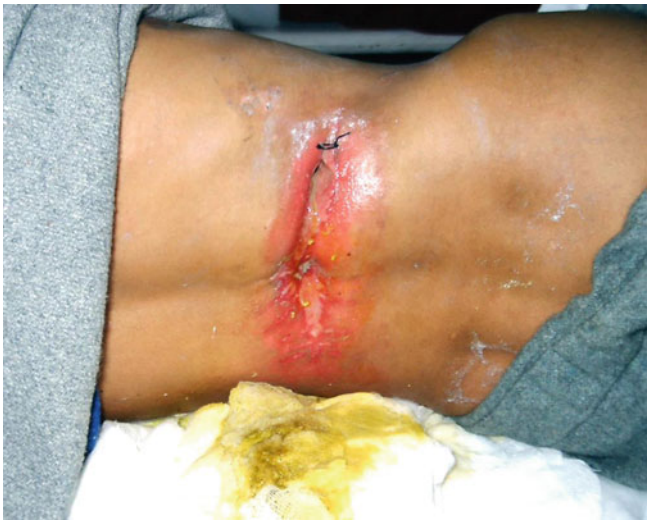

Fig. 5.9 A 26-year-old patient who suffered a gunshot wound through the abdomen. At emergency exploratory laparotomy, an enterotomy was repaired and mesenteric bleed controlled. A pancreatic injury was missed. He did not recover completely and presented with a discharge through the exit wound. It was amylase rich and had caused severe excoriation of the skin. Imaging revealed major ductal injury in the body of pancreas. Re-laparotomy, distal pancreatectomy and splenectomy along with extensive drainage, meticulous wound care and total parenteral nutrition resulted in the wound healing in 4 weeks

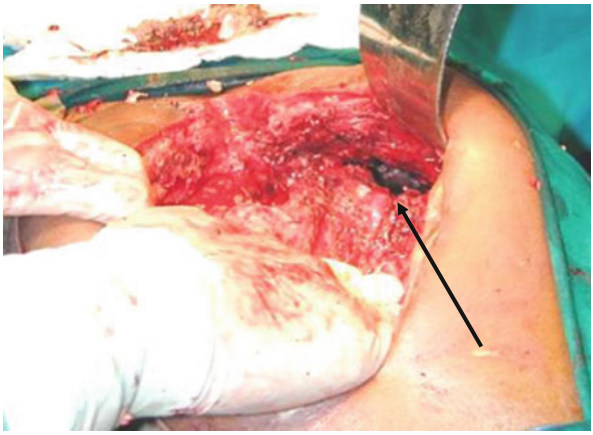

Fig. 5.10 A patient in whom a pancreatic injury to the body and tail of pancreas was missed. He was explored 10 days after the injury. His presentation was delayed and he had received conservative management. Operative photograph shows extensive pancreatitis and saponification (*arrow*). Only debridement, lavage and wide drainage could be done. The patient succumbed on postoperative day 6

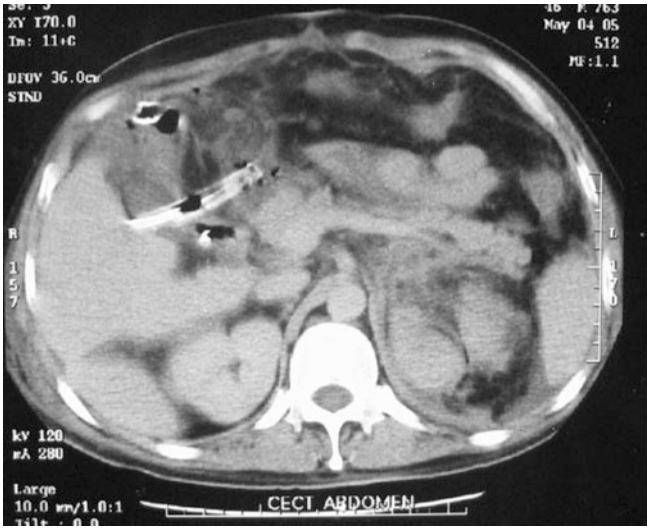

Fig. 5.11 Follow up CECT scan of a 46-year-old man following damage control surgery for grade V pancreatic injury (shattering duodeno-pancreatic injury). Patient underwent emergency exploratory laparotomy, control of haemorrhage, exteriorization of bile duct and duodenum over T-tube, pyloric exclusion via gastrotomy and drainage and feeding jejunostomy. He made a good recovery

valuable in planning the required operative intervention. Depending upon the extent of injury and if the duodenum is intact the various options include:

- Repair and extensive drainage
- Stenting
- Roux-en-Y pancreaticojejunostomy to preserve the pancreatic parenchyma. While theoretically feasible, it is rarely used. Here the pancreas is divided, the proximal segment closed, and the distal portion preserved with drainage into a Roux-en-Y pancreaticojejunostomy.

(iii) *Massive injury to the head of the pancreas, including the duodenum*: These patients are usually unstable and hence only damage-control measures can be applied (Fig. 5.11). These include:

- Control major bleeding given the intimate anatomical position of the vena cava, portal vein and mesenteric vessels to the pancreas. Higher mortality and morbidity rates in these patients are caused by uncontrolled haemorrhage rather than pancreatic injury. Every effort is made to control/repair these injuries first, directing consideration to the pancreatic injury only after haemostasis has been achieved.
- Exteriorizing the bile duct with a T-tube so as to form a controlled external biliary fistula. The bile duct can be cannulated or ligated. Ligation allows it to be dilated by up to 5 mm in 48 h and assist a biliary-enteric anastomosis in a previously undilated system at a later date.

- Anterior gastrotomy with suture closure of the pylorus/firing a stapler across the pylorus or distal stomach (pyloric exclusion) and gastrojejunostomy.
- Repair of the duodenum over a T-tube/large Foley catheter/Malecot catheter.
- Gentle repair and haemostasis of the lacerated head of pancreas.
- Feeding jejunostomy
- Extensive drainage

(iv) *The trauma Whipple*: There is no consensus on the absolute indications for a 'trauma Whipple'. Opting for a major surgery, such as pancreatoduodenectomy (PD) is not an easy decision for any surgeon. In the best of centres, it is associated with a high mortality approaching 50 % [31]. It is justified only in patients with severe combined injuries of the duodenopancreatic complex who report early and are relatively stable. Otherwise it is sensible to perform a damage control procedure as described earlier. Attempt is made to control haemorrhage and contamination in these patients who are usually in shock, coagulopathy and haemodynamically unstable requiring ionotropic support. PD may be performed as a second stage after recovery of the patient's physiological parameters in an intensive care environment [32].

PD for trauma is technically similar to that done for neoplasia. Resection is in fact often facilitated by the dissection started by the trauma itself and also by the damage control procedures required for exploration, such as the Cattell–Braash manoeuver. It differs from an electively done PD for neoplasia in the following aspects:

1. The main focus at laparotomy is early control of bleeding and contamination which is of utmost importance. Temporary duodenal repair is done if it is injured.
2. Resection of the uncinate process is not necessary because there is no indication for lymphadenectomy [31]. This simplifies the procedure, allowing the surgeon to work away from the mesenteric vessels and section the medial portion with a vascular stapling device [33].
3. The gallbladder should be spared initially, as it may be used in biliodigestive reconstruction if the biliary duct is too thin. Lastly, the pancreatic stump must be addressed. Trauma patients have normal, soft pancreatic tissue and a thin main pancreatic duct and hence the risk of pancreatic fistula increases significantly [34].
4. The common bile duct and pancreatic duct are not dilated and pose a challenge to the surgeon.
5. In elective PD, ligation of the pancreatic stump has not been shown to reduce the rate of pancreatic fistula formation and is not currently recommended. However, in the 'trauma Whipple', there are few reports where it was done or was the only possible option to the surgeon.

As for elective surgery, alimentary reconstruction with pancreato-jejunostomy (PJ) or pancreato-gastrostomy (PG) are feasible and safe. Although the literature favours PG over PJ, the surgeon's discretion and personal experience are final and he should do what is best in his hands. Animal models and human experience have shown that more than 80–90 % of the pancreas must be removed to result in diabetes or malabsorption; pancreatic head removal is well tolerated [31].

On the other hand, total pancreatectomy for the shattered pancreas has also been reported, obviating the problem of pancreatic fistula. However, it causes significant morbidity and brittle diabetes; hence this procedure should be used only in very select cases.

Since the procedure is uncommon, data regarding morbidity after trauma PD is scarce [31, 35]. Besides mortality, postoperative complications occur in 8–86 % [36]. The common complications include pancreatic fistula which occurs in 2–37 % of patients [31]. Others include septic complications, and pseudocyst or pseudoaneurysm formation leading to catastrophic bleeding, usually from the stump of the gastroduodenal artery. Up to 7 % of patients with fistula require additional surgery to treat the complication [31]. Pancreatic abscess is also important and contributes significantly to postoperative mortality. The incidence of pancreatic abscess ranges between 10 and 25 %; it is lethal in 27 % of cases. The best way to deal with this complication is image-guided percutaneous drainage [31].

5.10 Postoperative Details

Whether damage control surgery or PD, maximum consideration is directed towards preventing and correcting the 'lethal triad', i.e. monitoring and correcting metabolic acidosis; preventing hypothermia and warming the patient and correcting coagulopathy, if any. Close monitoring and maintaining normal haemodynamic parameters, adequate urine output, intravenous fluid replacement with crystalloid solution and blood products (as needed), and mechanical support of ventilation are necessary.

Death is most common with major injury, significant blood loss, delayed intervention or missed ductal injury. Acute respiratory distress syndrome (ARDS), multisystem organ failure and infection are the most common causes of delayed death in these situations.

5.11 Complications

Delayed diagnosis and delayed surgery while under observation are associated with higher rate of pancreas-specific morbidity and mortality and complications of pancreatic injury are numerous and range from minor pancreatitis prolonging the hospital stay to death.

5.11.1 Pancreatic Fistula

The most frequently reported complication is fistula formation. In isolated pancreatic trauma the incidence is about 20 % and increases to about 35 % in combined pancreaticoduodenal injuries [37]. If the drainage is unobstructed and the injury minor (arising from a minor duct), most fistulae will resolve spontaneously with

good nutrition and supportive care within 2 weeks of injury. If there is prolonged output of greater than 200 ml/day for more than 2 weeks, somatostatin analogues along with keeping the patient off oral feeds and on TPN have been reported to decrease fistula output and to facilitate closure, but not morbidity and mortality rates. Persistent fistulae should prompt MRCP followed by ERCP that can be therapeutic as well especially for proximal fistulae [23].

5.11.2 Pseudocyst Formation

Pseudocyst formation has been reported after pancreatic trauma. Since the gland is not diseased *per se*; a large number resolve with conservative management and observation. Symptomatic pseudocysts, those associated with compression of the common bile duct or gastrointestinal tract or those getting infected require treatment in the form of drainage or surgical intervention.

5.11.3 Vascular Complications

Vascular complications such as pseudoaneurysms occur due to complications of pancreatitis or secondary to surgical intervention [38]. The vessels commonly involved are splenic, gastroduodenal and common hepatic arteries. Untreated pseudoaneurysms can cause potentially life-threatening events—rupture leading to haemorrhagic shock and death. They can present as upper gastrointestinal bleed (haematemesis/malaena) or haemobilia. In a haemodynamically stable patient, CT angiography is preferred to diagnose the lesion. Therapeutic angiographic embolization with coils, glue or thrombin follows. Haemodynamically unstable patients can be directly taken for embolization [39, 40]. Surgical management is resorted to in those who are not amenable to or fail embolization.

5.11.4 Recurrent Pancreatitis

Ductal damage and healing by fibrosis can lead to chronic obstruction and raised intraductal pressure and can present months to years after trauma [41].

5.11.5 Infectious Complications

It is known that there is an increase in infectious complications in patients when pancreatic injuries occur along with hollow viscus injury (i.e. duodenum, small bowel and colon) with resultant increase in morbidity and mortality due to ensuing sepsis [36].

5.11.6 Miscellaneous

Wound dehiscence, burst abdomen and incisional hernias are known complications and need to be addressed as per merit. Abscess and infected walled-off collections can occur secondary to contamination from hollow viscus or from skin flora through the external drain. Patients present with persistent fever, laboratory parameters show leucocytosis and on imaging, air foci within peripancreatic collections are suggestive of infection unless external drainage has been attempted or done. Exocrine or endocrine insufficiency is also rare and usually occurs only in patients with a pancreatic resection greater than 80–90 %. Relative insufficiency may also occur and should be considered if symptoms of altered glucose homeostasis or gastrointestinal abnormalities manifest after injury.

5.12 Future and Controversies

The future will continue to bring better and faster patient evacuation modalities, and diagnostic modalities (e.g. faster and more precise CT technology, including CT cholangiopancreatography). Better non-invasive methods to identify ductal injury are likely to improve and morbidity rates will decrease. Also high volume centres with better expertise are likely to improve outcomes.

Editorial Comments

With an increase in vehicular accidents and ever increasing violence in life be it related to organized crime or terrorist activities, the incidence of pancreatic injury is increasing. The magnitude of the problem is enormous. Pancreatic injuries in most situations are complex and not restricted to the pancreas alone. Simple laceration or even duct transection in isolation is rather unusual. In the context of a blunt injury the degree of force needed to injure the pancreas (so well protected in its bed) simultaneously injures other adjoining structures. In penetrating trauma too, the pancreas is rarely injured without concomitant injury of the organs which overlie it. Therefore, in a patient with suspected pancreatic injury one must rule out injury to all the adjacent organs. Resuscitation in the emergency with fluid and blood is critical. Patients with blunt abdominal injury who cannot be stabilized must be suspected to have concomitant vascular injury causing bleeding. Such patients should be explored without delay. To proceed with investigations in such patients amounts to procrastination and could lead to death! The need of the hour is to establish vascular injury and to control it. Patients with penetrating trauma need an exploratory laporotomy. In the operation theatre, surgeons must take damage control measures so as to make unstable patients stable. This should

entail ligation of all bleeding vessels (important vessels needs repair), repair/resect all hollow viscus injury, and remove all devitalized tissues and foreign bodies (in penetrating trauma). Injuries of the pancreas should be identified by the presence of haematoma, bile staining of the retroperitoneum (or its presence in the peritoneal cavity) and adequate drainage should be provided for damage control. Patients who develop complications postoperatively should be properly investigated with suitable imaging (CT or MRI) and managed accordingly. In the event of pancreatic duct disruption management should continue with total parenteral nutrition, octreotide and antibiotics. Most patients improve with this strategy. Those who do not (have persisting pancreatic fistula, collection (s) with or without abscess, pseudocyst) can be managed by endoscopic or radiological intervention or by surgery. Pseudoaneurysm of the splenic artery is a complication that can be managed radiologically. Patients who remain stable in the emergency can be investigated with multidetector CT for evidence of parenchymal injury (superficial or full thickness). If pancreatic ductal integrity cannot be ascertained, an MRCP can be done to plan further management.

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Chapter 6
Controversies in Surgery for Pancreatic Cancer

H. Ramesh, Jacob Mathew, John Mathew Manipadam, and Saurabh Galodha

Pancreatic cancer continues to be a life-threatening disease with poor long term outcomes despite various treatments. Progress has been slow, although results of surgery have improved, and mortality rates have fallen. Surgery is still the modality with the highest potential to cure pancreatic cancer. We examine some of the key issues relating to the treatment of pancreatic cancer, largely to the description of issues related to pancreatic head cancer.

6.1 Controversies: the Top Seven Questions

1. What is the natural history of pancreatic cancer?
2. Is an R0 resection the key to improved survival?
3. How can the margins of resection be examined precisely?
4. Do vascular resections help?
5. Are multivisceral resections justifiable?
6. What should be the extent of lymphadenectomy?
7. Have laparoscopic and robotic technologies made a difference?

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6.1.1 What Is the Natural History of Pancreatic Cancer and the System of Spread of the Disease?

In 2016 there were 53,070 new cases of pancreatic cancer in the USA alone with 41,780 deaths [1]. Thus, pancreatic cancer has a poor overall prognosis. This may be due to the fact that even localized cancer may be systemic from its onset. The evidences in favour of a systemic disease are: (i) among 285 patients with margin-positive resection, 76 % had distant disease; [2] (ii) 70–85 % of patients who have undergone resection die of metastatic disease; [3] (iii) adjuvant radiation has no significant benefit in prolonging survival (indirect evidence); [4, 5] (iv) there is no advantage of chemoradiation over chemotherapy; [6, 7] (v) 15–32 % of patients on neoadjuvant therapy progress to systemic disease while on treatment; [8, 9] and not least, (vi) among specimens of extended lymphadenectomy, it has been shown that pancreatic cancer spreads by complex pathways to more distant lymph nodes [10].

While surgery continues to be the treatment of choice for localized pancreatic cancer, there is increasing evidence that a multimodality approach based on systemic therapy may be necessary to produce improvements in survival.

6.1.2 Is R0 Resection the Key to Improved Survival?

It is logical to presume that resection with negative margins (R0) can provide better local/locoregional control of the disease. Long term survivors invariably have R0 resections performed [11].

There is some controversy whether an R1 resection (microscopic involvement of the margin) for pancreatic cancer is justifiable. Despite excellent preoperative imaging, abutment of the tumour to the superior mesenteric artery is not always clearly defined, and surgeons may well discover it late in the course of the dissection that tumour free margins are difficult to achieve. While R0 resections lead to improved survival, it may also be true that the biology of the cancer may play a part. Hence, R1 resections must not be condemned as a surgical misadventure. An R2 resection (macroscopic residual disease) may also occur rarely, but every attempt should be made to avoid this eventuality.

The situation is rendered more complex by the fact that determination of R0 status is by no means standardized. The transection margins comprise (i) stomach or duodenum, (ii) pancreatic neck, and (iii) the bile duct and establishment of a negative margin is easy to achieve. However, circumferential margins are more unclear. This will be addressed in detail in the section on reporting of pathology.

There have been wide variations in R0 rates published from 20 to 80 %. Further, R0 resections did not confer any survival benefit and it was attributed to the poor biology of the disease—despite R1 resection rates of 17 %, survival in the R0 and R1 groups were similar (66 % and 68 %) [12]. Better histopathology approaches have created a realistic R1 rate, which may occur in up to 82 % of pancreatic head

cancers, and 72 % of bile duct cancers, but are less likely in ampullary cancers (25 %). Multifocal residual disease may occur. Overall, survival was better in R0 resections as determined by the new standardized pathology protocols [13].

The technical aspects of achieving an R0 resection are complex and hitherto undefined completely. Radicality has two components: (i) margins of the resection on the pancreaticoduodenectomy (PD) specimen, and (ii) margins on the lymphadenectomy. The issue is further complicated by the fact that there is no buffer of areolar or fatty tissue around the uncinate process of the pancreas which provides an opportunity for complete resection. The uncinate process of the pancreas may be densely applied to the proximal course of the superior mesenteric artery (SMA) and a tumour free margin may not be available despite peri-adventitial dissection of the uncinate process off the artery. The mesopancreas is defined as the soft connective tissue between the SMA and the region from the pancreatic head to the uncinate process, including the inferior pancreaticoduodenal artery (IPDA) as well as the lymphatic, nervous and vascular structures on the fusion fascia of the ligament of Treitz [14–16]. Clearance of the mesopancreas involves all tissue to the right of the SMA and can decrease the number of R1 resections with R0 resection rates of 93 % as compared to standard resection with 60 % R0 resection [17]. Dissections of the pancreatic head have failed to reveal a clear fascial envelope akin to the mesorectum [18, 19], but clearance of the area may be beneficial to the locoregional control of pancreatic cancer, although more data and larger studies are required [20]. Recent reports have described many approaches to clear this area. [21, 22] There may be one further anatomical fact which is not apparent from the published data. The mesentery of the uncinate process is continuous with the mesentery of the proximal jejunum, and even when the SMA is cleared, there may still exist a portion of the proximal jejunal mesentery which may harbour disease and fail to be cleared at surgery. Thus the artery may not represent the 'last frontier' in dissection of pancreatic cancer. However, there is recent data which suggests that the 'mesopancreatic stromal clearance' can be assessed by preoperative imaging [23], and patients in whom this clearance may not be possible could become candidates for preoperative chemo/chemoradiotherapy [23].

Perhaps the best evidence in favour of R0 resection is the description of improved survival figures with re-resection after a positive margin on frozen section, and the conversion from R1 to R0 status. Patients with R0 confirmed by frozen section, R0 after re-resection confirmed by frozen section, and R1 after re-resection despite frozen section had median survival figures of 29, 36 and 13 months [24]. Survival is also determined by the tumour biology (lymph node metastases) and treatment parameters such as major perioperative complications and blood loss [12], or tumour grade, performance status and tumour size as described by the guidelines published by the International Association of Pancreatology/European Pancreatic Club [25–27].

There is a lack of clarity as to terminology used to describe the circumferential margin. Up to 28 different names have been used and this has prevented uniformity of reporting and comparison of surgical approaches [28].

A final contentious issue is the margin (in millimetres) that is considered as adequate for R0 resection. While the American Joint Cancer Committee (AJCC)

guidelines describe uninvolved margins as R0, the Royal College of Pathology have described a 1 mm margin [29]. Patients with margins greater than 1 mm had survival figures twice as those with less than 1 mm. French data also recommended a 1 mm margin [30], but Chang et al. prescribed a 1.5 mm margin [31]. This emphasizes the need for accurate histopathological examination. A recent meta-analysis has also confirmed the need for a 1 mm margin [32].

There is no doubt that every surgeon embarking upon a PD must achieve the best possible local clearance of the tumour. While R0 rates are a measure of the quality of the surgery, and the experience of the surgeon (surgeons who have performed more than 60 resections have a lower R1 rate) [33], R1 resection may not be a marker of low quality surgery, but high quality pathological examination! [34].

6.1.3 How Can the Resected Margins Be Examined Precisely?

In 2006, Verbecke [35] and associates described a standard protocol for pathological examination of the PD specimen. This included a defined distance taken for microscopic involvement (currently 1 mm), colour inking of the margins (anterior, posterior, and superior mesenteric margins), axial slicing of the specimen and reporting of all the margins. There was a close correlation between R0 on the Leeds pathology protocol (LEPP) and survival. Some reports describe a posterior margin (retroperitoneal) and a distinct SMA margin (medial part of the uncinate process and further medial from the groove of the superior mesenteric vein [SMV]) [35–37]. In effect, the SMA margin and the retroperitoneal margins are the final frontier unless the SMV is involved.

A standardized approach to pathology reporting is advisable despite recent reports that survival may not depend entirely on the R0 status derived from such examination [38].

6.1.4 Do Vascular Resections Help?

In 1992, Fuhrman reported that *en bloc* resection of the SMV with the pancreatic head cancer is justifiable—a case of anatomical involvement rather than biological aggressiveness of the tumour [39]. Venous involvement may be classified (Ishikawa) [40] as type 1: normal; type 2: smooth shift; type 3: unilateral narrowing; type 4: bilateral narrowing; and type 5: bilateral narrowing with collateral veins. Histological involvement of the vein ranged from 0 % with types 1 and 2, 51 % in type 3, 74 % in type 4 and 93 % in type 5 [41]. Some critical aspects of venous resection in pancreatic cancer are: (i) sleeve resections may be required when the lateral aspect of the SMV alone is involved; however, there may be difficulty in repair of the vein due to kinking. A vein patch may be necessary; (ii) end-to-end anastomosis of up to 5 cm of the vein can be

achieved without difficulty with mobilization of the two ends and an adequate Cattell–Brasch technique; if the splenic vein is to be ligated, it can be done with impunity; reconstruction is only required if the inferior mesenteric vein (IMV) has been interrupted [42]. If the IMV is not patent, left-sided portal hypertension may result; (iii) if the reconstruction cannot be achieved by end-to-end anastomosis, then the following can be used for the repair: (a) left renal vein; [43] (b) internal jugular vein; (c) external iliac vein; (d) cryopreserved grafts; (e) polytetrafluoroethylene (PTFE); or (f) Dokmak peritoneal patch; [44, 45] (iv) in general, an autogenous vein is preferred, although a prosthetic graft can be used—postoperative aspirin may be necessary [46]. In general survival outcomes are better when the portal venous resection is considered preoperatively and planned rather than when it is decided on the table [47]. The key principle is not to separate the portal vein–SMV junction from the tumour bearing head of pancreas when preliminary dissection suggests abutment. In such cases, a full mobilization of the uncinate process is also completed leaving the tumour bearing head attached to a segment of the vein which is then resected *en bloc*; the best results have been described among patients who had a portal vein resection and had uninvolved margins [48]. This has been validated in a meta-analysis as well [49].

Turrini and colleagues suggested that the portal vein should be routinely resected during pancreaticoduodenectomy even if the vein was not involved by tumour. Their retrospective analysis suggested that patients with PD with portal vein resection who did not have invasion of the vein wall had superior survival to those who had a standard PD without venous resection [39, 50]. This represents a partial throwback to the regional pancreatectomy of Fortner where the portal vein was resected along with the hepatic artery/SMA and the mesocolon [51]. The Turrini approach needs to be validated by prospective studies before finding application in practice.

Arterial resections on the other hand are to be considered only in select situations. In general, survival is poor [52]. Occasionally reconstruction of the hepatic artery involved by an adenocarcinoma of the neck of the pancreas may be considered where a small area of involvement is the only impediment to the accomplishment of an R0 resection. Also, reconstruction of a replaced right hepatic or common hepatic (arising from the SMA) can be considered. If the origin from the SMA is uninvolved and a stump is available, end-to-end anastomosis or an autologous interposition graft with gastroepiploic artery, gastroduodenal artery, right gastric artery, middle colic artery, splenic artery, radial artery, great saphenous vein or cadaver iliac artery; occasionally the origin from the SMA is involved and in such cases, a long PTFE jump graft may be used from the aorta or the right iliac artery [53].

6.1.5 Are Multivisceral Resections Justifiable?

Locally advanced pancreatic cancer may involve adjacent organs. In view of the poor outcomes in pancreatic cancer, there is a widely held view that multivisceral resections may not provide any benefit. However, data has emerged that suggest that

additional organ resection is justified if the surgeon and centre are experienced in the procedure, and if an R0 resection can be accomplished at the end of the resection. The most common organs resected are the right colon, right kidney and a segment of the liver. Mortality rates were high initially [54], but are now comparable to a standard PD and superior to a palliative bypass [55, 56]. An additional nephrectomy may have the maximum negative outcome. Complication rates are higher, and R0 resection rates are no higher than with standard PD. The International Study Group for Pancreatic Surgery recommended that multivisceral (extended) pancreatectomy may be performed in selected cases [57].

6.1.6 What Should Be the Extent of Lymphadenectomy?

The extent of lymphadenectomy is a subject of much controversy. Published trials have failed to establish an advantage with extended lymphadenectomy. The value of these publications has been diminished further by the lack of uniformity in terms of nomenclature, definitions, classification of lymph node stations or the extent of the lymph node clearance. Four randomized trials [58–61], two consensus meetings [62, 63], and two meta-analyses [64] have failed to establish any benefit with extended lymphadenectomy. The optimum number of lymph nodes to be removed during a standard PD is 15 [65, 66]. A retrospective analysis of over 200 PDs with an average lymph node yield of 30.8 revealed that the number of lymph nodes involved, the number of lymph node stations involved, and involvement of station 14 may all have an adverse prognostic impact on survival [67].

A consensus was reached that the following groups of lymph nodes must be dissected during a standard PD.

1. Station 5: Suprapyloric
2. Station 6: Subpyloric
3. Station 8a: Hepatic artery superior
4. Station 12b: Right side of hepatoduodenal ligament close to common bile duct
5. Station 12c: Cystic duct lymph node
6. Station 13: Posterior pancreaticoduodenal
7. Station 14a, b: Right side of SMA from origin to inferior pancreaticoduodenal
8. Station 17: Anterior pancreaticoduodenal

In left-sided resections the following lymph node stations need to be removed.

1. Station 10: Splenic hilum
2. Station 11: Splenic artery node
3. Station 18: Along the inferior border of the body and tail of pancreas
4. Station 9: Coeliac axis node in patients with carcinoma of the body of pancreas

The nomenclature of lymph nodes is based on the classification of the Japanese Pancreas Society.

No consensus was reached as to whether the 8p lymph node (posterior to the hepatic artery) should be dissected, as also regarding the 16b1 (interaortocaval) lymph node. However, the latter may be an integral part of clearance of the mesopancreas if it is considered a valid option in PD [68]. Others have suggested that it may have a poor prognosis and if positive, resection can be abandoned [69].

6.1.7 *Have Laparoscopic and Robotic Technologies Made a Difference?*

The first laparoscopic PD was reported by Gagner in 1994 [70]. Over two decades later, laparoscopic PD is still not the standard of care. There are several reasons for this: (i) laparoscopic PD demands a high degree of technical skill in laparoscopy and also experience in pancreatic surgery so that oncological outcomes (which are the main objectives of the procedure) are favourable [71]; (ii) the learning curve is long and it may span as many as 40 cases [72]. If there is a low volume of <10 cases/year, then it is very difficult to achieve the necessary expertise for safe PD; (iii) intraoperative complications may lead to mortality [73]; and finally (iv) long term oncological outcomes are lacking.

Several series including meta-analysis have shown equivalence in intraoperative and perioperative outcomes with laparoscopic PD as compared to open PD. Operating times are generally longer, but blood loss is diminished. Margin positivity and lymph node harvest rates have been similar [74–78]. A nationwide survey found that the complication rates, hospital stay and mortality were lower in the laparoscopy group. This is probably because in the absence of randomized trials, there is likely to be bias in selection of tumours for laparoscopic PD. Patients with low grade tumours such as intraductal papillary mucinous tumours, mucinous cystadenomas, and those away from the superior mesenteric vessels were included in the laparoscopic group. However, it must be emphasized that even major vein resection and reconstruction has been reported [76, 79]. There have also been suggestions that laparoscopic PD is preferably avoided in high risk pancreatic anastomosis such as those with soft glands and narrow ducts [80].

The current status of laparoscopic PD is therefore still not clearly defined. The operation is feasible and safe in the hands of surgeons who possess laparoscopic skills in abundance, and may have lower complication rates in a selected group of patients. However, the indications require to be defined more clearly. One must remember that these technical ‘advances’ are superimposed on the open technique of PD which is also evolving.

