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Series Editor: T. K. Chattopadhyay

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Sujoy Pal *Editors*

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GI Surgery Annual

Series Editor

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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 TK Chattopadhyay and his team of co-editors. Professor TK 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 is indeed a pleasure to bring to you the twenty-fifth volume of the *GI Surgery Annual*. During its journey, the Annual has been quite popular among members of the association. I, as the editor, have enjoyed producing each issue over these years. It has been a very satisfying effort.

Advances in surgical gastroenterology have been so great that the Indian Association of Surgical Gastroenterology had decided to disseminate this information among its members through the *GI Surgery Annual*. In the early years of its existence, the Association had a fair number of its members living in far flung areas of the country who did not have ready access to the available literature. Mind you, this was before the days of the internet! Things have changed and indeed remarkably. What has not changed is the desire to acquire new knowledge for better patient care.

I and my co-editors are committed to further this cause.

Happy reading!

New Delhi, India — T. K. Chattopadhyay

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About the Editors

T. K. Chattopadhyay is Professor Emeritus in the Department of GI Surgery and Liver Transplantation, All India Institute of Medical Sciences, New Delhi. He initiated this series 25 years ago and has been the Editor-in-Chief of this series since its inception. Presently, he is Professor and Head of the Department of HPB Surgery, Institute of Liver and Biliary Sciences, New Delhi.

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Chapter 1
Esophagogastric Junction (EGJ) Carcinoma: An Updated Review

Rajneesh Kumar Singh

1.1 Introduction

Epithelial carcinomas constitute the majority of all cases of esophageal cancer. While squamous cell carcinoma (SCC) typically occurs throughout the esophagus (commonest middle third), adenocarcinomas mostly occur in the distal one-third and the esophagogastric junction (EGJ). All adenocarcinomas involving the EGJ are included under the group of EGJ carcinomas; these include esophageal carcinomas, gastric carcinomas and true carcinomas of the cardia. It is rare for lower esophageal SCCs to involve the EGJ; hence all discussion of EGJ carcinomas refers to adenocarcinoma. The incidence of adenocarcinoma has increased, while that of SCC has declined steadily in the Western population, in the last few decades [1, 2]. Hence EGJ carcinoma has become a tumour of increasing importance over the last few decades. The reasons for the increasing focus on these tumours include the rising incidence in the Western world, the controversies in classifications, the generally poor prognosis and major differences in the treatment and outcomes as compared to squamous cell carcinoma of the esophagus.

The other aspect in which esophageal adenocarcinomas differ from SCC is the well-characterized metaplasia-dysplasia-carcinoma sequence for which a large volume of scientific research has accumulated from across the world. This provides an opportunity to study the molecular mechanisms of carcinogenesis and early diagnosis and treatment of some of these tumours [3].

Adding to complexity in case of EGJ adenocarcinoma are the multiple terminologies used by different authors to denote one or all subgroups of EGJ carcinoma, varying from ‘junctional’ carcinoma, ‘cardia’ tumours, gastro-esophageal junction

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tumours, distal esophageal adenocarcinoma, etc. *One often needs have a careful look at the patient cohort represented while interpreting studies including these tumours.*

1.2 Classification

As opposed to the usual organ-based neoplasias, EGJ carcinomas are a heterogeneous group of zone-based tumours that arise from or involve the gastro-esophageal junction; these include esophageal, gastric and true cardia carcinomas. The heterogeneity in this group pertains to the epidemiology, etiopathogenesis, molecular pathology, differences in treatment and outcomes of the different subgroups. These within group differences in clinical behaviour were understood quite early, and several attempts were made to subclassify these tumours. Most of these classifications are topographical classifications, and the most commonly referred to is the one provided by Professor Siewert and his group. In the 1990s this classification was adopted by a consensus conference of the International Gastric Cancer Association and the International Society for Diseases of the Esophagus, and experts concluded that this should form the basis of definition, investigation and reporting management of EGJ adenocarcinoma [4].

EGJ carcinomas were defined by Siewert as a group of epithelial carcinomas arising from a zone 5 cm below or 5 cm above the EGJ and mandatorily involving the EGJ [5]. This needs an accurate definition of the location of the EGJ, considering the fact that anatomists, physiologists and endoscopists have all defined the EGJ differently [6]. Adding to this confusion is the shifting of the squamocolumnar junction due to columnar metaplasia of the lower esophagus, at least in some patients. The best accepted definition of EGJ for this purpose is that it lies at the proximal limit of the gastric mucosal folds (rugae). Siewert divided these into three subgroups based on the epicentre of the tumour [5]:

- *Type 1 tumours*: Distal esophageal adenocarcinoma infiltrating the EGJ and mostly associated with intestinal metaplasia, i.e. Barrett's esophagus (epicentre located more between 1 and 5 cm above the EGJ).
- *Type 2 tumours*: True carcinoma of the cardia arising from the epithelium of the gastro-esophageal junction and often referred to as 'junctional carcinoma' (epicentre located between 1 cm above to 2 cm below the EGJ).
- *Type 3 tumours*: Subcardiac gastric carcinoma located below the EGJ and infiltrating the gastro-esophageal junction and distal esophagus (epicentre located between 2 and 5 cm below the EGJ).

The Siewert classification was based on data from their large experience. The salient features separating the three types of tumours are as in Tables 1.1 and 1.2. Siewert type 1 adenocarcinoma is quite similar to esophageal adenocarcinoma, including a male preponderance, a strong history of reflux disease and mainly intestinal-type (Lauren) histology. The majority of these tumours are

Table 1.1 Demographic and morphologic tumour differences according to Siewert tumour type

Patients parameter	Siewert type 1	Siewert type 2	Siewert type 3
Age (mean) years	61	60	60
Male:Female ratio	9:1	5:1	2:1
Prevalence of associated Barrett's metaplasia	77%	10%	2%
Prevalence of grade 3/4 (undifferentiated tumours)	51%	55%	72%
Prevalence of tumours with intestinal growth pattern	79%	41%	38%

Adapted from [260]

Table 1.2 Pattern of nodal spread according to the Siewert tumour type

Location of nodes	Siewert type 1 (%)	Siewert type 2 (%)	Siewert type 3 (%)
Para-tracheal/subcarinal	15	0	0
Para-esophageal/lower mediastinal	50	12	6
Paracardial	50	65	50
Lesser curvature	32	66	85
Greater curvature	5	14	33
Celiac	8	25	39

Adapted from [261]

associated with chronic gastro-esophageal reflux disease, and most arise from Barrett's metaplasia. Siewert type 3 adenocarcinomas, however, are similar to distal (non-cardia) gastric cancers with only slight male majority, an almost equal proportion of intestinal and diffuse histological types and an insignificant association with reflux.

Lymphographic studies have shown that the lymphatic drainage from the lower esophagus goes both ways, upwards towards the mediastinum and downwards towards the celiac axis, while the lymphatic drainage from the gastric cardia and subcardiac region mostly drains towards the abdomen (celiac axis and the para-aortic lymph nodes) [4, 7]. The epicentre of the EGJ tumour determines the distribution of the nodal metastasis. The overall frequency of lymph node metastasis is about 90% for type 3 carcinoma, 70% for type 2 carcinoma and 65% for type 1 carcinoma. Type 1 tumours metastasize to nodes both in the mediastinal and upper abdomen, whereas the type 2 tumours mostly drain towards the abdominal nodes, especially the paracardial, lesser curvature and left gastric nodes, and only occasionally to the mediastinal nodes (Table 1.2). The recurrence pattern also varies according to the site, with peritoneal and nodal recurrence being more common with type 3 as compared to type 1 and 2 carcinomas [8].

Although the Siewert classification is useful in defining the prognosis, treatment and outcome of EGJ tumours, there are several practical difficulties encountered, in part due to the limitations of the investigations and often locally advanced nature of these tumours. In a Dutch study, Grotenhuis et al. had found that the overall

accuracy in correctly predicting tumour location (Siewert type) was not very high (70% for endoscopy/EUS and 72% for CT) [9]. In this study in 22% of patients, large tumours obscured the landmarks of the gastric folds on preoperative investigations and could not be compared with the pathologic assessment [9]. In another study from Italy, only 72.5% of patients could be accurately assigned a Siewert subtype using EUS and endoscopy [10]. In a Dutch randomized controlled trial on esophageal and EGJ adenocarcinomas, the authors found major differences between the classification of the tumour on endoscopy and on pathology of the resection specimen, in several patients [11].

AJCC in the 7th edition had named all tumours in 10 cm zone straddling the EGJ as EGJ carcinoma, and these were staged as esophageal carcinoma [12]. These included tumours whose epicentre was in the lower thoracic esophagus or EGJ or within the proximal 5 cm of the stomach cardia, which also involved the EGJ or esophagus.

However the eighth edition of AJCC has changed this to include only Siewert type 1 and 2 in the esophageal carcinoma staging schema [13]. Siewert type 3 tumours (2–5 cm below the EGJ) are to be staged as gastric carcinoma according to this recent classification. This change is viewed as an interim topographical classification of EGJ tumours till more genetic and molecular profile data enables these tumours to be classified according to more discerning criteria rather than the inaccurate topographical criteria presently in use.

1.3 Epidemiology and Risk Factors

Esophageal carcinoma is the eighth most common cancer worldwide and the sixth leading cause of cancer-related mortality, according to the GLOBOCAN database [14]. Most of the available epidemiologic data considers esophageal adenocarcinoma as a whole, and most databases do not categorize EGJ carcinoma separately. The incidence of esophageal adenocarcinoma has surpassed that of esophageal SCC in a number of Western countries, while SCC continues to dominate in Asian and African countries [15]. Esophageal adenocarcinoma is typically a disease of the obese Caucasian male often with chronic GERD. The rising incidence of esophageal adenocarcinoma has mirrored the increasing incidence of obesity and the high incidence of GERD in the Western countries [16, 17].

Although epidemiologic data based on subtypes of EGJ carcinoma is difficult to come by, the Siewert type 1 EGJ carcinoma probably has an epidemiology similar to esophageal adenocarcinoma, and the incidence rise has paralleled that of esophageal adenocarcinoma [18]. There is less reliable data about the incidence trends of Siewert type 2 and 3 EGJ carcinoma. A study from Sweden showed (among men) a much larger increase in the incidence of esophageal adenocarcinoma as compared to gastric cardia adenocarcinoma (10% versus 2.3%) [19]. However the different subtypes of EGJ carcinoma probably have different incidence patterns. A study based on the Surveillance, Epidemiology, and End Results (SEER) data from 1970 to 2010 has shown that the incidence of esophageal adenocarcinoma has shown a

sharp rise, while that of EGJ carcinoma has increased only a modestly, and there has been a sharp reduction in the incidence of (non-cardia) gastric carcinoma [20]. The parts of the world like China or Iran, with a high incidence of esophageal carcinoma in general, do not report a jump in the incidence of esophageal adenocarcinoma unlike that reported by the Western countries [21, 22]. A multi-ethnic study from the USA showed that among people of Asian origin, the incidence of esophageal adenocarcinomas was quite low [23]. This stands in contrast to the much higher incidence of gastric cardia adenocarcinoma and esophageal SCC in the same subgroup.

When publications of EGJ adenocarcinoma from the East and the West are compared, quite a few differences can be observed. The proportions of the three Siewert EGJ carcinoma subtypes are very different, being almost equal in European series (one-third each), while EGJ type 2 and 3 tumours are much more common in series from Korea and Japan, and the proportion of Siewert type 1 is less than 5% in the Eastern series [24]. These comparisons indicate that, in actual practice the presentation and hence the management of EGJ adenocarcinoma are quite different between these parts of the world. Indian reality is probably closer to the Eastern data rather than the Western data, as type 1 tumours are an unusual sight in our country.

1.3.1 GERD and Barrett's Metaplasia

A major risk factors of esophageal adenocarcinoma is Barrett's metaplasia of the esophageal epithelium. Barrett's metaplasia has been defined as intestinal type columnar metaplasia of the (lower) esophagus, seen at endoscopy and proven by biopsy, associated with chronic GERD [25–27]. Barrett's metaplasia is considered a precancerous lesion, and it is generally accepted that the intestinal metaplasia component is responsible for this risk, even though there is some disagreement on the malignant potential of non-intestinal columnar metaplasia [28]. Barrett's progression to carcinoma proceeds through a well-studied sequence of Barrett's metaplasia—low-grade dysplasia—high-grade dysplasia—adenocarcinoma. In a large prospective study, the annual incidence of these changes in Barrett's mucosa was as follows: low-grade dysplasia, 4.3%; high-grade dysplasia, 1.3%; and adenocarcinoma, 0.5% [29]. However a large number of patients still present with advanced stage of carcinoma at the time of diagnosis. One reason postulated is that up to 40% of patients do not report symptoms of GERD prior to diagnosis [30].

In EGJ carcinoma, however, the association with Barrett's metaplasia varies with the subgroup of tumours (Table 1.1). Siewert type 1 tumours have a strong association with Barrett's metaplasia as in the case of esophageal adenocarcinoma. Chronic GERD and Barrett's metaplasia have been found in 70–97% of patients with type 1 tumours [31]. On the other hand, type 2 tumours have a very low prevalence of Barrett's that is slightly more than type 3 tumours (Table 1.1). Type 3 tumours are thought to be similar in pathology to gastric carcinoma and do not have an etiologic background of Barrett's metaplasia.

1.3.2 Obesity

Several studies have documented a high incidence of GERD in obese patients. The risk is to the magnitude of 16% for every 1 kg/m^2 increase in BMI as calculated in one study [32]. These patients have a high risk of esophageal adenocarcinoma, probably through a mechanism of chronic GERD and metaplasia, while cardiac adenocarcinoma is only weakly associated with reflux disease [33]. Hiatus hernia also has a similar close association with GERD and esophageal adenocarcinoma [34].

1.3.3 Helicobacter pylori

H. pylori infection (especially CagA strain) is considered an important risk factor for adenocarcinoma of the distal stomach. This is believed to proceed through an orderly sequence of events such as chronic active gastritis, atrophic gastritis, intestinal metaplasia and gastric cancer [35]. Siewert type 3 adenocarcinoma seems to have a similar association with *H. pylori*. On the other hand, an infection with *H. pylori* seems to have a protective effect for esophageal adenocarcinoma and type 1 EGJ carcinoma, probably through its inverse effect on GERD [36]. With regard to the role of *H. pylori* in causation of cardia carcinoma (type 2 EGJ), however, the data is quite conflicting and inconclusive [18]. Eurogast Study Group meta-analysis found that there was lack of a consistent association between junctional cancers and *H. pylori* across the world [37]. While most studies from the West showed a negative association, quite a few studies from the East showed a positive association between EGJ adenocarcinoma and *H. pylori* infection [37].

1.3.4 Tobacco Smoking

Tobacco smoking is a well-established and moderately strong risk factor for esophageal adenocarcinoma in both men and women, with ever smoking conferring an approximately doubled risk of adenocarcinoma compared with never smoking (OR, 1.96) [38]. Further, the Northern Ireland Barrett's register reported an approximate twofold increased progression risk from Barrett's esophagus to adenocarcinoma associated with tobacco smoking. A similar association was reported with cardia cancer (type 2) as well [39].

1.3.5 Alcohol Consumption

A large study confirmed no association between alcohol intake and increased risk of esophageal adenocarcinoma [40].

1.3.6 Dietary Factors

The most comprehensive global report of diet, nutrition and esophageal cancer, published by Continuous Update Project of the World Cancer Research Fund International/American Institute for Cancer Research recently, found no good evidence for linking any conventional dietary factors with esophageal adenocarcinoma, except that vegetable intake had limited suggestive evidence for a reduced risk of adenocarcinoma [41].

1.3.7 Genetic and Molecular Studies

Over the last decade, attempts to classify the EGJ tumours based on genetic/molecular characteristics have covered a lot of ground and have provided a lot of exciting data. This is a rather complex area in which the picture has started becoming clearer only recently. The Cancer Genome Atlas (TCGA) project group had done extensive work on molecular profiling of gastric cancer in 2014 [42]. This study had classified gastric carcinoma into four subtypes on the basis of—(1) Epstein-Barr virus (EBV) infection, (2) microsatellite instability (MSI), (3) chromosomal instability (CIN) and (4) genomic stability (GS) [42]. Further work by the same authors has clearly shown that EGJ adenocarcinoma is distinct from esophageal SCC and needs to be viewed separately for therapeutic targets [43]. EGJ carcinomas were found to be quite similar to CIN type gastric carcinoma as opposed to other types of gastric carcinoma. These investigators found that among adenocarcinomas, there was an increasing prevalence of CIN as the location of the tumour moved proximally up to the esophagus and none of the esophageal adenocarcinomas was positive for MSI or EBV, unlike gastric carcinoma (Table 1.3). Some EGJ carcinoma were, however, MSI-positive and EBV-positive. With more and more genome-wide studies becoming available, it is becoming clear that topographical subgrouping (Siewert classification) of EGJ adenocarcinoma is a rather inaccurate way of classifying these tumours. In the not too distant future, the molecular profile of EGJ tumours will, possibly, determine the subgrouping, prognosis and treatment strategies adopted for these tumours.

1.4 Clinical Presentation

The majority of patients at presentation already have advanced disease. The commonest symptoms are dysphagia and odynophagia (i.e. painful swallow). It has been estimated that dysphagia occurs only after 75% of the lumen is obstructed by the tumour, though a small tumour may sometimes cause a tight stenosis through intense fibrosis. Hoarseness or Horner's syndrome occur with the invasion of the recurrent laryngeal nerve or cervical ganglia, respectively, and such patients are

Table 1.3 Molecular mutation profile of CIN type gastro-esophageal adenocarcinomas by anatomic location

	FHIT (%)	CDKN2A (epigenetic silencing) (%)	CDKN2A (total) (%)	WWOX (%)	ERBB2 (%)	MYC (%)	VEGFA (%)	APC (%)	ITGAV (%)	RUNX1 (%)	SMARCA4 (%)	SMAD4 (%)	CD44 (%)
Esophageal type AdenoCa	80	48	81	77	32	31	30	6	4	18	10	24	3
Gastric type EGJ Ca	39	26	52	34	26	19	13	11	11	4	2	15	6
Indeterminate EGJ Ca	58	38	70	59	38	29	21	12	8	0	8	44	4
Fundus/body Ca	28	5	24	37	23	23	10	21	14	3	2	18	12
Antrum/ pylorus Ca	48	6	38	34	31	22	12	16	14	0	5	21	7

Adapted from TCGA [43]

almost always inoperable. Cervical or supraclavicular lymphadenopathy is associated with distant spread and indicates inoperability in EGJ adenocarcinoma. Occult or overt GI bleeding can occur especially with ulcerated tumours. Other important symptoms that indicate advanced disease are chest pain, back pain, excessive weight loss (more than 10%) and long duration of dysphagia (more than 6 months). In addition severe comorbid illnesses, particularly cardiopulmonary, carry a risk of poor overall outcome. Submucosal infiltrating carcinoma at the EGJ may mimic achalasia, and as such is termed *pseudoachalasia.*

1.5 Investigations

1.5.1 Upper GI Endoscopy

The cornerstone of diagnosis, screening and surveillance is endoscopy by skilled observers. Barrett's mucosa is seen as an extension of the salmon-pink velvety gastric mucosa proximal to the squamocolumnar junction. Biopsies are mandatory to enable a pathologic diagnosis of intestinal metaplasia and any associated dysplasia. Any visible lesion in the mucosa should be biopsied, and in addition four-quadrant biopsies should be taken at every 2 cm along the Barrett's mucosa. To increase the accuracy of endoscopy, additions have been made like chromoendoscopy, high-magnification endoscopy, narrow-band imaging, autofluorescence, light-scattering spectroscopy, optical coherence tomography and confocal endomicroscopy. These techniques have been evaluated in individual studies and incorporated in various endoscopy systems. Having shown benefit in individual studies, these technologies have not been adopted across the board for reasons of high cost, absence of high-quality evidence of benefit and poor penetration across the world.

Endoscopy allows accurate characterization of the tumour's configuration, length and localization. At least six biopsies from non-necrotic areas of the tumour increase the yield to nearly 100%. Endoscopic views while crossing the EGJ and then the retroflexed views after entering the stomach are a good way of preoperatively subgrouping the tumours as per the Siewert classification. However about half the tumours in the Indian subcontinent are not passable with an endoscope due to the severity of the obstruction.

1.5.2 Endoscopic Ultrasound (EUS)

Most of the literature on EUS and esophageal carcinoma pertains to esophageal SCC and adenocarcinoma [44]. There is paucity of studies on the role of EUS in EGJ carcinoma. EUS is used for staging esophageal cancer and in the evaluation and management of patients with high-grade dysplasia (HGD) in Barrett's

metaplasia. It enables the endosonographer to evaluate the wall-layer pattern of the esophagus and to detect the presence of regional and celiac lymph nodes. EUS-guided FNA permits directed tissue sampling of adjacent nodes. The endoscope-based systems are divided into radial and linear array scanning systems. The radial echoendoscope uses a mechanically rotated transducer to generate a real-time 360-degree cross-sectional image perpendicular to the long axis of the instrument. The linear array echoendoscope has an electronically operated transducer that produces a 270-degree real-time image parallel to the long axis of the endoscope and is used to carry out a guided FNAC of adjacent nodes or lesions.

Tumours that do not admit an EUS scope due to stenosis are locally advanced in the majority of cases [45]. In these situations, dilatation of the tumour for the purpose of EUS staging is fraught with the risk of tumour perforation and should be weighed against the low benefit of EUS staging in therapeutic decision-making. These patients are best referred for neoadjuvant therapy in view of the locally advanced nature. EGJ tumours present a unique challenge to the EUS operator because of its location and frequent extension across the EGJ. The trouble is probably due to the imprecise results in the evaluation of gastric invasion because of the difficulty in positioning the probe on the entire circumference of the cardia region and in the gastric fundus. The invasion of the stomach is therefore frequently studied by the retroflexed endoscopy view alone. Hence the EUS assessment of T-stage of EGJ tumours is often inaccurate. A recent study on the role of EUS in EGJ carcinoma found a 48% concordance between EUS uT-stage and pathologic pT-stage (under-staged 23%, over-staged 29%) [46].

EUS is recommended to be performed in all patients with only loco-regional disease, and it may be helpful in the following clinical scenarios:

- Selected patients with high-grade dysplasia and early (T1a) tumours for non-surgical treatment—For accurate T and N staging [47, 48].
- Locally advanced esophageal carcinoma—Staging of T4 tumours to determine resectability [49].
- Locally advanced esophageal carcinoma—Staging for remote nodal disease and selecting out patients who may not undergo a R0 resection, e.g. upper mediastinal nodes in EGJ carcinoma [50, 51].
- Locally advanced esophageal carcinoma—To select patients for neoadjuvant therapy. Stage 2 and 3 patients are usually selected to undergo neoadjuvant treatment prior to surgery [52].

1.5.3 CT Scan

CT scan of the neck, thorax, abdomen and pelvis with intravenous and oral contrast is the standard of care investigation for staging of esophageal carcinoma. The fissure of the ligamentum venosum is seen on the CT separating the caudate lobe from the lateral segment of the left lobe of liver; it points directly at the EGJ [53].

The key findings on CT scan include:

- Wall thickening greater than 5 mm (circumferential or part of the wall).
- Dilated esophagus proximal to an obstructing lesion.
- Tumours infiltrating outside the wall may appear as soft tissue and fat stranding around the esophagus.
- Locally advanced tumours may cause displacement of the tracheobronchial tree. Unfortunately loss of fat plane between the airway and the esophageal tumour cannot be used as an indication of invasion, as no fat plane is normally evident even in patients without a tumour. It is known that the posterior tracheobronchial wall/membrane is unsupported by incomplete cartilage rings and hence normally indent during expiration. CT scans should therefore be acquired in full inspiration to avoid getting a false impression of a compression due to a mass lesion.
- Aortic invasion may be shown in the following findings on the CT scan:
  - The Picus angle is the angle of contact (loss of fat plane) between the esophageal mass and aorta. Angle of contact more than 90° is highly suggestive of invasion of aorta, an angle less than 45° is associated with no invasion, and angle in between 45° and 90° is indeterminate. Accuracy of these findings is about 80% [54].
  - Tumour invasion of the triangular space between the spine, esophagus and aorta may also be indicative of aortic invasion.
- Node metastasis—While nodes can be seen on CT scan, only a mediastinal node with a short-axis diameter exceeding 1 cm is considered abnormal, except for the nodes in the subcarinal region. However lymph nodes may harbour metastases without being enlarged, and hence the location of all visualized nodes should be noted. In addition, it is important to remember that nodes may be enlarged because of inflammatory or infectious etiologies. In a meta-analysis of staging investigations for carcinoma esophagus, the sensitivity and specificity of CT scan for nodal metastases were found to be rather low (0.50 (95% CI 0.41–0.60) and 0.83 (95% CI 0.77–0.89), respectively) [55].
- Distant metastasis can be present in advanced tumours. In a study Quint et al. found the pattern of distant metastasis as follows: abdominal nodes (45%), liver (35%), lung (20%), cervical and/or supraclavicular nodes (18%), bone (9%), adrenal glands (5%), brain and peritoneum (2% each), and stomach, pancreas, pleura, skin or body wall, pericardium or spleen (1% each) [56].

1.5.4 PET-CT Scan

Combined PET and CT scan has a higher sensitivity and specificity for tumour staging than 18F-FDG PET alone [57]. In these integrated scans, the CT scan has two main purposes. It provides an attenuation map to correct for the greater attenuation of photons coming from the deeper structures (as opposed to the photons

coming from the more superficial structures). This correction is not only important to improve the quality of the image and but also allows for an accurate quantitative measurement of metabolic activity. This is denoted as the standardized uptake value (SUV). The SUV is the ratio of metabolic activity in the region of interest to the decay corrected activity of injected 18F-FDG. The other purpose of the CT scan is to provide anatomic reference data that improves the interpretation of the metabolic findings on PET imaging by fusing anatomical with metabolic findings.

PET-CT for EGJ carcinoma faces a unique problem of varying avidity for 18F-FDG depending on various histologic features. While Siewert type 1 and type 2 tumours show intestinal differentiation in the majority of patients, type 3 tumours have pathology more like gastric cancer diffuse differentiation in the majority (Table 1.1).

Poor uptake of FDG (i.e. FDG non-avid tumours) is usually associated with diffuse Lauren type tumours, small tumour size, mucinous content and good differentiation. Up to one-third of gastric tumours can be PET non-avid [58]. These facts should be considered before interpreting PET literature for carcinoma esophagus as a whole.

A study on esophageal adenocarcinoma and EGJ carcinoma from India showed that PET-CT findings led to change in management in 16% of patients [59]. The utility of PET-CT can be summed up as follows:

- Prognostic value—Several studies have shown that there is a good correlation between higher maximum SUV (SUVmax) and poor overall and disease-free survival [60, 61]. Though the pre-treatment SUV values may have prognostic implication, there is a wide range of cut off values of SUVmax that are reported as significant across studies. In published literature there is no clear agreement on the optimal cut off value of the SUVmax.
- Staging—18F-FDG PET is less accurate than EUS for determining the T-stage and is not much better than EUS or CT scan for nodal staging [62]. Uptake in the primary lesion may obscure the involved loco-regional nodes. However 18F-FDG PET-CT is the best investigation for diagnosis of unsuspected distant metastasis and extra-regional involved nodes. In a meta-analysis van Vliet et al. showed that the sensitivity and specificity for detecting distant metastases by 18F-FDG PET were 71% and 93%, respectively, and by CT scan it was 52% and 91%, respectively [55].
- Response assessment during neoadjuvant therapy—Tumour response to neoadjuvant therapy can be quite variable, and only in about half of the patients, it may show a major response. Early PET-CT during neoadjuvant therapy allows early recognition of non-responders and institution of salvage therapy for them. While phase 2 studies have shown feasibility and good outcome of such an approach, randomized studies are awaited to adopt this widely [63, 64].
- Response assessment after neoadjuvant therapy—Schollaert et al. in a systematic review of 26 studies of post-treatment response assessment suggested that post-treatment 18F-FDG PET has good predictive value for long-term outcomes [65].

However, these studies are difficult to interpret because PET-CT was done at varying time-periods after neoadjuvant therapy (22 days to 6 weeks) and with widely different criteria for response measurement.

- Follow-up—PET can detect recurrent/metastatic disease in 8–17% of patients, sometimes even before disease can be diagnosed on standard imaging [66].
- Radiation planning—Good radiotherapy planning needs accurate delineation of gross tumour volume. Clearly distinguishing a small primary tumour from normal esophagus can be difficult with CT alone. Compared to CT for radiation planning, the addition of PET results in major changes in the gross tumour volume (GTV) and also influences the radiotherapy dose delivered to the neighbouring normal organs [67]. This is a relatively new field of work in which new data is emerging by the day.

1.5.5 Staging Laparoscopy and Peritoneal Lavage Cytology

CT scan and PET-CT scan have low sensitivity for small peritoneal metastatic nodules. Older series have reported sensitivity and specificity of CT scan in gastroesophageal adenocarcinoma for the diagnosis of liver metastases, 74% and 99%, respectively, and for the diagnosis of peritoneal carcinomatosis, 34% and 94%, respectively [68]. More recently, with advancement in technology, the sensitivity of CT scan has improved in this regard. In one series with 15% of peritoneal carcinomatosis, the reported sensitivity for CT scan was 75% for diagnosing peritoneal seeding with an impressively low rate of unsuspected peritoneal metastasis (less than 4%) [69]. In another large series, staging laparoscopy changed the treatment plan in 20% of patients [70].

Peritoneal lavage cytology seeks to diagnose free-floating tumour cells shed in the peritoneal cavity. In one large study, staging laparoscopy revealed overt peritoneal metastases in 22.6% of patients with gastric adenocarcinoma and 11.8% in those with esophageal adenocarcinoma. In the same study, positive peritoneal cytology in the absence of obvious peritoneal metastases was identified in another 3.1% of patients with gastric adenocarcinoma and 4.4% of patients with esophageal adenocarcinoma [71]. In another study with potentially resectable esophagogastric adenocarcinoma, 7.2% of patients had positive peritoneal lavage cytology aside from those with obvious peritoneal seedings [72]. The prognosis of positive peritoneal lavage cytology is as grim as grossly obvious peritoneal metastasis. Even though this is a subject of ongoing study, most such patients are offered only palliative chemotherapy.

Others have tried to identify patients at high risk of peritoneal spread who should be offered staging laparoscopy and peritoneal lavage cytology. In a study from MD Anderson, multivariate analysis showed that peritoneal carcinomatosis was associated with poorly differentiated histology, linitis plastica and suspicious CT findings, such as trace peritoneal fluid or nodules [73]. In a French series of esophagogastric adenocarcinoma, the factors associated with positive staging

laparoscopy were signet ring cell carcinoma, poorly differentiated carcinoma, T3/T4 tumours and linitis plastica-type tumour [74]. The National Cancer Care Network (NCCN) recommends laparoscopic staging with peritoneal washings (lavage cytology) for patients with Siewert type 2 and type 3 advanced tumours, clinical stage T3 or more or clinical node-positive tumours [75].

1.6 Staging

The eighth edition of the AJCC TNM classification of esophagogastric adenocarcinoma has made some important changes over the seventh edition (Tables 1.4, 1.5, 1.6 and 1.7) [13]. In an effort to overcome the limitations of the seventh edition, which was based entirely on patients treated by esophagectomy alone (without preoperative or postoperative chemotherapy and/or chemoradiotherapy), the dataset used to develop the eighth edition TNM stage groupings included patients who had received preoperative induction therapy (neoadjuvant) and/or postoperative adjuvant therapy. The availability of these data led to the ability to explicitly define cTNM and ypTNM cohorts and stages (Tables 1.5, 1.6 and 1.7).

The anatomic boundary between esophagus and stomach carcinoma has been redefined in the eighth edition. Tumours involving the esophagogastric junction with epicentre no more than 2 cm into the proximal stomach (originally Siewert

Table 1.4 AJCC 8th edition TNM categories

T category	• TX—tumour cannot be assessed • T0—no evidence of primary tumour • Tis—high-grade dysplasia (limited by the basement membrane) • T1—tumour invades the lamina propria, muscularis mucosae or submucosa – T1a tumour invades the lamina propria or muscularis mucosae (further divided into m1, m2 and m3 from superficial to deep) – T1b tumour invades the submucosa (further divided into sm1, sm2 and sm3 from superficial to deep) • T2—tumour invades the muscularis propria • T3—tumour invades adventitia • T4—tumour invades adjacent structures – T4a—tumour invades resectable adjacent structures as the pleura, pericardium, azygos vein, diaphragm or peritoneum – T4b—tumour invades unresectable adjacent structures, such as aorta, vertebral body or trachea
N category	• NX—regional lymph nodes cannot be assessed • N0—no regional lymph node metastasis • N1—tumour metastasis in 1–2 regional lymph nodes • N2—tumour metastasis in 3–6 regional lymph nodes • N3—tumour metastasis in 7 or more regional lymph nodes
M category	• M0—no distant metastasis • M1—distant metastasis

Table 1.5 (Clinical) cTNM stage grouping according to AJCC 8th edition TNM staging system for esophageal adenocarcinoma

	N0	N1	N2	N3	M1
Tis	Stage 0				
T1	Stage I	Stage IIA	Stage IVA		Stage IVB
T2	Stage IIB	Stage III			
T3	Stage III				
T4a					
T4b					

Table 1.6 (Pathology) pTNM stage grouping according to AJCC 8th edition TNM staging system for esophageal adenocarcinoma

		N0	N1	N2	N3	M1
Tis		Stage 0				
T1a	G1	Stage IA	Stage IIB	Stage IIIA	Stage IVA	Stage IVB
	G2	Stage IB				
	G3	Stage IC				
T1b	G1	Stage IB				
	G2					
	G3	Stage IC				
T2	G1		Stage IIIA	Stage IIIB		
	G2					
	G3	Stage IIA				
T3		Stage IIB				
T4a						
T4b						

Table 1.7 (Pathology following neoadjuvant treatment) ypTNM stage grouping according to AJCC 8th edition TNM staging system for esophageal adenocarcinoma

	N0	N1	N2	N3	M1
T0	Stage I	Stage IIIA	Stage IIIB	Stage IVA	Stage IVB
Tis					
T1					
T2					
T3	Stage II				
T4a	Stage IIIB				
T4b					

type 1 and 2) are now to be staged as esophageal cancers; tumours with epicentre located greater than 2 cm into the proximal stomach (originally Siewert type 3) are to be staged as stomach cancers even if EGJ is involved. Clinical stage grouping (cTNM) based on preoperative investigations has been introduced separately from pathologic TNM (pTNM) (Table 1.5). Additionally, patients who have

received neoadjuvant therapy followed by surgery are staged grouped (ypTNM) separately from pathologic TNM (pTNM) (Table 1.7). A major change in the eighth edition of AJCC TNM classification is the inclusion of certain stage groups that are unique to the post-neoadjuvant setting, e.g. ypT0N0–3M0 and ypTisN0–3M0. The TNM categories are similar to the seventh edition of AJCC TNM classification (Table 1.4) [76].

1.7 Treatment of Early Adenocarcinoma

Though there is no universally accepted definition of 'early' adenocarcinoma of the esophagus, most researchers currently include the following in 'early Barrett's carcinoma': high-grade intraepithelial neoplasia or high-grade dysplasia and mucosal (T1a) and submucosal (T1b) carcinoma [77, 78].

1.7.1 Rationale of Treatment

Esophageal adenocarcinoma progresses through stages of high-grade dysplasia—carcinoma in situ—invasive carcinoma. As the tumours cells breach the basement membrane of the epithelium and invade deeper into the esophageal wall, they gain access to the lymphatics that are abundant in the submucosal layer. Hence risk of lymph node metastasis increases progressively as the tumour invades deeper layers of the submucosa. In a large study, the incidence of nodal metastasis was 0%, 13%, 19% and 56% for tumour stages T1a tumours (limited to the mucosa), T1b-sm1, T1b-sm2 and T1b-sm3, respectively [79]. This may allow for the T1a tumours, limited to the mucosa, to be treated by local endoscopic therapies with no risk of tumour recurrence in the lymph nodes. Thus the options of treatment for T1a esophageal adenocarcinoma are esophagectomy and endoscopic resection/ablation. Esophagectomy has been the standard of care and historically the most accepted treatment for these patients. The advantage is of being able to take care of large segments of premalignant Barrett's metaplasia along with foci of invasive carcinoma and the disadvantages being the postoperative morbidity and mortality associated with major surgery like esophagectomy. On the other hand, endoscopic mucosal resection (EMR) has been used by several experts the world over and, in selected subsets, has shown outcomes equivalent to esophagectomy. A matched control study of two specialized esophageal centres comparing esophagectomy and endoscopic resection for pT1a tumours demonstrated excellent long-term survival rates (median follow-up: 4 years) in both groups, but morbidity (32 vs. 0%) and mortality rates (2.6 vs. 0%) were much higher after esophagectomy [80].

1.7.2 Staging

The risk of nodal metastasis is determined not only by the depth of penetration of the tumour but also by unfavourable histological features such as lymphovascular invasion, poorly differentiated histology or size more than 2 cm [81]. Thus there is need to accurately stage these early cancers prior to choosing definitive therapy. The modalities of diagnosis and staging of early tumours are endoscopic biopsy, EUS and endoscopic resection. Endoscopic biopsy is useful for diagnosis but can be falsely negative due to sampling error. Endoscopic resection gives better tissue samples than biopsy and may result in a change in diagnosis in up to 50% of patients with dysplasia and/or carcinoma [82]. Endoscopic resection also leads to better pathological staging of HGD and T1m and T1sm adenocarcinoma when compared to biopsy and EUS. The accuracy of EUS is low for staging of early esophageal adenocarcinoma, especially in distinguishing T1m from T1sm tumours. EUS results in under staging or over staging of the early tumours, in an important proportion of patients [83]. Therefore, most experts do not recommend the routine use of EUS before EMR, as clinical decision-making will be based more on the EMR findings. Endoscopic resection is the most accurate for diagnosis and staging of early EAC, if the lesion is suitable and adequate expertise is available. EUS may be done prior to endoscopic resection when suspecting deeper invasion, such as in case of lesions with ulcerated or depressed morphology or those that do not lift well after submucosal injection prior to EMR. Thus, EUS should be used in selected cases where the endoscopist suspects deeper invasion on the basis of the endoscopic appearance [84]. EUS, when performed, should be combined with FNA cytology of any suspicious nodes seen in the peri-esophageal region. With the low likelihood of distant metastasis in T1a cancer or HGD, PET-CT has no demonstrated benefit in these clinical settings. PET-CT may be of value in case of T1b disease, for detecting distant involvement [25].

1.7.3 Endoscopic Treatment of Early Carcinoma

Any endoscopic therapy in Barrett's mucosa begins with a close inspection and identification of mucosal irregularities including nodularity, ulceration or irregularity of mucosal contour. These are the areas that should be targeted for the highest yield of neoplasia. In the absence of any mucosal irregularities, the norm is to take several biopsies from the Barrett's mucosa (at least four quadrant biopsies every 2 cm), and further plan is based on the biopsy reports. If, however, endoscopy shows mucosal irregularity in the Barrett's mucosa, the next step in the management should be an endoscopic resection (either EMR or endoscopic submucosal dissection), to allow diagnosis and staging and for therapeutic benefit. As endoscopic submucosal dissection (ESD) is technically

demanding and requires experience, EMR is generally adequate to diagnose the depth of invasion, which is the most important parameter in clinical decision-making for early carcinoma. The pathology report of the endoscopic resection specimen would be useful to decide the subsequent treatment of the patient.

In patients with adenocarcinoma, the depth of invasion determines the curative potential of endoscopic therapy. In case of T1a adenocarcinoma with favourable histology (absence of lymphovascular invasion or well differentiated G1 and G2 tumour), if the margins of EMR resection are involved, then further endoscopic resection by EMR can be done multiple times till the entire lesion is resected. In general, if the post EMR T-stage is T1b or there are high-risk factors like lymphovascular invasion or poor differentiation, then surgical treatment is indicated. However in case of superficial submucosal invasion (T1b sm1), the literature is inconclusive with regard to the likelihood of concomitant lymph node metastasis [85, 86]. It seems there may be a subgroup of sm1 tumours with favourable histology, which can be treated by endoscopic resection with curative intent [87, 88].

Endoscopic resection alone is not adequate treatment for early mucosal (T1a) carcinoma. Several studies have documented that despite achieving complete resection with EMR, up to a third of patients subsequently develop recurrent HGD or carcinoma [25, 89]. Endoscopic ablative treatment of the remaining Barrett's mucosa markedly reduces this risk [90]. Therefore, after successful complete endoscopic resection, all patients should undergo subsequent ablation and eradication of the remainder of the Barrett's mucosa. The treatment options to achieve this eradication of remainder of Barrett's mucosa include complete endoscopic resection, radio-frequency ablation (RFA), cryotherapy and argon plasma coagulation (APC) [84]. The success of endoscopic ablative therapy is measured as complete eradication of all dysplasia, as well as all intestinal metaplasia, in the esophagus. After complete eradication of the Barrett's mucosa and neoplasia, patients need intermittent surveillance endoscopy, probably for life, to detect and treat any recurrence.

ESD has not been universally accepted for endoscopic resection of Barrett's neoplasia, quite in contrast to early squamous neoplasia of the esophagus. Indeed, the principle of ESD—allowing for en bloc resection of lesions irrespective of their size, at the cost of longer procedures, and a longer learning curve—is not compatible with the extensive and often multifocal nature of Barrett's neoplasia. Prospective studies of ESD for Barrett's neoplasia have shown disappointing results, with 39–74% histologically complete resection rates for HGD or EAC and 48–96% curative resection rates for EAC [91, 92]. This may change, however, in the future with increasing experience of high-volume centres in the Western world.

Endoscopic therapy has challenged the traditional approach to surgical treatment of early esophageal neoplasia. Pech et al. in a large study of 1000 consecutive patients with T1a Barrett's carcinoma treated with endoscopic therapy reported a 96.3% complete response rate [93]. They reported that out of 140 metachronous

lesions found at follow-up, 115 could be treated endoscopically with success, and only 12 patients needed surgery for failed endoscopic therapy. Overall survival at 5 and 10 years was 91% and 75%, respectively, with only two deaths related to esophageal cancer. Another study comparing the cost-effectiveness of endoscopic therapy with esophagectomy found that endoscopic treatment for early Barrett's esophagus adenocarcinoma was more cost-effective than esophagectomy [94].