What about robotic PD? The advantages of robotic surgery are the three dimensional binocular vision and the high numbers of degrees of freedom in the movements that can be executed. This helps to overcome some of the restrictions that laparoscopic surgery places during a complex procedure such as PD. The feasibility and safety of the procedure has been established in case series. Boggi showed that robotic PD can be done safely without conversions; increased operating time and high costs being the major problems [81]. A meta-analysis of over 200 cases of

robotic PD revealed comparable outcomes to open surgery. There was a marked heterogeneity among the cases. Patients could be categorized into (i) totally robotic technique, (ii) laparoscopic resection and robotic reconstruction, (iii) hand-port assisted laparoscopic resection and robotic reconstruction, or (iv) robotic resection and mini-laparotomy reconstruction. Conversion to open surgery occurred in 14 % of cases [82]. Zeh reported lower margin positivity rates in robotic PD [83] and attributed it to case selection—the use of the Pittsburgh model where (i) vascular involvement, (ii) tumour size >2.6 cm, and (iii) endoscopic ultrasound (EUS) staging showing advanced disease were associated with higher R1 resections [84]. In such cases, robotic PD was not used. It is arguable that these cases may well be candidates for neoadjuvant therapy.

Editorial Comments

The authors have dealt with some of the ongoing debates in pancreatic cancer surgery. There are other issues which too need attention and these are discussed below:

Borderline resectable cancer

This is a distinct clinical entity recognized in recent times. There is lack of prospective data by which one can advocate a suitable treatment strategy for the management of this entity. For the same reason, its definition has eluded broad consensus. By and large, these lesions fall between the obviously resectable and the locally advanced unresectable disease. Quite a few definitions are available. What is common in all is the use of a CT image to ascertain the relationship of the lesion with the vascular structures namely portal/superior mesenteric vein (PV/SMV), and superior mesenteric, gastroduodenal, hepatic and coeliac arteries.

A definition was initially proposed by the National Comprehensive Cancer Network (NCCN) in 2008 [85]. Soon after, the American HepatopancreatobiliaryAssociation (AHPBA), Society for Surgery of the Alimentary Tract (SSAT) and Society of Surgical Oncology (SSO) [86] developed a consensus statement, which was later accepted by the NCCN. According to this, borderline resectable cancer can be of three categories:

1. Venous involvement of the SMV/PV: either abutment, encasement or short segment occlusion with a suitable vessel proximal and distal to the involved vessels which can be used for resection and reconstruction.
2. Gastroduodenal artery encasement upto hepatic artery and short segment encasement/direct abutment of the hepatic artery without encroaching on the coeliac axis
3. Less than 180 degree involvement of the SMA.

The MD Anderson group [87, 88] have defined borderline resectable pancreatic cancer as follows:

Type A: One or more of the following: Tumour abutment up to 180 degree of the circumference of SMA or coeliac axis or abutment or encasement more than 180 degree of a short segment of hepatic artery (usually at the origin of the gastroduodenal artery) or short segment occlusion of the SMV, PV or SMV–PV junction such that resection and reconstruction is possible.
Type B: Above features of borderline resectable disease with CT findings suggestive but not diagnostic of extra-pancreatic metastatic disease and proven N1 disease either by laparoscopy or EUS fine needle aspiration cytology.
Type C: Features of borderline resectable disease but with marginal performance status or better performance status but with associated severe co-existing co-morbid conditions precluding operation.

I feel this classification is more confusing than elaborative. Borderline resectable disease is an anatomical description. Adding non-anatomical factors in the classification of this entity does not serve any meaningful purpose as has been pointed out by Choti in the discussion accompanying the article from MD Anderson [88]. This is not to suggest that this is less important. In fact, it is the reverse.

The other classification has been described by Ishikawa et al. in 1992 [40]. It is based on radiological image characteristics that ascertain the relationship of the tumour with SMV and PV. Accordingly there are 5 types.

Type 1: Normal anatomy
Type 2: Smooth shift without narrowing
Type 3: Unilateral narrowing
Type 4: Bilateral narrowing and
Type 5: Bilateral narrowing with presence of collateral veins

This classification is simple, comprehensive and yet useful in most clinical situations. True, it is silent on extension of the tumour on the SMA. However, if we consider tumour extension on both sides of SMV–PV (Types 4 and 5), almost invariably the SMA will be involved with very occasional exceptions.

More recently, Tran Cao et al. [89] have given another useful classification based on tumour vein circumferential interface (TVI) describing as no interface, or up to 180 degree of circumference or more than 180 degree of circumference or occlusion. This system can predict if a patient needs venous resection. The classification correlates well with histological evidence of venous involvement. Not surprisingly, this system has been reported to predict survival as well [89].

There is much attention focused on borderline resectable disease. In pancreatic surgery for cancer, the margin status plays a major role in the prognosis. The results are better following R0 than R1 resections. Results of R2

resection are no better than non-operatively treated patients [90]. Borderline resectable cancer has the potential for a R0 resection. Involvement of vascular structures in the region of the pancreatic head is related more to anatomical than biological characteristics of the tumour. Therefore, all attempts should be made to achieve an R0 resection, if need be by resecting the affected vessel. The definitions outlined above will help the surgeon undertake such measures. Pathological examination of the resected specimens will identify if the margin is truly negative (R0) or microscopically positive (R1). The results of R1 resection are inferior to R0 resection but are still acceptable, as has been mentioned by the authors [90–92]. It may not be out of place to mention here that not all anatomical abnormalities on imaging are attributable to tumour invasion of the vessels. On a number of occasions, I have found no involvement of the vessels even when preoperative imaging has suggested involvement. I am inclined to believe that desmoplasia (quite common in pancreatic malignancy) [93] can explain this phenomenon.

The other approach is to down stage the disease by using neoadjuvant protocols; thereby converting all such tumours to be resectable. The details of this approach are beyond the scope of this write up.

Artery first approach for pancreaticoduodenectomy (PD)

Even after 8 decades of the introduction of PD for pancreatic head cancer, the procedure is still evolving. This is related to better understanding of the pathobiology of this cancer, its image characteristics, technical advances in surgery and impact of resection margin. In the past tumours were resected only after it was ascertained that the PV/SMV is free of the disease. It was subsequently realised that venous involvement *per se* is not a contraindication for PD and resection and reconstruction of these veins can be done safely with results no different from standard PD [94]. Venous resection in a suitable patient is increasingly being done in contemporary surgical practice as long as a R0 status can be achieved. At present the focus has been on the SMA—whether it is involved or not. Its resection is technically feasible but it has increased mortality and morbidity. Moreover, it is not associated with better survival and hence it is not considered as a standard practice for PD. Thus the emphasis today is on accurate staging of the disease by high resolution CT imaging displaying the anatomy of the SMA and its relation with the tumour. Involvement of the SMA is a contraindication for PD [95]. For borderline resectable tumours, the artery-first approach is the most appropriate because it allows early detection of arterial involvement so that an irretrievable situation is avoided (not too uncommon a problem in the past when a surgeon used to proceed with a PD realising only at the end that the tumour has in fact involved the SMA—by that time a point of no return has already been reached!). This situation has to be avoided. The SMA first approach is a measure in that direction. There are a number of artery-first approaches described; each having its own advantage and disadvantage and are described below.

Posterior approach [96]: This is indicated for lesions located in the head and neck and for ampullary tumours extending to the head. Its advantage is early detection of arterial and venous involvement, detection of replaced/accessory right hepatic artery, and it allows adequate lymphadenectomy. However, it is difficult in the presence of severe inflammation.

Superior approach [97]: Tumours situated in the upper border of the pancreas can be best approached by this technique. All the relevant arteries can be identified by this approach (common hepatic, coeliac and superior mesenteric arteries).

Inferior supracolic (also called anterior approach) [98]: This is reserved for lesions of the lower border of the pancreas. The stomach and the neck of pancreas is resected early and this allows the so-called 'no touch' technique which facilitates *en bloc* resection without undue handling of the tumour.

Inferior infracolic approach [99]: Usually followed for lesions affecting the SMA at its origin but also can be done for lesions of the uncinate process. Its main advantage is early detection of a replaced right hepatic artery, early ligation of the inferior pancreaticoduodenal artery and superior dissection of the SMA especially its posterior aspect. It is particularly difficult to do in heavily built individuals.

Medial uncinate approach [100]: This is suitable for uncinate process lesions. It allows early detection of SMA involvement. Its advantage is ligation of the inferior pancreaticoduodenal artery can be done early due to which bleeding can be minimised. It is especially useful for lesions requiring total pancreatectomy. The main problem is identification of a replaced right hepatic artery.

Left posterior approach [101]: It is suitable for lesions confined to the ventral pancreas as well as uncinate process. SMA can be dissected even without Kocherization. Inferior pancreaticoduodenal artery ligation can be done early and it minimises bleeding. Since it skeletonises the SMA extensively, the incidence of postoperative bothersome diarrhoea is high (due to damage to autonomic sympathetic nerves).

Lymphadenectomy during PD

The most important factor to determine prognosis following PD is involvement of the lymph nodes. The other bad prognostic markers are positive resection margins of the pancreas and the retroperitoneal tissues. We now have better imaging, surgical techniques, pre- and postoperative therapies but the results of PD for adenocarcinoma of the pancreatic head is no better than what it was in the past [102]. Clearly, this reflects true biological behaviour of these cancers. In a meta-analysis of 4005 patients of PD, the overall survival was only 13 months with a 5-year survival of 6.8 % [103]. Almost similar results (median survival of 13–18 months and a 5-year survival of 15 %–30 %) have been reported by Wilkowski et al. [104]. Standard PD for cancer is associated with high recurrence rate possibly due to positive lymph nodes [27].

Therefore, it should be logical to do a more extensive lymphadenectomy. The International Congress in Italy advised excision of all lymph nodes and soft tissues along the proper hepatic artery, anterior surface of the vena cava and aorta; extending the same soft tissue excision along the portal vein up to the inferior mesenteric artery [62].

Lymphatic drainage of the pancreatic head occurs through the superior and inferior channels. The superior one drains in lymph nodes around the coeliac trunk and the inferior one drains into lymph nodes situated in relation to the origin of the SMA. In addition, there are certain lymphatic channels which drain into the cisterna chylae, either directly or through the para-aortic lymph nodes [105]. These latter channels, when disrupted can cause chyle leak following PD. The Japanese nodal staging system based on this lymphatic drainage patterns focuses on specific lymph node groups. The lymph nodes in the head region are located either anteriorly (station 17) or posteriorly (station 13). From these, the efferent vessels drain into lymph nodes along the SMA (station 14) before reaching the para-aortic nodes (station 16). Occasionally, lymphatics drain directly into lymph nodes along the hepatic artery proper (station 8) ultimately reaching the para-aortic nodes via the coeliac nodes (station 9).

Standard lymphadenectomy involves removal of all of the following lymph nodes—from above downwards these are lymph nodes along hepatoduodenal ligament (station 12), supra and infra pyloric lymph nodes (stations 5 and 6), those along the front of the common hepatic artery (station 8), anterior and posterior pancreatoduodenal lymph nodes (stations 17 and 13) and lymph nodes along the SMA (station 14) [106].

Extended lymphadenectomy on the other hand removes lymphatics starting from the porta hepatis on the right to the aortic opening of the diaphragm on the left. Dissection further continues to the splenic and both renal hila and then downwards up to the inferior mesenteric artery circumferentially removing tissues and lymph nodes around the origins of the coeliac and superior mesenteric arteries; in the process lymph nodes at station 7 (left gastric), station 9 (coeliac trunk), station 10 (splenic hilum), station 11 (splenic artery), station 16 (para-aortic) and station 18 (inferior border of pancreas) are removed in addition to what is removed in a standard dissection [58].

The fact that the local recurrence rate even after adjuvant therapy following surgical resection is high (ranging from 70 to 88 %) calls for wide clearance of the retroperitoneal soft tissues around the pancreatic head (the so-called mesopancreas consisting of loose areolar tissue, fat, lymphatics, capillaries and nerve plexus) and the related arteries as mentioned earlier. This improves not only the R0 resection rates, but also removes the affected lymph nodes in the draining areas [106]. So should one do a standard or an extended lymph node dissection? At least 7 prospective studies have assessed results (especially survival) of extended lymphadenectomy. None of these has found any

survival benefit [107]. However, the procedure has similar morbidity and mortality as a standard lymphadenectomy [108]. Extended lymph nodal resections can be associated with troublesome delayed gastric emptying and disturbing diarrhoea. In view of these, most experts recommend standard rather than extended lymphatic clearance. The consensus meeting of the International Study Group on Pancreatic Surgery (ISGPS) which was held in 2014 in Verona. made the following statements on this subject: (i) For classification of lymph node stations, the classification of the Japanese Pancreas Society should be followed; (ii) Extended lymphadenectomy should be avoided as it does not improve oncological outcome; (iii) lymphadenectomy should include removal of nodes at stations 5, 6, 12, 8, 13, 17 and 14 for pancreatoduodenectomy and stations 9, 10, 11 and 18 for tumours of the body of pancreas [63]. The disadvantage of lymphadenectomy is that it removes lymph nodes which are normal with potential immunoprotective function such as trapping the offending agent like the tumour cell and the bacteria. Therefore its unnecessary removal deprives the normal lymphocytes their important immune function against cancer cells [109].

The consensus statement of the ISGPS (mentioned above) as well as various other publications stresses that at least 15 lymph nodes should be removed and pathologically examined for accurate lymph nodal staging. Lymph node positivity has a variable impact on survival. While some have reported survival benefit in N0 patients, others have reported better survival in N1 patients. Still others have reported that the number of lymph nodes is not a predictor of survival [63]. The ratio of positive to total number of lymph nodes >0.2 is also considered to be a poor predictor of postoperative survival [63].

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Chapter 7
Splenectomy for Haematological Disorders

Kamal Kataria, Naveen Kumar, and Sunil Chumber

7.1 Introduction

The spleen in haematological conditions is enlarged often. This leads to destruction of cell lines and especially platelets, and becomes the cause of red cell destruction and iron overload in haemolytic conditions. Massive enlargement also places the spleen at risk of injury and exsanguinating intraperitoneal haemorrhage. Rarely, it becomes so large that it restricts the daily activities of the patient. Usually a total splenectomy is done for haematological disorders. Rarely, partial splenectomy may be indicated in some metabolic conditions such as Gaucher's disease.

7.2 Indications

There are four reasons to perform a splenectomy in haematological conditions. These are:

1. To treat a disease in which blood cells are destroyed in the pulp of the spleen.
2. To treat hypersplenism.
3. To stage Hodgkin's disease.
4. As a diagnostic procedure to establish the cause of splenomegaly in patients with non-distinctive haematological features.

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7.3 Platelet Disorders

7.3.1 Immune Thrombocytopenic Purpura (ITP)

ITP, classically known as idiopathic thrombocytopenic purpura, is characterized by a low platelet count despite a normal bone marrow and the absence of other causes of thrombocytopenia. Thrombocytopenia is a result of over-activated phagocytosis of platelets within the reticuloendothelial system after being complexed with auto-antibodies. It is characterized by purpura, epistaxis and gingival bleeding. Sometimes patients may present with haematuria or gastrointestinal bleeding. The diagnosis of ITP involves the exclusion of other relatively common causes of thrombocytopenia, viz. pregnancy, drug-induced thrombocytopenia (e.g. heparin, quinidine, quinine, sulphonamides), viral infections and hypersplenism. ITP is predominantly a disease of young women. However, its presentation is somewhat different in children—both genders are affected equally, onset is sudden, thrombocytopenia is severe, and complete spontaneous remissions are seen in approximately 80 % of affected children.

The management of ITP depends essentially on the severity of the thrombocytopenia. There is little need for intervention if the patient is asymptomatic and his/her platelet counts remain above 50,000/cmm. Patients with platelet counts, between 30,000 and 50,000/cmm, should be observed, as there is an increased risk for progressing to severe thrombocytopenia. The patients should be treated with glucocorticoids even if the platelet counts are less than 50,000/cmm when they present with symptoms such as mucous membrane bleeding, and high-risk conditions such as hypertension and peptic ulcer disease. Asymptomatic patients may also require glucocorticoids if the platelet count remains less than 20,000–30,000/cmm. Two-thirds of patients will show a clinical response with increase in platelet count to >50,000/cmm within 1–3 weeks of treatment. Of the patients treated with steroids, 25 % will experience a complete response. Platelet transfusion is indicated only for those who have severe haemorrhage. Intravenous immunoglobulin (IVIG) therapy is important for the treatment of acute bleeding, in pregnancy, or for patients being prepared for surgery, including splenectomy. The usual dose is 1 g/kg body weight/day for 2 days. This dose usually increases the platelet count within 3 days; it also increases the efficacy of platelet transfusions.

Splenectomy is also the treatment of choice for patients with an incomplete response to glucocorticoids and for pregnant women in the second trimester of pregnancy who have failed steroid treatment or IVIG therapy with platelet count <10,000/cmm without symptoms or <30,000/cmm with bleeding problems. There is no need of splenectomy in asymptomatic patients who are diagnosed with ITP more than 6 months ago and if their platelet count is >50,000/cmm.

Kojouri et al. in their systematic review of 436 published articles from 1966 to 2004 found that there was a complete response to splenectomy in 72 % of patients. The relapse rate in this review following splenectomy was 15 % of patients after a follow up of 33 months. They also found that age at the time of splenectomy was an independent variable that correlated most with the response, with younger patients showing improved responses [1]. Kuter et al. in their randomized trial evaluated the

role of romiplostim, a noval medical therapy for patients with no response to steroids, IVIG or splenectomy. Romiplostim, a thrombopoietin receptor agonist was associated with increased and maintained platelet count in patients with ITP who had or had not undergone a splenectomy. Many patients were able to reduce or discontinue other medications for their ITP [2].

7.3.2 Thrombotic Thrombocytopenic Purpura (TTP)

This rare disorder is characterized by microthrombi in the arterioles, capillaries and venules of many organs and leads to fever, transient neurological deficits and renal failure, accompanied by haematological changes. The aetiology is unclear, although it has been postulated that the disease is autoimmune in origin. The first line therapy is plasmapheresis, which is usually effective. Splenectomy is indicated only if plasmapheresis is ineffective.

7.4 Congenital Red Cell Disorders

Three types of congenital disorders that are associated with haemolytic anaemia and may warrant splenectomy are disorders of the erythrocyte membranes, haemoglobinopathies and erythrocyte enzyme deficiencies.

7.4.1 Disorders of Erythrocyte Membranes

Hereditary spherocytosis (HS) is an autosomal dominant disease affecting the production of spectrin, a red blood cell cytoskeletal protein. Loss of this protein leads to loss of the characteristic biconcave shape and red blood cells become rigid, small and sphere shaped. Due to this change in shape, RBCs become more susceptible to trapping and destruction by the spleen. The diagnosis is made by examination of a peripheral blood smear, increased reticulocyte count, increased osmotic fragility and a negative Coombs' test. The anaemia resulting from hereditary spherocytosis can be treated by splenectomy, but the erythrocyte morphology remains abnormal. Splenectomy should preferably be delayed until the age of 5 years to preserve the immunological function of the spleen and reduce the risk of opportunistic post-splenectomy infections (OPSI).

Other conditions similar to hereditary spherocytosis include hereditary elliptocytosis, hereditary pyropoikilocytosis, hereditary xerocytosis and hereditary hydrocytosis. All of these result in anaemia secondary to red blood cell membrane abnormalities and destruction in the spleen. Splenectomy is indicated in severe anaemia with these conditions, except hereditary xerocytosis, which results in only mild anaemia of limited clinical importance.

7.4.2 Haemoglobinopathies

A defect in the haemoglobin molecule may also result in haemolytic anemia. Thalassaemia and sickle cell disease are two examples of defective haemoglobin molecules, where the abnormal shape of the red blood cells leads to splenic sequestration and subsequent destruction.

Thalassaemia is an autosomal dominant trait, which results from a defect in haemoglobin synthesis. The disease is characterized by diminished production of structurally normal globin chains resulting in an excess of one type of chain. *Beta* thalassaemia is characterized by deficient synthesis of the beta chain, whereas *alpha* thalassaemia results from deficient synthesis of the alpha chain. These patients require blood transfusions at regular intervals and usually die at an early age. Splenectomy is reserved for symptomatic splenomegaly and recurrent splenic infarction.

Sickle cell disease results from substitution of valine for glutamic acid in the sixth position of the β chain of haemoglobin A. This substitution causes red cells to become rigid and crescent or sickle shaped within the microvasculature under reduced oxygen conditions. These crescent or sickle shaped cells are unable to pass through the microvasculature, resulting in thrombosis and microinfarction. Although this condition results from homozygous inheritance of the defective haemoglobin (haemoglobin S) but sickling can also occur when haemoglobin S is inherited along with other haemoglobin variants such as haemoglobin C or sickle cell β-thalassaemia. These episodes of vaso-occlusion and progressive infarction result in *autosplenectomy*. The spleen, which is often hypertrophied early in life usually atrophies by adulthood except in a few patients. Splenectomy usually does not stop the sickling process but it may improve the anaemia.

Hypersplenism and acute splenic sequestration are life-threatening disorders in children with thalassaemia and sickle cell disease. In these conditions, there may be rapid splenic enlargement, which results in severe pain and may require multiple blood transfusions. Hypersplenism related to sickle cell disease is characterized by anaemia, leukopenia and thrombocytopenia requiring transfusions.

Splenectomy may be an option to reduce transfusion requirements in this condition. Symptomatic massive splenomegaly that interferes with daily activities may also be improved by splenectomy. Finally, in children with sickle cell disease who exhibit a delay in growth or even weight loss, because of increased metabolic rate and whole body total protein turnover, splenectomy may relieve these symptoms.

7.4.3 Erythrocyte Enzyme Deficiency

The *pyruvate kinase* and *glucose-6-phosphate dehydrogenase* (G6PD) deficiencies are the main hereditary conditions responsible for haemolytic anaemia. Pyruvate kinase deficiency is an autosomal recessive disease that results in

decreased red blood cell deformability and the formation of *echinocytes*, a type of spiculated red blood cell. This change in shape increases the chances of trapping and destruction by the spleen. The resultant splenomegaly and haemolytic anaemia can be treated by splenectomy. Similarly, G6PD deficiency, which is a X-linked condition results in haemolytic anaemia especially after infection or exposure to certain foods, medications or chemicals. Primary treatment, therefore, is avoidance of exacerbation of the condition. Splenectomy is rarely indicated in this condition.

7.5 Malignancy

7.5.1 Hodgkin's Disease

It is a malignant lymphoma that is commonly seen in the second and third decades of life. Patients present with constitutional symptoms such as night sweats, weight loss and pruritus but, more commonly as asymptomatic cervical lymphadenopathy. It is characterized histologically as lymphocyte predominant, nodular-sclerosing, mixed cellularity or lymphocyte-depleted. The disease is pathologically staged according to the Ann Arbor classification.

Historically, surgeons used to do a splenectomy along with staging laparotomy for pathological staging to guide appropriate therapy. Now invasive staging methods have been replaced by non-invasive imaging techniques such as computed tomography (CT), fluorodeoxyglucose positron emission tomography (FDG-PET) and CT-lymphangiography—thus making invasive staging methods almost obsolete. Staging laparotomy remains appropriate for selected patients, such as those with early clinical disease stages (IA or IIA) in whom abdominal staging will significantly alter therapeutic management.

7.5.2 Non-Hodgkin's Lymphoma

Non-Hodgkin's lymphoma (NHL) is the most common primary neoplasm of the spleen, i.e. 50–80 % of patients with NHL will have involvement of the spleen. Approximately 75 % of these patients have clinically apparent hypersplenism. Splenomegaly or hypersplenism is a common occurrence during the course of non-Hodgkin's lymphoma (NHL). Splenectomy is indicated for NHL patients with massive splenomegaly leading to abdominal pain, early satiety, and fullness. It may also be indicated for patients who develop anemia, neutropenia, and thrombocytopenia associated with hypersplenism. The survival is improved significantly by splenectomy in patients with spleen-predominant features.

7.5.3 Leukaemia

Hairy cell leukemia is a rare disease characterized by splenomegaly, pancytopenia and neoplastic mononuclear cells in the peripheral blood and bone marrow. The cells that give the disease its name are B-lymphocytes that have a ruffling of the cell membrane. Treatment for cytopenias or splenomegaly typically begins with purine analogue chemotherapy [3]. Immunotherapy with monoclonal antibody, i.e. rituximab or recombinant immunotoxins (RIT) such as anti CD-22 or anti CD-25 may be used as second line therapy in refractory cases.

Splenectomy may provide relief from symptoms of splenomegaly and hypersplenism and lead to normalization of blood counts in half the patients and this post-splenectomy response may last 10 years in most patients [4].

Chronic lymphocytic leukaemia (CLL) is characterized by progressive accumulation of relatively mature but functionally incompetent lymphocytes. It is usually seen in the 5th decade of life with a slightly male preponderance. CLL is staged according to the Rai system and correlates well with survival. The Rai system helps clinicians determine when therapy should be started. The main treatment is medical therapy with nucleoside analogues (fludarabine and cladribine) or monoclonal antibodies (rituximab), which can be used in selected cases. The only known cure for CLL is bone marrow transplantation. Splenectomy is indicated in patients with refractory splenomegaly and pancytopenia, and results in improvements in blood counts in 60–70 % of patients.

7.5.4 Revised Rai Staging System (United States)

- Low risk (former stage 0):
  - Lymphocytosis, lymphocytes in blood >15,000/cmm, and >40 % lymphocytes in the bone marrow
- Intermediate risk (former stages I and II):
  - Lymphocytosis as in low risk with enlarged node(s) in any site, or splenomegaly or hepatomegaly or both
- High risk (former stages III and IV):
  - Lymphocytosis as in low risk and intermediate risk with disease-related anaemia (haemoglobin level <11 g/dl or haematocrit <33 %) or platelets <100,000/cmm

Chronic myelogenous leukaemia (CML) is a myeloproliferative disorder that develops due to neoplastic transformation of myeloid elements. In this condition, mature appearing neoplastic myeloid cells replace normal diploid elements of the bone marrow. Patients commonly present with fever, fatigue, malaise, effects of pancytopenia (infection, anaemia, easy bruising), and occasionally splenomegaly.

The defect in CML is fusion of fragments of chromosomes 9 and 22 resulting in Philadelphia chromosome. It usually presents with an asymptomatic chronic phase but may progress to an accelerated phase associated with fever, night sweats and progressive splenomegaly.

Most treatment modalities such as tyrosine kinase inhibitors and chemotherapy target *bcr–abl* gene product, i.e. tyrosine kinase. Bone marrow transplantation is an option but prognosis has improved dramatically with the advent of recent therapies, making transplantation less common. Splenectomy is reserved for patients with symptoms because of splenomegaly and hypersplenism as there appears to be no survival benefit when it is done during the early chronic phase.

7.6 Preoperative Preparation for Splenectomy

All patients undergoing elective splenectomy should have certain vaccinations to reduce the risk of sepsis. Vaccination against pneumococcus, *Haemophilus influenzae* type B (Hib) and meningococcus is recommended. Whenever possible, vaccines should be given at least 2 weeks prior to elective splenectomy. There is no evidence-based data to support long-term antibiotic prophylaxis and decisions in favour of or against their use should be made on an individual basis.

Nasogastric tubes are routinely placed in patients undergoing splenectomy. Urinary catheters are not placed in patients with ITP, but others may receive these. An epidural catheter is avoided.

7.6.1 Splenectomy

In adults, splenectomy may be done either by the open or laparoscopic method. In children, the open approach is preferred. The open method can be used in all indications, irrespective of the size of spleen whereas the laparoscopic method is suitable in patients with a normal sized spleen and adequate body habitus. A previous laparotomy makes the laparoscopic procedure difficult. Conversion to the open technique is also time consuming and often requires repositioning the patient in the supine position. The position is cumbersome in the laparoscopic technique, especially if it includes a cholecystectomy. The extraction incision in the laparoscopic method is often obvious, misplaced and ugly to look at after a few months. Overall, patients show rapid recovery and fewer wound problems after the laparoscopic method, which is no mean achievement.

The surgeon should himself position the lights as well as supervise the positioning of the patient before painting and draping. The position of the patient is often determined by the surgeon's preference as well as the age of the patient. Paediatric surgeons prefer a transverse incision while gastrointestinal surgeons prefer a subcostal or thoraco-abdominal incision.

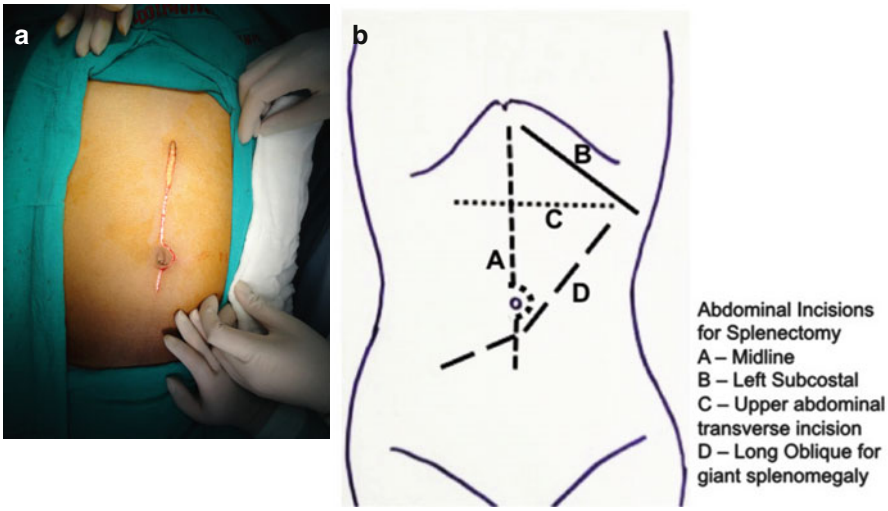

Fig. 7.1 (**a**) Midline incision is commonly used for splenectomy. Infraumblical extension is used in large spleens. (**b**) Other incisions used for open splenectomy

Irrespective of the habitus, age and pathology or size of spleen and the surgeon's experience, the supra-umblical midline incision provides good access, is made rapidly and without much bleeding. This is especially useful in patients who may be positive for Hepatitis B or C virus or have ITP with very low platelet counts. If the spleen is very large and extends into the lower abdomen, the incision may extend below the umbilicus. The left subcostal incision is made with difficulty and often causes bleeding and is not suitable for large spleens and cannot be extended when in difficulty (Fig. 7.1). At the end of the surgery, the midline incision can be closed easily using 2 sutures of 1–0 loop nylon without tension, after placing a drain in the splenic bed. Some surgeons use a pillow below the left side to tilt or throw-up the spleen but this rarely helps, and may cause more backache in the postoperative period.