1.7.4 Surgery for Early Carcinoma

Several studies have found that multicentric disease or multiple islands of preneoplastic epithelium could be present throughout the Barrett's mucosa in about half of the patients with early Barrett's cancer [95]. Removal of the entire Barrett's intestinal metaplasia in the distal esophagus therefore should be considered desirable in order to avoid recurrences. In addition adenocarcinoma invading the submucosa (T1b) has a high likelihood of local node involvement, though these are limited to lower mediastinum or lower. In a German study of early adenocarcinoma, 96% of the involved nodes were limited to the infracarinal location, in contrast to 86% in case of lower third early squamous cell carcinoma [78, 96].

The advantages of surgery are the ability to completely remove the lesion and the mucosa at risk, along with draining nodes. Further, endoscopic treatment has high metachronous/recurrent cancers within the Barrett's mucosa in up to one-third of patients, thus needing lifelong surveillance and treatment [97]. The other problems of endoscopic treatment are persistent sub-epithelial islands of intestinal metaplasia and stricture rate that can approach 30% [98].

The surgical options for early adenocarcinoma are as follows:

(a) Radical (transthoracic) esophagectomy
(b) Transhiatal esophagectomy (most widely practiced option)
(c) Minimally invasive esophagectomy
(d) Vagus preserving esophagectomy
(e) Merendino procedure
(f) Sentinel node navigation surgery

(a) *Radical esophagectomy* is the standard for comparison of all treatments directed at esophageal carcinoma. It removes all mucosa at risk and associated nodes, thus enabling the most accurate staging. The only randomized controlled study comparing transhiatal esophagectomy and radical transthoracic esophagectomy showed that patients with limited nodal metastasis benefit from radical surgery [11]. However this benefit is at the cost of increased mortality and morbidity compared to the less aggressive procedures. The pulmonary morbidity, ventilator requirement and ICU stay were significantly more than in the radical surgery group [99].

(b) *Transhiatal esophagectomy* is the most commonly utilized option for surgery of early adenocarcinoma. While experienced endoscopy centres have shown excellent and comparable long-term results with endoscopic therapy for HGD and T1a adenocarcinoma, it seems improbable that these can be reproduced across all hospitals treating early esophageal carcinoma. In one series of patients with early esophageal adenocarcinoma who underwent surgery for failed endoscopic treatment, the endoscopy failures were more likely to be associated with HGD, nodules, ulcers, multifocal dysplasia and persistent Barrett's metaplasia, and these patients were more likely to have undergone significantly more endotherapy sessions [100]. In a large retrospective series of transhiatal esophagectomy for early carcinoma from two Dutch centres, the operative mortality was 4%, and the overall 5-year survival was 68% [101]. Further comparison of the subgroup of (T1m1, T1m2, T1m3 and T1sm1) versus (T1sm2 and T1sm3) showed that the 5-year survival was 97% versus 57%, respectively. In multivariate analysis of the same series, lymph node metastasis was the only factor determining tumour recurrence.

(c) *Minimally invasive esophagectomy* is a term encompassing a wide variety of procedures. The common ones for early esophageal adenocarcinoma are laparoscopic transhiatal esophagectomy, minimally invasive McKeown esophagectomy or minimally invasive Ivor Lewis esophagectomy. The details of each operation are out of the scope of this chapter. The choice of the procedure would lie in the requirement of a formal lymphadenectomy and the final level of the anastomosis.

(d) *Merendino procedure* for early carcinoma has been described from a German centre and consists of a limited esophageal resection performed through a transabdominal and transhiatal approach after splitting of the diaphragmatic hiatus wide and includes a resection of the distal esophagus, proximal stomach and lymphadenectomy [102]. The reconstruction is done by interposition of a 10–15-cm-long pedicled isoperistaltic jejunal segment (retrocolic and retrogastric), between the esophagus and the stomach remnant. This centre showed that in this procedure, the same number of nodes can be harvested as a more radical transhiatal esophagectomy and gastric pull-up, with a lower postoperative morbidity and mortality. However these results have not been replicated by other centres, and the procedure has not been adopted widely [103].

(e) *Vagal-sparing esophagectomy* has been described both for early esophageal carcinoma as well as end-stage benign esophageal diseases. The concept of a vagal-sparing esophagectomy was introduced by Professor Akiyama from Japan [104]. In this operation the mediastinal nodes are not removed, and hence it is only suited for multifocal T1a adenocarcinoma or HGD. According to one group that has accumulated substantial experience in this procedure, the indications for a vagal-sparing esophagectomy are patients with HGD or an intramucosal adenocarcinoma with severe reflux symptoms or dysphagia, long segment Barrett's with a large, fixed hiatal hernia and poor esophageal body motility [105, 106]. These patients are poor candidates for esophageal preservation and should be considered for vagal-sparing esophagectomy.

1.7.5 Comparison of Endoscopic Treatment and Surgery for Early Adenocarcinoma

In the last couple of decades, several centres worldwide have accumulated large experience in endoscopy techniques for early esophageal carcinoma (intramucosal and HGD). One of the largest series of 1000 patients of intramucosal adenocarcinoma treated with endoscopic therapy had a mean follow-up of 56.6 months, 96% of patients had a complete response, and surgery was necessary in 3.7% after initial endoscopic eradication treatment had failed [93]. Metachronous lesions or recurrence on follow-up occurred in 140 (14.5%) patients; but endoscopic treatment was successful in 115 patients, resulting in an overall long-term complete remission rate of 93.4%. The calculated overall 10-year survival was 75% in this study. Hence surgeons are facing a stiff challenge from endoscopists for treatment of appropriately selected patients of early adenocarcinoma. Cost-effectiveness studies using decision-analysis models have also been in favour of endoscopic treatment [94]. In a propensity-matched scoring study, it was found that in patients with early-stage esophageal adenocarcinoma, survival appeared equivalent after endoscopic resection or esophagectomy, but endoscopic resection was associated with shorter hospital stays, fewer readmissions and less 90-day mortality [107]. Despite this large body of literature in favour of endoscopic treatment, it must be understood that there is no prospective randomized or good quality controlled study comparing the two modalities head to head. Then there is the important unanswered question with regard to patient management that is raised by Dubecz and Stein—'Is it really possible to choose between the 0 and 3% probability of a postoperative death and the 100% chance of the rigorous, lifelong follow-up after EMR?'

The decision to opt for endoscopic therapy or surgery has to consider the following factors:

- Stage and histology as determined by EMR pathology findings including depth, lymphovascular invasion, poor differentiation, etc.
- Risk of associated metastatic lymph nodes based on imaging and pathologic findings
- Patient fitness and risk of endoscopy versus surgery
- Experience available in the centre
- Patient wishes and informed consent

1.8 Treatment of Locally Advanced Tumours

1.8.1 Principles of Surgery

Surgery is justified in EGJ adenocarcinoma only if the patient is fit to withstand the surgery, and clinical judgement indicates that an R0 resection is possible. Palliative surgery is rarely justifiable in EGJ adenocarcinoma. Several studies have shown that the 5-year survival following a R0 (micro- and macroscopically

complete) resection is much better compared to a R1 or R2 resection (43–49%, 0–11% and 0–4%, respectively) [108–111]. Across published studies it has been consistently shown that an R0 resection is one of the most important factor associated with long-term survival. Incomplete resection (R1 or R2) is usually associated with high morbidity and mortality and is no better than medical therapy. Good quality surgical resection for EGJ carcinoma should aim to provide oncologic clearance with regard to the longitudinal resection margins (proximal and distal), circumferential resection margin and removal of all lymph node stations at risk of metastasis.

1.8.1.1 Longitudinal Resection Margins

The microscopic longitudinal spread of the tumour beyond the grossly visible tumour margins determines the longitudinal resection margins at surgery. Tam et al. in a prospective study of squamous cell carcinoma esophagus reported that the anastomotic recurrence rate was 20%, 8% and 0% when the resection margin was less than 5 cm, between 5 and 10 cm and more than 10 cm, respectively [112]. The studies on this issue in EGJ adenocarcinoma do not provide a clear answer. The interpretation of these studies is further confounded by the timing of the measurement, i.e. in vivo (during surgery) or ex vivo fresh preparation (of the specimen after resection) or ex vivo fixed specimen (and the number of days of fixation) [113]. It is well documented that the specimen shrinks longitudinally after resection and the in vivo measurement (during surgery) is much longer than in the resected specimen. The exact quantum of shrinkage is a matter of debate. In a study on patients undergoing esophagectomy, the overall shrinkage for the whole specimen after fixation was about 50% [114].

The recommended in vivo proximal resection margin for adenocarcinoma EGJ in four studies on Western patients have been 5 cm, 7 cm, 10 cm and 12 cm [115–118]. Barbour et al. found that 3.8 cm ex vivo (approximately 5 cm in vivo) proximal resection margin was independently predictive of better survival [116]. Hence, in the West, 5 cm in vivo proximal resection margin is the acceptable standard [116]. Mine et al. in a study on Siewert type 2 and 3 tumours in Japanese patients found that an ex vivo proximal resection margin (stretched resected specimen) more than 20 mm was independently related to better survival. The authors equated this to a 28 mm in vivo proximal resection margin [119]. Thus the Japanese recommendation is a 3 cm in vivo proximal resection margin for patients undergoing an extended gastrectomy for Siewert types 2/3 adenocarcinoma [119].

The distal resection margin for EGJ adenocarcinoma has been even less well studied. In a rare study dedicated only to this issue, the authors recommended a 5 cm in vivo distal resection margin in order to achieve consistently negative resection margins or, alternatively, advocate the routine use of frozen section examination [120].

It is clear from the available data that the increasing longitudinal spread of the tumour is also associated with other negative prognostic markers like depth of

penetration, nodal spread, differentiation of the tumour and Lauren classification [119, 121, 122]. Barbour et al. found that the benefit of survival associated with an ex vivo proximal margin more than 3.8 cm was limited to patients with T2 or greater tumours and less than/equal to six positive lymph nodes [116]. Lauren's diffuse type differentiation is more prone to microscopic infiltration (contiguous and non-contiguous) than intestinal type differentiation. Hence the German guidelines recommend an increased in vivo proximal resection margin of 5–8 cm for diffuse type tumours as opposed to 4–5 cm for intestinal type tumours [122]. The Japanese guidelines recommend a 3 cm in vivo proximal resection margin for T2 or deeper tumours with an expansive growth pattern and 5 cm for tumours with an infiltrative growth pattern [123]. It is clear that to fulfil the aim of R0 resection, it is important to achieve tumour-free resection margins. The length of in vivo resection margins may vary, to an extent, with several factors, and locally advanced stage tumours need a longer resection margin than early stage tumours. Thus it is reasonable to aim for 5 cm in vivo longitudinal resection margins (proximal and distal) and to confirm a tumour-free status with an intraoperative frozen section examination of the resection margins.

The implications of a positive resection margin also need to be better understood. One such situation that the surgeon may have to deal with is a positive frozen section margin during surgery. It should be understood that a positive frozen section margin has been independently associated with increased T-stage, signet ring cells, larger tumours, more infiltrative disease and increased N-stage [124, 125]. What then would be the value of a re-resection in the face of a positive frozen section margin? In a couple of comparative studies, it was found that re-resection improved prognosis but only in those with a low nodal burden (i.e. good biology tumours). Data suggests that the clinical situation in which the positive frozen section margin occurs is equally important in determining outcome when compared to the positive margin alone. While there is no doubt that achieving a negative margin by re-resection should be the aim in such a situation, it is to be understood that only patients with lower stage would benefit from such a re-resection.

The final pathology report with a positive resection margin after surgery is another vexing situation that the surgeon may have to face. There are several treatment options to consider in this case, including chemotherapy, radiotherapy or surgical re-resection. The existing reports of treatment outcomes in such a case are conflicting in their conclusions [126, 127]. Decision-making for the management of positive surgical margin must consider the clinical situation as a whole, and the risks versus benefit of additional treatment are to be carefully weighed. Patients with early stage disease with a positive margin should be considered for more aggressive surgery. However, in patients with more advanced disease stages with positive resection margins, careful thought should be exercised before considering aggressive re-surgery. This is in light of the fact that, in these patients, oncologic factors like advanced T-stage or N-stage are likely to play a greater role in tumour recurrence than a positive resection margin [124].

1.8.1.2 Circumferential Resection Margin (CRM)

The significance of the circumferential resection margin in esophageal cancer was highlighted a couple of decades back when Sagar et al. noted a 55% recurrence rate in patients with a positive CRM as opposed to 13% in those with a clear CRM [128]. Two meta-analyses since then have also concluded that a positive CRM is associated with a poor prognosis especially in patients with T3 tumours and in those following neoadjuvant therapies [129, 130]. Unfortunately there is disagreement on the definition of CRM. The College of American Pathologists defines the CRM as positive if tumour cells are present at the resection margin, whereas the Royal College of Pathologists label CRM as positive if the tumour cells reach to within 1 mm of the CRM [131]. Analysis of studies with CRM stratified for both criteria showed that the survival with positive American criteria was the worst followed by those with the positive Royal College criteria followed by completely negative CRM by both criteria [118]. As with the longitudinal resection margin, the benefit obtained from a negative CRM appears to be limited to the patients with few or no lymph node metastases. Griffiths et al. showed that CRM status had a greater prognostic effect in T3 tumours with a low metastatic lymph node burden when sub-stratified by percentage of positive lymph nodes (less than or more than 25%) [132].

The significance of CRM with regard to the surgical technique is that it is desirable to have a wide resection margin including some healthy tissue surrounding the tumour, as in the en bloc resection described by Skinner. Altorki and Skinner had compared the results of en bloc esophagectomy versus standard esophagectomy in patients with stage III disease and found that a standard esophagectomy was often associated with inadequate circumferential margin, a less radical lymph node clearance and poorer survival [133]. However en bloc esophagectomy, though desirable, has never been assessed in a randomized controlled trial for this issue, and other authors have questioned the significance of CRM over other more potent prognostic factors such as nodal status, especially after neoadjuvant therapy [134, 135].

1.8.1.3 Nodal Spread

Lymph node metastasis is recognized as a major prognostic factor in EGJ adenocarcinoma and is predictive of loco-regional or distant recurrence and survival. The main goal of lymph node dissection is to optimize tumour staging, to reduce loco-regional recurrence and improve survival. Therefore the lymphatic drainage of EGJ tumours is an important consideration in the surgical approach to these patients. The major nodal basins of interest can be grouped into the mediastinum (upper and lower) and the abdomen. In Siewert type 1 tumours, the majority of lymphatic drainage is towards the lower mediastinum, and a smaller proportion have involvement of nodes in the upper mediastinum and the abdomen. Siewert type 3 tumours have nodal metastasis almost exclusively in the abdomen like gastric carcinoma. The Siewert type 2 tumours have majority of the drainage towards the abdomen, but

a small percentage have involvement of lower mediastinal nodes. In a large cohort of patients, Siewert and his group reported the following distribution of node metastasis—Siewert type 1 (left paracardial (50%), right paracardial (53%), lower posterior mediastinum (50%), upper mediastinum (15%)); Siewert type 2 tumours (left paracardial (67%), right paracardial (63%), lesser curvature (66%), left gastric artery, splenic artery, and celiac axis (together 25%), lower mediastinum (12%)); and Siewert type 3 tumours (left paracardial (49%), right paracardial (52%), lesser curvature (85%), celiac axis (39%) and great curvature (33%)) [111]. Another study corroborated this increase in the incidence of mediastinal node metastasis from type 3 to type 2 and type 1 tumours (9.3%, 29.5% and 46%, respectively) and abdominal node metastasis from type 1 to type 2 and type 3 tumours (53.8%, 70.5% and 90.7%, respectively) [136].

It must be understood that the documentation of node metastasis in a given study is also dependent on the surgical approach and the extent of lymphadenectomy. Siewert type 2 tumours can uncommonly metastasize to the mediastinal nodes, but these are then a marker of poor prognosis. In a systematic review, Okholm et al. found that the node metastasis in lower mediastinal stations in type 2 tumours ranged from 7.5 to 23.8%, whereas upper mediastinal node involvement was less than 4% [137]. However it must be pointed out that Siewert type 2 tumours often are treated with transhiatal procedures and hence the mediastinal nodes are underdocumented in such studies [138]. In a Dutch study wherein transthoracic esophagectomy was done for Siewert type 2 tumours as a part of a larger randomized study, 22% of patients had upper mediastinal nodes, and the median survival of this subgroup was only 8 months [99, 139]. Siewert type 1 adenocarcinoma has an even higher incidence of upper mediastinal nodes when extended lymphadenectomy is performed. This was documented by Altorki et al. in a study of patients undergoing three-field lymphadenectomy [140]. The incidence of cervico-thoracic node metastasis (upper mediastinum and cervical) was 37% for esophageal adenocarcinoma, though EGJ adenocarcinoma was not separately specified. The cervico-thoracic nodal metastases were associated with large positive node burden in the abdomen and/or mediastinum. Patients with positive cervico-thoracic nodes had a poor 15% 5-year survival. In another study the pattern of nodal spread in locally advanced (T3 stage) esophageal adenocarcinoma and EGJ adenocarcinoma was documented in patients who underwent a three-field lymphadenectomy [141]. The cervical, thoracic and abdominal node metastasis were 35% and 70%, 70% and 20%, and 40% and 100%, in esophageal adenocarcinoma and EGJ adenocarcinoma, respectively. These factors must thus be considered to have an important role in therapeutic decision-making for these patients.

Increasing nodal burden strongly correlates with increasing T-stage. Pedrazzani et al. showed that in patients with T2, T3 and T4 tumours, high node burden (more than 6 positive nodes) was seen in 29%, 45% and 75% of patients, respectively, thus supporting the fact that the increasing tumour depth is associated with increasing node metastasis [136]. Furthermore, in this study, increasing number of involved nodes was linked to poor long-term survival (5 years survival was 0%, 26% and 54% in patients with more than 6, 1–6 and 0 involved nodes,

respectively), suggesting that even after R0 resection, the number of involved nodes determines the overall survival.

AJCC considers all regional nodes equal in significance, and N-stage is only determined by the number of positive nodes [142]. This is to emphasize that long-term survival is still possible with multimodality therapy in such patients, e.g. with celiac node metastasis. However celiac node metastasis in EGJ carcinoma is associated with large nodal burden and usually poor survival. The debate of the significance of the location of the nodal metastasis versus the total number of positive nodes is far from settled. A recent study with a large patient cohort from Europe, undergoing surgery after neoadjuvant therapy, reported that the patients with relatively distant lymph node metastases along the celiac axis and/or the upper mediastinum have a negative impact on survival [143]. The median survival for patients with both these stations positive for nodal metastasis had a median survival of only 8 months. However another study from the USA drew opposite conclusions. Sepesi et al. reported that only the number and not the location of positive nodes in patients with distal esophageal or EGJ adenocarcinoma was predictive of survival after preoperative chemoradiotherapy [144]. While another large international multicentre study of patients with R0 resection for esophageal adenocarcinoma showed that the total number of harvested nodes is also an independent predictor of survival, in addition to the number of involved lymph nodes and depth of tumour invasion [145]. This study found that removal of at least 23 lymph nodes was associated with improved survival. Hence, it appears that both the nodal burden (number) and the location of the positive nodes determine the prognosis for EGJ adenocarcinoma.

'Skip metastasis' is metastasis to lymph nodes distant from the primary tumour, without metastasis in the nodes in close proximity to the tumour, possibly due to the complex lymphatic drainage of the esophagus. These so-called skip metastases contribute to the fear of invisible micrometastases far from the primary tumour site and hence provide a rationale for a more extended lymphadenectomy. Some authors have estimated that metastases may be found in lymph nodes of the second or third anatomic compartment (namely, upper abdomen, mediastinum and cervical) while skipping the nodes of the compartment with the primary tumour, in up to 50–60% of esophageal cancer [146].

'Sentinel node' has been defined as the initial lymph node that receives lymphatic flow directly from the primary tumour and is usually the first site of metastatic deposit. The sentinel node concept hinges on the rationale when sentinel node shows no metastasis, and extensive lymphadenectomy may be omitted. Kitagawa and his team have investigated the role of sentinel node surgery in esophageal cancer [147]. Sentinel node-guided surgery is best suited for early esophageal cancers (T1 tumours), while advanced cancers are not considered suitable because the lymph vessels are often destroyed by the tumour and fibrosis due to neoadjuvant therapy. The sentinel node approach is as yet considered under investigation, and most of the work so far has been done in Japan on superficial squamous cell carcinoma. Currently, a Dutch trial (the SNAP study; NTR5245) on sentinel node procedure after an endoscopic resection of the primary tumour is ongoing and recruiting [148].

1.8.2 Surgical Approach Based on Siewert Type

The subject of surgical resection for EGJ carcinoma resembles a minefield with a wide variety of surgical procedures and the heterogeneity of the studies available to interpret the benefit of these procedures. Notwithstanding the controversies surrounding the Siewert classification, it serves as a good starting point to understand the surgical approaches to EGJ carcinoma and the pitfalls of those approaches.

1.8.2.1 Siewert Type 1

These tumours are frequently clubbed with esophageal adenocarcinoma (not involving the EGJ) and are referred to as Barrett's adenocarcinoma. Quite a bit of the conclusions about surgical approach to these patients is drawn from literature for esophageal adenocarcinoma in general. The objective of surgery is to achieve a negative resection margin (as discussed in the earlier section), complete resection of Barrett's mucosa and optimal lymphadenectomy. Thus subtotal esophagectomy with a 5 cm margin of stomach is the aim of surgery for these tumours. Several surgical techniques have been described to achieve such a R0 resection, all of which have been the subject of several studies with no consensus reached so far in the published literature. The controversial points can be revisited in brief as follows.