7.6.2 Open Procedure

In large spleens, on entry into the abdomen, the stomach and the transverse colon are lifted to enter the lesser sac after ligation of a few vessels; if small these can be cauterized or controlled with an ultracision energy source. Once inside with adequate access, the pulsations of the splenic artery are seen above the superior border of the pancreas and, towards the tail of pancreas, dividing into two main branches (Fig. 7.2). A short segment of the artery is isolated and two ties passed across and tied. Any fluid inside the lesser sac is now sucked and the stomach allowed to fall in place. Ligation of the splenic artery blocks the arterial flow and ensures the rest of the dissection can be done with relatively less blood loss. As the venous outflow is intact, squeezing of the spleen allows pooled blood to flow into the circulation and leads to autotransfusion of 100–300 ml of blood to the patient (Fig. 7.3). The

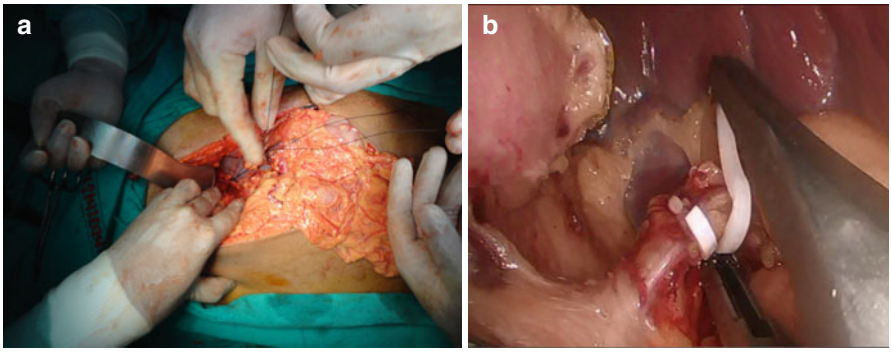

Fig. 7.2 (**a**) Early ligation of splenic artery in the lesser sac in an open procedure (**b**) Applying Hemolock clips in laparoscopic splenectomy

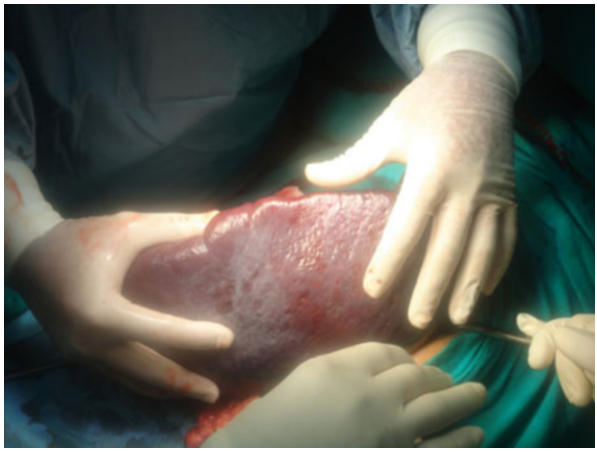

Fig. 7.3 Compression over a mobilized spleen for *autotransfusion* of blood

splenic vein is then ligated and divided. While early ligation of the splenic artery is not needed in patients with ITP, in the laparoscopic approach it is done even in patients with ITP. The tail of the pancreas must be identified and carefully preserved while the splenic artery and vein are dissected and isolated. The splenic artery and vein should be ligated separately to avoid the theoretical risk of an arteriovenous fistula.

Next, a hand is passed over the lateral surface of the now floppy spleen, it is lifted forwards and medially followed by division of the posterior layer of the lienorenal ligament from just above the splenic flexure towards the diaphragm. This allows the spleen to be delivered into the wound. Usually there are minimal adhesions with surrounding organs, which are divided. The 3–4 short gastric and left gastroepiploic vessels can then be divided. At the end of the procedure, a search should be made for accessory spleens in the region of the tail of pancreas, the lesser sac and in the gastrosplenic area (Fig. 7.4). Sometimes, enlarged lymph nodes may look like an accessory spleen, but these are usually pale in colour.

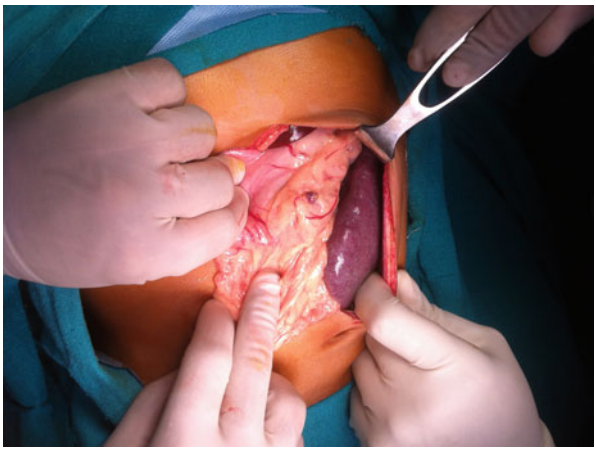

Fig. 7.4 Accessory splenunculus in the lesser omentum

7.6.3 Laparoscopic Procedure

Laparoscopic splenectomy is a reliable procedure for patients with small spleens (<15–20 cm in size). The important step is proper positioning of the patient on the operating table: in the right lateral semi-decubitus position at an angle of about $30–40^0$ with the head end raised. The left arm is elevated above the head, permitting a better approach to the spleen via the left thoracic aperture. By turning the table at the beginning of the procedure, the patient can be brought into a supine position with a slightly lowered pelvis (reverse Trendelenburg position) so that pneumoperitoneum can be established and the trocars inserted.

A total of 4–5 trocars are inserted. The camera is inserted through a 12 mm supraumbilical port. The next port is placed in the left subcostal area for elevation of the spleen with an endo-retractor. The main working trocar is inserted at the midpoint between the first two trocars and about 3 cm caudally. The fourth trocar is inserted 4 cm supraumbilical and to the right of the midline for the forceps or dissector. The fifth 5 mm trocar is positioned sub-xiphoid in the midline and retracts the liver (Fig. 7.5). More cannulas may be required if an additional procedure such as a cholecystectomy is to be done. The ultracision is very useful in dissection and coagulation during the procedure.

Early ligation or clipping of the splenic artery is done by entering the lesser sac. The splenic artery is doubled clipped with Hemolock clips in continuity (Fig. 7.2b). The gastrosplenic ligament and the short gastric vessels are divided next. Now, the posterior leaf of the lienorenal ligament is divided, although it may be better to leave its superior extremity towards the diaphragm to stabilize the spleen until after division of the hilar vessels. If not done earlier, the splenic artery can be isolated at this stage above the tail of the pancreas, clipped and divided. If the splenic artery has been tackled earlier, the main purpose of the dissection is to isolate the tail of the pancreas and the splenic vein. Only a vascular stapler is used to divide the splenic vein. The spleen is ready to be extracted after manipulating it into a bag.

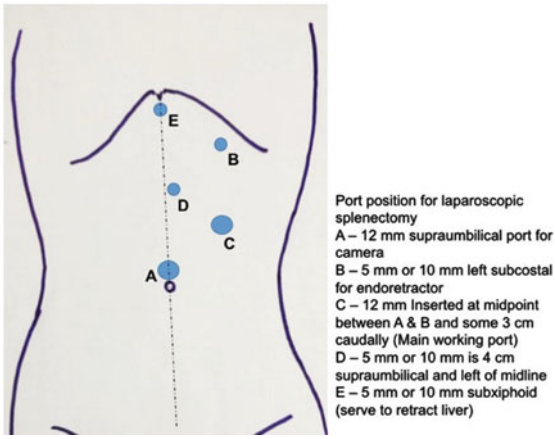

Fig. 7.5 Port placements in laparoscopic splenectomy

The spleen can also be extracted by enlarging a trocar incision or by morcellation since the exact pathology is not required for patients with ITP. One should take care not to lose any splenic fragments in the abdominal cavity to prevent postoperative splenosis. This is unpardonable in ITP.

7.7 Postoperative Management

7.7.1 Recovery

Patients are nursed in the recovery wards and receive adequate analgesia, avoiding non-steroidal anti-inflammatory drugs. The nasogastric tube is removed the following morning unless the output is high. Similarly, the drain can be removed unless the drainage is high. Patients may be started on oral fluids and later on a normal diet. If they are receiving steroids preoperatively, they can be shifted to oral steroids. Antibiotics are continued for a week and skin sutures/staples are removed after 2–3 weeks if the patients are on steroids.

7.7.2 Transfusion of Platelets in ITP

Most patients have a preoperative platelet count in the range of 10,000–50,000/cmm and require transfusion of platelets. We routinely arrange for 1–2 donors for preparation of single donor platelets. These are prepared on the day of surgery or 1-day

prior and irradiated before infusion. The infusion is started when the patient is on the operating table to obtain high levels during the initial phase of the operation. After the splenic artery is ligated/clipped, there is no need for any further infusion of platelets.

7.7.3 Postoperative Platelet Levels

The rise in platelets may occur as early as the day of the operation but in most patients the rise in platelet count occurs within 2–3 days of surgery. A major rise in platelet count does not occur beyond this time. There is a small number of patients who do not show a rise in platelet count (<5 %). However, it is important only to check if they have any source of bleeding. In the long term also these patients continue to have low counts and may require additional medical management in the form of IVIG and steroids (failure of surgery). Several patients after splenectomy show an exaggerated rise in the platelet count. These are monitored serially in the postoperative period and only when they rise above 600,000/cmm, we start low dose aspirin 75 mg once a day (others suggest waiting till the counts are above 750,000/cmm).

Patients with haemolytic disease are returned to their respective departments for long-term follow-up. Post-splenectomy, patients are more susceptible to fulminant bacteraemia, and this has been reported between 1 week and over 20 years after splenectomy. This is a result of the following changes that occur after splenectomy: (i) decreased clearance of bacteria from the blood; (ii) decreased levels of IgM; and (iii) decreased opsonic activity. The risk is highest in young children, especially in the first 2 years after surgery (80 % of patients) and when the disorder for which splenectomy was required was a disease of the reticuloendothelial system. In general, the younger the patient undergoing splenectomy and the more severe the underlying condition, the greater the risk for developing overwhelming post-splenectomy infection. Lethal sepsis is very rare in adults. There is a distinct clinical syndrome: mild, non-specific symptoms followed by high fever and shock from sepsis, which may rapidly lead to death. *Streptococcus pneumoniae, Haemophilus influenzae* and *Neisseria meningitidis* are the most common pathogens. Disseminated intravascular coagulation is a common complication. Awareness of this fatal complication has led to efforts to avoid splenectomy or to perform partial splenectomy or splenic repair for ruptured spleens (only in patients with trauma) to maintain adequate splenic function.

7.7.4 Postoperative Immunization

If immunization was not given before the splenectomy, it should be given within 1–2 weeks postoperatively. In various studies, it has been shown that the antibody titre was the highest when the polyvalent pneumococcal vaccine was administered

14 days post-splenectomy [5]. Additional booster doses of the pneumococcal and meningococcal vaccines may be recommended to maintain immunity. The need for booster doses depends upon the individual's situation and type of vaccine given previously. A booster dose of Hib vaccine is not routinely needed but is occasionally given to those who do not develop a good antibody response to the vaccine. Influenza immunization should be given yearly [6].

7.7.5 Preventive Antibiotic Therapy

Since the vaccine is effective against 80 % of organisms, some experts recommend antibiotics for a 2-year course, or treatment until the age of 16 years, or lifelong prophylaxis with penicillin. Antibiotic prophylaxis is essential in children under 2 years of age and should be continued until at least 6–7 years of age. In general, splenectomy should be deferred till the child is 6–7 years unless the haematological problem is severe. Two approaches are commonly used: (i) daily preventive antibiotic therapy and (ii) antibiotic therapy for fever.

1. *Daily therapy:* It is recommended for children who have a splenectomy done for sickle cell anaemia. The role of antibiotic therapy in adults is debatable due to the low risk of post-splenectomy opportunistic infections. The ideal duration of daily therapy for children remains unclear. Many experts advise treatment for 3–5 years after splenectomy (or until adulthood).
2. *Antibiotics for fever:* It is recommended that post-splenectomy patients with signs of chills, sore throat or cough should be treated with a full course of antibiotics. After taking the first dose, the person should seek care immediately at the nearest healthcare facility to determine if further testing or treatment is needed.

7.8 Complications of Splenectomy

Complications related to elective splenectomy in haematological conditions are relatively few, with atelectasis, wound infections, pancreatitis and postoperative haemorrhage being the most common. If splenectomy is done for thrombocytopenia, secondary bleeding may occur even though the platelet count usually increases early. Platelet transfusions should be given if primary haemostasis is inadequate (i.e. presence of oozing) and the platelet count remains low.

Thromboembolic complications may be more common following splenectomy but it does not correlate with the degree of thrombocytosis. The risk of portal vein thrombosis is 3 % and occurs most commonly after splenectomy for the massive spleens of haemolytic anaemia. Symptoms include fever, abdominal pain, diarrhoea and abnormal liver function tests. Treatment consists of anticoagulation and carries a poor prognosis. Rarely, the platelet count may decrease with a bleeding episode. This is often indicative of the presence of an accessory spleen. An ultrasound, CT

scan and an RBC destruction scan may help detect this and it will have to be removed surgically, if symptomatic.

7.9 Our Experience

In our surgical unit, 133 patients underwent splenectomy in the past 5 years. There were 75 women (56.4 %) and 58 men (43.6 %). The mean age of the patients was 31.5 years (range 4–65 years). Splenectomy was done in 56 patients for ITP, 17 for hereditary spherocytosis, 14 for autoimmune haemolytic anaemia and 11 for thalassaemia. Twenty-eight patients had splenomegaly with hypersplenism because of a non-haematological condition and also had a splenectomy done. Seven patients underwent splenectomy for metabolic disorders such as Gaucher's disease. Of the 98 patients who underwent splenectomy for haematological disorders, 19 (19.3 %) had a relapse. The remission rate was highest (62.5 %) in patients with ITP. The symptoms of hypersplenism were resolved in 76.9 % of patients.

7.9.1 Complications

Twenty-five of 98 patients who underwent splenectomy for haematological conditions had postoperative complications (Table 7.1).

Prolonged paralytic ileus was the most common complication in 5 patients. One patient had intra-abdominal bleeding requiring re-exploration. Four patients had high-grade fever and chills. On evaluation, there was no associated collection or lung infection, so the patients were diagnosed with overwhelming post-splenectomy infection (OPSI). Three patients responded to antibiotics but one patient succumbed on postoperative day 36 to multi-organ dysfunction syndrome.

Table 7.1. Postoperative complications in patients undergoing splenectomy for haematological conditions

Postoperative complication	Number	Percentage
Wound infection	4	4.1
Wound haematoma	1	1.0
Intra-abdominal bleed	1	1.0
Splenic fossa collection	4	4.1
Pneumonia	4	4.1
Prolonged ileus	5	5.1
Portal vein thrombosis	2	2.0
Overwhelming post-splenectomy infection (OPSI)	4	4.1

Editorial Comments

Splenectomy for haematological disorders has been done for over a century [7, 8]. The rationale for splenectomy for various disorders in this category is based on the function of the spleen—both haematological and immunological. Normally, the spleen destroys abnormal red cells (spherocytes, elliptocytes, sickle cells), pools nearly half of the circulating platelets and regulates blood volume [9]. It is thus not surprising that the spleen is involved in haematological disorders. The spleen is, in essence, an enlarged lymph node (with its own blood supply) and hence, a part of the reticuloendothelial system. As a result the spleen removes bacteria, aged blood cells and antibody coated cells, and also produces antibodies. These latter functions make the spleen an immunologically active organ [10]. This is the background for splenectomy being advocated for various haematological disorders.

Splenectomy, however, is not without problems. Apart from complications related to the surgery itself, absence of the spleen (asplenia) has several adverse consequences. The issue of overwhelming post-splenectomy infection (OPSI), once a dreaded complication is now extremely infrequent due to prophylactic vaccine and use of penicillin as well as suitable treatment when infection develops after spenectomy [11, 12]. The incidence of OPSI is 0.1 %–0.5 % with a mortality rate of nearly 50 % [11]. The risk is lifelong, particularly with *Streptococcus pneumonae*, *Neisseria meningitides* and *Haemophilus influenzae*. OPSI occurs most often in the first 3 years after splenectomy; more frequently in children below 5 years of age than in adults. The risk is also higher in patients with HIV, myeloma and leukaemia due to the immunodeficiency state [13, 14].

Thrombotic events both arterial and venous, are now being increasingly reported [6]. Venous thrombosis usually occurs in the portal system (splenoportal axis) in almost all haematological disorders requiring splenectomy including hereditary spherocytosis, thalassaemia and haemolytic anaemias [15, 16]. Pulmonary hypertension is another complication seen in asplenic patients with thalassaemia and sickle cell disease [17, 18].

Patients of haemolytic anaemia with hereditary spherocytosis and autoimmune haematological diseases are offered splenectomy because the spleen prematurely destroys all abnormal RBCs including antibody-coated cells. This controls the anaemia. This is the reason why splenectomy is considered the treatment of choice for these conditions. However, one must remember that splenectomy is not curative of the underlying pathology (abnormal cell) in these conditions. For prognostication one must ascertain that the spleen is the actual site of destruction by isotope study showing pooling of RBCs in it. Similarly one must demonstrate that the bone marrow is actively producing enough cells by doing a bone marrow biopsy which should be hypercellular. This is important to prevent cytopenia when the spleen is removed. Needless

to say that any accessory spleen must be meticulously searched for or removed to prevent the procedure from not providing the desired results [19].

When splenectomy is done for haematological disorders such as thalassaemia there is a higher incidence of thromboembolism [7]. Because of this, non-surgical measures have found favour [13]. The risk of thromboembolism is lower in idiopathic thrombocytopenic purpura (ITP) and hence splenectomy is considered curative in this condition. In spite of this, non-operative treatment has been advocated for ITP at least till such time that remission is not achieved [20].

Red cell abnormalities such as spherocytosis, elliptocytosis, pyruvate kinase deficiencies presenting with anaemia, cholelithiasis and leg ulcer respond well to splenectomy. However, it should be avoided in children below 5 years of age to avoid OPSI [21]. A cholecystectomy for gallstones should be done at the same time as the splenectomy [19].

Thalassaemia is an inherited disease resulting from reduced synthesis of a globin chain. This causes abnormal erythropoiesis and haemolysis. The result is enlargement of the spleen with hypersplenism. Due to persistent anaemia, patients require repeated blood transfusions. To avoid or reduce these, a splenectomy is done. To be effective, splenectomy should be done before the child is 6–8 years old [6, 9]. The risk of post-splenectomy thromboembolism and pulmonary hypertension is quite high in thalassaemia. On an average this complication occurs 8 years after splenectomy. In view of this, splenectomy should be avoided as long as possible even if the patients need increasing transfusion and iron chelation. The cause for the increased thrombosis is not known. Since the platelet count rises after splenectomy in some patients with thalasaemia some experts have advised the use of aspirin after surgery [15].

Sickle cell disease produces haemolysis and recurrent splenic infarction, which often leads to spontaneous asplenia (auto-splenectomy). Hypersplenism is quite common in this disease and it often needs splenectomy [22], because of a drop in haemoglobin level due to pooling of RBCs in the enlarged spleen. Splenectomy prevents further sequestration and helps the patient. However, this does not improve survival [23].

Disorders of platelet

Splenectomy for thrombocytopenia is a time-tested procedure and is the most effective means of treatment for it. It is effective because the spleen in this disorder has a dual role: Production of antiplatelet antibody as well as removal of antibody-coated platelets. Splenectomy thus decreases the antibodies and antibody-coated platelets resulting in an increase in platelet count. However, one must remember that inspite of this effect, splenectomy cannot cure ITP because the spleen can only remove the antibody-coated platelets which reach the spleen. In its absence the antibody-coated platelets continue to remain in circulation and sequester in the liver. This is the reason why splenectomy is

not always effective. The result is dependent upon the sites of sequestration; if it is in the spleen alone the efficacy of splenectomy is quite high but if it is also in the liver the splenectomy may not be as effective [1, 24]. Hence, relapse of ITP can occur in 30 %–35 % of patients [20]. After failure of corticosteroid therapy, splenectomy has been shown to improve both immediate (70 %) and delayed (7 %) results. Accessory spleens must be searched for and removed for better efficacy as in other haematological conditions. Patients below 40 years of age do particularly well after splenectomy in ITP. Increased haptoglobin which binds to free haemoglobin after release from RBCs seems to correlate well with long term efficacy in a large number of patients (80 %) [25]. Attempts are being made to see if splenectomy can be avoided. It appears that rituximab is effective if it is started relatively early in the course of the disease [26].

Splenectomy is also done for Hodgkin's and non-Hodgkin's disease. Earlier it was done for the purpose of staging. With the advent of CT scan to accurately stage the disease this indication has become less important [27]. Currently it is done for suspicion of lymphoma, reticulosis or infitrative disorders. In addition, splenectomy for Hodgkin disease has been reported to have a high risk of secondary leukaemia [28].

Myelofibrosis is another condition for which splenectomy is sometimes done. It is also done for symptomatic splenomegaly or hypersplenism but does not increase survival in this condition [29].

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Chapter 8
Role of PET-CT in Hepatobiliary Diseases

Kalpa Jyoti Das and Rakesh Kumar

8.1 Introduction

Positron emission tomography (PET) in conjunction with computed tomography (CT) has an important role as a functional imaging technology in mainstream oncology. The advantage of PET-CT as a one-stop shop in the diagnosis, staging, and monitoring of response and recurrence in various carcinomas has led to an increase in requests for this imaging modality. The cornerstone of PET-CT currently is flurodeoxyglucose (18F-FDG), a fluorinated analog of glucose, which mirrors the phosphorylation of the glucose pathway, but gets trapped inside the cells, as it is incapable of being metabolized further. Cancer cells have a high level of glucose metabolic activity and this forms the basis for the use of 18F-FDG PET-CT in oncology. There is increasing evidence of the usefulness of PET-CT in the assessment of hepatobiliary and pancreatic masses. We review the role of PET-CT in the evaluation of benign and malignant hepatobiliary diseases.

8.2 Role in the Evaluation of Hepatic Metastasis

Metastatic liver lesions account for more than 95 % of malignant liver disease, being more common than primary liver cancer [1]. Colorectal, breast and lung cancers are the most common cancers which metastasize to the liver (Fig. 8.1) [2]. Ultrasonography is the most commonly used imaging modality to diagnose metastatic liver disease. It is cheap and widely available. However, it is operator dependent and has a limited

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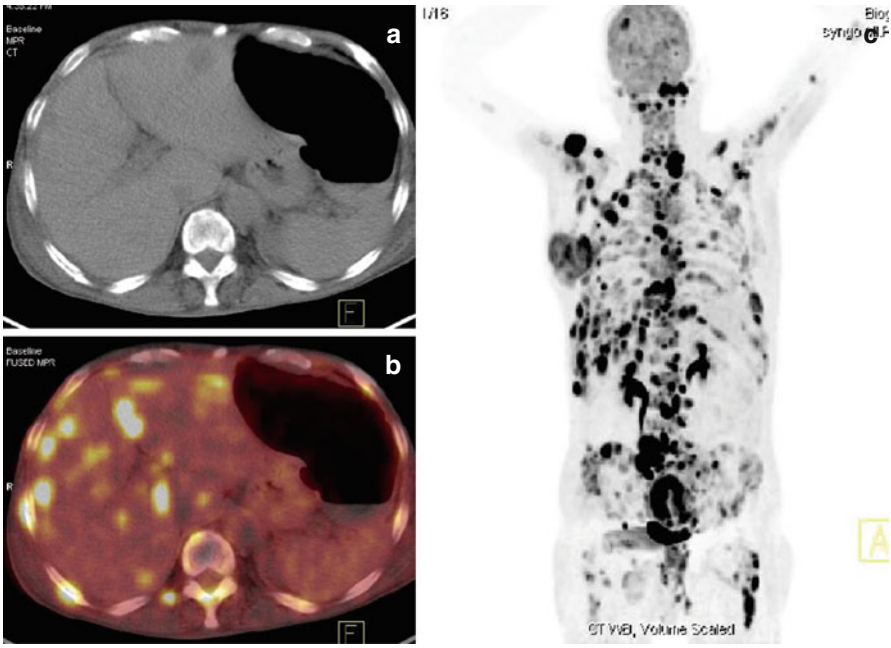

Fig. 8.1. PET/CT in a 49-year-old man with rectal adenocarcinoma revealed multiple hypodense lesions in CT (**a**) with corresponding increase in FDG uptake in the fused PET-CT images (**b**) The maximum intensity projection (MIP) images (**c**) showed extensive nodal, skeletal and bilateral lung metastases

role in obese patients. Although multiphase contrast enhanced computed tomography (CECT) remains the most sensitive technique, for the detection of metastatic lesions, there is growing evidence that 18F-FDG PET-CT has sensitivity equal to or superior to that of CECT [1]. Liver metastases are highly FDG avid enabling a high detection rate as corroborated by Lai et al. [3] who reported a sensitivity of 94 % for detecting hepatic metastases. Also D'Souza et al. [4] showed the superiority of PET-CT over CECT in the detection of untreated hepatic metastases with a sensitivity and specificity of 97 % and 75 %, respectively. Grassetto et al. [5] found that FDG PET-CT had an influence on the staging and selection of candidates for resection of liver metastasis. Fernandez et al. [6] reported the median 5-year overall survival was 58 % for preoperative FDG PET compared to 30 % after conventional imaging. Magnetic resonance imaging (MRI) has higher sensitivity for detection of liver lesions as compared to PET-CT but has lower specificity.

Veit et al. [7] showed 18F-FDG PET-CT to be more accurate than CECT in surveillance after radiofrequency ablation (RFA). Regional therapy to the liver metastases by chemoembolization can also be monitored with FDG PET imaging [8, 9]. In evaluation of FDG PET in colorectal liver metastases, Findlay et al. [10], showed that the responsive lesions had a lower tumour-to-liver ratio and lower standardized uptake values (SUVs) after 4–5 weeks of chemotherapy with fluorouracil. Langenhoff et al. [11] prospectively monitored 23 patients with liver metastases

following RFA and cryoablation and found that FDG-PET had a significant impact in measuring treatment efficacy. They also found that FDG-PET detected recurrences earlier than conventional diagnostic modalities.

Wong et al. [12] compared FDG PET imaging, with CT and MRI in monitoring the therapeutic response of liver metastases to 90Y-glass microspheres and found that changes in FDG uptake correlated better with the changes in serum levels of carcinoembryonic antigen (CEA) than CT and MRI.

8.3 Role in Hepatocellular Carcinoma (HCC)

The diagnosis of HCC relies heavily on ultrasound followed by CT, MRI and/or liver biopsy. The role of FDG-PET-CT is limited in HCC because of the relatively higher physiological FDG uptake and variable differentiation of tumour cells. FDG uptake in HCC is variable due to varying degrees of activity of the enzyme glucose-6-phosphatase in these tumors [13, 14], thereby limiting it's application in evaluation of intra-hepatic HCC [15]. The sensitivity of FDG PET for HCC is modest at 30 %–50 %, but has a higher sensitivity for other hepatobiliary primary and metastatic tumours to the liver [16, 17]. Bohm et al. [18] compared PET with ultrasound, CT and MRI, and found the sensitivity and specificity of PET superior to ultrasound and CT but not to MRI. The important advantage of PET scan consisted in the detection of extrahepatic tumour (64 %). Wudel et al. reported a sensitivity of 64 % for FDG PET in the detection of HCC [19]. Torizuka et al. [20] reported a significant correlation between the kinetic rate constant and SUV and the grade of tumour. A higher uptake and SUV was observed in high-grade HCCs compared to low-grade HCCs. Khan et al. [16] also concluded that PET imaging helps in assessing tumour differentiation and may be useful in prognostication of HCC.

One advantage of PET in primary HCC that accumulates FDG is its ability to detect unsuspected regional and distant metastases which may be indeterminate or missed on conventional CT (Fig. 8.2). Chua et al. [21] in a comparative study of 18F-FDG PET-CT versus CECT in the detection of metastatic liver disease reported a sensitivity and specificity of 96 % and 75 %, and 88 % and 25 %, respectively. In a subgroup analysis of their data, Chua et al. reported 94 % sensitivity and 75 % specificity of 18F-FDG PET-CT in the colorectal carcinoma group while CECT had 91 % sensitivity and 25 % specificity. In the non-colorectal group 18F-FDG PET-CT showed 98 % sensitivity and 75 % specificity while CECT had 85 % sensitivity and 25 % specificity. Sugiyama et al. [22] in their study reported a high detection rate of 83 % for metastases larger than 1 cm compared to 13 % for lesions equal or less than 1 cm. Seo et al. [23] demonstrated that the SUV and tumour to non-tumour ratio (TNR) were significantly higher in poorly differentiated HCCs than in well-differentiated and moderately differentiated HCCs. Inversely the percentage of P-glycoprotein (P-gp) positive area was significantly higher in well-differentiated HCCs than in poorly differentiated and moderately differentiated HCCs. The overall and disease-free survival rates were significantly lower in the high TNR group than in the low TNR group. In multivariate analysis, a high alpha-foetoprotein level and high TNR were independent predictors of postop-

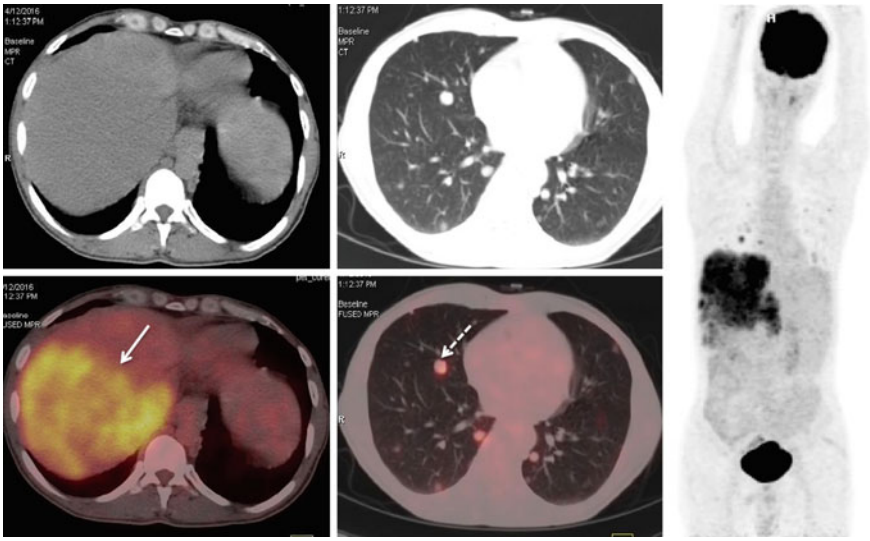

Fig. 8.2. A 42-year-old man with hepatocellular carcinoma. PET/CT for staging revealed a primary tumour in the liver (*white arrow*) with bilateral lung metastases (*white dashed arrow*), thereby upstaging the disease.

erative recurrence and overall survival. Khan et al. [16] also showed that well differentiated and low tumour grade HCCs had lower activity on PET. All these findings suggest that tumours exhibiting high FDG activity may be associated with more aggressive tumours and are indicative of poor prognosis.