Transthoracic Versus Transhiatal Esophagectomy

Though there are several non-randomized studies and meta-analyses, but there is only one randomized study on this issue. The several meta-analyses on this issue suffer from varied inclusion criteria and significant heterogeneity in the conclusions [149–152]. There seems to be very little agreement between the conclusions of these meta-analyses. Thus these do not form good quality evidence for basing clinical guidelines. However the only randomized trial from the Netherlands gave us more insight into the complexity of the problem [11, 99]. Both Siewert type 1 and 2 tumours were included in this well-conducted study. Perioperative morbidity (mainly pulmonary) was higher after transthoracic en bloc esophagectomy, but the in-hospital mortality was no different ($p = 0.45$). On the face of it, the overall long-term survival was equal in both arms—after transhiatal and transthoracic resection, 5-year survival was 34% and 36%, respectively ($P = 0.71$, per protocol analysis). However in the patients with a type 1 tumour, a survival benefit of 14% was seen with the transthoracic en bloc esophagectomy even though the p-value was not significant (51% vs. 37%, $P = 0.33$). Though one could question the validity of a subgroup analysis and the results could be a chance phenomenon, but this is the best quality evidence we

have on this issue. It is clear that a more extensive lymphadenectomy can be performed via a transthoracic approach, thereby resulting in more harvested lymph nodes, as seen in the Dutch HIVEX trial—the mean number of resected lymph nodes was 16 and 31 after transhiatal and transthoracic resection, respectively [99]. Though by no means conclusive, it seems that the increased risk of a transthoracic operation for a possible oncologic advantage is indicated for the fit and/or younger patients. Transhiatal surgery should be reserved for older patients with multiple comorbid conditions or the early tumours wherein radical clearance in the mediastinum is considered unnecessary [153].

Extended Lymphadenectomy Versus Standard Lymphadenectomy

The choice of whether to perform an extended mediastinal lymph node dissection and to what extent is largely governed by the choice of surgical approach. Extended lymphadenectomy can be viewed as the number of nodes to be resected or the stations of lymph nodes to be dissected. Various guidelines have slightly different recommendations for the minimum number of nodes to be resected (for assessing the pN status)—German guidelines, 16 nodes; UK guidelines, 15 nodes and NCCN (USA) guidelines, 15 nodes [75, 122, 154]. Some authors have advised minimum 23 lymph nodes to be resected for a survival benefit [155]. Worldwide esophageal cancer collaboration recommended that the greater the extent of lymphadenectomy, the better was the survival for patients with esophageal cancer, except at the extremes of stages. Further, this group recommended the resection of 10 nodes for pT1, 20 for pT2 and 30 or more for pT3/T4 stage tumours [156]. The extent of lymphadenectomy and the stations of nodes removed have been described varyingly by different authors. This was sought to be clarified by a consensus meeting of ISDE (International Society of Diseases of the Esophagus) in Munich in 1994 [157]. The extent of lymphadenectomy was grouped into the abdominal, thoracic and cervical fields. Thoracic dissection was further subdivided into standard two-field, extended two-field and total two-field lymphadenectomy. The details of these are beyond the scope of this review and can be accessed elsewhere. In esophageal adenocarcinoma only a few surgeons practise a three-field lymphadenectomy during esophagectomy [140]. The definite benefit of such an extended operation has been an improved staging and prognostication. However the impact of extended lymphadenectomy on survival has not been proven. It seems that patients with limited nodal metastasis derive the most benefit from extended lymphadenectomy. Subgroup analysis of the Dutch RCT showed that patients with 1 to 8 positive lymph nodes had a 5-year loco-regional disease-free survival advantage if operated via the transthoracic route (23% vs. 64%, $P = 0.02$), but not those who had no positive lymph nodes or greater than 8 positive nodes [11]. Presently the general consensus is that the most acceptable operation in a young fit patient of EGJ adenocarcinoma is a standard two-field lymphadenectomy best done as a part of en bloc esophagectomy, as was described by Skinner, DeMeester and others [133, 158–160].

Neoadjuvant Therapy and Lymphadenectomy

It has been shown that neoadjuvant treatment modifies the number and distribution of mediastinal lymph nodes. In these patients pathology examination shows fibrosis or sterile nodes in the previously affected lymph nodes. Using the CROSS trial database, Talsma et al. showed a decreased lymph node harvest after neoadjuvant therapy compared to surgery alone (14 vs. 18 lymph nodes) [161]. Additionally, in this study, the total number of resected nodes was not associated with survival in the neoadjuvant therapy group. However other studies have disagreed with these conclusions. Mariette et al. found that more than 4 positive nodes and a lymph node ratio of 0.2 or more were the only factors predictive of poor survival, on multivariate analysis in their series [162]. Additionally they found that neoadjuvant chemoradiation made no difference to the prognostic role of both the number and the ratio of node metastasis. Thus the importance of lymphadenectomy after neoadjuvant therapy is as yet an unanswered question that awaits a prospective controlled trial. According to the most recent NCCN guidelines, the optimum number of nodes to be removed after preoperative therapy (chemotherapy and/or radiotherapy) is currently unknown [75].

Minimally Invasive Esophagectomy

Several studies have shown that the most vexing problem with the radical transthoracic esophagectomy is the high incidence of postoperative morbidity [163, 164]. Pulmonary morbidity forms a large proportion of the postoperative complications. Several variations of minimally invasive esophagectomy have been practised by esophageal surgeons across the world in an effort to reduce pulmonary morbidity. The critics of minimally invasive surgery try to rationalize that the extent of mediastinal dissection and hence the surgical stress is same between open esophagectomy and minimally invasive esophagectomy. The Dutch conducted a multicentre randomized controlled trial (TIME trial) between open en bloc esophagectomy and minimally invasive esophagectomy. Pulmonary infection was seen in 34% and 12% of patients in the open and minimally invasive esophagectomy groups, respectively ($p = 0.005$). The operative mortality was low (one and two patients in each group) and statistically equal in both groups. A later follow-up study of the same cohort of patients found that minimally invasive esophagectomy was associated with a better quality of life compared to open surgery at 1-year assessment [165].

1.8.2.2 Siewert Type 2

These tumours are treated surgically either as esophageal adenocarcinoma or as gastric adenocarcinoma. A recent survey of surgeons across the world showed that for Siewert type 2 tumours, an extended gastrectomy was favoured by 66% of

respondents, followed by esophagectomy in 27% and total gastrectomy in 7% [1]. The controversies in choosing the surgical procedures for Siewert type 2 tumours can be understood as follows.

The Enigma of Siewert Type 2 Tumours

Tumours that are centred on the EGJ are topographically classified as Siewert type 2. The Siewert classification hinges on accurate subgrouping of these tumours by endoscopy and imaging. However this grouping is far from perfect, and the preoperative subgroups and pathologic subgroups often do not match. In the Dutch RCT of Siewert type 1 and 2 tumours, a large proportion of endoscopic Siewert type 1 tumours were subsequently re-classified by pathologist as Siewert type 2 tumours (proportion by preoperative endoscopy was 180:40 and by postoperative pathology was 90:115, respectively) [11]. Logically, Siewert type 2 tumours may actually include esophageal adenocarcinomas arising from short- or ultrashort segment Barrett's metaplasia, the sub-cardial gastric cancers and, possibly, the 'true' cardia cancers. Studies have documented that epidemiologically Siewert type 2 tumours are a mix of two types of tumours—gastric-type adenocarcinoma with a *H. pylori*-related aetiology, arising from severe atrophic gastritis and intestinal or diffuse subtype, and esophageal Barrett's type adenocarcinoma with a reflux-related aetiology and usually intestinal subtype [166–168]. When studies of EGJ adenocarcinoma from the East and the West are compared, very interesting contrasts emerge. The proportions of the three Siewert subtypes are very different: the proportions are almost equal (about one-third each) in European series, whereas majority of EGJ adenocarcinoma in Korea, China and Japan are Siewert types 2 and 3 [24, 151, 169]. In Eastern series, Siewert 2 tumours have oncological outcomes similar to Siewert 3 tumours and non-cardia gastric cancer [170]. In contrast, in a study of Western patients, node metastasis was seen in 8%, 16% and 30% of Siewert type 1, 2 and 3 tumours, respectively, and the median survival was 38, 28 and 24 months, respectively. This shows that at least in the Western studies, the three Siewert subtypes have different prognoses, as opposed to Eastern studies—good in Siewert type 1 tumours, intermediate for Siewert 2 tumours and poor in Siewert type 3 tumours (comparable to gastric cancer). Overall, it appears that the surgeons in different parts of the world face contrasting clinical situations when treating patients with EGJ adenocarcinomas.

Choosing a Surgical Procedure for Siewert Type 2 Tumours

The conventional choice for these tumours is either an esophagectomy with a 5 cm margin of stomach or a total gastrectomy extended to include the lower esophagus with a 5 cm margin. Some studies have recommended treating Siewert type 2 tumours like distal esophageal adenocarcinoma with an esophagectomy (preferably en bloc) [171–174]. Leers et al. presented their comparison

of distal esophageal adenocarcinoma and gastro-esophageal adenocarcinoma (Siewert type 2) and showed a similarity in the mediastinal node involvement in the node-positive patients (47% and 41%, respectively) and 5-year survival (45% and 38%, respectively) [173]. In another study the incidence of a positive longitudinal resection margin (R1 resection) was higher with extended gastrectomy than with esophagectomy (38% versus 7%, $p = 0.04$) [121]. A lower incidence of positive circumferential margin was noted with an esophagectomy, as compared to gastrectomy, in a Dutch study (11% versus 29%) [175]. NCCN has also recommended similar surgical procedures for Siewert type 1 and 2 adenocarcinoma [75].

Unlike what the preceding literature may make us believe, the issue of the surgical procedure of choice for Siewert type 2 tumours is far from settled. Siewert group had presented their large experience with extended total gastrectomy for Siewert type 2 adenocarcinoma [111]. They recommended 'an extended total gastrectomy including wide splitting of the diaphragmatic hiatus, transhiatal resection of the distal esophagus, and enbloc lymphadenectomy of the lower posterior mediastinum, in addition to a formal abdominal D2 lymphadenectomy'. They concluded that if R0 resection could be achieved, extended total gastrectomy gave survivals similar to transthoracic esophagectomy. In agreement with this conclusion, a few studies from the West and most studies from the East (Japan, Korea and China) have concluded that extended total gastrectomy provides good oncologic clearance (R0 resection) and survival in patients with Siewert type 2 tumours [24, 152, 169, 176, 177]. Most studies from the East have argued that Siewert type 2 and 3 tumours in this part of the world are similar to gastric adenocarcinoma and can be treated similarly provided negative margins can be achieved [24, 169]. Subgroup analysis of a Dutch RCT showed that for Siewert type 2 adenocarcinoma, transthoracic radical esophagectomy did not yield any survival benefit over a transhiatal esophagectomy [11]. A Japanese group conducted a randomized trial of left thoracoabdominal esophagectomy versus a transhiatally extended total gastrectomy for Siewert type 2 and 3 tumours with less than 3 cm esophageal involvement [178]. The 10-year overall survival rate was found to be similar (24% versus 37%, $p = 0.06$) in the two operation groups, respectively, and subgroup analysis showed that survival was also similar in the two Siewert types of tumours (types 2 and 3). Thus the Japanese recommendation is to surgically treat Siewert type 2 tumours with up to 3 cm esophageal involvement, with a transhiatally extended total gastrectomy and a transthoracic approach for tumours with a more extensive involvement of the esophagus [123]. A last but important bit of information to compare the two procedures (esophagectomy versus gastrectomy for Siewert type 2) concerns the morbidity and perioperative outcomes of the two procedures. In the Japanese RCT, the left thoracoabdominal esophagectomy had an increased morbidity as compared to transhiatally extended gastrectomy (49% versus 34%, respectively) [178]. Another follow-up study has shown that the health-related quality of life 6 months after transthoracic esophagectomy is significantly worse than that following total gastrectomy [179]. Thus gastrectomy seems a more attractive option from a morbidity and quality of life perspective.

Thus choosing a surgical procedure for Siewert type 2 tumours hinges on the following factors—extent of esophageal involvement (less or more than 3 cm), presence of mediastinal nodes, the bulk of the tumour, patient fitness to withstand a transthoracic procedure should it be necessary and the experience of the surgical team to carry out adequate mediastinal clearance through the transhiatal route. Even so, it is well acknowledged now that tumour biology is a greater determinant of the oncologic outcome rather than the surgical approach. In a large Dutch population-based study of EGJ tumours, it was concluded that perioperative chemoradiotherapy, and not surgical approach, influenced survival [180]. This, however, assumes that the surgeon aims to carry out a R0 resection with minimum possible morbidity. Thus the commonest surgical procedure for Siewert type 2 tumours is a transhiatally extended total gastrectomy with radical resection of lower mediastinal nodes and a D2 lymphadenectomy in the abdomen. While in most patients with Siewert type 2 tumours this procedure can accomplish this goal, there are patients where alternative (e.g. transthoracic) surgical approaches may have to be chosen based on the above described factors. In Siewert large experience about 20% of patients needed such an alternative (e.g. transthoracic) approach to type 2 tumours [111].

1.8.2.3 Siewert Type 3

These tumours are treated similar to gastric adenocarcinoma. The operation of choice is usually a total gastrectomy with D2 lymphadenectomy.

Resection Margins for Siewert Type 3 Tumours

As with other Siewert types, a 5 cm proximal and distal margin is appropriate for Siewert type 3 adenocarcinoma as well [116, 121]. Circumferential margins are easier to define for esophageal carcinoma, and so its usefulness pertains to esophageal portion of the specimen, in particular for Siewert types 1 and 2 [181]. Thus the circumferential margin is not so important a consideration in Siewert type 3 and gastric adenocarcinoma, wherein it should be easier to achieve a wide local margin. In most instances, resection can be achieved through an abdominal approach, and a thoracic approach is unnecessary. Total gastrectomy has been preferred over proximal gastrectomy by several international guidelines [75, 123]. The oncologic advantages of total gastrectomy are a longer distal resection margin and clearance of perigastric nodes along the distal stomach and the pylorus. In addition proximal gastrectomy is associated with problems of reflux and anastomotic strictures after an esophagogastric anastomosis [182]. Meta-analysis has shown that though proximal gastrectomy is associated with a similar long-term survival as compared to total gastrectomy but with a higher local recurrence rate (36.8% vs. 23%, respectively, $p = 0.004$) [183]. Despite this discouragement there are several surgeons who continue to practise proximal gastrectomy for small proximal gastric/ Siewert type 3

tumours. The resection nodes along the distal stomach and pylorus do not seem to provide much survival advantage. Some authors have argued that positive parapyloric nodes in Siewert type 2/3 tumours are associated with advanced disease and there is not much oncologic advantage gained by resecting these, by means of a total gastrectomy [184]. The other issue to consider is the long-term nutritional outcome. Total gastrectomy needs lifelong nutritional rehabilitation to get good long-term results, while proximal gastrectomy patients do much better in this aspect [185]. Hence some surgeons in some parts of the world practise and report radical proximal gastrectomy for small proximal gastric carcinoma and Siewert type 3 carcinoma [186]. A detailed review of this controversial issue is beyond the scope of this chapter, and the reader may be referred elsewhere for the same.

Nodal Spread of Siewert Type 3 Tumours

The nodal spread of Siewert type 3 tumours is mostly confined to the abdomen. Nodal pattern of spread reported in various studies has been as follows—only abdomen, 82–98%; abdomen and chest, 2–18%; and only chest, 0–2% [187–189]. The risk of mediastinal node metastasis correlates with the extent of esophageal involvement and the grade of the tumour. Hosokawa et al. showed that esophageal invasion 2 cm or more and histopathological grade 3 or 4 correlated with the involvement of mediastinal nodes [190].

The importance of the number of positive nodes or of lymph node ratio (LNR) has been studied extensively in gastric carcinoma [189]. LNR is defined as the ratio between involved and total resected nodes. While the total number of involved nodes is a main prognostic determinant, even the number of resected nodes seems to affect survival. A possible explanation for this could be the presence of micrometastases in the negative nodes (by routine pathology examination), which could explain the improvement in survival after extended lymphadenectomy in pN0 patients (by routine pathology). The worldwide esophageal cancer collaboration recommendation for the number of nodes to be resected, as per T-stage, is the same as other Siewert types (refer to earlier sections) [156]. Some studies have shown that, in inadequately staged patients, LNR correlated better with survival, than number of involved nodes [162]. Mariette et al. showed that in patient subgroups with less than 15 or more than 15 nodes removed, the LNR correlated better with survival in the former, while the total number of involved nodes predicted survival better in the latter group [162].

Lymphadenectomy for Siewert Type 3 Tumours

Today an abdominal D2 lymphadenectomy as defined by the Japanese guidelines would be considered the standard of care for a locally advanced Siewert type 3 tumour. However, the initial RCTs of D1 versus D2 lymphadenectomy for gastric carcinoma from the MRC group and Dutch centres led one to believe

that D2 surgery has no oncologic advantage and a greater postoperative morbidity [191, 192]. It has since been recognized by surgeons in the West that distal spleno-pancreatectomy is responsible for a major part of the morbidity and is not a necessary part of the operation. Jiang et al. in a meta-analysis showed that the morbidity and mortality of the two operations is similar in subgroups with pancreas and spleen preservation [193]. D2 patients with spleen and pancreas preservation also had a trend towards a lower risk of gastric cancer-related death. Most guidelines now recommend D2 lymphadenectomy for surgery of gastric carcinoma [194–198]. A detailed discussion about D2 lymphadenectomy is beyond the scope of this chapter, and the reader is advised to refer elsewhere for the same.

The definition of D2 lymphadenectomy has been different in the East and the West. In Japan it is defined by numbered nodal stations grouped according to the surgical procedure (total or subtotal gastrectomy). The Japanese guidelines recommendations are as follows—'D1 lymphadenectomy is indicated for T1a tumours that do not meet the criteria for EMR/ESD, and for cT1bN0 tumours that are histologically of differentiated type and 1.5 cm or smaller in diameter; D1 (plus) lymphadenectomy is indicated for cT1N0 tumours other than the above; D2 lymphadenectomy is indicated for potentially curable T2–T4 tumours as well as cT1Nplus tumours' [123]. According to NCCN D2 lymphadenectomy involves resecting perigastric nodes and nodes along the left gastric artery, common hepatic artery, splenic artery and splenic hilum. NCCN recommendation for localized gastric cancer and Siewert type 3 carcinoma is gastrectomy with D1 or modified D2 lymph node dissection, with the aim of examining at least 15 nodes for proper staging [197]. NCCN guidelines emphasize that D2 dissection should be performed by experienced surgeons in high-volume centres.

Extended Lymphadenectomy

Though para-aortic lymph node dissection is not carried out as part of lymphadenectomy in the West, it has been extensively studied in Japan. Yonemura et al. studied and grouped the major lymphatic pathways from the stomach [199]. They classified the route of lymphatic drainage into four groups: (1) left subdiaphragmatic pedicle, (2) celiac pedicle, (3) superior mesenteric pedicle and (4) retropancreatic pedicle. It was found that lymph flow from upper-third gastric cancer was characteristically along the left subdiaphragmatic pedicle, especially for the cardia cancers. The nodal stations for this pathway were the upper para-aortic nodes to the left of aorta up to the level of the left renal vein. Two RCTs conducted in Japan have, however, not found any survival advantage in routinely adding para-aortic node dissection to a D2 lymphadenectomy [200, 201]. However patients with isolated para-aortic node metastasis have a better survival than those with liver or peritoneal metastasis (18% vs. less than 5%) [201]. Selective para-aortic lymphadenectomy in the regions described may be considered and is a subject of active research in Japan [199].

1.9 Multimodality Treatment

Surgery is still the primary treatment for resectable EGJ adenocarcinoma, but most patients across the world, especially in India, present with locally advanced disease, and long-term survival with surgery alone is poor (5-year survival is about 25%) [202]. There is reasonable consensus that since surgical resection alone is insufficient, additional therapy must be considered. But there is little agreement on the optimal multimodality therapy, and practices vary across the world.

Several multimodality strategies such as preoperative chemotherapy or chemoradiotherapy, perioperative chemotherapy, postoperative chemoradiotherapy and adjuvant chemotherapy have been investigated in several studies. While interpreting the myriad studies on this issue, one has to keep in mind that most studies have included EGJ carcinoma as part of predominantly esophageal or gastric cancer studies. EGJ carcinoma usually constitutes a minority in these studies, and very few studies have focussed on EGJ adenocarcinoma as a separate entity. Indeed, some studies have included only certain subtypes of EGJ adenocarcinoma. While interpreting the results of these studies, it should also be kept in mind that there are several important differences in aetiology, stage at presentation, treatment tolerance and outcomes from different parts of the world. Results from one part of the world cannot necessarily be extrapolated to another—e.g. Eastern countries have consistently reported better outcomes as compared with the West. As the molecular biology of EGJ adenocarcinoma becomes clearer, we are gradually realizing that while Siewert's classification may be quite helpful for determining the appropriate surgical approach, it has only limited utility in the pre-, post-, or perioperative treatment.