RFA is used for the treatment of focal hepatic tumours. RFA often poses difficulty in assessing the completeness of tumour ablation. Dierckx et al. [24] in their review of literature support the notion that FDG PET performed early after RFA provides additional information about the efficacy of local tumour ablation by differentiating post-treatment changes from a residual or recurrent malignant tumour. Anderson et al. [25] found that FDG-PET was superior to anatomical imaging in the surveillance of patients treated with RFA for malignant hepatic tumours. 18F-FDG PET detected recurrent tumours at the ablation site or new metastases more often than conventional CT and MRI. Paudyal et al. [26] reported that 18F-FDG PET could detect recurrence earlier in patients with HCC treated with RFA, as compared with CT. Zhao et al. [27] evaluated the efficacy of transcatheter arterial chemoembolization (TACE) combined with RFA in 13 patients with HCC by FDG PET-CT and found that FDG PET-CT detected residual disease in 10 of 11 positive cases and hence was more accurate than CT alone (detected only five cases) in the detection of recurrent intrahepatic HCC (Fig. 8.3).

Several studies have suggested a potential role for FDG-PET in assessing the prognosis of HCC. Paudyal et al. [28] observed that the prognosis of patients correlated with the intensity of SUV uptake in HCC. The overall survival in patients with SUV ≥ 2 was significantly worse than in those with SUV <2 ($p = 0.005$ and $p = 0.03$), respectively. Similarly, Seo et al. [23] found that in patients with HCC

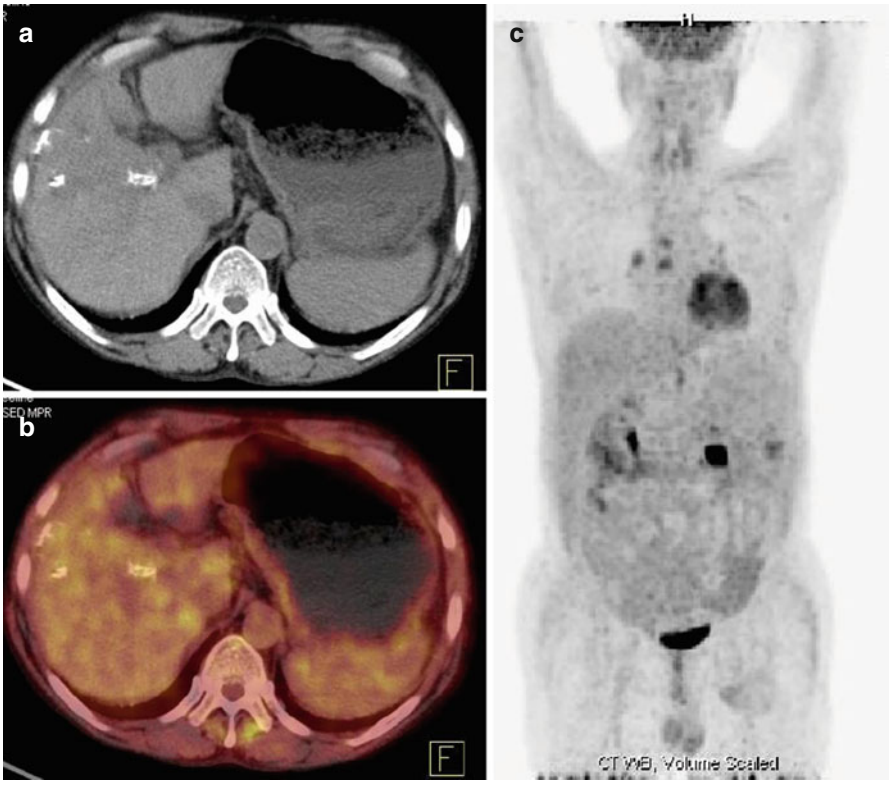

Fig. 8.3. A 55-year-old man, after transarterial chemoembolization of a hepatocellular carcinoma with alpha foetoprotein level of 14.6 ng/ml. CT (**a**) showed an ill-defined hypodense lesion with multiple calcific areas and PET-CT (**b**) showed mild FDG uptake in the region suggestive of minimal residual disease. MIP (**c**) did not reveal any distant metastases

who underwent a curative resection, a high T/N ratio was an independent predictor of postoperative recurrence and poor survival. Another study of 59 patients with HCC who underwent orthotopic liver transplantation and were followed up for more than 1 year showed that 18F-FDG PET was an independent and significant predictor of recurrence-free 3-year survival [29].

8.3.1 Limitations

Expression of hexokinase and glucose-6-phosphatase is highly variable in HCC and depends on the degree of tumour differentiation leading to a variable FDG uptake masking the tumour from the normal liver parenchyma, accounting for poor detection rates reported in a few studies [16, 18]. Alternative tracers such as 11C-acetate [30] and 18F-fluorocholine have been explored to improve the detection of these lesions.

Well-differentiated HCCs negative on 18F-FDG demonstrated an uptake with 11C-acetate, while poorly differentiated HCCs tend to preferentially accumulate FDG. Moderately differentiated HCCs show a mixed affinity in various parts of the tumour between the two tracer molecules [31]. Though at present, only a few studies have compared 18F-fluorocholine PET-CT and 18F-FDG PET-CT, the results suggest improved accuracy of 18F-fluorocholine PET-CT in detecting both intrahepatic and extrahepatic recurrences. In an assessment of dual-tracer (11C-acetate and 18F-FDG) PET-CT, Park et al. [32] found the overall sensitivities of FDG, 11C-acetate and dual-tracer PET-CT in detecting 110 lesions in 90 patients with primary HCC were 61 %, 75 % and 83 %, respectively. However, the short half-life of 11C-acetate limits its applicability only to centres with an on-site cyclotron. In the setting of chronic hepatitis C and cirrhosis, PET lacks utility for detecting primary HCC.

8.4 Role in Cholangiocarcinoma

Cholangiocarcinoma (CCA) is the second most common hepatobiliary malignancy after HCC. CCA may be intrahepatic or perihilar/extrahepatic based on its location within the biliary tree. Early diagnosis of CCA is challenging and is usually done with the help of ultrasound, and CT or MR cholangiography. Although FDG PET-CT has no major advantage over CECT, MRI or MR cholangiography, it is better for detecting metastases, both regional and distant. The prognosis remains poor due to difficulties in early diagnosis and late clinical presentation.

In a prospective study, Kim et al. [33] found the sensitivity and specificity of PET-CT in the detection of the primary tumour to be 84 % and 79 %, respectively. In a retrospective study of patients with CCA, Kluge et al. [34] found that FDG PET had sensitivity, specificity and diagnostic accuracy of 92 %, 93 % and 93 %, respectively. Another study by Jadvar et al. [35] found that FDG PET-CT had a sensitivity and specificity of 94 % and 100 %, respectively.

However, few studies have reported differences in detection rates for intrahepatic and extrahepatic tumours [33, 36]. The sensitivity is dependent on the morphological characteristics and location of the lesion, with nodular forms and peripherally located lesions being easier to detect than infiltrating and hilar lesions. Petrowsky et al. [37] reported a sensitivity of 93 % versus 55 % and specificity of 80 % versus 33 % in detecting intrahepatic versus extrahepatic CCA. Corvera et al. [36] proposed that the higher detection rate of intrahepatic CCA was due to their larger size compared to other types of CCA. Anderson et al. [38] found that the sensitivity for nodular type of CCA was significantly higher than for infiltrating type of CCA (85 % versus 18 %). These data suggest that FDG PET is accurate in predicting the presence of nodular CCA but is less effective for the infiltrating type.

Similar to HCC, studies have shown PET to be superior to CT in detecting distant metastases from CCA. In a prospective study, Kim et al. [33] found PET-CT had significantly higher accuracy than CT in the diagnosis of regional lymph nodes metastases (75.9 % versus 60.9 %, $p = 0.004$) and distant metastases (88.3 % versus 78.7 %, $p = 0.004$; Fig. 8.4). Seo et al. [39] also found FDG PET to be a more accurate and

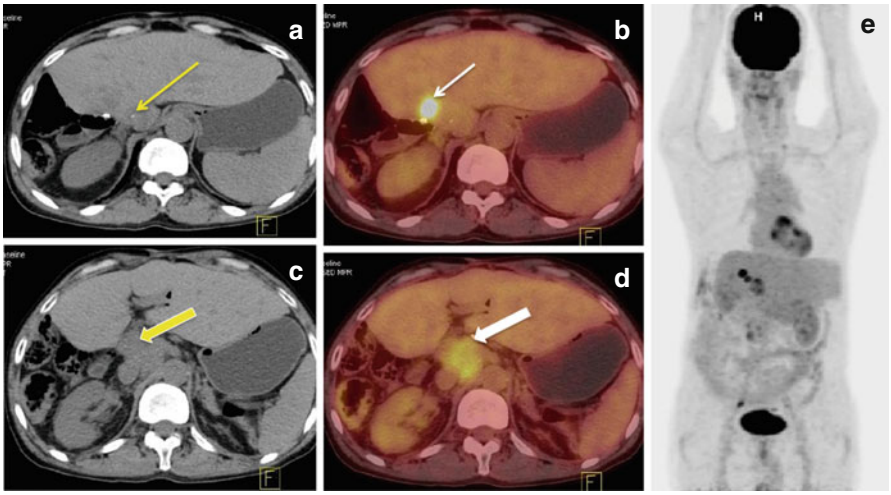

Fig. 8.4. PET-CT in a postoperative case of hilar cholangiocarcinoma revealed recurrent disease involving the liver (*yellow and white straight arrow*; **a**, **b**) and abdomino-pelvic lymph nodes (*yellow and white block arrows*; **c**, **d**)

specific for detection of lymph node metastases. The diagnostic accuracies of FDG-PET, CT and MRI for detection of lymph node metastasis were 86 %, 68 % and 57 %, and the sensitivities were 33 %, 43 % and 43 %, and the specificities were 100 %, 76 %, and 64 %, respectively.

8.5 Role in Gall Bladder Carcinoma

Gallbladder cancer (GBC) is a common cancer of the biliary system especially in northern parts of India. It is estimated that GBC is discovered incidentally in 1–3 % of cholecystectomies. Early diagnosis of GBC remains difficult, as these tumours are often asymptomatic. Though ultrasound and CT are most commonly used for the detection of GBC, these may fail to distinguish malignant from benign gallbladder disease. Radical surgical excision of the tumour and local lymph nodes with an R0 resection remains the most effective tool in the management of patients with gallbladder cancer. Surgery does not offer any survival benefit in patients with distant metastasis. When GBC is suspected and detected before surgery, it is often because the tumour is already locally advanced or has metastasized. The prognosis for GBC remains poor with a 5-year survival rate of 15–20 % [40].

Very few studies have assessed the role of FDG PET-CT in GBC; the reported sensitivity for detection of GBC is 75–100 % [37, 40–42]. Shukla et al. [41] in their study to assess the role of 18F-FDG PET-CT prior to radical resection for incidental GBC found a slightly better accuracy (91.6 % versus 87.5 %) than multi-detector (MD) CT in determining tumour resectability in patients without distant metastases. Studies have also supported the potential value of PET in detecting distant metasta-

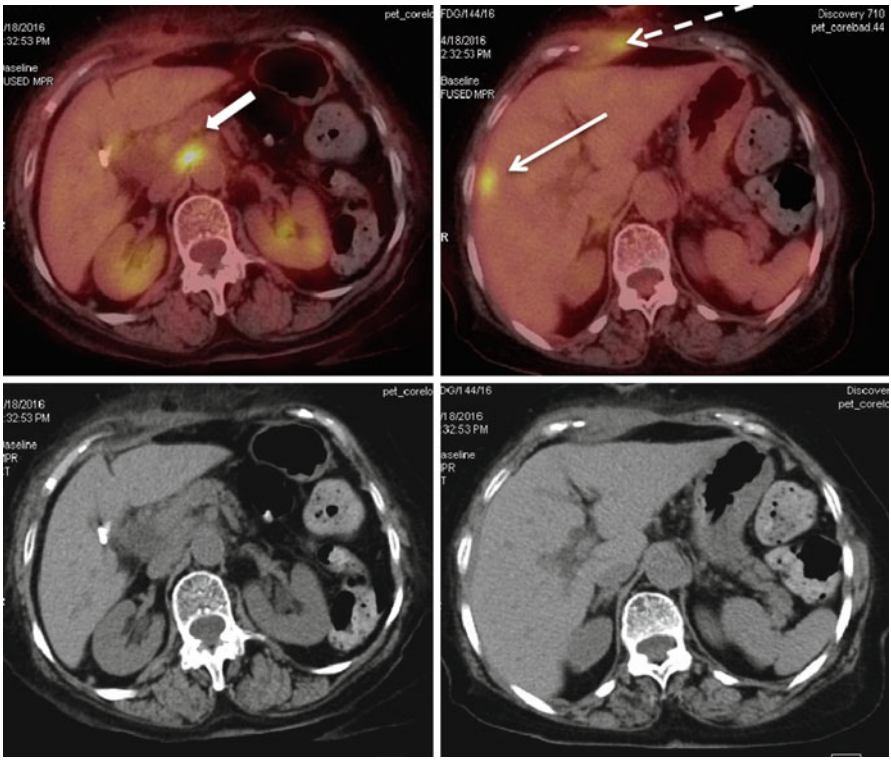

Fig. 8.5. A 73-year-old lady with gall bladder carcinoma following cholecystectomy. PET-CT (*upper row*) and CT (*lower row*) revealed FDG uptake at the port site (*dashed arrow*), corresponding to the soft tissue thickening seen in CT with FDG avid liver (*straight arrow*) and peripancreatic lymph nodes (*block arrow*)

sis. Petrowsky et al. [37] found PET-CT to be valuable in detecting unsuspected distant metastases, which were not diagnosed by standard imaging; all distant metastases (12/12) were detected by PET-CT, but only 3/12 by CECT. Anderson et al. [38] detected metastases in 50 % of patients with GBC. PET-CT led to a change in stage and treatment in 23 % of patients with GBC [36]. Oe et al. [42] studied 12 patients to distinguish between malignant and benign gall bladder wall thickening and reported a sensitivity of 75 % and specificity of 100 % of PET for the diagnosis of GBC—4 of 12 patients with gall bladder wall thickening on conventional imaging showed FDG uptake, and three of those were subsequently found to have GBC, whereas all the PET negatives were diagnosed to have cholecystitis.

PET-CT has been shown to be helpful in identifying recurrence when CT failed to differentiate scar tissue from malignant recurrence [43–45]. Kumar et al. reviewed 62 PET-CT studies in 49 patients with GBC with suspected recurrence, and found that PET-CT had a sensitivity of 97.6 % and specificity of 90 % in detecting tumour recurrence (Fig. 8.5) [45]. Locoregional disease was seen in 16 (37.2 %) PET-CT studies, distant metastases in 13 (30.2 %), and both locoregional disease and metas-

tasis in 14 (32.5 %) studies. PET-CT showed a better specificity than conventional imaging for detection of recurrence of GBC. Studies have also supported the prognostic impact of PET-based staging of GBC. Butte et al. [44] studied 32 patients with incidental GBC and found a significant difference in the mean survival of patients with negative, locally-advanced and metastatic findings on PET-CT (13.5 versus 6.2 versus 4.9 months, respectively).

8.5.1 Limitations

Studies have shown poor sensitivity for detecting regional lymph node metastasis in GBC. Petrowsky et al. [37] found regional metastases using PET in only 12 % of patients. Overall, the evidence supporting the use of PET in GBC is still limited.

8.6 Role in Pancreatic Adenocarcinoma

Pancreatic adenocarcinoma accounts for about 85 % of pancreatic cancer. Surgical resection remains the primary curative option but is possible in around one-fifth (20 %) of new cases. Surgeons often underestimate the extent of disease and resectability. Although CT scan helps in determining resectability, surgery has the ultimate say in successful removal of the tumour without damaging adjacent tissues. Thus imaging modalities improve staging of pancreatic cancer, thereby avoiding non-therapeutic exploratory surgery. PET scan has of late shown encouraging results in pancreatic cancer.

Studies have reported that PET has moderately higher sensitivity of detecting pancreatic cancer (84–97 %) compared to CT (76–80 %) [46, 47]. Henrich et al. demonstrated a comparable sensitivity (89 %) to CT [48]. Schick et al. [49] showed that endoscopic ultrasound (EUS) had a slightly lower sensitivity than PET in detecting pancreatic malignancies. However, DeWitt et al. [50] reported that EUS had a higher detection rate of 90 % for all pancreatic malignancies. Mertz et al. [51] in a comparative study of EUS and PET found EUS to be more sensitive in detecting vascular invasion and PET in detecting metastatic disease. Sendler et al. [52] in their study showed that PET accurately detected only 71 % of true pancreatic malignancies.

Another potential use of PET in pancreatic cancer is in differentiating benign from malignant cystic lesions and patients with chronic pancreatitis presenting with pancreatic head mass. Sperti et al. [53] during a 4-year period, studied 56 patients with a suspected cystic tumour of the pancreas and found that 18-FDG PET is more accurate than CT in identifying malignant pancreatic cystic lesions. The sensitivity and specificity for CT and 18-FDG PET in detecting malignant tumours were 94 % and 97 %, and 65 % and 87 %, respectively.

Besides the complementary role of PET in diagnosing primary pancreatic lesions, it is valuable for staging and surveillance of pancreatic cancer. Heinrich

et al. [48] showed that PET was able to detect more metastasis compared to CT. Bang et al. [47] showed that more than one-fourth of patients with pancreatic cancer had a change in the stage of the disease after PET identified distant metastases not previously seen on CT.

A study comparing pre- and post-treatment scans showed PET to be more accurate in determining tumour response [47]. In a small study of ten patients, PET demonstrated changes in the tumour after treatment not seen on CT or identified through tumour markers [54]. In a retrospective study by Sperti et al. [55] following up pancreatic cancer patients after resection, PET was more sensitive in identifying recurrence compared to CT. These studies suggest that PET has a role in monitoring after treatment of pancreatic cancer.

To summarize PET imaging alone has a reported sensitivity of 82–100 % and a specificity of 67–100 % in the diagnosis of pancreatic adenocarcinoma [56, 57].

8.6.1 Limitations

The main limitation of PET-CT is the lack of anatomical detail to determine surgical resectability, specifically vascular infiltration and invasion of surrounding organs. Another limitation may be in differentiating benign inflammatory processes from malignancies. Pancreatic adenocarcinomas have hypoxic tumour cores and this may result in poor uptake of 18F-FDG [58].

Strobel et al. [59], in considering pancreatic cancer resectability, found that PET was able to detect metastases to the liver, lung and bone but failed to detect arterial infiltration in all five patients with known tumour infiltration of the coeliac trunk or superior mesenteric artery. Sendler et al. [52] showed that PET falsely identified four of seven patients with chronic pancreatitis to have malignant disease. The potential for false-positive PET findings resulting from non-malignant pancreatic diseases should also be a subject for further research. In addition to the hypoxic tumour core [60] resulting in poor uptake of 18F-FDG, background inflammatory changes within the pancreas (such as chronic pancreatitis) may also result in increased 18F-FDG uptake, making detection of small pancreatic lesions difficult [61]. The paucity of relevant data suggests that PET-CT is not routinely used in the diagnosis or surveillance of pancreatic adenocarcinoma. Prospective data of PET-CT in detecting pancreatic lesions has shown it to be no worse than traditional investigative modalities such as endoscopic retrograde cholangiopancreatography (ERCP), EUS or abdominal US [49]. Interestingly, no comparison with conventional CT was made in the study but other prospective data do not suggest a major advantage for PET-CT compared with multi-row detector CT in the diagnosis which assesses cells undergoing active proliferation, staging or surveillance of pancreatic tumours [62]. 18F-fluorothymidine (FLT), which assesses cells undergoing active proliferation, has been proposed as a new radiotracer. There is one report of 18F-FLT being used in five patients with pancreatic adenocarcinoma compared with standard 18F-FDG PET-CT [63]. Despite the small numbers of patients, the results do not suggest any advantage over 18F-FDG.

8.7 Evaluation of Islet Cell and Other Endocrine Tumours of the Pancreas

Pancreatic neuroendocrine tumors (PNETs) are rare, accounting for 1–2 % of all pancreatic neoplasms. Most NETs, including islet cell tumours, express somatostatin receptors (SSTR) and can, therefore, be imaged effectively with somatostatin analogs (Fig. 8.6). The pancreas carries all the SSTR subtypes. [68]Ga DOTA-NOC PET-CT is increasingly used for NETs, also often found primarily in the pancreas. However, pancreatic tissue usually does not show significantly increased uptake of [68]Ga DOTA-NOC. The normal biodistribution of [68]Ga DOTA peptides in the pancreas appears as a faint, almost undetectable, uptake along the head, body and tail. Also the physiological uptake of DOTA-NOC

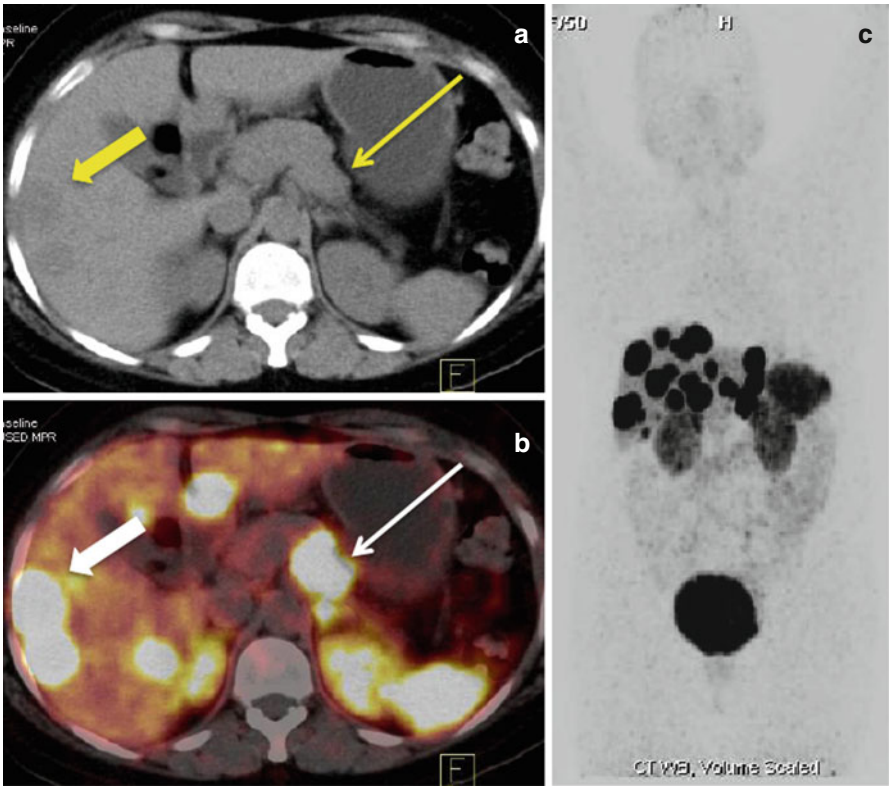

Fig. 8.6. A 50-year-old lady with pancreatic neuroendocrine tumour who underwent 68Ga DOTA-NOC PET-CT to asses response to chemotherapy. CT images (**a**) show a hypodense lesion in the body of pancreas and (*yellow arrow*) multiple hypodense lesions in the liver (*yellow block arrow*). (**b**) 68Ga DOTA-NOC PET-CT images revealed somatostatin receptor expression in the body of pancreas (*straight arrow*) and multiple liver metastases (*block arrow*). MIP (**c**) images showed multiple 68Ga DOTA-NOC uptake in the liver

predominantly in the uncinate process of the pancreas carries a risk of false-positive interpretation of a lesion in the uncinate process. Castellucci et al. [64] in a retrospective study found that increased uptake of tracer in the head of pancreas was stable over time (24 months) regardless of the intensity or shape of the uptake and inferred that this should be interpreted with caution and with reference to the specific clinical signs and symptoms. In the absence of any biochemical and clinical symptoms, they indicated that the diffuse or even focal uptake is likely due to physiological variability in SSTR expression by pancreatic endocrine cells and to variability in their anatomical distribution in the organ. Al-Ibraheem et al. [65] in their study also demonstrated that [68]Ga DOTA-TOC uptake in the head of the pancreas is a common finding and most likely represents a physiological condition, especially if the uptake is similar to the uptake in the liver. Therefore, any suspicion of a tumour in the head of the pancreas in [68]Ga PET-CT should be compared with other imaging modalities such as MRI and correlated with fine needle aspiration (FNA) biopsy. Partelli et al. in their study of combined [68]Ga DOTA-NOC and 18F-FDG PET-CT in the management of patients with PNETs found that routine use of combined [68]Ga-DOTA-NOC and 18F-FDG PET-CT does not significantly influence the treatment strategy in patients with PNET despite dual tracer functional imaging often revealing tumour heterogeneity [66].

8.8 Benign Liver Tumours

These are extremely frequent and mostly asymptomatic. The most common benign tumours are haemangiomas, focal nodular hyperplasia (FNH), hepatocellular adenomas and hepatic cysts. FDG PET is not routinely indicated in patients with benign liver lesions; however, it is useful as part of the imaging work-up in patients with a history of malignancy. Kurtaran et al. [67] showed that FNH had normal or even decreased accumulation of FDG compared with background liver tissue. Ho et al. [68] found that FNH can show mildly increased levels of 11C-acetate uptake. Haemangiomas showed poor FDG uptake [69], with an SUV ratio of less than 2. Tan et al. [70] found increased FDG uptake in non-neoplastic lesions such as cryptococcosis, abscesses and secondary inflammation from cholecystitis. Increased metabolic activity was also seen in some benign neoplasms such as hepatic adenomas and haemangioendotheliomas. Delbeke et al. [17] found that all benign hepatic lesions including adenoma and FNH, had poor uptake unlike liver metastases and HCCs which showed avid FDG uptake. Liver abscesses may be a source of false-positive findings on FDG PET. Hepatic hamartoma can be difficult to distinguish from metastasis on anatomical imaging, hamartomas do not show FDG accumulation; therefore, PET is useful to confirm a benign lesion.

8.9 Overall Limitations

18F-FDG is not a specific tracer. Not all FDG avid tissue is malignant. Infective, inflammatory and some benign lesions also reflect increased FDG uptake. Besides the lack of anatomical details, another limitation of stand-alone PET is the spatial resolution compared to CT and MRI. This restricts the role of PET in determining resectability of liver tumours. Also the integrated CT of PET-CT is of non-diagnostic quality, acquired at lower radiation to minimize exposure, decreases the image quality rendering it suboptimal for assessing structural details or vascular invasion. Thus, PET should be used to complement other structural imaging techniques. High rate of false-negative results may be seen in small lesions due to partial volume averaging, leading to underestimation of the uptake (for example small ampullary carcinoma, CCA of the infiltrating type and miliary carcinomatosis) or in necrotic lesions with a thin viable rim, falsely classifying these lesions as benign. Also because of the relative hypocellularity of mucinous adenocarcinoma the sensitivity of FDG PET for their detection is lower than for non-mucinous adenocarcinoma. Other false-negatives include differentiated NETs and HCC. The uptake of FDG in tumour is glucose dependent. Elevated serum glucose levels can result in decreased FDG uptake due to competitive inhibition. Besides the high incidence of glucose intolerance and diabetes in the Indian population and its association with pancreatic pathology represents a potential limitation of 18F-FDG in the diagnosis of pancreatic cancer. Inflammatory lesions such as acute or chronic pancreatitis, may show markedly increased FDG and can be erroneously marked as malignancies.

False positive interpretation of FDG activity can also be encountered after radiation therapy, along infected incisions, biopsy sites, drainage tubing and catheters.

8.10 Summary

The present literature suggests that PET-CT is not appropriate for making the initial diagnosis of most primary hepatobiliary and pancreatic tumours. However, FDG PET-CT has a promising role in whole-body staging, tumour grading, prognostication and surveillance in hepatobiliary malignancies. FDG PET imaging also appears helpful in differentiating malignant from benign hepatic lesions. FDG PET can be effectively used in differentiating post-therapy changes from recurrence. Integration of diagnostic CT with PET improves detection of lesions, better differentiation of physiological from pathological foci, and better localization of the pathological foci of metabolism translating into more optimal patient care. Also PET-CT fusion images can be used to guide procedures such as biopsy, surgery or planning for radiation therapy.

PET-CT has a high sensitivity in detecting highly FDG avid hepatic metastases and is superior to contrast enhanced CT. PET is not helpful in identifying HCC because of variability in FDG uptake, but has a prognostic role with aggressive tumours exhibiting high FDG activity. In addition PET-CT may be helpful in detecting extrahepatic disease which can impact therapeutic decisions. FDG PET-CT has no significant advantage over contrast enhanced CT, MRI or MR cholangiography in the diagnosis of primary biliary tumours; its advantage being limited to detecting metastases. PET also has a complementary role in diagnosing primary pancreatic lesions but has a higher sensitivity in identifying recurrence compared to CT. In conclusion, though PET has limited role in the initial diagnosis of primary biliary tumours, its sensitivity varying according to type and location of tumors, it has a definitive role in staging, prognostication, response monitoring and surveillance.

Editorial Comments

Surgery is being increasingly used in the management of various hepatobiliary diseases. Consequently, various imaging modalities including PET-CT are used to choose suitable patients (those without suspected or confirmed disease outside the scope of surgical treatment). Imaging is done for the diagnosis, staging, planning of multimodal therapy, assessment of response and surveillance of the disease. In the context of this article, PET-CT gives not only the morphology of the disease but also its physiological characteristics. The principles involved in PET are: (i) detection of positrons which a radiopharmaceutical releases (tracer); (ii) the tracer is bound to molecules involved both in health and disease; and (iii) quantitative detection of these molecules. Eighteen flurodeoxyglucose (18F-FDG) is the molecule used widely in clinical practice because it is taken up by all cells. Once it reaches the cells, it is metabolized by phosphorylation. Phosphorylated FDG is incapable of further metabolism and hence stays inside the cells, more in neoplastic than normal cells and this can be detected on a gamma camera. This image can be combined with CT images (PET-CT). Thus functional and morphological characteristics can be incorporated in a single scan. The advantage is that while PET alone may not accurately localize a lesion, a PET-CT can. The other advantage of PET-CT is that it is superior to CT for assessment of tumour response. This is because tumour reduction may not be apparent for some time after chemotherapy and hence CT may not detect any response. PET, on the other hand, by virtue of its functional character can show a reduction in size within 24 h [71]. Apart from this, PET-CT can detect occult secondary tumours not detected by a conventional CT.