1.9.1 Pre-/Perioperative Chemotherapy (Table 1.8)

Two of the accepted approaches for the treatment of locally advanced EGJ cancer are perioperative chemotherapy, which is mostly used in Europe, and preoperative chemotherapy that is commonly used in the USA. The strongest evidence for neoadjuvant chemotherapy in EGJ carcinoma comes from the French ACCORD RCT [202]. This is because this trial has a large proportion (64%) of patients with EGJ adenocarcinoma (Table 1.8). It showed a significant improvement in R0 resection rates and overall survival (Table 1.8). The much larger MAGIC trial (RCT) was reported earlier than the French trial, but the proportion of patients with EGJ carcinoma is much smaller (11%) [203]. This trial too showed a consistent improvement in overall and disease-free survival (Table 1.8). Another phase 3 RCT from US Radiation Therapy Oncology Group (RTOG) 8911/Intergroup (INT)-0113 trial showed surprising contradictory results [109, 204]. The percentage of EGJ patients was not reported. No difference in median OS or R0 resection rates was noted between the two arms. Some of the factors that could have impacted the surprising

Table 1.8 Randomized controlled trials of pre-/perioperative chemotherapy followed by surgery

Trial	Treatment regimen	Patients enrolled	Histology	EGJ patients enrolled	R0 resection rates	Survival
ACCORD-07/ FNCLCC-FFCD [202]	CF × 2–3 → surgery → CF × 3–4 vs. surgery alone	224 (250 planned)	AdenoCa 100%	64%	87% vs. 74% ($p = 0.004$)	5-year OS, 38% vs. 24% ($p = 0.02$)
MAGIC [203]	ECF × 3 → surgery → ECF × 3 vs. surgery alone	503	AdenoCa 100%	11%	69% vs. 66%	5-year OS, 36% vs. 24% ($p = 0.009$)
RTOG8911/ INT-0113 [109, 204]	CF × 3 → surgery → CF × 2 vs. surgery alone	440	AdenoCa 54%, SCC 46%	NR	63% vs. 59%, ($p = 0.51$)	5-year OS, 19.4% vs. 19.8%
MRC—OEO2 [108]	CF × 2 cycles → surgery vs. surgery alone	802	AdenoCa 66%, SCC 31%	10%	60% vs. 54%, ($p = 0.0001$)	5-year OS, 23% vs. 17%, ($p = 0.03$)
EORTC 40954 trial [205]	CF × 2 → surgery vs. surgery alone	144 (planned—282)	AdenoCa 100%	53%	82% vs. 67%; ($p = 0.036$)	Estimated median survival, 64 vs. 52 months; 2-year OS—73% vs. 70% (not significant)
MRC—OEO5 [206]	ECF × 4 → surgery vs. CF × 2 → surgery	897	AdenoCa 100%	80%	66% vs. 59% (not significant)	Median survival 26·1 vs. 23·4 months; HR 0.90 (95% CI 0.77–1.05, $p = 0{\cdot}19$)
FLOT4-AIO (phase 2 of RCT) [207]	ECF/ECX × 3 → surgery → ECF/ECX × 3 vs. FLOT x 4 → surgery → FLOT × 4	300	AdenoCa 100%	52%	74% vs. 85% ($p = 0.02$); [pCR rate 6% vs. 16% ($p = 0.02$)]	Not yet reported

CF cisplatin and 5-fluorouracil; *SCC* squamous cell carcinoma; *ECF/EFX* Epirubicin, cisplatin and infusional 5FU/capecitabine *OS* overall survival; *FLOT* docetaxel, oxaliplatin, 5FU and leucovorin

results of this trial include the following: after chemotherapy about 20% of patients did not undergo surgery; postoperative radiotherapy was not part of the planned treatment but was used in case of margin positive resection.

The OEO2 trial from the UK showed the benefit of two cycles of preoperative chemotherapy [108]. However it was predominantly an esophageal carcinoma trial, and only 10% had carcinoma of the cardia. The European Organization for Research and Treatment of Cancer (EORTC) 40,954 trial was a much smaller RCT of preoperative chemotherapy, and it included 53% EGJ carcinoma [205]. In this study there was a significantly improved rate of R0 resection (82% vs. 68%; $p = 0.036$); however, there was no difference in survival in between the two arms. The trial was closed early due to slow accrual, and hence the results are poorly powered to conclude anything. The recent MRC OEO5 RCT studied whether intensifying the chemotherapy beyond the OEO2 regimen has any benefits [206]. Four cycles of neoadjuvant ECX (epirubicin, cisplatin and capecitabine) was compared with two cycles of neoadjuvant CF (cisplatin, 5-fluorouracil), and it was found that survival was not any different. Newer chemotherapeutic regimens using docetaxel have raised the hopes of many investigators. The FLOT regimen (docetaxel, oxaliplatin, leucovorin, 5FU) has been tested in a phase 2 RCT reported recently, and the pathologic complete response rate was better for perioperative FLOT chemotherapy versus ECX chemotherapy (16% vs. 6%, $p = 0.02$) [207]. The long-term results of survival outcomes in this trial are awaited.

1.9.2 Preoperative Chemoradiotherapy (Table 1.9)

It is seen that even after adequate surgical treatment, a large number of patients with EGJ adenocarcinoma get loco-regional recurrences on follow-up. Potentially preoperative chemoradiotherapy can reduce local recurrences and improve rates of pathologic complete response (pCR). High rates of pCR have been associated with improved survival across various studies. Most studies on this issue, till recently, had given contrasting conclusions, and the advantage of preoperative chemoradiotherapy remained an unkept promise, so far. This was often because of small sample size of trials, variable regimens of chemoradiotherapy followed and several other shortcomings.

Of late, perhaps the strongest evidence for the benefit of neoadjuvant chemoradiotherapy comes from the Chemoradiotherapy for Esophageal Cancer Followed by Surgery Study (CROSS) [208]. This trial randomized patients with resectable esophageal or EGJ tumours ($n = 366$) to preoperative radiation (41.4 Gy in 23 fractions) along with chemotherapy (weekly carboplatin/paclitaxel) or to surgery alone. Majority were adenocarcinoma (75%), and 24% were EGJ adenocarcinoma. Neoadjuvant chemoradiotherapy was associated with increased rates of R0 resection (92% vs. 69%), improved median OS (49.4 vs. 24 months, $p = 0.003$) and increased 5-year OS (47% vs. 35%). The survival benefit of chemoradiotherapy was more with squamous cell carcinoma as compared to adenocarcinoma with higher

Table 1.9 Randomized controlled trials of preoperative chemoradiotherapy therapy followed by surgery

Trial	Treatment regimen	Patients enrolled	Histology	EGJ patients enrolled	R0 resection rates	Survival	Pathology—complete response
Walsh et al. [262]	CF and XRT (40 Gy) vs. surgery alone	113 (58 vs. 55)	AdenoCa 100%	Cardia 35%, distal esophagus 51%	Not reported	Median OS, 16 vs. 11 months ($p = 0.01$) 3-year OS, 32% vs. 6% ($p = 0.01$)	25%
Urba et al. [263]	CF/vinblastine and XRT (45 Gy) vs. surgery alone	100 (50 vs. 50)	AdenoCa 75%, SCC 25%	Mid/distal esophagus 92%	45/50 vs. 45/47 (not significant)	Median OS, 16.9 vs. 17.6 months; 3-year OS, 30% vs. 16% ($p = 0.15$)	28% (SCC 38%, AdenoCa 24%)
Burmeister et al. [264]	CF and XRT (35 Gy) vs. surgery alone	256 (128 vs. 128)	AdenoCa 62%, SCC 37%	Lower third of esophagus 79%	80% vs. 59% ($p = 0.0002$)	DFS 16 vs. 12 months ($p = 0.18$); median OS, 22.2 vs. 19.3 months ($p = 0.44$)	16% (SCC 27%, AdenoCa 9%)
CALGB 9781 [265]	CF and XRT (50.4 Gy) vs. surgery alone	56 (475 planned) (30 vs. 26)	AdenoCa 75%, SCC 25%	Not reported	Not reported	Median DFS, 3.47 vs. 0.01 years; 5-year DFS, 28% vs. 15%; 5-year OS, 39% vs. 16%	40%
CROSS [208]	Carboplatin/Taxol and XRT (41.4 Gy) vs. surgery alone	366 (178 vs. 188)	AdenoCa 75%, SCC 23%	EGJ 24%, distal esophageal 58%	92% vs. 69% ($p = 0.001$)	Median OS, 49.4 vs. 24 months ($p = 0.003$); 5-year OS, 47% vs. 34%	29% (SCC 49%, AdenoCa 23%)
FFCD 9901 (stage I/II Ca Eso only) [210]	CF and XRT (45 Gy) vs. surgery alone	195 (97 vs. 98) (planned 380)	AdenoCa 29%, SCC 70%	Thoracic esophageal 100%		5-year DFS, 35.6% vs. 27.7%; 5-year OS, 41.1% vs. 33.8%	33%

CF cisplatin and 5-fluorouracil, *SCC* squamous cell carcinoma, *XRT* external beam radiotherapy, *DFS* disease-free survival, *OS* overall survival

pathologic complete response rates (49% vs. 23%; $p = 0.008$). Long-term follow-up study of the CROSS patient cohort has shown that chemoradiotherapy considerably reduces loco-regional recurrences, peritoneal carcinomatosis and distant recurrences [209].

Postoperative morbidity and mortality following preoperative chemoradiotherapy has remained an area of concern. While the CROSS trial data showed no increase in postoperative morbidity and mortality between the two arms, other studies have come to different conclusions on this issue [208]. The French FFCD 9901 RCT showed that while the postoperative morbidity was similar between groups (55.6% v 52.8%; $p = 0.72$), the chemoradiotherapy group had a significantly higher in-hospital postoperative mortality (11.1% v 3.4%; $p = 0.049$) [210].

1.9.3 Postoperative Chemoradiotherapy

The US intergroup RCT (INT 0116) was a predominantly gastric carcinoma of adjuvant chemoradiotherapy following surgery versus observation after surgery. EGJ carcinoma formed only 20% of the 556 patients included in this trial. Survival was significantly improved in the chemoradiotherapy arm (3-year OS 50% vs. 41%, $p = 0.005$; 3-year DFS 48% vs. 31%, $p = 0.001$) [211]. In a follow-up study of the same cohort, it was shown that the benefit persisted after 10 years [212]. Even today this study forms the basis of adjuvant chemoradiotherapy for gastric cancer resection in the USA. The major criticism of this study has been suboptimal surgery for trial patients, according to today's standards. Only 10% of patients had undergone a D2 lymphadenectomy. Hence it was considered that the adjuvant chemoradiotherapy was possibly only compensating for inadequate surgery, and thus its benefit following a formal D2 resection is open to question.

1.9.4 Postoperative Chemotherapy

Adjuvant chemotherapy following resection has been extensively studied in East but only for gastric carcinoma. Very few EGJ tumours have been included in these studies. However since Siewert type 3 adenocarcinoma is treated like gastric carcinoma, it is logical to get to know about the gastric cancer-related adjuvant therapy trials. The best quality and the most impactful of these studies are the Japanese ACTS-GC trial, the Korean CLASSIC trial, the Dutch CRITICS trial and the Korean ARTIST trial [213–216]. Japanese ACTS-GC trial was a phase 3 RCT that showed a major benefit with adjuvant chemotherapy using S-1 versus observation only, in patients undergoing good quality D2 resection for gastric carcinoma [213]. The OS at 3 years was 80.1% vs. 70.1% (HR of 0.68 (95% CI, 0.52–0.87)). The study also reported that S-1 reduced lymph nodal ($p = 0.01$) and peritoneal ($p = 0.009$) recurrence significantly. Though in Japan this is the current standard of care adjuvant

chemotherapy following D2 gastrectomy for gastric cancer, there are questions about its availability as well as efficacy in the rest of the world. The Korean CLASSIC trial (RCT) studied adjuvant capecitabine plus oxaliplatin treatment after curative D2 gastrectomy versus observation [215]. The updated results of this study reported a 5-year OS of 78% vs. 69% (HR 0.66 (0.51–0.85), $p = 0.0015$) and a 5-year DFS of 68% vs. 53% (HR 0.58 (0.47–0.72) $p < 0.0001$) [217]. The Dutch CRITICS trial and the Korean ARTIST trial both studied adjuvant chemotherapy versus chemoradiotherapy for resected gastric cancer, albeit in European and Korean populations, respectively [214, 216]. Both studies showed that the addition of radiotherapy did not benefit the overall subjects of the trials. However the Korean ARTIST trial subgroup analysis of node-positive patients showed that this subset may benefit from the addition of postoperative radiotherapy (3-year DFS was 77.5% vs. 72.3%, $p = 0.0365$) [214]. The ARTIST-II RCT is designed to answer this question, and the study is currently ongoing.

1.9.5 Preoperative Chemoradiotherapy Versus Peri-/Preoperative Chemotherapy (Table 1.10)

The German Preoperative Chemotherapy or Radiochemotherapy in Esophagogastric Adenocarcinoma Trial (POET) is the only phase III study to exclusively enrol EGJ tumours to address this question [218]. Chemoradiotherapy arm had significantly improved rates of pCR (15.6% vs. 2.0%; $p = 0.03$) and pN0 (64.4% vs. 37.7%; $p = 0.01$) after resection [218]. Unfortunately, the trial was closed prematurely because of poor accrual. Thus statistically significant differences could not be demonstrated; however, there was a trend towards improved 3-year survival after preoperative chemoradiotherapy (47.4% vs. 27.7%; $p = 0.07$). Long-term results of this trial showed an improved DFS (HR 0.37, CI 0.16–0.85, $p = 0.01$) but only a statistically non-significant trend to improvement in OS (5-year OS 39% vs. 24%, $p = 0.055$) [219]. Another trial from Sweden/Norway addressed this issue but included all esophageal carcinoma, and Siewert type 1/2 tumours were only 17% of the study population [220]. This study showed that while the addition of preoperative radiotherapy helped in achieving a higher pathological complete response rate, higher R0 resection rate and a lower frequency of lymph node metastases, but there was no improvement in the overall survival.

1.9.6 Response-Guided Therapy

Tumour response to preoperative therapy is not a universal phenomenon. One needs to identify the nonresponsive patients as early as possible to avoid futile and toxic therapy and change to alternative therapy or surgery as early as possible. Currently the most useful predictive investigation for this purpose is the 18F-FDG

Table 1.10 Randomized controlled trials of preoperative chemoradiotherapy therapy vs. preoperative chemotherapy

Trial	Treatment regimen	Patients enrolled	Histology	EGJ patients enrolled	R0 resection rates	Survival	Pathology—complete response
POET [219]	CF and XRT (30 Gy) → surgery vs. CF → surgery	119 (60 vs. 59)	AdenoCa 100%	100%	72% vs. 69% (not significant)	3-year OS 47% vs. 27% ($p = 0.07$)	15.6% vs. 2% ($p = 0.03$)
NeoRes [220]	CF and XRT (40 Gy) → surgery vs. CF → surgery	181 (91 vs. 90)	AdenoCa 72%, SCC 28%	17%	87% vs. 74% ($p = 0.04$)	3-year OS 47% vs. 49% ($p = 0.77$)	28% vs. 9% ($p = 0.02$)
Burmeister et al. [266]	CF and XRT (35 Gy) → surgery vs. CF → surgery	75 (39 vs. 36)	AdenoCa 100%	Not reported	R0 resection rate—84% vs. 80% ($p = 0.61$) R1 resection rate—0% vs. 11% ($p = 0.04$)	Median OS 32 vs. 29 months ($p = 0.83$)	31% vs. 8% ($p = 0.01$)

CF cisplatin and 5-fluorouracil, *SCC* squamous cell carcinoma, *XRT* external beam radiotherapy, *OS* overall survival

PET scan. In the German MUNICON-I trial, metabolic responses were studied with 18F-FDG PET in 110 patients with locally advanced EGJ adenocarcinoma, 2 weeks after induction chemotherapy with cisplatin/fluorouracil [63]. Non-responders underwent immediate surgery, and responders had a total of 12 weeks of further chemotherapy. The PET non-responder patients in this study had a better median survival when compared to historical control non-responders from another study who received chemotherapy irrespective of PET response (25.8 vs. 18 months, respectively). The MUNICON-II trial added chemoradiotherapy in case of early detection of PET non-response, while the responders continued the chemotherapy [64]. Both groups then underwent surgery. By comparing the groups of non-responding patients in the current trial and the previous published MUNICON-I trial, salvage chemoradiotherapy did increase the histopathologic response rate, but this study could not demonstrate an increased R0 resection rate that was the primary endpoint of the study. The prognosis of the subgroup of PET non-responders remains poor, indicating their different tumour biology. The CALGB 80803 trial has recently reported its results in abstract form [221]. This was a crossover study of FOLFOX (5FU, leucovorin, oxaliplatin) chemotherapy vs. carboplatin/paclitaxel (CP). The objective was to determine that changing chemotherapy during preoperative chemo-radiation based on response to induction chemotherapy by 18F-FDG PET imaging can lead to improved pathologic complete response (pCR) in resectable esophageal and EGJ adenocarcinomas. For PET non-responders who crossed over to alternative chemotherapy during chemoradiotherapy, the pCR was 15.6%, as compared to 5% pCR in historical controls. According to the authors, the study met the efficacy criteria for improvement in pCR rates in patients who were PET non-responders and crossed over to alternative chemotherapy. Response-guided treatment is a field of active research currently, and many more studies are in the process of being reported [222]. The problems of PET response criteria and the timing of PET scan are yet without a clear answer.

1.9.7 How to Choose Multimodality Therapy for EGJ Carcinoma

It is now universally agreed that multimodality therapy is definitely needed in locally advanced but resectable EGJ carcinoma, as the results of surgery alone leave a lot to be desired. The potential advantages of upfront or preoperative therapy over postoperative (adjuvant) therapy are as follows: better compliance and delivery of the therapy as the patient is better preserved before the stress of surgery; better vascularized tissues before resection which ensure a good response to the therapy; sterilization of tumour margins and hence a better R0 resection; and reconstructed organs and tissues that are not at risk from the radiotherapy. While there is evidence for some of these points, the others are assumed as part of good practices.

The issue of compliance for pre- versus postoperative chemotherapy is well illustrated by the low postoperative compliance (40%) in the perioperative regimens like the MAGIC protocol [203]. However the differences in compliance with adjuvant (postoperative) chemotherapy are obvious between the studies of adjuvant therapy for gastric carcinoma from the West versus those from the East (46% in the Dutch CRITICS trial versus 67% in the Korean CLASSIC trial and 71% in the Japanese ACTS-GC trial) [213, 215, 216]. These may be explained by the several differences between the populations including earlier tumour stage, racial differences and possibly different biology. The same story unfolds in case of compliance between preoperative and postoperative chemoradiotherapy. In the Intergroup 116 trial, the compliance (as per plan) with postoperative chemoradiotherapy was 64% [211]. However the CROSS trial compliance of 91% for preoperative chemoradiotherapy illustrates that it is possible to get good compliance with good practices and well-planned protocols [208].

The choice of therapy before surgery is between pre-/perioperative chemotherapy and preoperative chemoradiotherapy. Comparison between these two modalities has shown a higher pathologic complete response (pCR) with chemoradiotherapy. Across the literature pCR has been consistently related to good long-term outcome following neoadjuvant therapy. Unfortunately, due to heterogeneity in methodologies and varying regimens used, these differences in pCR have not shown up consistently as improvement in survival in comparative studies (Table 1.10).

Several authors have shown concern about the increase in postoperative morbidity and mortality due to the preoperative therapy. The worry is more with preoperative chemoradiotherapy than with chemotherapy. Though a meta-analysis in 2014 had concluded that neither of the two therapies increase the risk of postoperative morbidity or mortality (except for neoadjuvant chemoradiotherapy for SCC), it remains an issue of worry for quite a few surgeons [223]. Several authors have shown an increase in anastomotic complications, cardiopulmonary morbidity and postoperative mortality following preoperative chemoradiotherapy [224, 225]. On the other hand, well-planned studies like the CROSS trial have shown no such increased risk. It seems that the risk can be mitigated with diligence and attention to detail in planning the preoperative chemoradiotherapy.

Which patients should get neoadjuvant therapy is a moot question. All investigators agree that T3 or more tumour depth and node-positive tumours should be treated with neoadjuvant therapy. Whether T2N0 patients should get neoadjuvant therapy is controversial [226]. The proponents point out the fallacies of preoperative staging of EGJ carcinoma and that it is acceptable to overtreat such an aggressive tumour than to rely on inaccurate clinical staging of T2N0 tumours. The German guidelines allow for use of neoadjuvant therapy in T2 staged adenocarcinoma [122]. The NCCN guidelines also recommend primary esophagectomy only for T1b-T2 N0 low-risk tumours (well differentiated, less than 2 cm size) [75]. For all the rest, preoperative chemoradiotherapy is recommended as the first treatment choice. ESMO guidelines recommend surgery as the treatment option of choice for limited disease (T1–T2 N0) [227].

In most of Europe and the USA, preoperative chemo-radiation is the standard practice currently, for Siewert types 1 and 2 tumours. Siewert type 3 tumours are treated either with perioperative MAGIC type chemotherapy or postoperative chemo-radiation. In the UK currently, OEO2 regimen is used for Siewert types 1 and 2 and esophageal adenocarcinoma, and the MAGIC regimen is commonly used for Siewert type 3 and gastric carcinoma. The original MAGIC trial regimen has been modified over the years—cisplatin has been replaced by oxaliplatin, 5-FU by capecitabine and the inclusion of epirubicin has been questioned recently.

1.9.8 Upcoming Trials

The Neo-AEGIS trial is an RCT including esophageal and junctional tumours, which compares neoadjuvant chemoradiotherapy according to CROSS, with perioperative chemotherapy according to the MAGIC regimen [228]. The TOPGEAR trial studies patients with gastric or junctional cancer randomized to either ECF treatment according to the MAGIC regimen or perioperative ECF treatment with the addition of preoperative chemoradiotherapy [229]. The ESOPEC trial compares the exciting perioperative FLOT chemotherapy to the CROSS type chemo-radiation [230]. The ACTS-GC trial provided good evidence of benefit of adjuvant S-1 in gastric carcinoma in the Japanese and Korean population. The PRODIGY trial has been testing if the perioperative chemotherapy strategy similar to MAGIC (except using docetaxel, oxaliplatin and S-1 preoperatively and only S-1 postoperatively) is better than the already proven postoperative S-1 strategy, in Korea [231].

1.9.9 Targeted Therapy

In the last decade or so, molecular targeted therapies have received increasing attention, as the mechanism of action is different from that of cytotoxic agents. Most of the studies have included only advanced incurable carcinoma, and EGJ carcinoma population has been often mixed with gastric or esophageal carcinoma patients.

HER2 is a member of the human epidermal growth factor receptor family. The TOGA trial (trastuzumab for gastric cancer) had about 20% proportion of EGJ adenocarcinoma [232]. This cohort of patients provided us with very good information on this issue. HER2 was amplified or overexpressed in 32% of patients with EGJ adenocarcinoma. Intestinal differentiation had a 31% HER2 positivity, while diffuse type had only 6% positivity, and there was no difference in HER2 expression in the Asian and European patients [233]. The TOGA trial showed addition of trastuzumab increased survival of the palliative chemotherapy group

by 2.7 months (regardless of HER2 expression), and this benefit was increased to 5.2 months when considering a subgroup of patients with high expression of HER2 [232]. The advantage of adding trastuzumab to perioperative chemotherapy consisting of 5-FU, leucovorin, docetaxel and oxaliplatin is being investigated in a phase II study (HerFLOT study), in patients with locally advanced gastric adenocarcinoma or EGJ carcinoma [234].

Ramucirumab is another promising targeted agent that is an anti-vascular endothelial growth factor receptor 2 (anti-VEGFR-2) antibody. Ramucirumab is a monoclonal antibody VEGFR-2 antagonist that prevents ligand binding and pathway activation in endothelial cells. Apart from trastuzumab this is the only other agent that has shown promise in RCTs, so far. Ramucirumab has been tested in two RCTs (RAINBOW and REGARD) as second-line treatment in combination with chemotherapy in advanced gastric and EGJ carcinoma and has shown significant gain in survival by about 2 months [235, 236].

1.10 Palliation of Advanced EGJ Carcinoma

In patients with unresectable or metastatic EGJ carcinoma, the best outcomes of palliative treatment are achieved through an individualized approach by a multidisciplinary team in an institutional setup. It is difficult to find studies exclusively dedicated to palliation of advanced EGJ adenocarcinoma. Hence most of the recommendations come from studies of palliation of esophageal or gastric carcinoma.

1.10.1 Supportive Treatment

Supportive care is the treatment administered with the intent to improve quality of life (QOL) and alleviate symptoms. The predominant symptoms that contribute to the reduction in QOL are dysphagia, pain, malnutrition and occasional bleeding. Malnutrition is the end result of a multitude of factors. There is substantial evidence that malnutrition is immunosuppressive and has a negative impact on survival [237, 238]. Malnutrition should be identified early and intensive nutrition interventions introduced to maintain or improve QOL. Drugs like megestrol acetate and corticosteroids can play a general role in increasing appetite and weight gain. Intensive nutritional therapy often includes enteral tube feeding (nasogastric, feeding jejunostomy, etc.). However it should be understood that oral feeding (even little) leads to a better QOL than only tube feeding [239]. Hence esophageal stents play a major role in palliation, with the additional advantage that the patients can quickly return to an oral diet. Pain treatment needs a specialized approach by pain physicians and clinics. Pain is often treated with opioid analgesics, and local radiotherapy is sometimes useful (e.g. for bone metastases).

1.10.2 Stents

In a recent meta-analysis including 16 randomized controlled trials, it was summarized that the most widely used method for palliation of dysphagia is endoscopically placed self-expandable metal stents (SEMS) when compared to other alternative methods of loco-regional modalities, like radiotherapy, laser thermal or photodynamic therapy [240]. SEMS are best used in palliation of dysphagia in patients with a short anticipated life expectancy (about 3 months). The SIREC randomized trial compared SEMS placement (with a partially covered Ultraflex) with brachytherapy (1 × 12 Gy) for the palliation of dysphagia in 209 patients with advanced esophageal cancer [241]. Though the dysphagia improved much faster after SEMS placement than after brachytherapy, but this difference reduced gradually over time. Brachytherapy was superior to SEMS in providing dysphagia relief after about 3 months of follow-up [241].

SEMS have improved over time from uncovered to (fully or partially) covered stents to minimize tissue ingrowth and larger stent diameters to reduce the risk of stent migration and bolus impaction. Due to the problem of tumour ingrowth, the use of uncovered SEMS has been abandoned in palliation of esophageal carcinoma. Though SEMS for esophageal carcinoma may be associated with complications in some patients, but data for EGJ carcinoma is usually not reported separately. The common reported complications (average reported incidence) are pain (8.7%), haemorrhage (7.6%), migration (11%), perforation (3.3%), reflux (15%), obstruction (9%) and ingrowth/overgrowth (14%) [242]. Spaander et al. analysed pooled data from RCTs and prospective and retrospective studies and showed that major adverse events occur in 18%, 21% and 10% of patients with partially covered SEMS, fully covered SEMS and self-expanding plastic stents (SEPS), respectively, while recurrent dysphagia develops in 41%, 29% and 37% of these patients, respectively [242]. RCTs have not shown any difference in the performance of fully versus partially covered SEMS [243].

The placement of anti-reflux SEMS for palliation of EGJ cancer has been associated with an increased risk of stent migration and gastro-esophageal reflux, more than in other parts of the esophagus [240, 244]. This is attributed to inadequate anchoring of the distal end of the stent that protrudes into the stomach. Anti-reflux stents are designed to prevent reflux through either a glove of polyurethane membrane extending into the stomach or a membrane at the lower end functioning as a valve. Despite the anticipated superiority of anti-reflux stents, a meta-analysis was not able to establish statistical significance for reflux relief [240]. Other more recent studies have also shown conflicting results with some showing improvement and others no effect on control of reflux symptoms [244, 245]. Some authors have voiced concern about the increased complication rate associated with the anti-reflux stents [244]. Even haemorrhage may be more common due to the stent corroding the posterior wall of the stomach, and angulation of the stent may lead to poor dysphagia relief.

A combination of different modalities of palliation can prolong the dysphagia-free period, decrease the need for re-interventions and improve quality of life. This approach may, at times, even improve overall survival [246]. In recent studies

attempts have been made to study if the short-term and immediate benefits of SEMS can be combined with the long-term benefits of external beam radiotherapy. Historically there have been concerns about the potential problems of scattering effect of SEMS, but smaller studies have shown the feasibility of such an approach, and the results of large studies (ROCS trial) are awaited [247, 248].

1.10.3 Concurrent Chemoradiotherapy

Concurrent chemoradiotherapy has been shown to improve overall survival compared with radiotherapy alone, albeit at the expense of additional, yet manageable, toxicity [249]. It is the preferred treatment option for patients with incurable esophageal carcinoma, provided the patients can tolerate the toxicity. The dose of radiotherapy to be used in case of definitive chemoradiotherapy is 50.4 Gy in the USA and some European centres and more than 60 Gy in many European and Asian centres [250, 251]. However this can only be followed in patients who are either not fit for surgery despite having a localized disease or in patients who have locally advanced tumours of questionable resectability. The dose of definitive radiotherapy is presently a subject of a few ongoing RCTs.

1.10.4 Chemotherapy

Chau et al. concluded that despite the differences in molecular characteristics between esophageal, EGJ and gastric adenocarcinoma, palliative chemotherapy combinations are similarly effective in all of these tumours [252]. The usual workhorse for palliative chemotherapy of these patients is a combination of a fluoropyrimidine, such as 5-fluorouracil, with a platinum agent, such as cisplatin. The landmark REAL-2 RCT in advanced adenocarcinoma from the UK compared epirubicin-cisplatin-5-fluorouracil (ECF) with ECX (substituting 5-fluorouracil with capecitabine), EOF (substituting cisplatin with oxaliplatin) and EOX (substituting CF with oxaliplatin-capecitabine) [253]. All combinations were found to give similar results, except EOX, which had a better median survival [253]. The study concluded that oxaliplatin and capecitabine have comparable efficacy to CF and can be used as replacements. There have been questions raised about the additive value of anthracyclines (epirubicin) to the doublet chemotherapy. Though triplet therapy was supported by an initial Cochrane meta-analysis, Mohammad et al. in a more recent meta-analysis showed that anthracycline did not add much to survival advantage when added to CF doublet therapy [254, 255]. Another study (CALGB 80403) showed that FOLFOX (5-FU, leucovorin and oxaliplatin) was better tolerated than the toxicity of anthracyclines [256]. Addition of docetaxel to CF chemotherapy (FLOT regimen) has led to better response rates but at the cost of increased toxicity [257]. This has led investigators to study modified FLOT regimens with encouraging results so far, and more results are eagerly anticipated [258].

1.10.5 Targeted Therapy

As discussed in a prior section on targeted therapy in this chapter, several molecular targets have been identified and studied, mostly in patients with advanced EGJ and stomach carcinoma. So far only two agents have been shown to improve survival in RCTs, i.e. trastuzumab (targeting HER 2) and ramucirumab (anti-VEGF2). Trastuzumab has been tested as part of first-line treatment in advanced EGJ and stomach cancers, in the TOGA trial [232]. This study has established that HER2 testing should be offered to all patients with advanced gastro-esophageal and gastric cancer, and these can then be considered for treatment with trastuzumab and chemotherapy in HER2-positive tumours. Ramucirumab has been tested as part of second-line chemotherapy, with survival benefit in metastatic esophagogastric adenocarcinoma [235, 236].

1.10.6 Other Interventions for Palliation

Brachytherapy is a method of delivering intraluminal high radiation doses to esophageal tumours while reducing the exposure to adjacent healthy, at-risk organs. As mentioned in the earlier section on stents, the SIREC RCT showed that brachytherapy is better palliation (than primary SEMS) for patients whose expected survival is more than 3 months [259]. However the long-term benefit of brachytherapy in the SIREC trial was partly explained by follow-up procedures like additional SEMS placement in 45% of the patients in the brachytherapy treatment arm [259]. The other issues complicating palliative brachytherapy are the lack of availability and expertize even in major centres and the potential to cause major complications like perforation, fistulization, etc. Photodynamic therapy (PDT) and laser treatments have been used for palliation of advanced esophageal carcinoma, but have not been widely adopted. A Cochrane meta-analysis of endoscopic ablative therapies found that laser therapy and PDT had increased rate of re-interventions than palliation of dysphagia with SEMS [246].

1.10.7 How to Choose Good Palliation for Indian Patients

The foundation of good palliation rests on all round supportive care that is often not given due importance. Palliative interventions should be chosen through individualized decision-making in multidisciplinary team meetings. A simple starting point of palliation is good supportive care along with nasogastric tube feeding, followed by reassessment for other interventions. The pragmatic options for dysphagia relief are SEMS and chemoradiotherapy. Though SEMS provide quick relief of dysphagia in EGJ tumours, these are associated with troublesome reflux (even with anti-reflux stents) and the ever-present risk of stent migration. Chemotherapy provides slow relief of dysphagia, and hence maintaining the patient on nasogastric tube feeding

is of utmost importance. Chemotherapy has oncologic benefits with survival advantage, and radiotherapy is usually used for slowly bleeding tumours. Palliation of patients with reasonable fitness and expected survival should include combination of the discussed modalities, with the aim of relieving symptoms and increasing survival at the cost of least possible morbidity. At the end of the day, palliation is all about trying to understand the patient's problems and expectations and fulfilling these objectives to improve the quality of life with the armamentarium at hand.

1.11 Summary

It is apparent from the preceding sections that EGJ adenocarcinoma is still work in progress. Including the Siewert classification, we have come a long way in the understanding of EGJ carcinoma. The Indian reality is that most of our patients present with advanced tumours and only a modest proportion are suitable for potentially curative therapy. Nevertheless the potentially curative treatment for locally advanced EGJ tumours consists of multimodality therapy in the ambit of multidisciplinary care. It is thus essential that the decision-making for these patients is routed through tumour boards or multidisciplinary clinics. While surgery is central to the treatment of locally advanced EGJ tumours, major advances are being made in the modalities of neoadjuvant therapy. However, the future of EGJ carcinoma rests with the cancer genome projects running across the world, which would enable accurate molecular classification of these tumours and better targeted treatment.

As always, the future promises to be better than the past, provided we learn from the past and embrace changes for the future with scientific temper and rational thought.

Editorial Comments

The author has given a comprehensive review on the subject of adenocarcinomas of the esophagogastric junction (EGJ carcinoma). I will restrict myself to a few comments.

EGJ adenocarcinomas seen in the East are quite different from those seen in the West. While type 2 and 3 cancers are more frequent in the East, type 1 is more common in the West. This is possibly because of the lower incidence of reflux disease and obesity and a higher frequency of *Helicobacter pylori* infection [267]. The incidence of EGJ adenocarcinomas has been rising in the West, but the prognosis has not improved. This is related to the advanced stage of presentation of the disease. The seventh edition of the UICC staging system has revised cancer staging across EGJ cancers. However, this has not resulted in a uniform pattern of lymphadenectomy. While surgeons in the West perform a less radical lymphadenectomy, surgeons in the East do a more extensive lymphadenectomy [268]. These tumours are bigger in size with greater depth of penetration and higher lymphatic and vascular metastases [269]. Histological grading and vascular invasion are well-known predictors for recurrence of disease. Timing of recurrence has been shown to affect survival, while early recurrence is uniformly fatal; late recurrence is somewhat better [270].

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Chapter 2
Superior Mesenteric Artery Syndrome

V. P. Bhalla, V. K. P. Singh, R. Vats, and D. Goel

2.1 Background

Duodenal compression between the aorta and superior mesenteric artery (SMA) is a rare condition. It is traditionally referred to as the superior mesenteric artery syndrome (SMAS) or Wilkie's syndrome.

The prevalence of SMAS is reportedly 0.013–0.3% based on upper gastrointestinal barium series [1, 2]. The wide variation in its prevalence and its frequent association with neurosis [3] has often led to skepticism about its existence [4]. Some have questioned whether the syndrome is "fact or fantasy" [5]. An extensive review of literature shows that SMAS is a clearly defined distinct disease entity. The condition results from structural developmental aberrations or as a result of an acquired illness or condition [6] or may even result from a combination of both factors.

Many different terms have been used to describe the compression of the third part of the duodenum by the SMA. These include:

- Vascular compression of duodenum
- Chronic duodenal ileus [7]
- Cast syndrome [8]
- Cast syndrome incognito [9]
- Gastromesenteric ileus [10]
- Chronic intermittent arteriomesenteric ileus [11]
- Arteriomesenteric duodenal obstruction [12]
- Chronic duodenal pseudo-obstruction [13]

Harold Ellis suggests the term superior mesenteric artery syndrome to be most appropriate for the duodenal obstruction caused by the SMA [14].

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2.1.1 Nutcracker Syndrome

The nutcracker syndrome is a distinct entity, and the term is used to describe the compression of the left renal vein by the SMA. It is often erroneously used as being synonymous with SMAS. Duodenal and left renal vein compression can occur simultaneously particularly when they both lie in an anteroposterior position at the same vertebral level instead of the normally placed left renal vein lying above the duodenum. The term nutcracker syndrome should not be used for duodenal compression by the SMA but used for the left renal vein compression [15].

2.2 History

The Austrian anatomist Carl von Rokitansky is credited with the earliest description of the compression of the third part of the duodenum by the superior mesenteric artery in 1861 based probably on extensive autopsy studies [16]. It is said that Rokitansky supervised more than 70,000 autopsies and personally performed more than 30,000 [17]. There is however no record of the exact incidence of SMAS in these autopsies (Fig. 2.1).

Fig. 2.1 Carl von Rokitansky. Source: Wikipedia

Kundrat (1881) postulated that the root of mesentery is the possible anatomic structure responsible for the partial or complete duodenal stricture [18]. A German physician Albrecht in 1899 postulated that mesenteric traction was the etiology of external constriction of the third part of the duodenum [19]. Until the twentieth century, there was no clear distinction between functional ileus and mechanical obstruction of the duodenum, leading to frequent use of the term ileus to describe the syndrome of emaciation, duodenal obstruction, and bilious vomiting.

In the early part of the last century, Bloodgood used the term *gastromesenteric ileus* to describe a life-threatening condition of acute gastroduodenal dilatation which was ill understood at that time. Most of the cases studied and reported with the aid of hand-drawn accounts of operative and autopsy findings may have been secondary to an infective condition or postoperative ileus (Figs. 2.2 and 2.3). However some cases were due to an abrupt cutoff of the third part of the duodenum. He suggested that the condition could be surgically treated by duodenojejunostomy [10], and a year later the first successful duodenojejunostomy for duodenal obstruction was performed by Slavely [20].

Wilkie in 1921 studied operative and postmortem findings of patients with *duodenogastric ileus* [7] and observed that "the great dilatation of the duodenum was found to end abruptly at the crossing of the superior mesenteric artery. There was no evidence of any acute infective process anywhere which might have caused an acute toxic dilatation of the stomach" (Fig. 2.4).

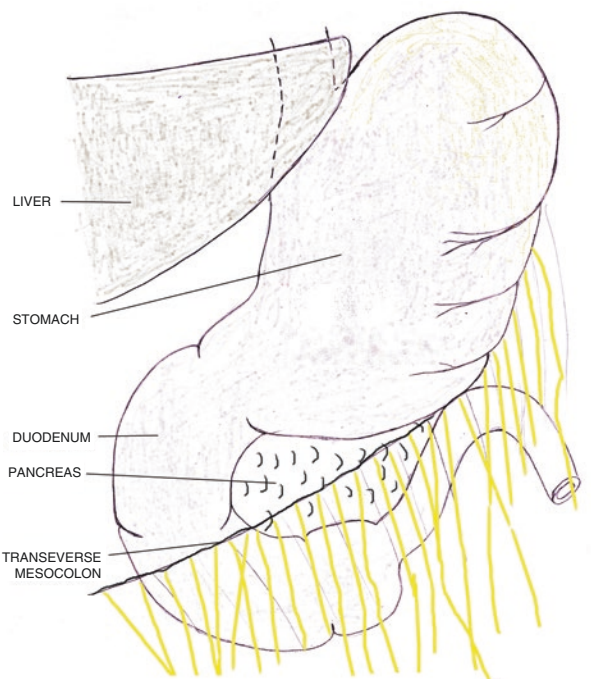


Fig. 2.2 Drawing of image of "gastromesenteric ileus" as reported by Bloodgood. Source: Drawing by author

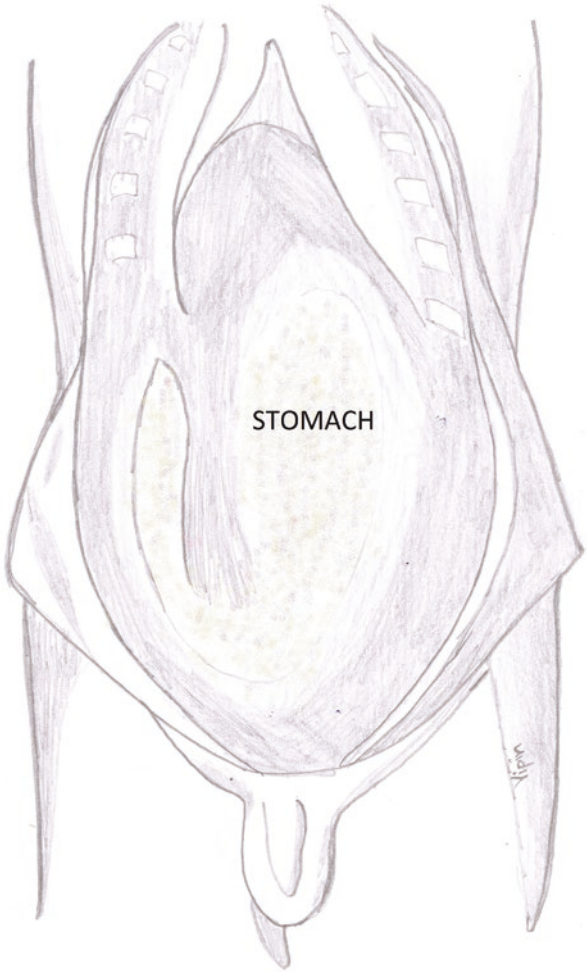


Fig. 2.3 Drawing of autopsy finding of gastric dilatation as reported by Bloodgood. Source: Drawing by author

In so reporting he suggested that what was till that time thought to be ileus due to infection, postoperative state, and/or trauma was in fact a mechanical obstruction due to the crossing of the SMA over the duodenum (Fig. 2.5).