For colorectal liver metastases

PET-CT is usually done for staging. It has the ability to detect disease outside the liver not detected by conventional imaging. This can prevent unnecessary abdominal exploration for liver resection. PET-CT can also identify liver lesions for local therapy (ablation or surgical) and tumour response to

chemotherapy. Comparative studies have shown that PET-CT scores over CT but MRI is better in detecting hepatic metastases [72]. Sometimes prior chemotherapy can reduce the sensitivity of PET-CT for detecting colorectal metastasis. This is due to a substantial decrease in metabolic activity within the tumour. The decreased SUV does not allow the lesion to be dectected [73]. PET-CT scan can often change the management strategy by avoiding laparotomy (for extrahepatic disease), guiding palliative chemotherapy or even allowing more extensive resection than contemplated [74]. For post-ablation surveillance also, PET-CT is more helpful than CT because following ablation a contrast enhancing rim is always seen in the periphery of the ablated area. This is difficult to assess by CT [7].

For hepatocellular carcinoma (*HCC*)
No more than 50 % of HCC are PET positive. This is because the normal liver like the malignant tumour has high glucose-6-phosphatase resulting in dephosphorylation of FDG which leaves the cell and enters the circulation and thus escapes detection [75]. To improve detection of HCC, other radiotracers such 11C-acetate and 18F-flurocholine are being used with promising results. The degree of differentiation of the HCC can be assessed by these newer techniques: well differentiated tumours are negative on FDG PET but positive with acetate PET. Poorly differentiated tumours have just the opposite features. Moderately differentiated tumours have a mixed uptake in various parts of the tumour between the two tracers [68]. Thus, dual tracer PET is likely to provide better imaging in HCC. Acetate has a short half-life and hence is used less frequently (only in centres which have their own cyclotron). Choline PET can solve this because of its longer half-life [76]. Since choline is present in all cell membranes it has a high 18F-flurocholine uptake [76]. HCC with a known rapid turnover of cells are particularly easy to detect with choline PET [76]. Except these newer developments, FDG PET has a very limited role in the management of HCC.

For gall bladder and biliary malignancy
The literature is rather sparse on this aspect. However, PET-CT has been shown to be better than CT but its superiority over MRI remains to be established. PET-CT has been shown to be better in terms of defining the primary lesion as well as detection of lymph nodal metastasis and distant disease. Intrahepatic cholangiocarcinoma [33] and gall bladder cancer are not better delineated by PET-CT [37]. PET-CT can be useful in differentiating benign from malignant hilar strictures [77].

For pancreatic lesions
Adenocarcinomas of the pancreas are hypoxic tumours. As a result uptake of FDG is poor and hence PET-CT is not very useful [78]. Furthermore, in the background of chronic pancreatitis, detection of foci of malignancy are difficult [61].

A new radiotracer, 18F-fluothymidine (18FLT) has been introduced but its utility, as of now, remains doubtful [63]. PET-CT has not been used much in pancreatic adenocarcinomas due to the above reasons. In one study PET-CT did not fair badly in comparison to ERCP and EUS [49]. Heinrich et al. [62] have also shown FDG PET-CT to be as good as CT in the diagnosis of pancreatic adenocarcinoma. The distinct advantage with PET-CT is detection of distant metastasis not detected by CT. It changes management, avoids unnecessary operation and thus decreases the cost significantly [48].

For cystic lesions of pancreas
One of the major problems of a cystic lesion of the pancreas is to determine whether the lesion is benign or malignant. Various diagnostic aids have been used to solve the problem. These include CT, MRI, EUS or laparoscopic ultrasound, cytological assessment of cyst fluid and estimation of tumour markers in the cyst fluid. To these, PET-CT can be added and has been shown to be more sensitive than conventional CT [79].

For NET of the pancreas
NETs can be functioning or non-functioning. Most functioning tumours present early even before they attain sufficient size for early detection by conventional imaging such as CT and MRI. Thus, functional imaging by PET remains the only modality to detect these tumours early. Apart from FDG, other tracers can be used such as C11 hydroxytroptophan, 18F flurodopamine, gadolinium-labelled somatostatin analogue, 11C hydroxyephedrine or 11C metomidate [58], Dodecane Tetra acetic Acid Na-Octreobid (DOTA NOC) and Dodecane Tetra acetic Acid Thy Octreotide (DOTA TOC). An analysis of the comparative efficacy of these tracers is not possible because not enough data is available. What can be reasonably argued is that PET-CT is more accurate than CT, MRI or even octreotide scan [80]. However, liver lesions are detected with equal sensitivity with both PET-CT and MRI [81].A newer development is fusion of MRI and PET [81] which has been shown to be more useful in the detection of liver, lymph node and bone metastasis than CT, MRI and PET-CT [81].

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Chapter 9
Hyperthermic Intraperitoneal Chemotherapy

Nikhil Gupta and Shivendra Singh

9.1 Introduction and Historical Perspective

Peritoneal metastasis in abdominal malignancies is associated with a dismal prognosis. In the past, it was considered inoperable and the patient was considered a candidate for palliative chemotherapy alone. The outcome of systemic chemotherapy is poor with the average survival being 6–8 months. With the introduction of newer agents including biologicals, survival of stage IV patients has increased from 6 months to as high as 22 months [1]. On detailed analysis of these studies, it has been found that the results of systemic chemotherapy were more profound in patients with liver or lung metastases. It was rarely effective in peritoneal carcinomatosis (PC) possibly due to the poor blood supply of the peritoneum. Moreover, this approach is associated with poor quality of life due to impending complications and is ineffective in improving survival. Surgery has been used as a palliative modality for PC for long. Extensive debulking for locally advanced ovarian cancers was described as early as the 1930s by J.V. Meigs [2]. The concept of 'debulking' was to reduce the tumour burden and eventually decrease the incidence of complications such as obstruction and perforation. He reported that in stages II and III ovarian cancers, residual tumour less than 1.6 cm was associated with better survival [3]. Another malignancy in which palliative surgery was used was pseudomxymoma peritonei (PMP) of appendiceal origin. The rationale behind debulking surgery in this group was that distant metastases were rare and the most important reason for morbidity and mortality was local disease causing bowel obstruction or perforation. In 1969, Alabama et al., showed improved survival with cytoreductive surgery (CRS) and adjuvant chemotherapy in patients with PMP. He introduced the concept of intraperitoneal chemotherapy by administering alkylating agents [4]. After this

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there was a sudden increase in trials trying to establish the role of intraperitoneal (i.p.) chemotherapy in these cancers. A trial on animals comparing intravenous (i.v.) and i.p. route of administration of cisplatin showed significantly higher intraperitoneal levels of the drug compared to i.v. levels [5]. In the 1970s and 1980s, multiple studies reported the use of intraperitoneal chemotherapeutic drugs administered at a concentration much higher than what could be safely administered intravenously. Most of the phase I and II trials showed efficacy of CRS and i.p. chemotherapy in ovarian tumours. The concept of whole body hyperthermia in reducing the tumour burden levels was utilized in peritoneal malignancies and machines were developed to instill hyperthermic intraperitoneal chemotherapy (HIPEC) [6]. Soon results of adequate CRS and HIPEC started coming in and surgeons realized that adequate cytoreduction is a must for the benefit of HIPEC. The pioneering work of Dr Paul Sugarbaker in the field of CRS and HIPEC for gastrointestinal malignancies gave a glimmer of hope for a select group of patients with peritoneal metastasis [7–9].

Although there is enough literature now to suggest that CRS and HIPEC is superior to systemic chemotherapy, it has not made its way into the routine management of stage IV cancers as most treating surgeons and medical oncologists still consider this strategy to be experimental. Moreover, the surgery is quite extensive with relatively high morbidity. Initially, a similar thinking governed the management of patients with liver metastasis from colorectal cancers. However, now surgery is considered the treatment of choice for resectable liver metastasis of colorectal origin with the aim of complete cure in selected subgroups of patients. Management of peritoneal surface malignancies requires a dedicated multidisciplinary team comprising of a proactive surgeon, medical oncologist, anaesthesiologist, radiologist and intensivist.

9.2 Rationale Behind CRS and HIPEC

There are three routes by which a malignancy spreads: blood, lymphatics and transcoelomic. The last one is responsible for PC. Usually PC can occur either due to exfoliation of cells through a tumour which has breached the serosa or during surgery. Thus it should be treated as local and not systemic disease. Unfortunately, systemic chemotherapy was considered by most as the treatment of choice for patients with peritoneal metastasis. With the latest drugs, the survival was up to 16–20 months [1]. One of the main limiting factors governing dosimetry and thus efficacy of systemic chemotherapy is haematological toxicity. In other words, the actual dose given intravenously is not as much as the dose one wants to give based on cytotoxicity studies, but rather the dose tolerated by the patient's haematological reserve.

In CRS with HIPEC, all the visible disease is removed (taking care of macroscopic disease) and chemotherapy is given at higher temperature intraperitoneally (taking care of microscopic disease). There are few drugs that have a high intraperitoneal and low plasma concentration when given intraperitoneally.

Moreover, the absorption into plasma is also slow thus giving more time for the anticancer drug to act on cancer nodules. This gives us an opportunity to give the maximal dose of chemotherapy to the tumour cells without any major effects on the haematological reserves. Another important characteristic that an i.p. drug should possess is its ability to cross the cancer nodules and act on them. It has been found in various studies on rodent models that drugs such as adriamycin have a limited penetration in tumour nodules; the maximum being up to 1–2 mm. This finding has a major impact on the premise on which the concept of CRS and HIPEC is based. An adequate CRS (defined as CC-0 or CC-1) is a must for HIPEC to work. This means that HIPEC would be effective only when the residual tumour size is less than 2.5 mm. Various clinical studies have established that completeness of CRS is one the most important factors affecting survival after HIPEC.

9.3 Rationale Behind Hyperthermia

The rationale of HIPEC is the synergistic cytotoxic effect of heat (ideally 42–43 °C) and the chemotherapeutic agent itself on tumour cells. Hyperthermia has anticancer activity. A temperature above 41 °C causes selective cytotoxicty of malignant cells by various mechanisms such as protein denaturation, impaired DNA repair and inhibition of oxidative metabolism. It causes vasodilatation with improvement in tumour oxygenation improving the effects of chemotherapeutic agents. Various rat models have shown that adding hyperthermia to doxorubicin increased its concentration in the peritoneum and doubled it in the small bowel thus confirming that heat increases local tissue concentration.

A study published in 2009 compared patients of PC with those receiving CRS and HIPEC to those receiving CRS and systemic chemotherapy. The 5-year survival was 51 % with CRS and HIPEC compared with 13 % for the non-HIPEC group [10].

9.4 Rationale Behind Bidirectional Chemotherapy

When i.v. chemotherapy is added during the HIPEC, it is known as bidirectional chemotherapy and is an important aspect of HIPEC in gastrointestinal malignancies. 5-fluorouracil (5 FU) when administered intravenously, rapidly diffuses into the peritoneal cavity where HIPEC fluid is present and stays there for a longer duration than it would have stayed in the plasma. Its metabolism is reduced within this compartment as the enzyme responsible for its metabolism is present in the liver. Thus, the HIPEC compartment acts as a storage reservoir for 5 FU and gives it longer duration to act on the cancer nodules compared to its i.v. administration. The time at which i.v. chemotherapy should be started during HIPEC is a matter of debate and further studies are required to define it.

9.5 Rationale Behind Increasing Intra-abdominal Pressure

Raising the intraabdominal pressure has been postulated to increase the concentration of the chemotherapeutic drug in the tumour nodules especially of cisplatin and doxorubicin. Its utility is still not proven except in cases of malignant ascites of unknown aetiology where laparoscopic HIPEC is given at 10–15 mmHg.

9.6 Role of Type of Carrier Solution and Vasoactive Agents

Various carrier solutions such as hypotonic, isotonic and hypertonic solutions for delivery of chemotherapeutic agents inside the abdominal cavity have been studied. An ideal solution is one which increases the exposure of tumour nodules to chemotherapeutic drugs. In the setting of HIPEC, hypotonic solutions were found to be associated with a higher incidence of peritoneal bleeding and thrombocytopenia. In early postoperative intraperitoneal chemotherapy (EPIC), a high molecular weight solution is preferred as it maintains artificial ascites and thus drug concentration for a longer duration.

Vasoactive agents have been used both intraperitoneally and intravenously to increase the peritoneal fluid concentration of chemotherapeutic agents. However, there is no consensus yet on this.

9.7 Open, Semi-closed or Closed Techniques

Various techniques of administering HIPEC have been proposed: open, semi-closed and closed. In the open technique, the hyperthermic solution is administered in the open abdomen and it is manually stirred with the aim to uniformly distribute the hyperthermic solution to all quadrants and the whole of the peritoneal surface. However, there is a theoretical risk of exposure of the operating personnel to the chemotherapeutic drugs. Till date, no study has proven this risk in caregivers. Another problem with the open technique is difficulty in maintaining the desired temperature of the hyperthermic solution. In the semi-closed technique, the abdomen is covered with a plastic sheet and a small opening is made through which the surgeon manually manipulates the solution. In the closed technique, the abdomen is closed and then HIPEC administered. This has the benefit of achieving the desired temperature earlier, it is safer for the caregivers but may result in non-uniform distribution of the HIPEC solution. Till date no trials have confirmed the benefit of one technique over the other.

9.8 Types of Intraperitoneal Chemotherapy Regimens

9.8.1 Neoadjuvant Intraperitoneal and Intravenous Chemotherapy

This technique is used in patients in whom PC is diagnosed at staging laparoscopy. Patients are given both i.p. and i.v. chemotherapy with the aim to reduce or eradicate PC, checking the tumour biology and preventing dissemination of the disease to the extra-abdominal spaces. Definitive surgery is done after 3–4 cycles of such therapies. Both radiological and clinical responses have been shown with this technique. However, it is not without complications. First, there might be adhesions present due to prior surgical intervention and these might prevent uniform distribution of drug. Moreover, extensive adhesive response from this technique might render future definitive CRS difficult and increase morbidity and mortality.

9.8.2 Intraoperative HIPEC and Intravenous Chemotherapy

This is the most widely used technique. Here i.p. chemotherapy is given at the time of definitive surgery and is added after CRS.

9.8.3 Early Postoperative Intraperitoneal Chemotherapy (EPIC)

EPIC is usually given immediately after definitive surgery. Drains are placed during the primary surgery and chemotherapy is given through the drainage catheters usually from postoperative days 1–5. Drugs are given through one drain over 1 h and all the drains are clamped for the next 23 h. The position of the patient is changed for effective mixing of the drug in all the quadrants of the abdomen. The drug is allowed to flow out of the drains over the next one hour. This process is repeated for the next 4 days. Since adhesions have not formed, it allows for uniform distribution of the drug throughout the peritoneal cavity and prevents entrapment of cancer cells inside the fibrin deposits.

9.8.4 Adjuvant Intraperitoneal and Systemic Chemotherapy

Very few studies have been done using this approach. It is usually used in the setting of incomplete cytoreduction in ovarian tumours. Patients are given i.p. chemotherapy through a port inserted at the time of the first surgery. Additional systemic chemotherapy is also given. This technique can also be used as a bridge between primary surgery and a definitive or second look surgery later.

9.9 Role of Laparoscopy

CRS and HIPEC require an abdominal incision from the xiphisternum to the symphysis pubis. The present literature suggests that nearly 50 % patients are deemed unresectable following exploratory laparotomy done with the aim of doing CRS and HIPEC for PC. The main reasons for incomplete cytoreduction are extensive small bowel serosal and mesenteric deposits, pelvic disease and hepatoduodenal disease. A negative laparotomy causes a lot of morbidity to the patients and also delays administration of systemic chemotherapy. The present staging modalities such as CT and PET scan have poor sensitivity in detecting peritoneal disease especially on the small bowel mesentery or serosal surfaces. Moreover, PET scan is a poor modality to identify metastasis from mucinous tumours. Various studies have shown the benefit of staging laparoscopy in identifying PC in gastrointestinal malignancies such as carcinoma gall bladder and carcinoma head of pancreas. Staging laparoscopy when used preoperatively to assess the extent of disease in established PC has shown a positive predictive value of 82.9 % in predicting complete cytoreduction [11]. This has a great impact in reducing the number of negative laparotomies. The maximal benefit has been in finding unresectable small bowel disease or extensive pelvic disease.

However, the limitations of laparoscopy in this subset of patients are that most patients have undergone prior surgery, sometimes more than once. Thus there are intraperitoneal adhesions which prevent complete visualization of the small bowel. Moreover, disease in the hepatoduodenal ligament is also difficult to see during laparoscopy. Despite these limitations, staging laparoscopy should be considered before contemplating CRS and HIPEC wherever possible.

9.10 Procedure of CRS and HIPEC

After staging laparoscopy is done to assess the extent of disease on the small bowel and in the hepatoduodenal ligament, the abdomen is entered through a long midline incision from the xyphoid process to the pubic symphysis. The presence of macroscopic tumour deposits is recorded in 13 abdominal regions according to the peritoneal carcinomatosis index (PCI) chart. The procedure involves removal of the peritoneum from all the five regions—right and left hemidiaphragm, right and left paracolic gutters and pelvic peritoneum (Fig. 9.1). All the disease involving the small bowel and its mesentery is also removed. This may require resection and anastomosis of the small bowel. In order to achieve complete cytoreduction, adjacent organs may need to be resected such as anterior resection of the rectum for deposits on the sigmoid colon and in the pouch of Douglas, distal gastrectomy, cholecystectomy, splenectomy and various types of colectomies. The other components of CRS are excision of both the greater and lesser omentum and removal of the Glissonian capsule (in case of involvement by a mucinous tumour). The objective of CRS is to leave no macroscopic tumour behind (CC-0; complete

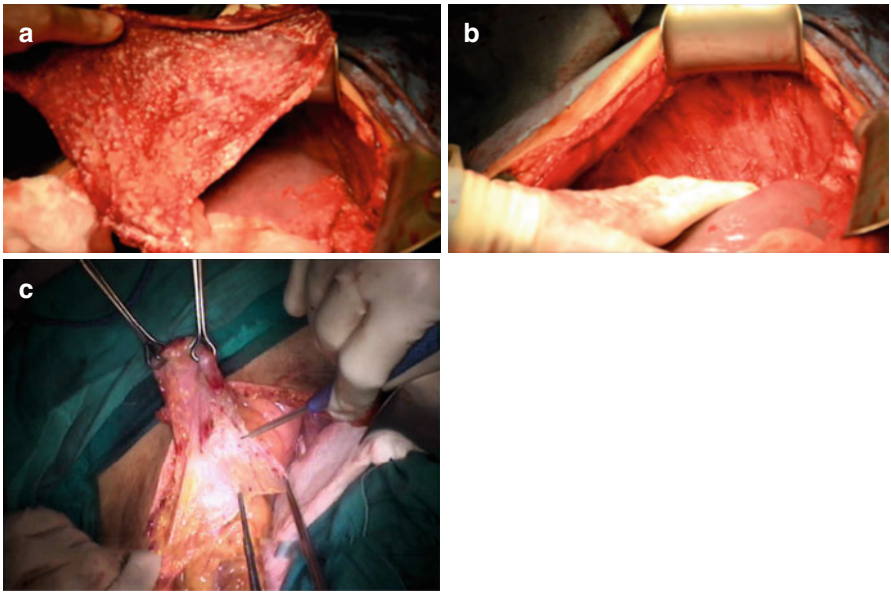

Fig. 9.1 (**a**) Patient of pseudomyxoma peritonei with extensive diaphragmatic deposits; (**b**) after complete peritonectomy; and (**c**) pelvic peritonectomy of the same patient

cytoreduction); but, if this cannot be achieved, attempts are made to leave no residual tumour exceeding 2.5 mm in thickness (CC-1) as previously discussed. The main benefits of HIPEC are in patients in whom CC-0 and CC-1 are achieved [12]. However, some investigators have shown some benefit of HIPEC for CC-2, although this is not proven. The limiting factor for complete cytoreduction in most cases is extensive small bowel involvement as this would require multiple resection and anastomoses. Another factor which might prohibit complete cytoreduction is extensive involvement of the hepatoduodenal ligament.

HIPEC is carried out according to the open or closed technique. We prefer the closed technique using the Belmonte machine (Fig. 9.2). Perfusion is started with a minimum of 2 l of isotonic dialysis fluid, with an inflow temperature of 43–44 °C. As soon as the temperature in the abdomen is stable above 40 °C in all the quadrants, the chemotherapeutic agents are added to the perfusate and circulated for 90 min. Drugs used for i.p. chemotherapy depends upon the primary disease. Even the duration of HIPEC depends on the type of drug used (30 min for oxaliplatin and 90 min for doxorubicin and mitomycin C). The position of the patient is changed to allow for complete mixing of the drug in the whole abdomen. In the open technique, the whole of the drug is mixed manually so that it comes in contact with all the peritoneal surfaces. The patient is also given i.v. chemotherapy to increase the effect of i.p. chemotherapy (bidirectional chemotherapy). Before closing the abdomen, drains are inserted in all the five peritonectomy regions for EPIC.

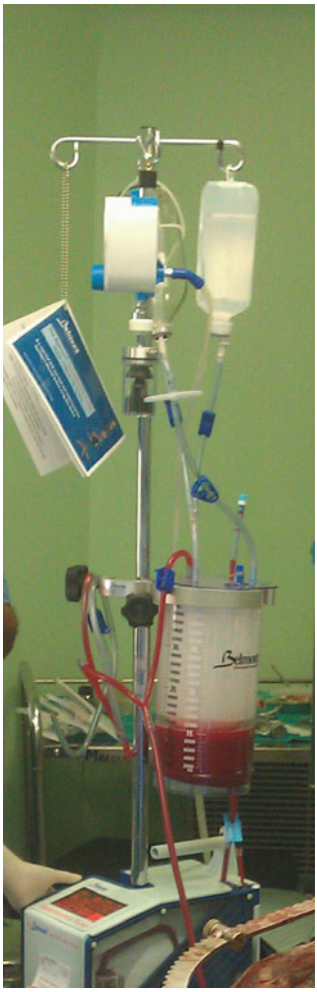

Fig. 9.2 Belmonte machine to administer hyperthermic chemotherapy

9.11 Drugs Used in HIPEC

9.11.1 Appendiceal Tumours and PMP

CRS and HIPEC is the standard of care for PMP tumours. Mitomycin C (MMC) is the drug to be used in these tumours. The side-effects of MMC are mainly neutropenia, bowel perforation and anastomotic dehiscence [5]. 5 FU is used both in the setting of bidirectional chemotherapy and in EPIC. Other drugs used in PMP are oxaliplatin, doxorubicin, taxanes and platinum compounds.

9.11.2 Colorectal Neoplasms

The most commonly used drug is MMC. However, the European literature is replete with the use of oxaliplatin in HIPEC. Oxaliplatin has a lower area under the curve (AUC) and thus it is more easily absorbed systemically compared to MMC. Thus, the dwell time of this drug is only 30 min compared to MMC whose dwell time is 90 min. 5 FU is used as a bidirectional agent and as an EPIC agent in patients with colorectal cancer.

9.11.3 Gastric Cancer

MMC and cisplatin are the most commonly used drugs for gastric cancer with PC. Cisplatin is also used for ovarian malignancies. It has a low AUC, and is nephrotoxic and ototoxic. Metal binding agents such as sodium thiosulphate and amifostine are used to prevent tubular damage. Other drugs used are taxanes.

9.11.4 Malignant Peritoneal Mesothelioma

This is a very aggressive disease. The only survival benefit is with CRS and HIPEC. The most commonly used drugs are MMC, doxorubicin and cisplatin. Taxanes are used as EPIC agents. Doxorubicin has a good antitumour profile when used intraperitoneally as it has a high AUC ratio. However, when used in higher doses it causes extensive peritoneal inflammatory reaction which may lead to bowel obstruction. Thus it is used in low doses (15 mg/m^2). Because of its inflammatory peritoneal reaction, it is also commonly used in patients with intractable malignant ascites with good results.

9.12 Monitoring

During HIPEC, the urine output should be monitored and should be more than 1 ml/kg/h. Care should be taken to avoid spillage of the chemotherapeutic drugs. Patients may be considered for parenteral nutrition during the early postoperative days as feeding orally would be delayed due to prolonged ileus post-HIPEC. After EPIC, patients are more prone to leucopenia. White cell counts should be monitored daily and if required granulocyte-macrophage colony-stimulating factor (GM-CSF) should be used. We use GM-CSF at the start of a decrease in the leucocyte count.

9.13 Complications of CRS and HIPEC

CRS with HIPEC is an extensive surgery involving surgical resection and introduction of chemotherapeutic drugs into the peritoneal cavity. Both components add to the morbidity of the surgery.

The overall morbidity and mortality of CRS and HIPEC is 22–34 % and 0.8–4.1 % [13]. Various series have shown that the mortality varies according to the primary disease. The overall complications associated with CRS and HIPEC are haematological toxicity especially neutropenia, digestive fistulas, pneumonia, postoperative bleeding, septic infections such as intra-abdominal abscess, wound infection and renal insufficiency. Respiratory complications are 6–14 %, gastrointestinal complications including digestive fistulas occur in 8–18.2 %, renal 1–10 % and haematological 6–20 %. Various factors associated with higher morbidity and mortality are old age, hypoalbuminaemia, poor performance status, high PCI score, high grade histology of tumour, associated bowel, diaphragmatic and pancreatic resections and the surgeon's experience. A high PCI score has consistently been associated with higher morbidity. The reason for this association may be the need for extensive resections, associated bowel resection and poor general condition due to advanced disease. Surgeon experience has also been cited as an important factor determining the morbidity and mortality. One study showed that the complications in the first 70 cases were much higher compared to the next 70 cases (30 % versus 10 %) [14]. The learning curve of this procedure is not merely due to technical improvements but improved patient selection also plays an important role [15].

Haematological toxicity is a common problem after HIPEC especially after the use of MMC. At our centre, neutropenia occurs in around 40 % of patients. Therefore, we closely monitor the leucocyte count especially after the third postoperative day.

Pulmonary complications are a major concern after CRS especially after subdiaphragmatic peritonectomy. It was hypothesized that after subdiaphragmatic peritoneal stripping, the incidence of leakage of HIPEC fluid inside the pleural space increases. This increases the incidence of postoperative pneumonia, pleural effusion and respiratory distress. Although this theory has been quashed in a review by Preti et al. [16], the only factor responsible for postoperative pulmonary complications was excessive blood transfusion. According to Muller and colleagues, the incidence of pulmonary complications can be decreased by restricting intraoperative fluids, intensified management of hyperglycaemia and reducing blood loss [17].

Oxaliplatin is associated with a higher incidence of intra-abdominal bleeding and mild hepatotoxicity and cisplatin is associated with a higher incidence of nephrotoxicity.

9.14 CRS and HIPEC for Colorectal Cancer

PC is a frequent occurrence in patients with CRC (upto 8 % at the time of primary surgery and upto 25 % at the time of recurrent CRC) [18]. Systemic chemotherapy alone is associated with a mean survival of 8–10 months. Complete CRS and HIPEC

is associated with a significant increase in survival in patients of PC from CRC. Verwaal et al. did a randomized controlled trial comparing systemic chemotherapy (5 FU and leucovorin) and palliative surgery with CRS and HIPEC for PC from CRC. The median survival was 12.6 months with chemotherapy versus 22.3 months following CRS and HIPEC with systemic chemotherapy. They concluded that CRS and HIPEC gives better results in this group of patients compared to systemic chemotherapy alone [19]. Further follow-up over 8 years showed that the 5-year disease-free survival was 45 % for patients with optimal cytoreduction compared to those who either received systemic chemotherapy alone or those who underwent incomplete cytoreduction. The major drawback of this study was the use of only 5 FU as a part of the systemic chemotherapy protocol. Had oxaliplatin been used, the results might have been different. The same protocol was used as an adjunct to CRS and HIPEC.

Glehen published a multicentre study showing the results of CRS and HIPEC in PC from CRC. The study included 506 patients. The median survival was 19.2 months and patients who had complete CRS had a median survival of 32.4 months [20].

Another multicentre study by Elias et al. showed a median survival of 30.1 months following CRS and HIPEC with a 5-year overall survival of 27 %. They concluded that CRS and HIPEC should be the gold standard treatment for limited PC from CRC [21].

9.15 CRS and HIPEC for Appendiceal Neoplasms

Appendiceal neoplasms are a rare entity arising primarily from appendiceal epithelium. Histopathologically, they can be divided into three categories: (i) disseminated peritoneal adenomucinosis (DPAM), (ii) peritoneal mucinous carcinomatosis (PMCA) with intermediate (well differentiated) features, and (iii) PMCA [22]. DPAM is associated with a better prognosis than PMCA. Overall, the disease has a good prognosis because of the absence of extra-abdominal metastasis and a lower propensity to involve the small bowel. Complete CRS is associated with very good results. Sugarbaker and Chua et al. reviewed 2300 patients of PMP of appendiceal origin and found that following CRS and HIPEC, the median survival rate was 16.3 years! The overall 3, 5, 10 and 15-year survival rates were 80 %, 74 %, 63 % and 59 %, respectively [7].

9.15.1 Selection Criteria for CRS and HIPEC for Colorectal and Appendiceal Neoplasms

1. Patients with colorectal malignancy with peritoneal disease
2. No evidence of extra-abdominal disease
3. Good performance status
4. PCI score less than 20
5. Patients with good response to neoadjuvant chemotherapy
6. Limited liver metastasis (up to 3 which can be removed without a major hepatectomy)

9.15.2 Contraindications to CRS and HIPEC

1. Poor general condition
2. Presence of extraperitoneal metastases
3. Huge and diffuse PC
4. Presence of extensive liver metastases (relative)
5. Evidence of ureteric or biliary obstruction
6. More than one site of small bowel obstruction (relative)

9.16 Concept of Second Look Laparotomy

All studies have shown that patients who benefit most from HIPEC and CRS are those with less bulky peritoneal disease. However, detecting early PC is not possible with the presently available clinical or radiological means. It is possible to see these only at laparotomy. There is a certain high-risk group which is more prone to develop peritoneal recurrence after definitive surgery. So a second-look laparotomy may be done with the aim of diagnosing PC at an early stage in these patients and then treat it with CRS with HIPEC. However, this is a major undertaking and only a specific subgroup of patients should be considered for a prophylactic 'second look laparotomy'. These include

1. Obstructing or perforating colonic lesions
2. Lesions with positive circumferential resection margin
3. Positive cytology either before or after definitive resection
4. Krukenberg metastasis
5. Rising carcinoembryonic antigen level on follow-up may be one of the indications for peritoneal disease which may not be evident on routine radiological imaging.

A multicentric RCT (Prodige 15) was started in 2011 to assess the role of systemic chemotherapy or second look laparotomy in a high-risk group of patients. The main outcome measure is the rate of peritoneal recurrence after 3 years [23].

9.16.1 Repeat CRS and HIPEC

Even after CRS and HIPEC, the disease can recur in 31–57 % of patients with most recurrences occurring in the abdomen. These patients, if they have a good ECOG status, can be considered for repeat CRS and HIPEC. In a study by Gough et al., repeat CRS was done in 71 % of patients of appendiceal and ovarian malignancies [24]. Yan et al. analyzed 402 patients of PMP; [25] 28 % of these patients had

disease progression on follow up and 88 % of these patients underwent repeat CRS and HIPEC. The 5-year survival was much better in the repeat surgery group compared to those who did not undergo surgery. In all the studies, complete cytoreduction and low grade tumour histology were the only factors responsible for increasing the survival. Similarly for CRC, disease recurrence occurs in most of the cases (40–60 %) following CRS and HIPEC. Repeat CRS and HIPEC can be done in carefully selected patients with a decent outcome [20].

9.17 CRS and HIPEC for Non-colorectal/Appendical Neoplasms

CRS and HIPEC is being used for various non-colorectal diseases including gastric cancer, ovarian cancer and peritoneal mesotheliomas. The indications of CRS and HIPEC in Gastric Cancer include

1. T4 disease
2. Cytology positive
3. Limited peritoneal disease (PCI<6)

Malignant peritoneal mesothelioma is a very aggressive disease with a uniformly fatal outcome. It is associated with ascites and intra-abdominal mesenteric or small bowel nodules. It has three variants: epitheloid, sarcomatoid and mixed. The epitheloid variant is associated with a superior outcome. CRS and HIPEC with or without EPIC and systemic chemotherapy is the treatment of choice for peritoneal malignant mesothelioma. Patients with PCI score <20 are considered to be ideal candidates. The prognosis dips progressively as the extent of small bowel involvement increases. CC-0 and CC-1, epitheloid variants and presence of ascites in the absence of small bowel involvement are associated with improved survival. Many surgeons insert a port at the time of initial CRS and i.p. pemetrexed is given postoperatively along with intravenous cisplatin. This has also been shown to increase survival. With morbidity and mortality of 30 %–40 % and 2 %–4 %, respectively, a median survival of 30–92 months has been achieved following adequate CRS and HIPEC [26].

9.18 Our Experience

Rajiv Gandhi Cancer Hospital has a dedicated machine (Belmonte) to administer hyperthermic chemotherapy. Over the past 3 years, we have operated upon over 60 patients with PC. The primary disease was mainly from the colon, appendix, small bowel and peritoneal mesothelioma. More recently, we have started offering CRS and HIPEC to patients with gastric cancer too. CRS and HIPEC were done in 41

patients and CRS alone in three patients. EPIC has been given in ten patients. Staging laparoscopy was done in the patients whenever possible. Various additional visceral resections done include colectomies (most common), small bowel resection, total abdominal hysterectomy and bilateral salpingo-oophorectomy, cholecystectomy, splenectomy, liver metastatectomy, gastrectomy and pelvic lymph node dissection. The mean PCI score was 13.7 (3–29) and CC-0 and CC-1 status was achieved in nearly 90 % of patients. Two patients died following neutropenia and sepsis and 45 % of patients had morbidity with neutropenia being the most common.

9.19 Conclusion

CRS and HIPEC is a promising therapeutic technique to improve the long-term survival and may even cure selected patients with PC secondary to tumours arising from the ovaries, appendix, colorectal or upper gastrointestinal tract. The key to successful HIPEC is proper patient selection, and adequate CRS with limited blood loss. A dedicated multidisciplinary team yields the best long-term results in this difficult group of patients.

Editorial Comments

Management of carcinomatosis peritonei has been evolving. What was once considered a picture of extreme gloom has now some means of treatment with prolongation of life. This has been possible with the introduction of cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC). In 1980 Spratt et al. [27] described the procedure in the management of diffuse carcinomatosis from an appendiceal mucinous neoplasm. Later, Fujimoto and others described this technique for the management of peritoneal carcinomatosis occurring in gastric cancer [28]. Subsequently through tireless efforts, Sugarbaker made this a viable option for the management of this intimidating intraperitoneal complication of various malignancies [29]. This method of treatment entails total reduction of all carcinomatosis (defined as no more than 0.25 cm residual mass) and simultaneously treating all (if any) residual disease with hyperthermic chemotherapy instilled directly in the peritoneal cavity. Cytoreductive surgery encompasses extensive peritoneal stripping from 13 locations known to be the sites of adherent carcinomatous tissue, excision of various organs involved in the pathology (commonly the omentum, small and large bowel, uterus, ovary, pancreas and urinary bladder). Following extirpation, HIPEC solution is instilled in the peritoneal cavity. Because of the blood–peritoneal barrier, relatively high concentration of the chemotherapy agent is allowed to stay in contact with viable cancer cells making them vulnerable. This barrier allows only minimal

absorption of the cytotoxic drugs producing minimal toxicity. Increased temperature of the instilled fluid is cytotoxic to the cancer cells, has a better effect of the drugs (increased temperature augments the action of the drugs) and allows deeper penetration of the drug [30]. Thus, this approach has a sound scientific basis. It is not surprising therefore to see CRS and HIPEC emerging as a standard of care for a large number of patients with this condition who would otherwise succumb to their disease with conventional chemotherapy. The results are so gratifying that an opinion statement has been issued by the American Society of Peritoneal surface malignancies in 2014 stating the expected median survival with CRS and HIPEC of 30 months for peritoneal carcinomatosis from colorectal cancer [31]. Inspite of these, CRS and HIPEC still await wide acceptance by the oncology community largely due to non-confirmation by randomized trials, the extensive surgical procedure and significant morbidity, if not mortality associated with it. In addition, the technique of CRS has a direct bearing on mortality and morbidity. With experience both these improve highlighting a learning curve for this procedure. The prognostic factors for CRS and HIPEC are: complete cytoreduction (CC-0) which is defined as no residual disease or R0–R1. CC-1 is defined as no more than 0.25 cm residual disease (R2a). The CRS status is important because HIPEC in incomplete CRS does not improve survival as compared to adjuvant chemotherapy [32]. Experience with CRS and HIPEC in gynaecological cancer has shown better results when complete cytoreduction (no macroscopic residual disease) has been achieved than in an incomplete one (>1 cm of residual disease)—median survival of 128 months in the former as against 48 months in the latter [33].

The site of the primary tumour is also a prognostic factor. Thus, appendiceal carcinomatosis has a better prognosis, because the gelatinous mucin in this disease is relatively easy to clear than the sticky, densely adherent material seen with stomach, colon and ovarian malignancy. Also these tumours do not commonly involve the peritoneum.

Tumour differentiation also determines prognosis. While well differentiated tumours can often have complete cytoreduction [30], moderately or poorly differentiated tumours cannot because the latter type of cancers produce less mucin and hence are more invasive [34]. This is why oncologists often use systemic chemotherapy before CRS and HIPEC. In addition, certain carcinomatosis cannot be completely removed such as those with biliary obstruction due to disease in the hepatoduodenal ligament, those causing multiple sites of bowel obstruction, and these along a wide segment of the mesenteric end of the bowel. Unfortunately these defy detection by preoperative imaging and are detected at surgery.

The other prognostic factor is the total tumour volume. This is related to the site of origin of the primary. While those from the appendix have a low volume [35], those due to colorectal, gastric and ovarian malignancy have a higher volume and are not amenable for complete cytoreduction and hence

have poorer results after CRS and HIPEC [36]. To measure the volume of disease, various scoring systems have been proposed. One such system is the peritoneal cancer index (PCI) which has been discussed by the authors. In this system the peritoneal cavity is divided into 13 zones. Each of these is given a score 0 (no tumour), or 3 (confluent tumour or tumour >2.5 cm). Scores of all the zones are added up to make the final score. This score has a bearing on morbidity and mortality seen with CRS and HIPEC—obviously related to the tumour volume. In view of this, some authors have reserved this modality of treatment for patients with a PCI score of <15–20 [37]. I will mention another scoring system. This is a prognostic score introduced by Verwaal et al. and is detailed below: [38]

Prognostic score=0.592C + 1.875R + 0.448D + 0.487H + 0.343 Re

C = 1 if colon cancer or 0 if not
R = 1 if colon cancer or 0 if not
D = 1 if well/moderately differentiated or 2 if poorly differentiated
H = 1 if no signet cell or 2 if there is signet cell

Re = No. of affected regions [1–7], i.e. pelvis, right lower abdomen, omentum + transverse colon, small gut including its mesentery, subhepatic space and stomach, right subphrenic and left subphrenic spaces.

It was argued by the authors that rather than the volume it is the ability to achieve complete removal (cytoreduction) which is more important. Poor prognosis observed in this study was related to the presence of signet ring cells, and poorly differentiated tumour occurring in more than five anatomical locations.

Elevated circulating tumour markers such as CA19-9, CA 125 and CA 15.3 can also predict poor prognosis (survival <12 months) and hence such patients are unlikely to benefit from CRS and HIPEC [39].

While significant advances have taken place resulting in improved morbidity and mortality, unfortunately, most patients are still not suitable for CRS and HIPEC because of extraperitoneal disease, extensive small bowel and mesenteric involvement, poor general health and large tumour volume. Moreover, often patients are referred for this form of therapy after pursuing an unduly long period of chemotherapy without achieving meaningful arrest of disease progression. It is prudent to send patients for HIPEC at an early stage when the possibility of CRS is high and when HIPEC is likely to be effective.

We have now started to learn the pathophysiology of this dreadful complication of various intra-abdominal malignancies. We have only now realized the importance of the blood–peritoneal barrier which makes HIPEC an effective tool in the management of patients with peritoneal carcinomatosis. However, the pattern of disease is complex and difficult to manage with plenty of problems but CRS and HIPEC can be rewarding in the end.

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Chapter 10
Advances in Gastrointestinal Surgery

T.K. Chattopadhyay

10.1 Oesophagus

10.1.1 Fast Track Oesophagectomy: Is It a Viable Option?

Surgery remains the cornerstone of treatment for operable oesophageal cancer. In view of the magnitude of the operation most such patients require postoperative intensive care in specialized units. This invariably, increases the hospital stay and cost.

To decrease hospital stay a fast track approach has been suggested wherein all patients after extubation are shifted to a monitoring unit (telemetry unit) rather than to an intensive care unit (ICU). The monitoring team includes a surgeon, an internist, trained nurses and family members. With their help patients are made ambulant soon after surgery and their vital signs, chest tube drains, urine output and fluid balance are monitored. Early ambulation is specifically encouraged because it has been shown to reduce postoperative stress and fatigue. It is usually possible to achieve ambulation within 4 h. During ambulation, care of all lines is ensured including chest tubes, the nasogastric tube, abdominal drains, the feeding jejunostomy tube and urinary catheter. When cared for with adequate monitoring in a telemetry unit early ambulation can reduce the length of hospital stay and consequently cost of treatment.

Fast track surgery for oesophageal cancer has been drawing attention for more than a decode now [1–12]. Recently a comparative study has been published in the *Annals of Surgery* [13] that included 322 patients operated before the introduction of fast track oesophagectomy (group A) and 386 patients after (group B). Group A patients were shifted to a traditional ICU set up while group B patients were shifted to a telem-

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etry unit. They compared a large number of parameters including the patients' demographic data, tumour characteristics, type of operation, complications and mortality, length of hospital stay, and cost of treatment in the hospital. They also included readmission and re-operation rates, as well as 30- and 90-day mortality rates in the two groups. They found that the fast track patients (group B) had a shorter hospital stay (8 *versus* 12 days in group A), and the difference was statistically significant. Surgery ICU stay was also shorter in group B than group A (1.2 *versus* 4.5 days, $p < 0.001$). Telemetry days were also less in group B than group A (9.7 *versus* 12.7 days, $p = 0.001$). Postoperative cardiac (arrhythmia) and pulmonary complication rates were also lower in group B patients than group A (19 % *versus* 27 %; $p = 0.013$ and 27 % *versus* 20 %, $p = 0.016$, respectively). Interestingly even though patients in group B had higher stages of tumour and higher rate of neoadjuvant therapy, they fared better than patients in group A. Thus, it is time people treating oesophageal cancer surgically change their strategy to a fast track approach for faster hospital discharge and decreasing costs for their patients and the healthcare system.

10.1.2 Current Understanding of Distal Oesophageal Spasm (DES)

DES, though not included in most textbooks of gastroenterology, was described as early as 1889 by Osgood who considered it a peculiar form of oesophagismus [14]. It is increasingly being reported and is associated with contractions with conduction velocity of >8 cm/s in conventional oesophogeal manometry [15]. However, this criteria is too non-specific. Currently, high resolution manometry (HRM) showing at least 20 % premature contractions following swallowing and normal relaxation of the lower oesophageal sphincter (LES) is used to diagnose the condition [16]. Premature contraction occurs during the latency period of less than 4.5 s (measured from the time to the contratile deceleration point in the distal oesophagus) [16]. For diagnosis of DES at least two such premature contractions should occur with LES relaxation and distal latency.

10.1.2.1 Aetiopathogenesis

Essentially, DES is a motility disorder. It can be either primary or secondary to reflux disease of the oesophagus [17] or opiate over use [18]. It is thought to be associated with eosinophilic oesophagitis; some investigators however, consider this relationship [19] to be speculative [20]. Funaki et al. [19] have reported increased immunoglobulin E in the serum of a patient but no eosinophilic infiltration in the mucosa. However, the patient responded to steroid therapy. This is the only evidence to suggest a relationship of DES with allergy, which may also have a relation with eosinophilic oesophagitis. As anti-epileptic treatment resolved DES in one patient, epilepsy has also been suggested to be an aetiological factor [20].

Pathologically, DES is associated with impaired inhibitory activity [21]. This causes premature contractions of the distal oesophagus. A similar inhibitory effect is also noted in achalasia. That is why some authors claimed that DES ultimately progresses to achalasia [22].

10.1.2.2 Clinical Presentation

The disease is seen both in children and older people. Dysphagia, chest pain and reflux symptoms are the common presenting symptoms and in children refusal to eat food is common [21].

10.1.2.3 Diagnosis

Being an uncommon disease, it is usually diagnosed late. A study reported a delay of 2 years in the diagnosis of the condition (time between the first symptoms and diagnosis) [17]. Manometry is the corner stone of diagnosis. However, conventional manometry is non-specific and unreliable. HRM is the investigation of choice [16]. The present diagnostic criteria requires at least 20 % of swallows to be associated with premature contractions and with normal LES relaxation on a Clouse plot [23].

Diagnosis of DES by conventional oesophageal manometry was made with a contractile velocity of 8 cm/s and an amplitude of >30 mmHg. These criteria have now been changed. The present criteria are:

(a) Contractile velocity >30 cm/s with an amplitude of >100 mmHg or
(b) Contractile velocity of >32 cm/s with an amplitude >100 mmHg or
(c) Contractile velocity of >7 cm/s to 8 cm/s with an amplitude <100 mmHg.

Using these modified criteria, conventional manometery has an improved specificity [21].

Other diagnostic aids used in DES are endoscopic ultrasound (EUS) and disposable trans-nasal endoscope (DTE). EUS evidence of increased oesophageal thickness (due to increased thickness of the muscularis propria of the oesophagus) is suggestive of DES [24]. In DTE, following a wet swallow, oesophageal contraction and clearance are evaluated 1, 8 and 16 cm above the LES. Both DES and achalasia patients show relaxation of the LES, contraction of the lower oesophagus and consequent fluid retention [25].

10.1.2.4 Therapeutic Options

DES can be managed in a number of ways. Drug therapy is the oldest method of treatment. Nitric oxide, a potent post-ganglionic inhibitor has been advocated for the medical management of DES. Calcium channel blockers have been reported to be useful in relieving symptoms of DES [21].

Injection of botulinum toxin is another therapeutic option. It is a potent blocker of acetylcholine and as a result oesophageal muscle contraction disappears and patients get relief of symptoms [26]. The relief can be long lasting. If and when symptoms recur the injection may have to be repeated. Lastly, peroral endoscopic myotomy (POEM) is increasingly being used in the management of DES. POEM was initially used for the treatment of achalasia. Its use has now been extended to the management of other motility disorders of the oesphagus including nutcracker oesophagus and DES. While 98 % success is seen with POEM in achalasia its efficacy is 71 % in non-achalasia motility disorders [27].

10.1.3 Oesophageal Cancer

10.1.3.1 Extensive Lymphadenectomy: Survival Is No Better

Oesophageal cancer is a lethal disease and surgery remains the mainstay of its treatment. The overall 5 year survival is poor (only 10 %). If a patient is treated with a curative intent the 5 year survival can be increased to 30 % [28]. This may partly be related to the increasing use of preoperative chemotherapy and/or radiotherapy [29, 30].

Surgeons are concerned about the poor results. As the disease spreads through lymphatics this may be responsible for tumour recurrence and poor survival [31]. Hence, lymph nodes were removed routinely to improve the 5-year survival [32]. The procedure has significant mortality and morbidity [33]. Notwithstanding this, a group of physicians from 12 centres in China, Europe and the USA have recommended that for T1 lesions at least 10 lymph nodes should be removed. For T2 and T3/T4 at least 20 and $\geq$20 lymph nodes, respectively, should be removed [34].

Has this strategy improved patient survival? This can be answered by well controlled studies. Fortunately, a number of studies have addressed this issue and are discussed below:

The first nation-wide study was from Sweden [35]. It included 1044 cases of oesophageal cancer and survival in relation to lymphadenectomy was assessed. What was found is contrary to what has been suggested for some time for the surgical management of oesophageal cancer. The overall 5-year survival reported in this series showed no improvement in survival in patients in whom more lymph nodes were removed (7 to 14) than when <7 lymph nodes were removed. Extended lymphadenectomy for early cancer (Tis–T1) in fact led to worse survival. This adverse effect of extensive lymphadenectomy on survival was seen in all T stages of the disease. The authors also showed that poor survival was associated with a higher rate of lymph mode involvement as well as a higher positive to negative ratio of the lymph nodes. Thus, it is obvious that an extensive lymphadenectomy does not determine the survival but the possibly biological behaviour which determines the outcome!

The second study is from high volume centres in the United Kingdom [36]. The authors of this study included 606 patients who underwent oesophagectomy for cancer. The data was gathered prospectively and is comprehensive. Excellent quality control of all aspects of surgery, pathology and follow-up were ensured. They reported a recurrence rate of 36 % leading to death despite lymphadenectomy, questioning its efficacy in preventing recurrence. The 5-year overall survival in this series was similar in patients who had fewer lymph nodes removed (0–10 nodes) and in those who had more lymph nodes removed (21–52 nodes). Interestingly, this trend was seen in patients who received preoperative chemotherapy too. The authors of this study, as those of the Swedish Study [35] also observed poor survival in patients with higher number of positive nodes as well as a positive to negative ratio of the lymph nodes. They concluded that lymphadenectomy does not improve survival. They attribute this to the disseminated state of the disease in patients who had lymph node positive disease. They also believe that lymph node negative cases do not require lymphadenectomy.

What emerges from this study is that lymphadenectomy allows only proper staging of the disease and to detect lymph node positivity a limited lymphadenectomy is more than sufficient. The authors have quoted poor results of lymphadenectomy in other diseases too, including breast cancer [37, 38], endometrial cancer [39, 40], and pancreatic, gastric and rectal cancer [41–43]. The lymph node metastasis can be considered only as a prognostic tool and an extensive lymphadenectomy does not improve survival. Moreover, extensive lymphadenectomy for oesophageal cancer as in other cancers mentioned above significantly increases the morbidity.

10.2 Intestine

10.2.1 Management of Postoperative Ileus with Gastrografin

Postoperative ileus is a common problem after abdominal surgery. The clinical features of this condition are quite similar to those of postoperative small bowel obstruction. However, it usually resolves spontaneously in 3–4 days. Occasionally, it persists longer and results in delayed recovery, higher morbidity, increased stay in hospital and a higher cost of treatment.

The condition can be attributed to surgery-induced inflammation, autoimmune nerve dysfunction, electrolyte disturbances and stimulation of opioid receptors. All these factors are responsible for gut wall oedema and poor contraction of the intestine [44].

Gastrografin minimises oedema and restores intestinal contractility. It is a water soluble hyperosmolar substance useful in the management of postoperative adhesive small bowel obstruction [45]. Gastrografin by virtue of its hyperosmolality draws out fluid from the wall of the gut to its lumen, thereby decreasing the odema related autonomic dysfunction and opioid receptor stimulation. The intraluminal shift of fluid in turn improves contractility. Gastrografin itself acts like an osmotic

laxative. Its clinical benefit was reported in 1985 [46]. Some subsequent studies have produced confusing results [47, 48].

A recent prospective, randomized trial with excellent quality control has assessed the efficacy of gastrografin in the management of postoperative ileus [49]. The authors included all patients undergoing colorectal resections including those who needed an ileostomy or its closure. They defined postoperative ileus when two or more of the following five features were present:

1. Nausea/vomiting
2. Inability to tolerate oral feeds
3. Abdominal distension
4. Inability to pass flatus or faeces
5. Image evidence of ileus

They studied 351 patients for evidence of ileus and detected it in 88 patients. They included 80 patients for randomization in a 1:1 ratio in the treatment and control groups. The treatment group received 100 ml of undiluted gastrografin mixed with saccharine and a flavouring agent and the control group received 100 ml of placebo consisting of 1 ml concentrated anise solution (2 % anise oil, 72 % ethanol, 26 % water), 40 ml glycerol and 59 ml distilled water; well validated earlier [50].

The primary outcome of the study was duration of postoperative ileus and the secondary outcome was length of hospital stay from the time of diagnosis of ileus and the 30 day re-admission rate.

The duration of ileus was similar in both the treatment and control groups (83.7 *versus* 101.3 h; p = 0.19) and resolution of ileus was compared in the two groups.

Feature	Gastrografin (h)	Placebo (h)	p value
Nausea, vomiting	64.5	74.3	0.4
Consumption of oral diet	75.8	90.9	0.3
Time to passage of flatus and faeces	18.9	32.7	0.04
Abdominal distension	52.8	77.7	0.13

Clearly, the use of gastrografin was associated with earlier resolution of lower bowel symptoms (distension and inability to pass flatus/faeces). However, it does not help relieve upper bowel symptoms (nausea, vomiting, feed intolerance) faster than placebo.

10.2.2 Inflammatory Bowel Disease: Biological Therapy and Its Complications

Tumour necrosis factor (TNF) has a major mediatory role in the pathogenesis of inflammatory bowel disease (IBD). Its inhibitors are therefore being increasingly used in the management of IBD. However, TNF also controls chronic infections

such as tuberculosis. Thus, the use of an anti-TNF agent can cause a flare up of this chronic infection. In addition, an anti-TNF agent can initiate carcinogenesis. These aspects are discussed below.

10.2.2.1 Infectious Complications

Various infections commonly seen with the use of TNF blockers include tuberculosis, histoplasmosis (causing an acute hepatitis-like picture), leishmaniasis, legionellosis (causing features of pneumonia), viral infections, penumocystis and actinomycosis [51]. However, it is difficult to ascertain the exact incidence of infectious complications in patients with IBD receiving anti-TNF drugs because such patients are often on steroids or other immunomodulators. Hence, the available data is unreliable. While a report published in the *Annals of Rheumatic Diseases* in 2014 [52] has shown a higher rate of infectious complications including tuberculosis with anti-TNF therapy and immune modulator therapy, Dula et al. reported similar rates of infectious complications [53]. In a multi-institutional study from USA, of 33,234 patients receiving anti-TNF agents for different chronic inflammatory diseases such as IBD, rheumatoid arthritis, ankylosing spondylitis and psoriasis, opportunistic infections such as tuberculosis, pneumocystis and actinomycosis occurred in the majority of such patients [54]. A significant number of these patients were concurrently on steroids (69 %) and methotrexate (25 %). In a study from Korea including 873 patients with IBD receiving anti-TNF agents, 25 developed tuberculosis [55].

Thus, infectious complications are a genuine problem and should receive due attention. Patients with IBD likely to receive anti-TNF drugs should be screened for tuberculosis by doing a chest X-ray, Mantoux test and interferon gamma release assay (IGRA; suggested by European guidelines [56]). It is unfortunate that this is often not done to detect latent tuberculosis infection (LTBI) before anti-TNF therapy is started [55]. Seven patients in another study did not receive anti-tuberculosis therapy even though screening detected LTBI [57].

Once LTBI is proven, anti-TNF treatment should be with-held and chemoprophylaxis against tuberculosis started. Anti-TNF therapy should be started 3 weeks later [56]. Tuberculosis can occur after starting anti-TNF treatment even in patients who do not have LTBI [56–58]. Thus anti-TNF treatment not only re-activates LTBI but also predisposes to the development of tuberculosis *de novo* [57].

What should be done when active tuberculosis develops during anti-TNF therapy? In a study of 683 patients receiving anti-TNF therapy for rheumatological or skin diseases, 13 patients developed active tuberculosis. In 6 of 13 patients anti-TNF therapy was restarted either during or after antitubercular treatment. None of these patients developed recurrence of tuberculosis at a follow up of 30 months [59].

In addition to the previously mentioned infections, herpes zoster, cytomegalovirus and hepatitis B virus infection can also occur during anti-TNF therapy. Hence, patients with hepatitis B infection are advised to receive antiviral therapy before, during and for at least 12 months after anti-TNF therapy is completed [51]. Hepatitis C infection, on the contrary, does not cause a problem during anti-TNF therapy [60].

10.2.2.2 Malignancies and Anti-TNF Therapy

Lymphoma and melanoma have been linked to the use of anti-TNF therapy. However, a recent meta-analysis has failed to substantiate this observation [61]. While anti-TNF monotherapy does not lead to an increased risk, combination therapy with thiopurines or methotrexate has a higher risk of the occurrence of malignancies [62].

Patients who have a previous history of cancer can have an increased risk of recurrence of their malignancy. Unfortunately, data on this aspect is scarce and a firm opinion cannot be provided at present.

10.2.2.3 Miscellaneous Complications

Various adverse effects that can occur with the use of anti-TNF agents include hypersensitivity skin rash, arthralgia, leukopenia, congestive cardiac failure and autoimmune hepatitis. All these adverse effects disappear on withdrawal of the anti-TNF agents [63].

Adverse effects on the outcome of pregnancy have been reported even though anti-TNF therapy has been widely considered safe. The second trimester onwards the drug reaches the foetus through the placental circulation [64]. In a recent review by the US Food and Drug administration (FDA), thiopurine with or without anti-TNF was not found to be hazardous to either the mother or the foetus [65]. In a case–control study, no difference was observed in the outcome of the pregnancy with or without anti-TNF therapy [66]. However, severe neutropaenia has been reported in four newborns whose mothers were on infliximab for ulcerative colitis—all the babies developed skin infection. Surgical complications in patients receiving anti-TNF agents have been a subject of some debate. Two recent publications have not observed any surgical complications of resection and anastomosis of the bowel in patients with Crohn's disease who received infliximab [67, 68]. Similarly patients with ulcerative colitis who received infliximab did not have any increased risk of complications. However, anti-TNF therapy has been shown to cause higher complications following both ileal pouch–anal anastomosis and ileostomy closure. It is difficult to be certain whether these were due to the biological agents or severe form of the disease [69]. Complications of newer drugs such as matalizumab and vedolizumab have also been studied. The former is effective in Crohn's disease but its use is limited due to progressive multi-focal leuco-encephalopathy [70]. The latter has been in use for more than 5 years. Its adverse effects are no greater than those of a placebo [71]. Usteknumab, originally used in psoriasis, is now used for Crohn's disease too. Over a long period of follow-up (over 5 years) only mild side-effects have been reported, but these did not require stoppage of therapy [72]. Its role in Crohn's disease is promising [73].

10.2.3 Recent Trends in the Management of Acute Diverticulitis

Diverticulitis is a common problem in western countries. However, it has been uncommon in India. Things are changing. The incidence of diverticulitis in India is rising, albeit slowly, possibly due to changes in lifestyle. The treatment of this condition has seen major changes all over the world.

Patients with diverticulosis have been reported to have a 4 % life-time risk of acute diverticulitis [74]. The common complications associated with the condition are abscess, perforation, fistula formation and colonic obstruction. Following an episode of acute diverticulitis, upto one-third of patients can have a recurrent attack [75]. With increasing cost of medical care, the financial burden of management of this condition is enormous, at least for those requiring in-hospital care [76].

Though changes have occurred in the management of acute diverticulitis, there is little consensus even among experts in the field [77]. Experts do agree that CT scan of the abdomen and pelvis should be done to assess severity of acute diverticulitis. They also agree on the value of total white cell count, polymorph count and C-reactive protein in the diagnosis of acute diverticulitis. However, there is no consensus among experts on the use of antibiotics in acute diverticulitis. There seems to be a trans-atlantic divide on this issue. While experts from the USA favour the use of antibiotics, those from UK, Ireland and Europe do not.

Two recent papers have addressed the use of antibiotics. The first study from Scandinavia reported no benefit of antibiotics on resolution of symptoms, development of complications, time of discharge from hospital and recurrence [78].

The second study from The Netherlands', a randomized trial, too did not report any benefit of antibiotics with reference to the above parameters [79]. Following these reports, antibiotic use has been discontinued in Germany, Denmark, Italy and The Netherlands for uncomplicated acute diverticulitis. Such patients however need to be closely followed up. The American Gastroenterological Association (AGA) has also framed their new guidelines [80]. This policy can be judiciously followed for all uncomplicated cases only. Patients with immune compromised states, diabetes and sepsis should receive antibiotics. Patients with complicated diverticulitis such as those associated with abscess formation, perforation and peritonitis should be managed with antibiotics. Small abscesses can be managed with drainage under radiology guidance, thus avoiding surgical exploration. At present the emphasis is on shifting from the traditional open approach to a minimal access approach. Even for faecal peritonitis, laparoscopic surgery has been advocated by some experts [77]. Surgery should include segmental colectomy, Hartmann's procedure, diverting ileostomy, thorough peritoneal lavage and abdominal drainage. The other contentious issues are discussed below.