Concluding his famous article on "Chronic Duodenal Ileus," [7] Wilkie made the following conclusions:

1. "Chronic duodenal ileus from compression of the third part of duodenum by the root of the mesentery is a clinical and pathological entity.
2. It may be associated with duodenal and gastric ulcer, and with biliary and pancreatic lesions.
3. Visceroptosis, and congenital lack of fixation of the proximal colon, predispose to its development.
4. Fixation of the proximal colon may relieve symptoms in certain cases.

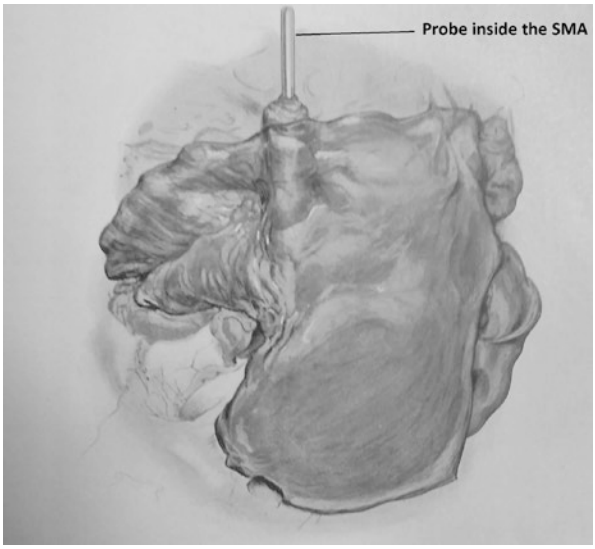


Fig. 2.4 Wilkie's postmortem specimen of "duodenogastric ileus." Reprinted with Permission of John Wiley & Sons, from Wilkie DPD. Chronic duodenal ileus. Br J Surg. 1921;9:204–14; permission conveyed through Copyright Clearance Center, Inc.

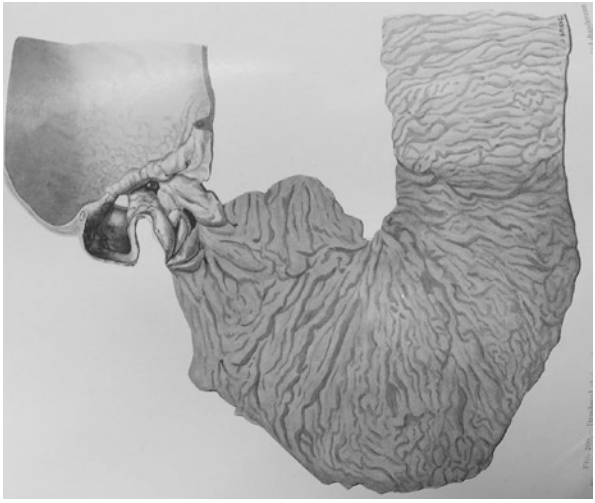


Fig. 2.5 Mechanical duodenal obstruction by SMA—Wilkie. Reprinted with Permission of John Wiley & Sons, from Wilkie DPD. Chronic duodenal ileus. Br J Surg. 1921;9:204–14; permission conveyed through Copyright Clearance Center, Inc.

5. Drainage of the dilated duodenum by duodenojejunostomy is the most certain method of treatment, and the only one suited for well-developed and late cases.
6. Acute dilatation of the stomach, either idiopathic or post-operative, is probably merely a gross manifestation of a previously present chronic condition."

These observations are still relevant to our current management of the SMAS.

In 1927, Wilkie reported on 75 cases of the SMAS and some who were treated successfully by duodenojejunostomy. For his contributions to the understanding of this enigmatic condition, the SMAS is often referred to as Wilkie's syndrome [21].

2.3 Etiopathogenesis

2.3.1 Embryological Basis of the SMAS

To understand the anatomical basis of the acute-angled compression of the third part of the duodenum between the SMA and the aorta, it is important to study the embryological development and rotation of the gut and its blood supply which when altered predisposes to the development of SMAS. The SMA, duodenum, ligament of Treitz, and the body habitus as determined by the spinal curvatures are most important to this understanding.

2.3.1.1 SMA

The developing midgut is supplied by the SMA. It develops from the embryological aorta to supply blood to the embryonic yolk sac. The developing gut extends into the yolk sac extension in the umbilical cord, and the SMA accompanies the bowel and supplies blood to Meckel's diverticulum. By the mid-fifth week, the midgut and the SMA lie in the body of the developing embryo (Fig. 2.6).

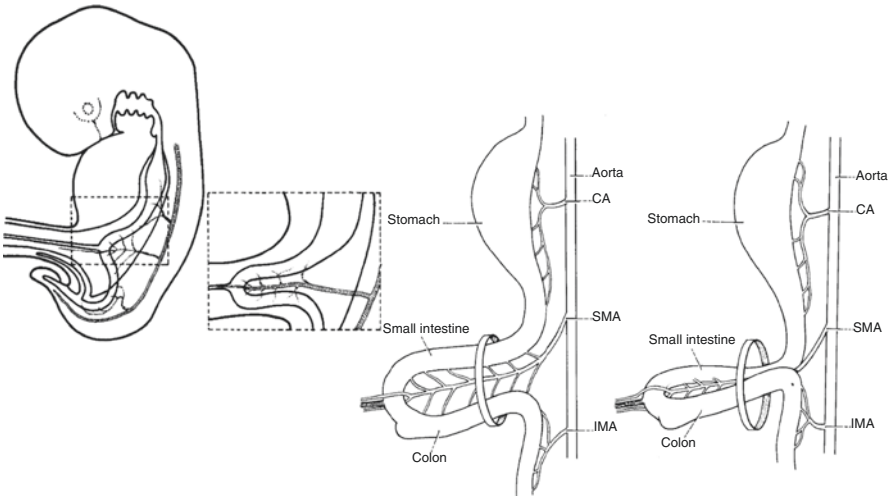


Fig. 2.6 Early development of gut and its blood supply. Reprinted from Akin ST, Skandalakis JE, Gray SW. The anatomic basis of vascular compression of the duodenum. Surg Clin North Am 1974;54:1361-70, with permission from Elsevier

2.3.1.2 Rotation of the Developing Gut

By the end of the fifth week, the embryonic gut grows faster than the body and herniates into the umbilical cord. While doing so, it rotates 90° anticlockwise, and the SMA comes to the left of the duodenum and colon.

By the tenth week, the gut begins to retract into the abdomen. The small intestine returns first pulling along with it a part of the duodenum, and passing below the SMA, the duodenojejunal junction comes to lie to the left of the SMA within the angle formed by the SMA and the aorta.

The colon and rest of the bowel also retract, and the transverse colon comes to lie in front of the SMA. The final adult position of the bowel is achieved around birth with both the ascending and descending colon fusing with the posterior abdominal wall (Fig. 2.7).

2.3.1.3 The SMA Angle

Unlike quadrupeds where the SMA hangs at right angles to the aorta, the erect posture of humans makes the SMA hang at an acute angle with the aorta and makes the duodenum very susceptible to be pinched between the two (Fig. 2.8).

2.3.1.4 The Suspensory Ligament of Treitz

The suspensory ligament of the duodenum was first described by Treitz [22] in 1853. Ever since it has been referred to by his name. Treitz believed that the ligament arises from the area of the duodenojejunal flexure and is inserted cranially in

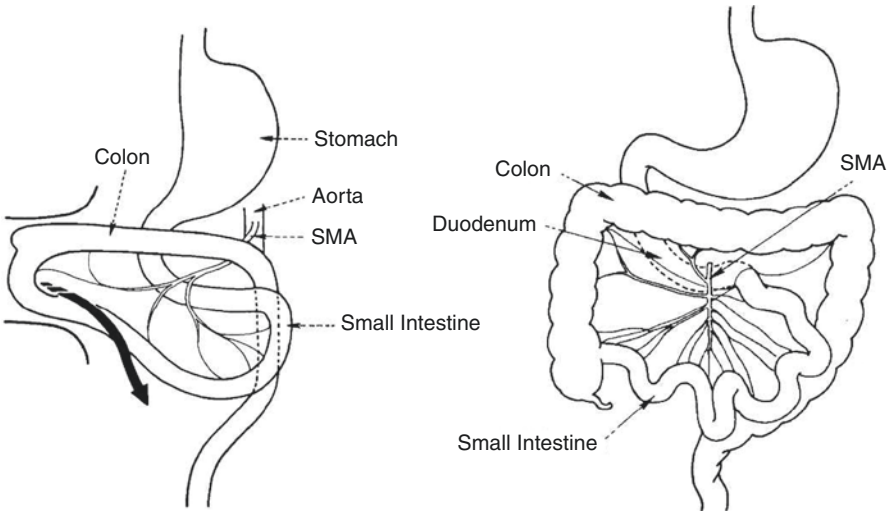


Fig. 2.7 Stages of rotation of the gut. Reprinted from Akin ST, Skandalakis JE, Gray SW. The anatomic basis of vascular compression of the duodenum. Surg Clin North Am 1974;54:1361-70, with permission from Elsevier

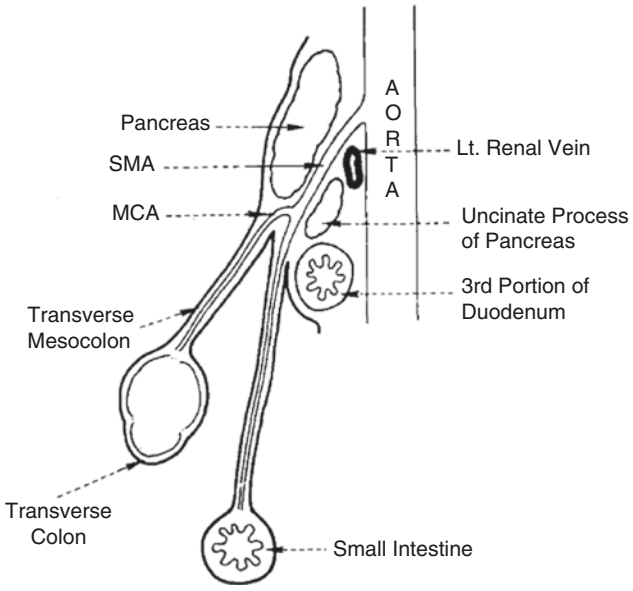


Fig. 2.8 Diagrammatic relations of aorta and SMA. Reprinted from Akin ST, Skandalakis JE, Gray SW. The anatomic basis of vascular compression of the duodenum. Surg Clin North Am 1974;54:1361-70, with permission from Elsevier

the connective tissue surrounding the origin of the celiac trunk and inferior mesenteric artery extending to the right border of the esophageal hiatus. He also described a slip of skeletal muscle derived from the diaphragm which forms part of the suspensory ligament proper which was also shown to contain smooth muscle scattered within it. Smooth muscle cells within the ligament of Treitz are believed to be derived from the circular muscle layer of the duodenum. The diaphragmatic skeletal muscle slip has been referred to as *Hilfsmuskel* which arises from the right border of the esophageal hiatus and extends caudally to join the termination of the suspensory ligament. The development and structure of these two components of the ligament have been a subject of lively debate among anatomists. The presence of smooth and skeletal muscle cells in the ligament suggests that there are two separate sites of embryological origin of different parts of the suspensory ligament of Treitz (Fig. 2.9).

In a significant Indian contribution to the study of the ligament, an ICMR-funded study by Inderjeet et al. [23] confirmed the century-old findings of Treitz. With the help of elegant anatomical dissection, they showed in detail the structure and attachment of the two components of the ligament and the different ways the ligament is attached at both ends. They also determined the nerve supply of the various parts of the ligament, the clinical importance of which is still not clearly understood (Fig. 2.10).

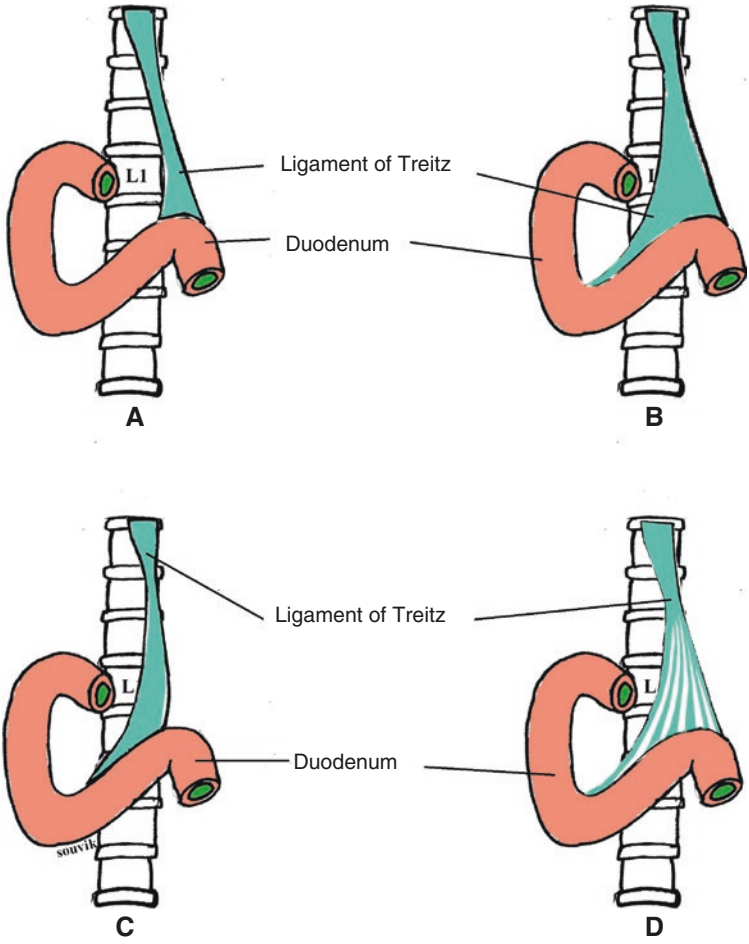


Fig. 2.9 Variations of ligaments of Treitz

Ligament of Treitz Variations

There is a wide variation in the structure and attachment of the suspensory ligament of Treitz, which can explain the origin of the SMAS in some cases [24]. When the ligament stretches too far right on the duodenum, it can tent the SMA and the aorta. Also, a shortened ligament of Treitz attached to the duodenojejunal flexure can pull up the duodenum pushing it higher and allowing it to be kinked between the SMA and the aorta.

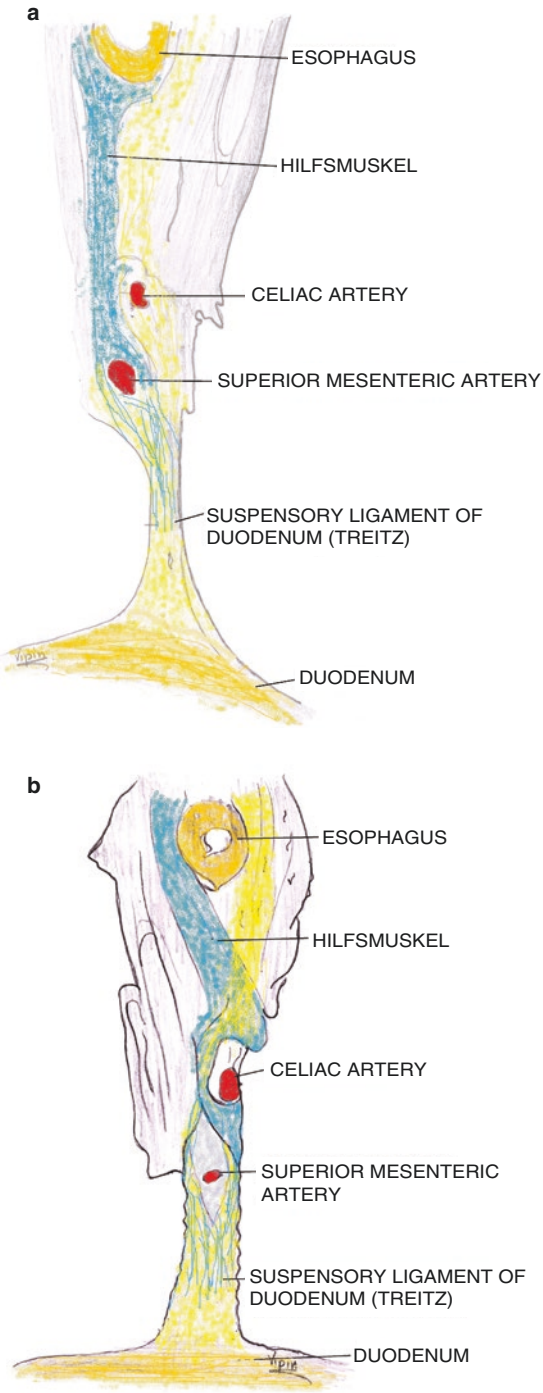
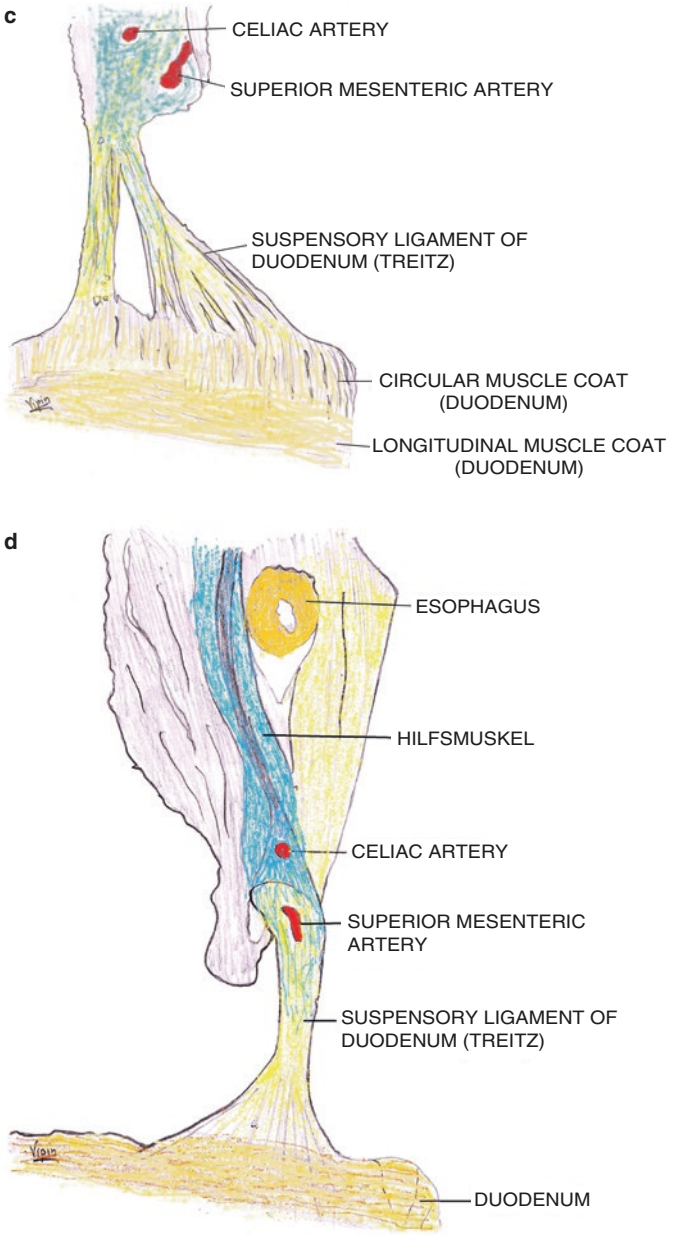


Fig. 2.10 (**a**–**d**) Line diagram of Inderjeet's dissection specimen of the suspensory duodenojejunal ligament. Source: Drawing by author



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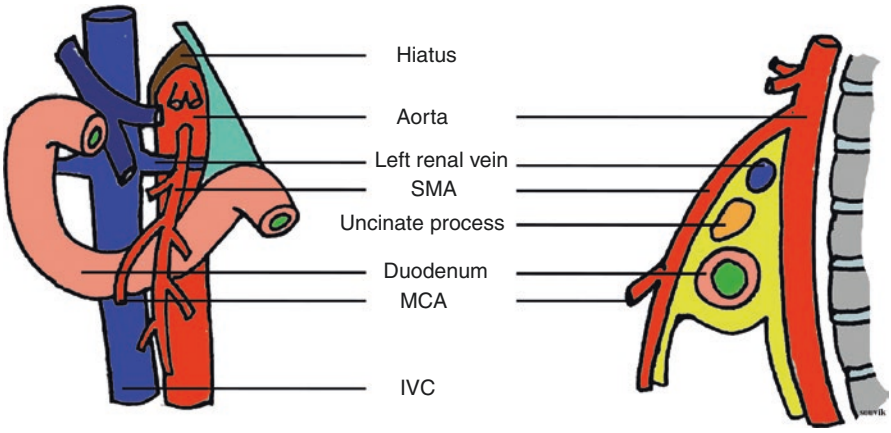


Fig. 2.11 The relation of SMA, duodenum and aorta

2.3.1.5 Lie of the Duodenum

The duodenum derives its name from the belief that it is equal in length to the width of 12 fingers held side to side. The SMA originates at the first lumbar segment, while the duodenum lies across the spine at the level of the third vertebra. It is susceptible to compression of its third part between the SMA anteriorly and aorta and vertebral column posteriorly. Duodenum is held in place by being fixed at the pylorus, by the fused mesentery of the second and third part of the duodenum, and by the ligament of Treitz (Fig. 2.11).