Elective colectomy for uncomplicated diverticulitis successfully managed non-operatively is no longer advised. This is based on the fact that approximately 10 % of patients undergoing colectomy develop complications whereas those not undergoing surgery have a 20 % risk of a subsequent episode in 5 years. Surgical complications include wound infection, anastomotic dehiscence and cardiac complications (related to age) [81]. The long term complications of surgery are quite significant (25 %) and include bleeding, abdominal pain, altered bowel movement and, not infrequently, faecal incontinence [82]. In view of these, routine sigmoidectomy is avoided and is reserved to improve the quality of life in patients who suffer from frequent attacks interfering with their day-to-day life.

Colonoscopy has been recommended after an attack of diverticulitis. This is because CT findings often are similar in both diverticulitis as well as colonic cancer [83, 84]. This practice too has been challenged. Westwood et al. [85] showed that colon cancer was present in only 0.5 % of 205 patients with uncomplicated acute diverticulitis who had their colon evaluated. The low incidence of colon cancer in the setting of uncomplicated diverticulitis does not warrant a routine colonoscopy.

In another study, colon cancer was detected in 2.1 %, 1 year after CT proven acute diverticulitis. When patients with uncomplicated and complicated diverticulitis with colon cancer were compared, patients with an abscess had a seven-fold higher risk of cancer. It was four-fold for those with localized perforation, and 18-fold for those associated with a fistula [86]. Hence, the authors advised routine colonoscopy for all left-sided diverticulitis. In a systematic review, the prevalence of colon cancer was reported to be 2.1 % [87]. When this data was compared with a calculated rate of 0.68 % in those >55 years of age, the risk appears marginally higher in patients with diverticulitis. It is only in complicated diverticulitis associated with an abscess that colonoscopy can detect colon cancer [88]. Uncomplicated diverticulitis does not have a higher prevalence of colon cancer [89]. They reported that colon cancer was detected more often (10.8 %) by colonoscopy when diverticulitis was complicated with an abscess, fistula or obstruction. Similar observations have been made by other studies too [90, 91]. Thus, patients with CT confirmed uncomplicated diverticulitis do not require a routine colonoscopy. On the other hand in those with complications (abscess, fistula, perforation or obstruction), a colonoscopy is indicated because the malignancy rate is higher in them.

High fibre diet, though not studied well in the context of diverticulitis, has been advocated because of its beneficial effects [92]. Nuts and popcorn have also been recommended [80], but the evidence is not strong. For the same reason seeds too can be advised to patients.

The use of aspirin, non-steroidal anti-inflammatory drugs (NSAIDS), mesalamine, rifaximin and probiotics in acute diverticulitis is contentious.

The effect of aspirin on diverticulitis is not known. Observational studies have suggested only a mild increase in the risk of diverticulitis. As aspirin is a known preventive agent against myocardial ischaemia, its use in patients with diverticulitis and coronary artery disease can be more beneficial with little increased risk of a mild attack of diverticulitis [80].

NSAIDs are better avoided because of the increased risk of diverticulitis, although the evidence again is not very strong.

Mesalamine, a potent anti-inflammatory drug has not been found to be effective when used in diverticulitis. It does not decrease the recurrence rate, indications for surgery or pain subsidence. Therefore, it use is not recommended.

Rifaxamin, an antibiotic, has not been found to be effective in diverticulitis and its use is not recommended. Probiotics, though not recommended in the AGA guideline, have been shown in a randomized controlled trial, along with mesalamine, to be effective [92].

Finally is the issue of recurrent diverticulitis. The risk of recurrence after an initial attack has been thought to have a bearing on management. Retrospective hospital-based data in the 1960s suggested that after the initial acute attack about one-third of patients develop recurrent attacks and one-third of these would develop further recurrences [93]. Subsequent attacks were reported to be more severe and this led to the recommendation that after two attacks the patients should be operated. In recent reports this risk has been shown to be less (13–23 %). Also, the subsequent attacks are no more complicated than what was perceived earlier. Actually, the incidence is only 6 % [94–96]. Thus to advise surgery based on the above beliefs is not tenable. Recent studies have not shown increased morbidity or mortality of surgery even in patients who have had two or more attacks of diverticulitis [97]. This evidence has allowed the American Society of Colon and Rectal Surgeons to revise their guidelines so as not to proceed with surgery after recovery from uncomplicated diverticulitis [98, 99].

10.3 Liver

10.3.1 Quantitative Liver Function Tests (QLFT): Need of the Hour

Whenever the function of any organ deteriorates, it results in disease with all its hazards. Specialists involved in the management of disease essentially evaluate the degree of functional impairment for accurate stratification of the severity and the management. In the evaluation of heart disease the ejection fraction is determined. Similarly for diseases of the kidney, creatinine clearance is estimated and for diseases of the lung a pulmonary function test assesses the underlying functional impairment so as to plan appropriate treatment and provide an assessment of the possible outcome. For diseases of the liver we have a plethora of tests, each of these tells us about one aspect of its function. Some of these tests do not even assess function, e.g. hepatic venous pressure gradient (HVPG) assesses the degree of portal pressure not portal flow. Similarly, a fibroscan or even a liver biopsy deals only with structural change. None of these evaluates the functional status of the liver. Thus, there is a need for a test which evaluates comprehensively the function of the liver.

The test should preferably be simple, non-invasive and reproducible. The quantitative liver function test meets these criteria and is based on scientific principles. In this test specific substances which are removed from the blood by the liver through uptake, metabolism and excretion are used. These substances can be exogenous such as indocyanine green (ICG), antipyrine, nitroglycerine, propranolol, lidocaine, midazolam, etc. or endogenous such as bile acids (cholic acid), amino acids and lipoproteins. These agents when administered either orally or parenterally reach the liver through the portal venous or hepatic arterial blood. Once these reach the liver, they are metabolized and excreted. The hepatic clearance is related to the hepatic blood flow. Thus clearance of these agents reflects all the above functions (hepatic blood flow, hepatic uptake and metabolism). Clearance of a substance can be calculated from the equation: [100, 101]

$$\text{Clearance}\left(\text{ml/min/kg}\right) = \frac{\text{Dose in mg}}{\text{AUC}\left\{\left(\left[\text{mg/ml}\right]\text{min/kg}\right)\right\}}$$

When the substance is removed completely in a single cardiac cycle (E) the hepatic blood flow equals clearance of the substance: [101]

Clearance (ml/min/kg) = Hepatic blood flow (ml/min/kg) × E where
E = 1 when the entire agent is cleared in single hepatic pass.

Apart from blood flow, clearance tests measure hepatic uptake, its perfusion and function.

Blood flow measurement is preferably done with the use of agents which are extracted to a high degree by the hepatocytes (E >0.7). High extraction substrates, as these are called, include bile acids, sorbitol, nitroglycerine, ICG, lidocaine, propranolol, galactose, etc. The clearance of low extraction substrates (E <0.3) represents metabolic efficiency of the hepatocytes. Since the clearance is dependent on hepatic metabolism, liver flow will not influence it. The agents in this category are methionine, erythromycin, diazepam, caffeine, antipyrine, phenylalanine, aminopyrine, etc. [102].

This information has been used in the dual cholate test (DCT) for quantitative evaluation of liver function. Cholate is administered simultaneously orally and intravenously [103]. The intravenous cholate (24 cholate) is tagged with ^{13}C. The oral cholate is D4 cholate and its serum concentration is then measured. The area under the serum concentration is then plotted against a time curve of D4. This quantifies clearance of D4 from the portal circulation (portal hepatic filtration rate). The serum concentration of ^{13}C-24 cholate when plotted against its time curve represents clearance of ^{13}C-24 cholate from the systemic (hepatic arterial) circulation. The ratio between ^{13}C and D4 cholate measures the portal systemic shunt. Thus, dual cholate test gives information regarding clearance of a high extraction agent (cholate) both from the portal and systemic circulation and also the degree of portosystemic shunting. From the data thus obtained, a disease severity index (DSI) can be obtained [104]. DSI range and cut-off values are similar in various liver diseases.

DSI has also been shown to correlate well with the degree of fibrosis seen in a liver biopsy [105]. DSI can also predict development of varices and help in formulating a preventive strategy.

Why is quantitative liver function assessment important? Currently liver function tests take into account bilirubin, liver enzymes and international normalized ratio (INR). However, these do not provide an accurate status of the liver function, e.g. patients with grossly elevated alanine aminotransferase (ALT) do not necessarily have poor liver function. The reverse is also true; patients with near normal ALT level can have poor liver function and hence can have a poor clinical outcome. Yet, these inaccurate parameters are used in Child-Turcotte-Pugh (CTP) and Model for end stage Liver Disease (MELD) scores. These two well described scoring systems can be valid only in the presence of cirrhosis. They fail to provide information of hepatic function before cirrhosis develops [106].

Structural changes seen on a liver biopsy have been, until now, the gold standard in the clinical work up of a patient with chronic liver disease including cirrhosis. Since liver biopsy is an invasive procedure it is worrisome to patients. Thus non-invasive methods such as serum biomarkers of fibrosis or elastography are being used. Unfortunately though these tests can ascertain cirrhosis, but fail to identity pre-cirrhotic stages of the disease.

Currently, HVPG is being used to prognosticate the clinical manifestations of portal hypertension such as ascites, development of varices and hepatic encephalopathy. As it is invasive, the same concerns as with a liver biopsy remain. Consequently, a non-invasive test such as the dual cholate test seems to be an alternative because it can assess the portal circulation and ascertain portal systemic shunting.

10.3.1.1 Utility of QLFT

1. Diagnosis of early liver disease before cirrhosis sets in: Various currently used tests (Elastography, HVPG and collagen content) have been compared with DSI obtained from the dual cholate test. DSI is the only test which correlates most with the Ishak score [107]. Thus, DSI can detect patients in the precirrhotic stages so that preventive strategies can be considered.
2. Hepatic steatosis is common in chronic hepatitis C, and with alcoholic and non-alcoholic liver disease. This (steatosis) influences the imaging characteristics of fibroscan and elastography. DSI on the other hand is independent of steatosis [108].
3. Frank cirrhosis can be diagnosed with MR elastography. However, it has limitations. Its accuracy in obese patients is poor. Moreover underlying disease pathology (such as inflammation and impaired portal circulation) interfere with elastography. The dual cholate test in this regard is accurate. DSI estimated from this test correlates well with cirrhosis (DSI above 19). The test can be done very quickly (in 60 min) and is cost-effective when compared with liver biopsy, elastography, HVPG, etc. [105, 109]

4. Risk of future complications of cirrhosis can also be predicted better with dual cholate test (with calculated DSI) than with the other methods [107].
5. Efficacy of treatment of hepatitis C can also be evaluated with DSI (estimated from the results of dual cholate test). It has been shown that with treatment of hepatitis C infection, the hepatic flow rate and DSI improve, pointing to an effective and successful antiviral treatment [110]. This happens even before improvement in bilirubin, albumin, INR, MELD or CTP score.
6. Dual cholate test can also identify graft failure after liver transplantation. However, it is not yet certain if this can be utilized in the treatment of graft failure [111].
7. High grade varices can be predicted with dual cholate test (DSI >19 or cholate shunt above 35 %). It can, hence, be used in the primary prophylaxis against variceal bleeding [109].

10.3.2 Porto-Pulmonary Hypertension

Pulmonary hypertension occurring in patients with portal hypertension with or without cirrhosis is termed porto-pulmonary hypertension (PPHT). This occurs in 5 % of patients with end stage liver disease [112]. Patients at particularly higher risk of this disease are those who have autoimmune hepatitis. Hepatitis C infection, surprisingly, has a low incidence of PPHT [113].

The pathophysiology of PPHT involves increased vascular resistance of the pulmonary arterial bed due to intimal hyperplasia caused by endothelin and other vasoconstrictors such as thromboxane, interleukin, angiotensin, glucagon, serotonin, etc. These substances are normally removed by the liver. When the liver is not functioning normally as in patients with cirrhosis and portal hypertension when portosystemic shunts are formed [114], these substances accumulate and reach the pulmonary circulation. In addition, PPHT can be due to the hyperdynamic circulation associated with cirrhosis when increased cardiac output along with reduced systemic vascular resistance can cause this condition [115]. The net result of increased cardiac output is damage to the intimal cells of the pulmonary bed when endothelins are released along with the other vasoconstrictors mentioned earlier resulting in profound vasoconstriction. Patients can be asymptomatic in the initial stages but as the disease progresses they may develop dyspnoea, orthopnoea and platypnoea. Apart from respiratory symptoms, patients can have fatigue and syncopal attacks. The latter symptoms occur very late and have a poor prognosis. Palpitation and precordial discomfort can also be present. Clinical signs include tricuspid regurgitation, right heart failure with raised jugular venous pressure, pedal oedema and signs associated with portal hypertension (prominent subcutaneous veins, ascites, spider naevi, gynaecomastia, splenomegaly, ascites, pedal oedema and in the late stages, encephalopathy).

The diagnosis of PPHT is established by Doppler echocardiography. The pulmonary and right ventricular pressures are raised. In case the pulmonary artery pressure

cannot be measured accurately and if the right ventricular pressure is more than 40–50 mmHg, right heart catheterization should be done to confirm the diagnosis. In PPHT, right heart catheterization characteristically shows mean pulmonary artery pressure (PAP) of more than 25 mmHg. The pulmonary vascular resistance (PVR) is more than 240 dynes/s/cm^{-5}. Pulmonary capillary wedge pressure is less than 15 mmHg. Based on the pulmonary artery pressure, PPHT is graded as mild (25–34 mmHg), moderate (35–45 mmHg) and severe (>45 mmHg). While PAP can be raised due to a hyperdynamic circulation, PVR is increased only due to vascular resistance. Thus, elevated PVR indicates true PPHT while only elevated PAP indicates false PPHT [116]. The treatment of PPHT can be general and specific. General measures include diuretic therapy and beta-blockers particularly for bleeding. Specific measures include pulmonary vasodilators such as bosentan (endothelin receptor blocker) [117], sildenafil (phosphodiesterase inhibitor) [118] and prostanoid (prostaglaudin inhibitor) [119]. All these agents reduce PVR and PAP by smooth muscle relaxation-induced vasodilatation.

The prognosis of PPHT is bad. However, the degree of pulmonary hypertension is not correlated with the degree of liver disease (Child–Pugh or Model for End-stage Liver Disease [MELD] score). The mean survival is only 15 months. Medical treatment is not effective in the long-term and liver transplantation is the only hope. Even for this the severity of PPHT is crucial. While mild PPHT can have low (almost 0 %) mortality following transplantation, it can be 100 % with severe PPHT with PAP exceeding 45 mmHg. Moderately severe PPHT (35–45 mmHg) too has a very high mortality (50 %) [120]. For this reason, all candidates for liver transplantation should be screened properly for this condition.

10.3.3 Hepatopulmonary Syndrome: Its Pathogenesis, Diagnosis and Management

Hepatopulmonary syndrome (HPS) is commonly associated with chronic liver disease with or without portal hypertension. The three cardinal features of HPS are presence of liver disease with or without portal hypertension, increased alveolar–arterial oxygen gradient [p(A–a)O_2 gradient] >15 mmHg at room air and the presence of intrapulmonary vasodilatation (IPVD).

The condition occurs in patients with chronic liver disease [121]. Abnormalities in gas exchange are seen in <20 % of patients [122]. HPS can occur not only in chronic liver disease but also in extrahepatic portal venous obstruction, Budd–Chiari syndrome and various acute and chronic inflammatory diseases of the liver [123].

Patients with HPS can be asymptomatic but progressive dyspnoea is the commonest presenting feature. It can be associated with cyanosis and/or clubbing. If these are detected in the setting of chronic liver disease, a clinical diagnosis of HPS can be made with reasonable certainty. Patients can have shortness of breath with relief on lying down (platypnoea), dyspnoea on lying flat (orthopnoea) or difficulty in breathing which worsens in the erect position. These occur due to dilatation of the

pulmonary vasculature particularly at the base of the lungs due to which ventilation–perfusion mismatch occurs. The diagnosis of HPS is confirmed if abnormal gas exchange and IPVD can be demonstrated in the absence of significant lung disease. On arterial blood gas analysis, $p(A–a)O_2$ gradient in the upright position is increased in HPS (>15 mmHg). IPVD is established using microbubble transthoracic echocardiography (MTTE). In this test, saline is shaken to form microbubbles and is then injected in a peripheral vein. Normally, the microbubbles reach the right atrium, right ventricle and then the pulmonary artery where the bubbles get trapped in the pulmonary capillaries (microbubbles have bigger diameter than the capillaries; 10 μm versus 8–9 μm). These bubbles then get absorbed by the alveoli. In HPS on the other hand, microbubbles appear in the left atrium within 3–6 cardiac cycles suggesting intrapulmonary shunting due to IPVD and neoangiogenesis.

The other investigation done to confirm HPS is microaggregated albumin (MAA) labelled Tc99m scan. The MAA has a diameter of 20 μm and hence gets trapped in pulmonary capillaries (diameter 8–9 μm). In HPS due to the presence of IPVD and right to left shunt due to formation of collaterals by vascular endothelial growth factor (VEGF) induced shunt, these aggregates get shunted to the heart and reach the kidney and brain through the systemic circulation. These molecules are retained in the brain and kidney, and can be detected by Tc99m scan. This indirectly proves IPVD and right to left shunting.

Common investigations such as chest X-ray or high resolution CT of the chest can show evidence of IPVD [124, 125]. Pulmonary angiography is advised when large IPVDs are suspected. This can be used for angioembolization. Pulmonary function tests can detect an abnormality particularly diffusing capacity of carbon monoxide (DLCO) [126]. However, routine pulmonary angiography is not necessary. Notwithstanding the utility of the tests (MTTE and Tc99m MAA) often regarded as gold standard, simple investigations can be done to at least screen patients for possible HPS. These include oxygen saturation by pulse oximetry in the supine and erect posture (the difference is reported to be 100 % sensitive and 88 % specific with O_2 saturation cut-off less than 96 %) [127]. Enlargement of the left atrium and ventricle on a simple chest X-ray has also been suggested [128]. Serum biomarkers are also being evaluated to diagnose HPS. These include vascular cell adhesion molecule ($VCAM_1$) and von Willebrand factor [123].

To better understand HPS, one has to consider the pathophysiological factors which cause this condition. Central to the pathophysiological mechanisms are IPVD and arteriovenous shunting which impair gas exchange leading to ventilation–perfusion mismatch and diffusion abnormality. Pulmonary vasodilatation occurs due to production of NO from activated endothelial nitric oxide synthase (eNOS) and inducible nitric oxide synthase (iNOS). Vasodilatation also occurs due to production of carbon monoxide (CO) and Haem Oxygenase (HO). While eNOS is activated by endothelin 1 bound to its receptor which occurs in patients with cirrhosis, iNOS activation occurs in intravascular monocytes or macrophages. These latter cells are presented to the lungs where they get attached to pulmonary endothelial cells following bacterial translocation and endotoxaemia which occur in patients with chronic liver disease and cirrhosis [129, 130].

However, VEGF is also produced which gets bound to its receptor in pulmonary endothelial cells [131], leading to angiogenesis and formation of pulmonary arteriovenous shunts. The net result is a ventilation–perfusion mismatch, pulmonary A–V shunting causing diffusion abnormality and arterial hypoxia which is the hallmark of HPS. HPS has been graded based on the paO_2 value: mild (>80 mmHg), moderate (60–79 mmHg), severe (50–59 mmHg) and very severe (<50 mmHg) [132].

Various agents have been used to treat HPS including L-NAME (Nebulised NG nitro L arginine methyl ester, a NO inhibitor), pentoxyphylline, norfloxacin, aspirin, indomethacin, somatostatin, mycophenolate (angiogenesis and NO inhibitor), etc. [123] However, none of these are effective. Even TIPS has been tried but this too was not useful. Thus, at the moment no medical treatment can be suggested for HPS. Liver transplantation is the only hope for cure. HPS has been shown to resolve within 6–12 months after liver transplantation in over 80 % of patients [125]. 5-year survival of 76 % has been reported, a figure not very different from patients undergoing liver transplant without HPS. This has made HPS a MELD exception category in prioritising patients for liver transplant with a better survival with this policy [123]. In fact reversal of HPS after liver transplant has been reported in all patients in a recent publication [133]. However, the severity of HPS has a bearing on the results of liver transplant. Patients with HPS with a paO_2 <44 mmHg have a very high post-transplant mortality [134] and hence this is considered a contraindication for liver transplant. Pre-transplant paO_2 <60 mmHg and positive MAA scan showing a brain uptake of more than 20 % are considered predictors of death following liver transplant [135]. Such patients should be managed with lifelong oxygen for palliative purposes only [125]. Angioembolization of pulmonary A–V shunts can also be done.

10.3.4 Organ Transplantation and Infection

Organ transplantation is the best treatment option for end-stage disease of an organ. According to WHO, nearly 1,15,000 solid organ transplants occur each year globally [136]. The major problem after transplantation is the high risk of infection which has a direct bearing on post-transplant morbidity and mortality. It is therefore imperative to be aware when it occurs and what is its cause. Infection develops due to an impaired defence of the host coupled with exposure to pathological organisms. Along with these, complications of transplantation such as anastomotic disruption (mostly incomplete) can add to the risk. Recipients with associated co-morbid conditions such as diabetes, or when the transplant has been done for primary sclerosing cholangitis in the case of liver, and urinary reflux in kidney have an inherent higher risk of infection.

As mentioned earlier, ineffective host defence is an important factor for infection in the post-transplant period. This defence mechanism can be impaired due to various factors such as a breach in the anatomical barrier (due to skin incision, anastomosis

of draining ducts), compromised flow of the draining system such as anastomotic leakage leading to intra-abdominal collections, use of corticosteroids causing lowered cell-mediated immunity, use of immunosuppressants leading to defective immunity (both humoral and cellular), etc. Depression of the bone marrow is another factor associated with the risk of infection in the transplant setting. This is seen with the use of mycophenolate, cotrimoxazole, and antivival agents such as ganciclovir. B cell function and immunoglobulin production is depressed with rituximab and T cell depletion is associated with the use of antithymocyte globulin. Biological agents such as eculizumab and belatacept hamper complement function and T-cell activation [137].

The offending pathogens can originate either from the patient or from the environment, be hospital acquired or from the donor. Examples of the former include organisms in oral secretions, respiratory secretions (colonized), gastrointestinal tract, from the skin and concomitant chronic infection (viral, fungal, tubercular, etc.). Environmental (atmospheric) organisms are essentially fungi and water borne pathogens which include *Salmonella*, *Cryptosporiduim*, etc. Donor related infections typically include cytomegalovirus (CMV), Epstein–Barr virus (EBV) and hepatitis B virus infection (HBV).

It is also important to know the timing of these infections (following transplantation), its source and type. Surgical site infection occurs due to colonization in the skin by both bacteria and fungi. This commonly occurs soon after the operation and following any subsequent intervention. Pneumonia too occurs soon after transplant and is caused by a number of organisms (*Aspergillus*, *Pseudomonas*, *Pneumocystis*, *Nocardia*, *Mycobacteria*, *Staphylococous*, etc.). These colonize the respiratory tract. It can also occur following aspiration (colonized with respiratory organisms as well as oral flora). Fungal infections can also develop in patients after an attack of viral infection of the lungs. Reactivation of latent pulmonary infection can occur relatively late, some weeks or months after transplantation. The organisms responsible include *Mycobacterium tuberculosis*, *Histoplasma*, *Coccidioides*, etc.

Following antibiotic use patients can develop diarrhoea which could be due to *Clostridium difficile*, *Cryptosporidium* or norovirus. When diarrhoea occurs soon after transplant, an intra-abdominal source including biliary and urinary tract should be searched. The organisms in such situations can be either cutaneous or gastrointestinal in origin. Infection of the central nervous system can occur due to food-related organisms such as *Listeria monocytogenes*. These are latent in plasma and get reactivated. They typically occur several weeks after transplantation. Certain viral infections (HBV, hepatitis C virus, CMV, herpes zoster virus, varicella zoster virus) occur soon after transplantation [138].

Care of a transplant patient is provided by clinical evaluation, diagnostic aids and good clinical decision making. Good clinical observation often detects the site of infection. Often the transplanted organ is the site of infection. A focused history taking and physical examination can often be rewarding. This can then be supported by some simple laboratory tests such as haemogram, urine examination (both routine and culture) and culture of the blood and sputum. Other than the transplanted organ the common sites of infection are respiratory, intra-abdominal,

urinary and gastrointestinal tracts. Following immune suppression CMV infection can get re-activated within a year after transplant. Sometimes when the diagnosis cannot be confirmed with the above tests one has to do more elaborate diagnostic tests. It is not rare to see multiple infections occurring simultaneously, e.g. viral pneumonia with bacterial respiratory tract infection or *Clostridium difficile* infection with urinary tract infection. These can at times re-activate latent CMV infection.

Thus, one has to carefully look at various aspects of a transplant recipient who develops infection. It should include details of the immunosuppressants including their doses, microbiological evaluation of the offending pathogens, presence of latent infection in the recipient, and even donor-related latent infections [139]. Surgery-related factors should also receive due attention such as vascularity, anastomotic integrity, and collection of body fluids such as bile, urine, etc.

Sometimes features suggestive of infection can occur with graft dysfunction and rejection. At times the two can be superimposed. Drug reactions too can be a confounding factor such as colitis with the use of mycophenolate, and mental aberration with cyclosporine and other calcineurin inhibitors. Allergy to various antibiotics is quite common and hence should also be considered.

Though transplantation has become a standard of care for end-stage disease of an organ, it can be associated with a serious risk of infection in a large number of patients. These infections are related to a compromised host defence and are caused often by aggressive and opportunistic pathogens. Adequate knowledge of both these is important in clinical practice. The high infection rate can be triggered by complications related to the transplant operation [140–142].

10.3.5 Acute Liver Failure

Acute liver failure (ALF) occurs in the absence of any pre-existing liver disease. The disease, though rare, can be associated with a high mortality. It is characterized clinically by jaundice, coagulopathy and encephalopathy [143].

It can be due to multiple aetiological factors which include viral hepatitis (A, B and E), a variety of drugs such as anti-tubercular drugs, paracetamol, non-steroidal anti-inflammatory drugs (NSAIDs), antifungal, antiepileptic, and herbal medicines, as well as veno-occlusive disease, Wilson's disease and pregnancy-associated liver disease. There can be other rare causes of ALF such as heat stroke, and ischaemic and autoimmune hepatitis, Amanita phalloides poisioning, etc. [144] While paracetamol toxicity is the predominant cause in the West, viral hepatitis, particularly hepatitis E virus infection, is the leading cause in the Indian subcontinent.

The disease can occur in different forms depending on the duration between appearance of jaundice and encephalopathy. If the duration is less than 1 week the disease is hyperacute. Duration ranging from 1 to 4 weeks makes the disease acute and when this duration is between 4 and 12 weeks, it is subacute. Sometimes, pro-

gression of the disease can occur within hours. In view of this, patients should be managed systematically—starting with medical treatment with appropriate strategy for prognostication and thus allowing a timely decision for emergency liver transplantation (ELT).

The primary medical management of ALF is fluid replacement so that blood volume is restored to maintain hepatic perfusion.

Specific therapy should be instituted whenever possible. N-acetyl cysteine is started irrespective of whether the cause of ALF is paracetamol or not. For viral hepatitis, antivirals have been used but their efficacy in ALF has not been borne out in trials [144].

Similarly, for autoimmune hepatitis, steroid use is advised provided sepsis is adequately treated. In other forms of ALF also management of sepsis is extremely important. Both antibiotics and antifungals are advised in severe ALF because unabated infection can make patients unsuitable for ELT [145]. Treatment of coagulopathy of ALF is somewhat tricky. Correction of coagulopathy is not recommended unless undue bleeding has already occurred or if an invasive measure such as intracranial pressure monitoring is contemplated. This is because the decision for ELT is related to the value of the international normalized ratio (INR) and its correction will influence the decision.

Encephalopathy is related to raised intracranial pressure caused by excessive ammonia crossing the blood–brain barrier leading to swelling of astrocytes and raised intracranial pressure. Its management includes care of the airway by endotracheal intubation, measures to reduce ammonia and reduction of intracranial pressure. Reduction in ammonia is achieved by lactulose. L-ornithine L-aspartate has also been used because of its ammonia lowering effect. However, no survival benefit has been documented with its use [146]. Similarly, rifaximin has not been shown to be useful in lowering the ammonia level in patients with ALF. Patients with a high ammonia level in the blood (150 μM/L) should have the intracranial pressure monitored especially in young patients with a high risk of intracranial bleeding [147]. Continuous venovenous haemofiltration has been shown to lower the blood ammonia level [148].

These patients should be placed in the head up position, given i.v. sedation and muscle paralysis with elective ventilation. To reduce cerebral oedema and intracranial pressure either mannitol or hypertonic saline should also be given.

The clinical benefit of hypothermia has not been proven [149]. Both hypo- or hyperthermia has potential risks and hence should be used with caution. High volume plasma exchange is being reported to have some utility. It aims to eliminate the circulating inflammatory cytokines which are responsible for continuous damage to the hepatocytes. With its use, the ELT rate is likely to come down as spontaneous recovery occurs in some patients [150].

The use of liver support devices, as of now, has not been found to be useful in the management of patients with ALF [151]. Transplantation of hepatocytes is another strategy being explored. The purpose is to support the patient until

liver transplantation is done or allow such patients to recover without liver transplantation [152]. Patients who benefit most from ELT are those who have ALF due to metabolic diseases of the liver. With improvement in care there is increasing evidence of success of recovery of ALF without ELT. Thus, there is a need for proper and timely evaluation and listing a patient for ELT. The Kings College or Clichy criteria have been found useful. The King's College Criteria [153] are:

For paracetamol-induced liver failure, arterial pH <7.3 irrespective of the degree of encephalopathy or all of the following, if present, are indications for ELT.

1. Prothrombin time >100 s (INR >6.5)
2. Grades 3 or 4 encephalopathy
3. Serum creatinine >3.4 mg/dl

For non paracetamol-related acute liver failure, prothrombin time >100 s (INR >6.5) irrespective of the grade of encephalopathy or any three of the following; if present, are indications for ELT.

1 Age <10 years or >40 years
2 Non-A, non-B hepatitis, idiosyncratic drug reaction
3 Jandice to encepholoapathy duration >7 days.
4 Prothrombin time >50 s (INR >3.5)
5 Serum bilirubin >18 mg/dl

The Clichy criteria [154] developed in patients with fulminant viral hepatitis uses grade 3 or 4 encephalopathy and factor V level <20 % in patients less than 30 years of age or <30 % in patients older than 30 years. Subsequently, MELD score has also been used but has not been found more useful than the above two. Similarly, sequential organ failure assessment (SOFA) score [155] has been used but its efficacy is yet to be ascertained. A new scoring system has been suggested by the acute liver failure study group [156] using grade of encephalopathy, INR, serum phosphate and bilirubin levels and serum M30 level (marker of apoptosis; increased in ALF). The score has been shown to be better than King's College criteria or MELD score. However, the problem is M30 estimation is not available at most centres.

ELT is an option in ALF. However, its indications for paracetamol toxicity and viral hepatitis have been decreasing. The results of ELT, though much better now, are still inferior to the results of LT in the elective setting. The 1- and 5-year survival rates in the USA and Europe have been reported to be 78 % and 74 %, and 72 % and 57 %, respectively [157, 158]. Most deaths occur in the first year following transplant and the causes are infection, primary non-function, surgical complications and rejection. Results in the long term tend to be similar irrespective of the indication for ELT. Such patients may develop psychological abnormalities and it, not uncommonly, leads to suicides. In view of this, pretransplant psychological evaluation has been recommended [159].

10.3.6 Contemporary Issues in Liver Transplantation

Liver transplantation has become the standard of care for various conditions causing end-stage liver disease. However, due to the shortage of donor organs not all prospective recipients can be offered the therapy. In the context of deceased donor liver transplantation, allocation criteria are used to offer the organ to someone who is sick. Despite this, the mismatch between demand and supply is steadily rising. There are also a number of other issues that have been highlighted in the recent past. Some of these are discussed below.

10.3.6.1 MELD Score and Prognosis

Model for end-stage liver disease (MELD) score is used to allocate organs more fairly. With its use, results have improved and most countries have adopted MELD score as the listing criterion. One of the problems with this score is that there is a high dropout rate as well as mortality in those waiting for transplantation. There are also disparities related to male gender, those who are poor as well as those suffering from hepatocellular carcinoma (HCC). There are certain factors which are not considered in the MELD score and efforts are being made to incorporate these in the MELD score to improve it further. One such variation is MELD sodium. The high serum concentration of sodium has been associated with a higher mortality in patients on the waiting list. MELD sodium has been shown to be highly predictive of 90-day mortality [160]. It is presumed that patients with a low MELD but a high sodium and thus a higher risk of mortality while on the waiting list can benefit from the revised MELD incorporating serum sodium concentration in the equation.

Similarly, low albumin level has been shown to be associated with a higher mortality during the waiting period particularly when the MELD score is <20 [161]. A five variable MELD has been developed to address serum sodium and albumin concentration and has been called 5V MELD. This is better in predicting mortality on the waiting list [162].

Risk stratification of patients on the waiting list is also being discussed because it has been observed that patients with ascites, encephalopathy and varices with a low MELD score (<18) often die before transplantation [163]. If these patients were given additional points to enable them to be listed with a higher priority it might prevent or decrease mortality during the waiting period. However, these parameters are subjective and it is difficult to quantify them for any mathematical calculation!

To predict 6 month mortality in waitlisted patients, Jara et al. [164] evaluated the role of LiMax (maximum liver function capacity) using [13]C methacetin. The test assesses the ability of the liver to metabolize methacetin, the gaseous metabolized product is removed by the lung and hence can be measured in the breath. The use of LiMax test is considered to be helpful in the prediction of mortality in worsening liver function. Acute on chronic liver failure (ACLF) is another problem. If patients are not transplanted it has a high mortality. The CLIF (chronic liver failure) consor-

tium of EASL (European Association for Study of Liver) has recognized this and developed CLIF consortium acute decompensated MELD, MELD Na [165].

10.3.6.2 Transplantation in Various Categories

Elderly patients have lower survival rates after liver transplantation. This is true both in USA and Europe particularly for patients older than 65 years with a higher MELD (>28) [166, 167]. With propensity matching, competing risk analysis and modeling of MELD <28, this poor outcome has been blunted [166–168]. Hospital stay, postoperative results and overall cost have not been shown to be affected by advanced age of the recipients. Thus, it is not surprising that nearly 18 % of liver transplants done in both USA and Europe in 2013 were among those >65 years of age [169, 170]. Thus, it appears that not all elderly patients do badly after transplantation. Properly selected patients can do as well as younger patients. The moot point is how to select them?

Transplantation in patients who have depleted muscle mass—*sarcopenia*, has poor results. Sarcopenia is objectively assessed using CT scan by measuring thickness of the psoas muscle. Patients with cirrhosis because of abnormal energy metabolism and poor protein synthesis have severe sarcopenia. The overall health of such patients can be indirectly measured by cardiopulmonary tests which can accurately predict both 90-day mortality and post-transplant survival. Thus, before transplantation, all patients with *sarcopenia* should receive adequate nutritional supplementation and active physiotherapy. Such patients are likely to have better outcomes. Since sarcopenia is a modifiable state, all patients should be given a fair chance to improve their nutritional status. The importance of preoperative build up cannot be ignored because in those with sarcopenia, postoperative recovery is unduly prolonged and they often require prolonged ventilatory support. These patients also have a high infection rate following transplantation. Overall they have a higher postoperative mortality [171].

Obesity is endemic in developed countries and many patients develop NASH (non-alcoholic steatohepatitis). In the USA 35 % of transplant patients are obese (BMI >35 %) [172]. Unlike in the past, results in the obese have been shown to be better in terms of post-transplant survival [173]. For still better results, bariatric surgery either during the transplant or subsequently has been suggested [174].

NASH is a growing problem and is estimated to be the commonest cause of chronic liver disease in the USA [175]. Patients with NASH are being transplanted more frequently [176]. However, patients with NASH have a high rate of post-transplantation cardiovascular events and death. In addition, they have a high incidence of postoperative infections. In spite of these their survival is good [177].

Patients with hepatitis C virus (HCV) infection do badly after liver transplantation. If not treated, recurrence of HCV infection is the rule rather than the exception, with subsequent re-infection of the graft leading to graft loss and eventual death. With the availability of effective antiviral therapy this is changing. To achieve this goal, one has to aim for sustained viral response (SVR) [178]. Newer drugs can

achieve this and prevent recurrence of HCV infection related graft loss, and thus avoid the need for re-transplantation. The newer drugs are taken orally and are well tolerated. These include sofosbuvir, simipevir and doclatasvir. These drugs can be given in combination or alone with or without ribavirin [179].

Patients with alcoholic hepatitis can also be offered transplantation. Most centres require patients to be off alcohol for at least 6 months before transplantation. This policy has been questioned by some because it is arbitrary, does not correlate with recidivism and more importantly denies transplantation to patients who develop alcoholic hepatitis [180]. However, the concern for recidivism remains with all its consequences. In the context of donor shortage this issue continues to be debated.

Patients with HCC are being transplanted more often on both sides of the Atlantic. These patients are offered the MELD exception criteria to be eligible for transplant [181]. The 5-year survival in excess of 77 % justifies that these patients accrue extra points [182]. Results of transplantation have been so good that it is being increasingly offered to patients with HCC beyond the Milan criteria. Such patients are down staged using locoregional therapy before transplantation. Waiting time before transplantation acts as a biological marker. Those who wait longer and survive prior to transplantation have lower recurrence and better survival rates. Patients who have aggressive tumours deteriorate rapidly in the waiting period and become ineligible for transplantation. Thus, it has been suggested that patients have a mandatory waiting period with local/locoregional therapy (to prevent progress and reduce size). Those who progress should be delisted and the others transplanted [183]. A revised MELD for HCC has also been devised which incorporates tumour size, number, alphafoetoprotein (AFP) level, MELD and response to locoregional therapy [184]. Hopefully, this will select patients who will benefit the most.

MELD disparity is being recognized, particularly in connection with the geographical location of the patients, poor socioeconomic strata, race and male gender. To tackle this, ‘Share 35’ has been introduced which offers the organ to the ‘sickest first’ patient, cutting across geographic barriers (regional sharing of available organs), reduce travel time of the donor organ, and reducing death during waiting. The impact of Share 35 has been reported by Trotter et al. [185] They reported an increase in number of transplants, more transplants for MELD >35, broader regional sharing and decrease in mortality while waiting for transplant. The flip side of this strategy is the high organ travel time, increased cold ischaemia time, more organs discarded, potential increase in hospital stay and impact on local donations. Some of these appear to be unavoidable. Gentry et al. have reported no difference in cold ischaemia time, short term wait list mortality, 6 month post-transplant survival and organ discard rate [186].

Simultaneous liver kidney transplantation (SLK) is on the rise due to introduction of MELD which gives priority to patients with associated kidney injury. In fact, SLK transplantation constitutes about 8 % of deceased donor liver transplantation [187]. However, 12 % of patients listed for dual SLK transplant ultimately undergo liver transplantation alone. In this group undergoing liver transplantation alone, the kidney function recovers completely in 33–87 % of patients post-transplant [188]. It is difficult to predict which patients will recover and which will not. It has been

shown that SLK transplants can achieve over 75 % 5-year survival as against only 55 % without it [188].

Lastly, the issue of immunosuppression. Following transplantation, most centres use immunosuppression with tacrolimus or cyclosporine. The main problem associated with their use is renal toxicity. To prevent this as well as graft rejection, everolimus has been introduced with good long term renal function [189]. The drug is well tolerated by patients. At this point it is not clear if everolimus can be used alone or in combination with tacrolimus. Since everolimus has anti-neoplastic property, its use in HCC may be beneficial [190].

The crucial issue of discontinuation of all immunosuppressive drugs has also been addressed in two reports. About 42 % of patients in one study have been without any immunosuppressive agents without any biopsy evidence of rejection over a 3-year period since cessation of immunosuppressive therapy [191]. The predictors of success include time since transplant—higher the period greater is the chance of better results. In one study, phytohaemagglutin stimulation index has been shown to be associated with better results in one study [192].

10.4 Biliary

10.4.1 IgG Cholangiopathy

This entity, described recently, [193] is being reported increasingly. While the initial description was reported with reference to pancreatitis, various other organs now appear to be affected by the same causative factor—IgG. These include the salivary and lachrymal glands, pancreas, bile duct, prostate and testis [194]. In susceptible individuals IgG4 induces a severe inflammatory reaction producing an inflammatory mass. Most of the symptoms are related to this, the commonest being obstructive jaundice when the pancreas is affected. In most cases it mimicks malignant biliary obstruction. Patients are diagnosed with this condition only incidentally following a biopsy report or following histological examination of an excised specimen. Immunohistochemistry using anti-IgG4 staining reveals IgG cholongiopathy. Higher levels of circulating IgG4 in the serum are usually present.

The diagnosis is essentially one of exclusion. If malignancy can be excluded, high serum IgG4 level may suggest the presence of the disease. Apart from the mass effect, the inflammatory reaction can cause dysfunction of the affected organ. In the pancreas it can cause either exocrine or endocrine abnormalities leading to steatorrhoea or diabetes. Affected patients are usually in their sixth decade or older. The diagnosis can be suspected by the HISORT criteria (Histology, image characteristics, serology, other organ involvement and response to treatment) [195]. The disease has a relatively indolent course without any generalized symptoms. Not much is known about how the condition develops. While there is overproduction of IgG4, the reason for this is not known as yet. It is possible that an antigen-specific IgG4

accumulates in individuals (or organs) exposed to chronic stimulation of the antigens [196]. Chronic exposure may be related to various environmental pollutants such as dust, petroleum products, etc. The IgG4 then gets attached to the antigens. It has specificity to bind and hence does not cause any systemic reaction. IgG4 is derived from B cells and plasma cells. In patients with IgG cholangiopathy the B cells and plasma cells have been reported to be rich in IgG4 [197]. That the high levels of IgG4 are pathological is evident from the fact that IgG4 disappears from the circulation following immunosuppression with corticosteroids. IgG4 positive B and plasma cells have been seen in pathological specimens of IgG cholangiopathy [198]. CD20 is a marker of B cells and hence it has been suggested that anti-CD 20 therapy (rituximab) can be used in patients with IgG cholangiopathy. In fact, one study has already shown its efficacy [199]. While the diagnosis of IgG4 cholangiopathy is based on raised serum IgG4 level, a typical histological picture and features on imaging, there are limitations of each of these tests. First, the IgG4 may be normal in about 30 % of cases [200]. In addition, IgG4 may be elevated in primary sclerosing cholangitis, cholangiocarcinoma and pancreatic carcinoma. The hallmark histopathological feature of IgG cholangiopathy is a lymphoplasmacytic infiltrate which stains positively for IgG. However, this may not be seen; possibly because of the non-uniform nature of the disease [201]. Specific imaging characteristics are lacking for IgG cholangiopathy. However, it can exclude malignancy which is an important differential diagnosis of this condition. The other tests that can be used for diagnosing it are IgG levels in biliary specimens and a PET scan [202, 203].

The course of the disease (IgG4 cholangiopathy) is variable. While many patients recover spontaneously others may continue to progress and the fibrosis becomes severe. Most patients are treated with corticosteroids. Both high dose (40–60 mg/day) and low dose (10–20 mg/day) oral steroids are effective [204]. IgG cholangiopathy is expected to respond to corticosteroid therapy in 4 weeks failing which there is a need to reconsider the diagnosis. Those who respond should continue steroids for 3 months after which the same can be tapered and ultimately kept on a low maintenance dose for a longer period (the duration is not yet defined). Apart from steroids, azathioprine and mycophenolate have also been tried with similar results [205]. Immunosuppressive therapy should be started early when the fibrosis is minimal as it may be ineffective when extensive fibrosis is present. Immunosuppressive therapy can be associated with a higher incidence of lymphoma or other malignancies. Since IgG cholangiopathy mimicks features similar to malignancy this has to be considered seriously especially if the response to corticosteroid therapy is not evident in a month's time and a radical procedure such as pancreatoduodenectomy may have to be considered.

10.4.2 Pathogenesis of Carcinoma of the Gall Bladder

Carcinoma of the gall bladder (GBC) is essentially a disease of the developing world with high rates reported from India, Pakistan, South America and certain east European countries. The risk factors for GBC include gallstones, chronic

inflammation, female sex, obesity and high parity. Adenomas and abnormal pancreatobiliary junction are other uncommon risk factors [206]. Considering the association between cholelithiasis, cholecystectomy, at least for patients who have symptomatic gallstones will prevent the development of GBC. This approach has been used in Chile since 2006 in patients between 35 and 49 years of age. Whether this prevention strategy is effective or not will be known soon when the results are analysed and published [207]. Even when cancer is detected in such patients in the gall bladder specimen, it is at an early stage and simple cholecystectomy offers cure in 90 % of patients [208]. Gallstones which are large have a higher risk of cancer, presumably because of the longer contact time with the gall bladder mucosa inducing inflammation and causing carcinoma [209]. Chronic inflammation associated with gallstones is thought to induce cancer through inflammatory pathways involving COX2, nuclear factor kappa beta (NFKB), reactive oxygen species (ROS), cytokine (IL-6) and prostaglandins. All these occur due to a change in cellular proliferation and apoptosis. Consequently, there is increased DNA methylation and angiogenesis which leads to malignant transformation of the inflammed epithelium [210].

GBC can form in one of two ways—either dysplasia to carcinoma or adenoma to carcinoma sequence. In the former, there is dysplasia developing due to chronic irritation because of gallstones or cholecystitis which causes metaplasia of the affected epithelium. Dysplastic epithelium progresses to *in situ* cancer. In the second, malignant transformation occurs in the adenoma. Dysplasia in the gall bladder is preneoplastic. In a study of 210 early GBC, intraepithelial dysplasia and carcinoma *in situ* have been noted adjacent to the tumour in 80 % of cases. This is indirect evidence that neoplasia occurs in the damaged epithelium and not in adenomas [211]. It is to be stressed here that adenomas in the gall bladder are rare. Roa and Aretxabala reported an incidence of only 0.001 % in all cholecystectomies done for symptomatic gallstone disease [212]. The same authors reported adenomas occurring in 2.8 % in a series of 210 early GBC [213]. Nearly one-fourth of these adenomas had adenocarcinomas. These adenomas progress to carcinoma in a time bound manner as has been reported by Roa et al. [214] In their series adenomas were observed at 50 years, adenomas with malignant change at 58 years and frank adenocarcinomas at 64 years of age. Histological characteristics of dysplasia of gall bladder mucosa are: pseudo-stratification, nuclear enlargement, hyperchromatic nucleus and loss of polarity. In carcinoma *in situ* the nucleii are bigger, and chromatic distribution is irregular along with presence of nucleoli. In adenocarcinomas there are micropapillary projections and atypical mitosis [214]. These three categories (adenoma, adenoma with malignant change and adenocarcinomas) seem to be progressive in nature as they develop in 50, 58 and 64 years, respectively. Thus, it appears it takes about a decade each to change to frank adenocarcinoma from adenoma through malignant change in an adenoma [214].

Various morphological abnormalities are also noted in patients of GBC [208]. These include increase in the length and thickness of the gall bladder. Thickness greater than 10 mm has a 2 year survival of only 14 %. The presence of cholesterolosis results in a lower risk of developing malignancy. In nearly 40 % of patients the cut section of the gall bladder does not show any discernible tumour. Features of chronic

cholecystitis are often difficult to differentiate from those of malignancy. Location of the tumour (hepatic side or the visceral side) has a bearing on the prognosis. While the former has a favourable prognosis the latter has a more aggressive course. Dysplasia can extend to Rokitansky sinuses also, from which frank cancer can arise. In view of this, a suitable surgical strategy should be adopted for the prevention of such tumours.

Lastly, various molecular events are attributed to gall bladder carcinogenesis. Most of these are poorly understood. The ones that are reasonable and agreeable to researchers are: an abnormal growth signal, absent apoptosis, relentless cell replication, angiogenesis, local invasion and systemic dissemination. Each of these factors is associated with a specific genetic influence. There are listed below:

1. Abnormal cellular growth is controlled by HER2 (amplification of ligand), EGFR, K-RAS, BRAF, PIK3CA (gain of function mutation in receptor and/or downstream signaling) or SMAD4 (loss of function mutation in growth inhibition) [215–217].
2. Limitless replication (uncontrolled cell cycle) through gain of function with increased expression of positive cell cycle regulator like cyclin E, cyclin D1 or loss of function with decreased expression or mutation of negative regulator like p2, p16, p53 and retinoblastoma gene.
3. Evasion of apoptosis occurs due to over expression of anti-apoptotic caspases and Bcl2, or increased resistance to apopotois due to COX2 over expression. HER2 amplification too helps prevent apoptosis.
4. Increased cell survival due to survival signalling pathway controlled by PI3K, AKT, mTOR, JAKI/STAT1, NF-KB and wnt/beta-catanin.
5. Angiogenesis occurs due to over expression of angiogenic signalling genes, thrombospondin 1, COX2 and VEGF.
6. Tissue invasion and metastasis are due to over expression of E-cadherin [218] and erythrocyte complement receptor 1 (ECR1). Loss of epithelial and gain of mesenchymal phenotype can also help this process. Genes responsible for this are COX2, TGF beta and NFKB. Loss of differentiating gene, IDH1 and over expression of stem cell marker CD44 also facilitate the process. Some of these molecular markers have a bearing on prognosis, e.g. Erb is associated with poor prognosis [219]. Many of these can be used for targeted therapies such RAS, RAF, MAP kinase, EGFR/HER2, JAK/STAT1/NFKB, TGF beta, etc.

10.4.3 Extrahepatic Bile Duct (EHBD) and Gall Bladder (GB) Cancer

10.4.3.1 Adjuvant Chemoradiotherapy

Both EHBD and GB cancer are lethal diseases. Most patients suffering from these diseases present late and are not candidates for surgical resection; the only effective and potentially curative option. Even in those who undergo surgical resection,

recurrence is a real problem. Adjuvant chemotherapy and/or radiotherapy have been suggested to decrease the rates of recurrence. However, their role is doubtful [220–224]. The response to adjuvant therapy may partly be related to the pattern of recurrence. Local recurrence occurs more often in EHBD cancer and hence radiotherapy or chemoradiotherapy can be expected to be beneficial as suggested by Nakeeb et al. [225] For GB cancer, chemoradiotherapy has been reported to be superior to chemotherapy [226]. However, a meta-analysis has reported beneficial effects of chemotherapy over either chemoradiotherapy or radiotherapy [227]. A recent phase II trial used adjuvant capecitabine and gemcitabine followed by radiotherapy and concurrent capecitabine for both these cancers. The study included 79 patients (54 EHBD and 25 GB cancers). All patients underwent surgical resection (54 R0 and 25 R1). Postoperatively, all patients received intravenous gemcitabine 1000 mg/ m^2 on days 1 and 8 along with capecitabine 750 mg/m^2 twice a day from days 1 to 14. A 7 day break was allowed to all patients, thus making the regimen a 3-week cycle. Following completion of the first cycle all patients were re-investigated. Those patients, who did not progress, received 665 mg/m^2 of capecitabine twice daily for 7 days per week along with radiotherapy (45 Gy to regional lymph nodes and 54–59.4 Gy to the preoperative tumour bed). Radiotherapy was given for 5 days per week till the total planned dose was delivered. Capecitabine was continued till the end of radiotherapy.

All patients were then followed up at intervals of 3 months for 5 years. Repeat imaging (CT/MRI) was done every 6 months for 2 years. Overall, 86 % of patients completed the planned treatment. The 2-year survival was 65 % for the entire group (67 % for R0 and 35 months for R1 patients). Similarly, the median survival was 35 months for all patients, 34 months for R0 and 35 months for R1 patients. Local recurrence was noted in 14 patients, of whom 9 also had concomitant distant metastasis. Distant metastasis alone occurred in 24 patients. Grade III toxicity occurred in 52 % of patients while grade IV toxicity was seen in 11 % of patients. The most common side-effects were neutropenia (44 %), hand foot syndrome (11 %) and diarrhoea (8 %).

The key findings of the study which merit special mention are:

1. High rate of R0 resection reflecting improved surgical care in these challenging cases.
2. R0 and R1 resections fare equally following adjuvant chemoradiotherapy dismissing the conventional notion that R1 resection has a poor survival in both EHBD and GB cancer [224, 228, 229].
3. That chemoradiotherapy is effective and results have shown an acceptable local recurrence rate of 11 % unlike what has been reported earlier [220, 230, 231].
4. This is the only truly multicentre trial with good quality control with regard to every aspect of disease management such as surgery, imaging, pathology and radiation.
5. The trial has two similar malignancies such as EHBD and GB cancer avoiding other tumours, thus minimizing heterogenity. This conclusion is derived from the observation that R0 resection rates are similar in the two diseases and patterns of failure following adjuvant therapy (chemoradiotherapy) too are similar.

10.5 Pancreas

10.5.1 Newer Scoring Systems for Assessment of Severity of Acute Pancreatitis and Its Management

Acute pancreatitis is a disease of variable severity—mild, moderate or severe. Fortunately, most patients develop mild pancreatitis and the disease resolves without any long term sequelae. However, 5–10 % of patients have severe disease with severe systemic inflammatory response, organ failure (single or multiple), and pancreatic necrosis with or without infection. While mild pancreatitis needs no aggressive treatment, severe pancreatitis more often requires treatment in an intensive care unit (ICU) with careful monitoring of various organ specific parameters (neurological, respiratory, circulatory, haematological, renal and hepatic). Therefore, it is important to identify patients who are likely to progress to severe disease. There is evidence that events occurring in the first 24 h ultimately determine severity. Various prognostic criteria have been developed for identification of patients who are likely to develop acute severe pancreatitis. These include Ranson's criteria, APACHE II score, CT severity score, Bedside index of severity in acute pancreatitis (BISAP) and Harmless acute pancreatitis score (HAPS). Ranson's criteria can be completed only at the end of 48 h of hospitalization. The APACHE II score (initially developed in critically ill patients) requires arterial blood gas analysis and the patients' past medical details. While the first (blood gas) is not done in the emergency, the second (past history) is often not available. CT severity index is established after a CT scan which is not routinely done in most cases of acute pancreatitis. Often it is not required and may not be possible to do because of associated renal dysfunction. Thus, we require predictive tests which are simple, can be done timely and as effective as the others. Two simple yet useful scoring systems are now available. These are BISAP and HAPS [232–235]. BISAP score has five criteria which include (i) blood urea nitrogen >25 mg/dl, (ii) impaired mental status <15 on the Glasgow coma scale, (iii) presence of systemic inflammatory response (fever, tachycardia, hypotension, tachypnoea, (iv) age >60 years, and (v) presence of pleural effusion on chest X-ray. Each of these parameters is allotted 1 point. Scores of 1 and 2 suggest mild disease from which patients recover without mortality. However, scores of 3, 4 and 5 have been associated with mortality in excess of 5 %, 12 % and 22 %, respectively [233]. This score can also identify patients with organ failure beyond 48 h [233]. The HAPS score includes only three parameters: (i) absence of rebound tenderness or guarding; (ii) normal haematocrit; and (iii) serum creatinine value [235]. HAPS has been shown to be predictive of the milder form of disease [236]. Both high urea and haematocrit levels reflect fluid deficit and help identify patients with severe disease. Thus this can be used to triage patients and select the appropriate ones for admission to hospital possibly in an ICU for better treatment and monitoring. High levels of both blood urea and haematocrit values in the first 24 h or failure of reduction of these are highly predictive of severe disease and death [237, 238]. Further, an increase in serum creatinine in 48 h has been shown to be highly predictive of pancreatic necrosis [239].

While discussing various prognostic markers one is reminded of the utility of clinical judgment in identifying patients with severe disease—patients with heightened inflammatory response as manifested by impaired mental status, tachypnoea, tachycardia and hyperpyrexia. Such patients should be managed preferably in an ICU. The laboratory findings mentioned above should help clinicians select patients properly for further management.

It is obvious that the first 24 h of the onset of illness are extremely important. Severe disease can be identified during this time frame. The main problem is hypovolaemia (raised haematocrit and blood urea) leading to hypoperfusion of the pancreas. This has to be tackled aggressively to improve results. The mainstay of treatment of severe acute pancreatitis is to avoid further hypoperfusion of the pancreas.

Aggressive fluid therapy is the key. In the emergency room, soon after the diagnosis of severe acute pancreatitis is made, about 1–2 l of fluid should be infused. This does need to take into consideration the patient's age, and cardiac, pulmonary and renal status. Fluid overload should be avoided by careful clinical observation (prominent jugular veins, presence of rales on chest auscultation or cardiac signs). Thereafter fluid should be infused at a rate of 250–300 ml per hour. The aim should be to achieve urine output in excess of at least 30 ml per hour in an adult weighing 60 kg. Fluid therapy should be monitored both clinically and by laboratory tests such as blood urea nitrogen and haematocrit. Based on the efficacy or otherwise of fluid therapy further replacement should be decided periodically but at least on a 12 hourly basis.

While giving fluids, it is better to use Ringer lactate than normal saline, because of its better efficacy in averting systemic inflammatory response [240]. Prophylactic antibiotic use has been debated for a long time while managing acute necrotizing pancreatitis. However, there is no evidence that these do any good. In fact in one meta-analysis antibiotics failed to decrease infection of pancreatic necrosis or mortality [241]. Similar observations were made in a later meta-analysis and a Cochrane review [242–244].

It has to be emphasized that aggressive fluid therapy in the early stage of disease (within 24 h) is the cornerstone in the management of severe acute pancreatitis. The primary objective should be restoration of the already depleted circulatory volume with the secondary aim being improvement of perfusion of the pancreatic microcirculation. The guide to successful fluid therapy is improvement of blood pressure, heart rate and optimal urine output. Needless to say this simultaneously reduces central venous pressure, blood urea nitrogen and haematocrit.

10.6 Miscellaneous

10.6.1 Closure of the Midline Abdominal Incision: Do We Need to Change the Way It Is Done?

Traditionally midline laparotomy incisions are closed using continuous, running sutures of monofilament non-absorbable material such as prolene (or delayed absorbable material such as polydiaxone [PDS]). The technique involves placing

sutures about 1 cm from the fascial (aponeurotic) edge of the incision about 1 cm apart. The incisional hernia rate (a measure of efficacy of the closure technique) in such patients was 10–23 %. In a high risk group of patients for occurrence of hernia this was 38 % [245, 246]. The high rate of incisional hernia has a bearing on the quality of life of patients because of pain, obstruction of the hernial contents and the incidence of strangulation necessitating re-operation [247, 248]. The cost of care understandably increases significantly in those requiring re-operation.

An alternative method of closing the incision has been tried by a Swedish group where the incision is closed with a running suture using small bites [249]. The bites were placed 5–8 mm from the incised aponeurotic margin. The authors have reported a decreased rate of incisional hernia. To validate this result, a prospective, multicentre, double blind randomized trial (STITCH trail) was done in The Netherlands [250]. It compared the large versus small bite suturing techniques of closure of midline fascial/aponeurotic incisions. In the large bite group (also referred to as mass closure) sutures were placed 1 cm from the incision and 1 cm from each other using No 1 double loop PDS. The sutures were started from either end to the centre of the incision where both the sutures overlapped for about 2 cm. In the small bite group, the bites were placed 5 mm from the margin of the incision at an interval of 5 mm. The suture used in this group was 2-0 PDS. A similar running method was used as in the conventional group starting at both ends and overlapping in the centre for 2 cm.

All patients were followed up at 1 month and 1 year following the operation. Integrity of the closure was evaluated by both physical and ultrasound examination. The patients' quality of life was also assessed periodically [251, 252]. The primary outcome measure was development of incisional hernia and the secondary outcomes were postoperative complications, hospital stay and quality of life. Incisional hernia occurred in 21 % of patients in the large bite group and 13 % in the small bite group. The difference was statistically significant ($p = 0.02$) with an odds ratio of 0.52 and confidence internal of 0.31–0.87 ($p = 0.13$). Hernias were detected by clinical assessment, ultrasound examination or both. The mean size of the defect was similar in the two groups (3.4 ± 4.4 cm). The complications were also similar in the two groups. Re-admission rate and adverse events were also similar. Pain in the immediate postoperative period also did not differ significantly. Thus, the small bite suturing technique was considered superior to the traditional large bite technique with lower incisional hernia rate and similar pain and quality of life. I strongly feel that the small bite technique should now be the standard of closure of midline abdominal incisions.

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Oesophagus

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