The duodenum crosses the vertebral column at the level of lower border of the third lumbar vertebrae and in some cases at the upper border of the fourth lumbar vertebrae. The fourth lumbar vertebra itself is the most anterior part of the vertebral column. SMA arises from the aorta anteriorly at the level of the first lumbar vertebrae. The middle colic vessels arise one vertebral level lower. The middle colic vessels cross the duodenum at the third duodenal segment, and these may also cause compression of the duodenum due to the sheer weight of the loaded transverse colon.

A lower duodenal position may not be advantageous either, as the spine curves anteriorly at L4 thus reducing the gap between the SMA and aorta at this level.

The average angle between the aorta and SMA was found to be 42° in an autopsy series and may range from 28 to 65°. The aortomesenteric distance ranges from 10 to 34 mm [25] (Fig. 2.12).

In this angle lie left renal vein, uncinate process of pancreas, and third part of the duodenum and craniocaudally with the *retroperitoneal fat pad* which sits just at the angle. This mass of fat and lymphatic tissue surrounds the origin of the SMA and provides protection against duodenal compression. Variations in the state and size of this pad of fat can also greatly influence the angle size.

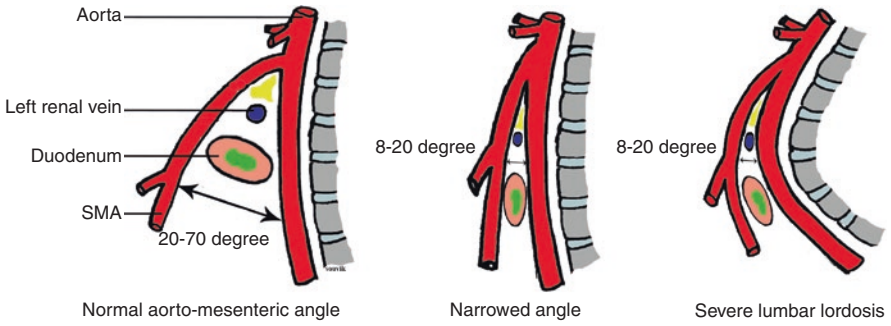


Fig. 2.12 Aortomesenteric angle variation

2.4 Etiology

2.4.1 Embryological Causes

The embryological factors responsible for the vascular compression of the third part of the duodenum have already been referred to in the preceding sections on development of the duodenum, SMA and surrounding structures. These are summarized as follows [4]:

- Incomplete rotation and higher than normal lie of the duodenum
- Congenitally short small bowel mesentery
- Narrow angle of the SMA offtake from the aorta
- Aberrant SMA
- Variations in the insertion and length of the ligament of Treitz
- Excessive mobility of the right colon
- Changes in the curvatures of the developing vertebral column

Progressive increase of spinal lordosis stretches the SMA angle. In women childbearing increases lumbar lordosis and may explain why SMA syndrome is encountered more frequently in females over the age of 30 years.

The embryological hypothesis is supported by the identification of a very rare familial variant of SMAS and by a report of SMAS occurring in identical twins [26].

2.4.2 Acquired Causes

Many authors believe that superior mesenteric artery syndrome is an acquired condition which results from a primary illness which alters the aortomesenteric angle. This alteration may be seen in patients with the following conditions.

2.4.2.1 Excessive Weight Loss due to Malnutrition [27]

Malnutrition due to any cause can result in the narrowing of the aortomesenteric angle by a reduction of the pad of fat in the angle and associated change of habitus. Anorexia nervosa classically described in adolescent females presents with anorexia and extreme malnutrition, weight loss and cachexia. Whether it is cause or effect of SMAS is a subject of debate [28]. SMAS should be considered in all young adolescent girls with an anorexia nervosa like illness associated with vomiting and postprandial epigastric discomfort [29]. This may present a unique challenge for the psychiatrist to diagnose SMAS in patients with anorexia nervosa presenting in his OPD [30, 31].

In patients with extensive burns, arteriographic studies have shown that the angle formed by the SMA with the aorta may decrease to as little as 15° as patients lose weight rapidly from debilitating burn injuries [32].

2.4.2.2 Following Spinal Surgery

Surgery for correction of scoliosis, relative lengthening of the spine [33], and other spinal operations may cause acute-onset SMAS in the immediate post-op period. SMAS can also develop following spinal fusion causing narrowing of the aortomesenteric angle. Slender body habitus and body mass index less than 18 kg/m^2 are independent risk factors for SMAS in spinal fusion surgery for scoliosis [34]. The incidence of SMAS after spinal surgery is reported as 2.5% [35, 36].

In contemporary times, Christopher Reeves, the actor who portrayed Superman, is believed to have died in 2004 due to cardiac arrest because of SMAS resulting from spinal cord injury and quadriplegia [37].

2.4.2.3 Following Restorative Proctocolectomy

Cases of SMAS have been reported after proctocolectomy and ileal J pouch-anal anastomosis due to traction on mesentery by the translocated terminal ileum causing tension and caudal pull of small bowel mesentery [38]. The ileal J pouch is supplied by the SMA, which may be stretched and cause a decreased aortomesenteric angle and consequent compression of the third part of the duodenum.

2.4.2.4 Following Bariatric Surgery

Bariatric surgery is an important cause of SMAS [39]. This is due to the post-procedure weight loss. It should therefore be considered in the differential diagnosis of all post-bariatric surgery patients presenting with epigastric discomfort and vomiting few weeks or months following the procedure.

2.4.2.5 Enforced Bed Rest and Application of Body Cast [40]

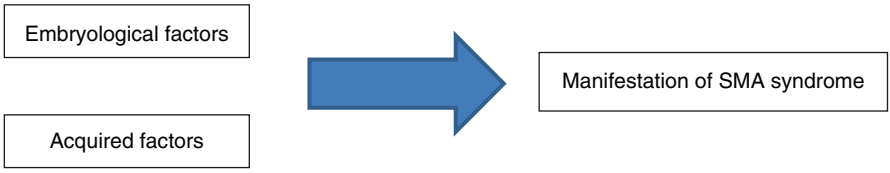
SMAS has been reported in patients with conditions requiring enforced bed rest as in acute traumatic quadriplegia [41]. Prolonged bed rest in the supine position results in continuous, unrelieved pressure on the SMA and duodenum by the weight of the overlying transverse colon [4]. Also, the presence of a body cast may alter the angle of mesenteric traction and increase the possibility of duodenal compression [4].

2.4.2.6 Rapid Spurt in Growth and Height [42]

Height spurt in adolescent individuals makes them susceptible to a decrease of the aortomesenteric angle and makes them susceptible for SMAS.

2.5 SMAS: Congenital or Acquired?

Whether SMAS is congenital or acquired is currently the subject of debate. It is probably more than just a simplistic choice of one or the other being a cause of SMAS. The truth may lie somewhere in the middle in that secondary acquired factors may cause the disease to manifest in patients who already possess some embryological features predisposing them to the development of SMAS. Possibly both factors need to contribute for SMAS to manifest.



2.6 Clinical Features

SMAS is a rare disease. It is commonly seen in the second and third decade of life and is more common in females compared to males [1, 21]. Presentation of SMAS may be acute or chronic [43].

Acute presentation is less common than the chronic variety and is a serious surgical emergency. While it may be precipitated by conditions like prolonged bed rest in supine position and application of plaster cast and other causes enumerated earlier, it may sometimes occur without any precipitating cause and be discovered during a laparotomy for upper GI obstruction where the abrupt duodenal cutoff by the SMA becomes apparent [11, 44].

In a comprehensive review of the subject [4], half of the patients with SMAS with an acute presentation had suffered for 6 months or less. There is a more common chronic form which develops slowly and may be diagnosed after years. A very unusual patient is reported as having had the condition for 23 years before diagnosis [4].

It is usually difficult to make a diagnosis on clinical grounds alone. Clinical symptoms are a combination of features of distal duodenal obstruction, malnutrition, and cachexia and of the underlying acquired causes of SMAS.

2.6.1 Distal Duodenal Obstruction

Distal duodenal obstruction classically presents with upper abdominal discomfort and pain associated with nausea and vomiting which may occasionally be induced. Pain in the upper abdomen may be a dull ache to start with and progress to persistent crampy pain relieved by vomiting. The vomitus is typically green, and this helps to distinguish the symptoms clinically from a gastric outlet obstruction. So, a clear distinction can be made between distal duodenal obstruction and gastric outlet obstruction by the color of the vomitus. A recent change in the character of pain may indicate a developing complication like gastroesophageal peptic ulcerations.

Early satiety, abdominal distension, weight loss, and postprandial pain which worsens on lying supine and which is relieved on lying prone or in a left lateral decubitus position are other symptoms of the disease.

The Hayes maneuver which entails applying pressure below the umbilicus in a cephalad and dorsal direction helps relieve the obstructive symptoms by elevating the root of the SMA and slightly easing the constriction. This symptomatic relief by a change in position is almost pathognomonic of SMAS.

2.6.2 Malnutrition and Cachexia

The persistent nausea and vomiting do not allow adequate dietary intake and lead to a state of both protein and calorie deficiency with a loss of muscle mass and body weight.

2.6.3 Symptoms of Underlying Specific Diseases

When SMAS is a result of a clinical condition associated with weight loss and malnutrition, the symptom complex associated with the underlying disease can cause confusion and a delay in diagnosis. After bariatric surgery, for example, the upper abdominal symptoms following surgery need to be differentiated from the symptoms of distal duodenal obstruction. The distinction between the two is vital, for the latter condition can be corrected.

2.6.4 Complications

SMAS is associated with significant morbidity and mortality. Severe malnutrition, dehydration, and dys-electrolytemia including hypokalemia, hypochloremia, and metabolic acidosis are quite common. Peptic ulcer disease with associated complications of bleeding and perforation and presenting with shock has also been reported [45]. Peptic ulcer disease is a common accompaniment of SMAS and is seen in 40–50% of cases. Gastric dilatation and vomiting can be complicated with aspiration pneumonia.

2.7 Diagnosis

A diagnosis of SMAS is rarely made on clinical grounds alone, and in 95% of cases, the diagnosis is delayed and requires radiological assistance. A high index of clinical suspicion and confirmation of the same on imaging is required to confirm the diagnosis of vascular compression of the duodenum.

2.7.1 Plain Radiograph of the Abdomen

The investigation of any gastrointestinal obstruction begins with a plain abdominal radiograph. This can identify the dilated stomach and dilated proximal duodenum. A prominent gastric and duodenal air-fluid level proximally and the absence of air distally and a clear demarcation line in the duodenum are particularly suggestive of SMAS.

2.7.2 Contrast Upper GI Studies

Hines et al. [42] laid down the radiological criteria for establishing the diagnosis of SMAS on upper GI contrast studies.

These are:

1. Dilatation of the first and second part of the duodenum with or without gastric dilatation
2. Abrupt vertical and oblique compression of the mucosal folds
3. Antiperistaltic flow of barium proximal to the obstruction producing “to-and-fro” movements on fluoroscopy
4. Delay in transit of 4–6h through the gastroduodenal region
5. Relief of obstruction when the patient is placed in a position that diminishes the drag of the small bowel mesentery

Positional maneuvers may produce relief through widening of the aortoduodenal angle and aid in diagnosis [46]. These include knee to chest, prone left lateral decubitus position, and the previously mentioned Hayes maneuvers. Passage of contrast depends upon the severity of the duodenal compression. Fluoroscopy along with upper GI contrast studies shows a characteristic "to-and-fro" motion of the peristaltic waves [1].

Upper GI contrast studies combined with aortic and SMA angiography have been used in the past and for a long period were considered the diagnostic modality of choice for diagnosing SMAS [47]. Narrowing of aortomesenteric angle and duodenal compression at the point where the SMA crosses the duodenum are the hallmark features of the SMAS, and these could be well visualized by combining the two. The current gold standard for diagnosis of SMAS is an abdominal MDCT angiography.

2.7.3 CT Angiography

CT with intravenous and oral contrast provides a rapid, highly accurate, noninvasive visualization of both the vascular and intestinal structure. Multi-planar CT with three-dimensional rendering provides accurate axial reconstruction of the aortomesenteric distance and the sagittal reconstruction of the aortomesenteric angle [25, 48].

2.7.4 Aortomesenteric Distance

The normal mean radiographic aortomesenteric distance is 10–28 mm, and this can reduce to 2–8 mm in SMAS [49]. Indian figures for aortomesenteric distance have been studied by Desai et al. [47]. The aortomesenteric distance is measured as the mean of three readings of the distance between the aorta and the SMA at the level of duodenal crossing where D1, D2, and D3 are measured at the level of the upper, middle, and lower border of the duodenum, respectively.

2.7.5 Aortomesenteric Angle

As the aortomesenteric angle narrows, so does the aortomesenteric distance. The normal aortomesenteric angle is 25–60° with a mean of 45°. In SMAS the angle is reduced to 15° with a range of 6–22°, resulting in occlusion of third part of duodenum.

Neri et al. measured the aortomesenteric angle during normal expiration 2 cm below the beginning of aortomesenteric bifurcation [49]. Desai et al. measured the aortomesenteric distance at the mid-duodenal level [47]. The most appropriate measurement results from starting at the midpoint of the SMA origin and extending the two lines 2.5 cm in the axis of the aorta and SMA.

2.7.6 MR Angiography

MR angiography is as accurate as CT angiography for diagnosing SMAS. Less radiation exposure may be considered an advantage in children.

2.7.7 Color Doppler

Low cost and wide availability make the ultrasonographic color Doppler examination a useful diagnostic modality for the measurement of the aortomesenteric angle even in asymptomatic patients and is also useful when the upper GI series are inconclusive in symptomatic patients. An additional benefit of the US color Doppler is that it can also be performed in a standing position. Its use is greatly hampered in the obese and in a gaseous abdomen. Color Doppler characteristics such as noninvasiveness, repeatability, non-exposure to radiation, and low cost make it one of the initial diagnostic modalities. Ultrasound color Doppler imaging is useful as an epidemiological screening tool for detection of reduced aortomesenteric angle and SMAS [49].

2.7.8 UGIE

Endoscopic examination avoids exposure to radiation, which is of benefit for young patients [47]. Duodenal dilatation, stasis, and antiperistaltic waves seen on endoscopy suggest a diagnosis of SMA syndrome. While UGIE per se is not a modality of choice for diagnosing SMAS, it is useful for excluding other causes of distal duodenal obstruction [50, 51].

2.7.9 EUS

EUS has been used for the diagnosis of SMAS. The SMA is difficult to visualize as are attempts at measuring the aortomesenteric angle. The role of EUS as a modality for measuring the aortomesenteric angle needs further evaluation [52].

2.8 Differential Diagnosis

The differential diagnosis of SMAS will include all causes of distal duodenal obstruction. These have been well classified [53].

Congenital

Duodenal duplication/diverticula, duodenal web, annular pancreas, malrotation of gut

Acquired

Intraluminal

Hematoma, duodenal bezoar

Luminal

Benign

Crohn's disease, duodenal tuberculosis, post-bulbar peptic ulcer, disseminated histoplasmosis

Neoplastic

Mucosal

Duodenal polyps, duodenal adenocarcinoma, duodenal lymphoma, vascular hemangioma

Intramural

Gastrointestinal stromal tumor, lymphoma, hemangioblastoma, Brunner cell hamartoma

Extraluminal

SMA syndrome

Chronic midgut volvulus

Pancreatic pathologies: Pancreatic pseudocyst, chronic pancreatitis, benign cystic and solid tumors of pancreas, periampullary carcinoma, pancreatic adenocarcinoma, pancreatic neuroendocrine tumors

Lesion of hepatobiliary system

Hepatic masses, gallbladder pathologies, choledochocoele

Colonic lesions

Retroperitoneal process

Fluid collection, lymphoma, primary retroperitoneal collection

Chronic idiopathic megaduodenum had been reported in families with symptoms simulating SMAS [54].

2.9 Treatment

The response to treatment of SMAS depends on whether it is an acute- or chronic-onset SMAS. Whatever the type of onset, the aim of the initial treatment remains conservative after resuscitation. Conservative treatment alone is most likely to work in the acute-onset cases where removing the reversible cause say a plaster cast will result in rapid improvement in the patient's condition.

2.9.1 Resuscitation

The initial management of patients with SMAS is to manage the obstruction-associated features such as fluid volume and nutritional depletion and electrolyte imbalance using standard laid down protocols. Every effort should be made to identify an underlying cause. If one is found, it must be immediately corrected.

Gastroduodenal decompression: This is of importance as a chronically distended stomach and duodenum lose its tone. This not only affects its ability to overcome the obstruction but also delays the functioning of a drainage procedure postoperatively.

2.9.2 Nutritional Correction

The chronic protein calorie deficit needs to be corrected by both enteral and or parenteral therapy. If adequate nutrition is not achieved by the oral route, enteral nutrition is achieved by a naso-jejunal tube advanced endoscopically or radiographically beyond the point of duodenal obstruction. In some cases, total parenteral nutrition may be required. The presumptive aim of such efforts is to achieve weight gain and restoration of the retroperitoneal fat pad and attendant expansion of the aortomesenteric angle. That the change in the aortomesenteric angle by restoration of the retroperitoneal pad of fat is significant is demonstrated by CT angiography in one of our cases (Figs. 2.13 and 2.14).

2.9.3 Positional Maneuvers

Lying in the left lateral decubitus, knee-chest, and prone position may alleviate the associated symptom of pain and facilitate passage of food beyond the point of obstruction particularly in patients who have been bedridden for a long time. The Hayes maneuver described earlier also helps relieve the constriction on the duodenum.

2.9.4 Response to Conservative Treatment

A fair trial of conservative therapy should be given to all patients. The success rate of non-operative management is variable and depends upon the etiology and extent of obstruction at the time of presentation. Patients with prolonged and severe symptoms or those who fail to achieve weight gain with nutritional support and conservative management fall in a category where surgery may be required. There are no guidelines for the duration of conservative treatment before surgery is advised, and this decision must be personalized for an individual patient.

2.9.5 Surgical Management

Operation for SMAS is advised if there is a failure of conservative treatment. This is more likely to happen with long-standing disease. By the time the patient presents for surgery, he is often severely cachexic and malnourished.

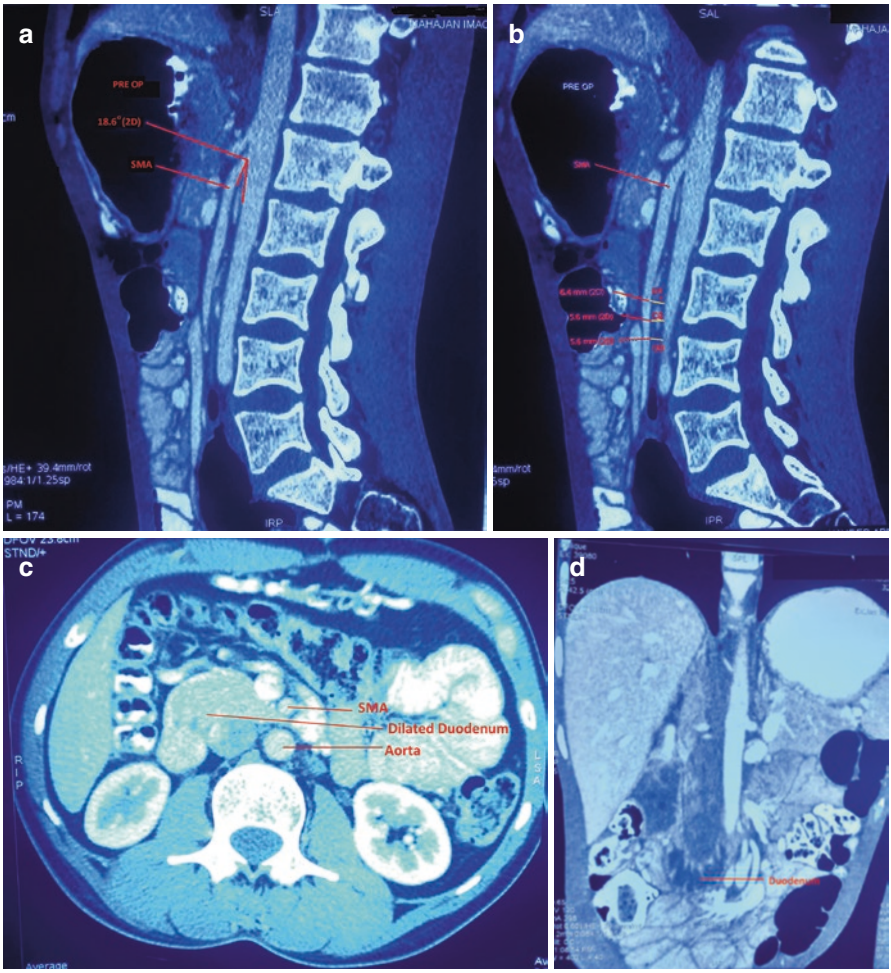


Fig. 2.13 (**a–d**) Pre-op pictures of SMA. Source: These are CT images of patient treated in the authors' unit (Identity concealed)

The initial step again is to resuscitate the patient. Treat dehydration and dys-electrolytemia, and build up nutrition with enteral or parenteral nutrition. Preoperative buildup and use of an incentive spirometry are important for good operative outcome. Several operative procedures have been described.

2.9.5.1 Release of ligament of Treitz

Complete severance of the ligament of Treitz alone has been used with some success. In addition to the advantage of not opening the bowel, the severance of the ligament of Treitz and duodenal mobilization can be done laparoscopically with all advantages of minimally invasive surgery.

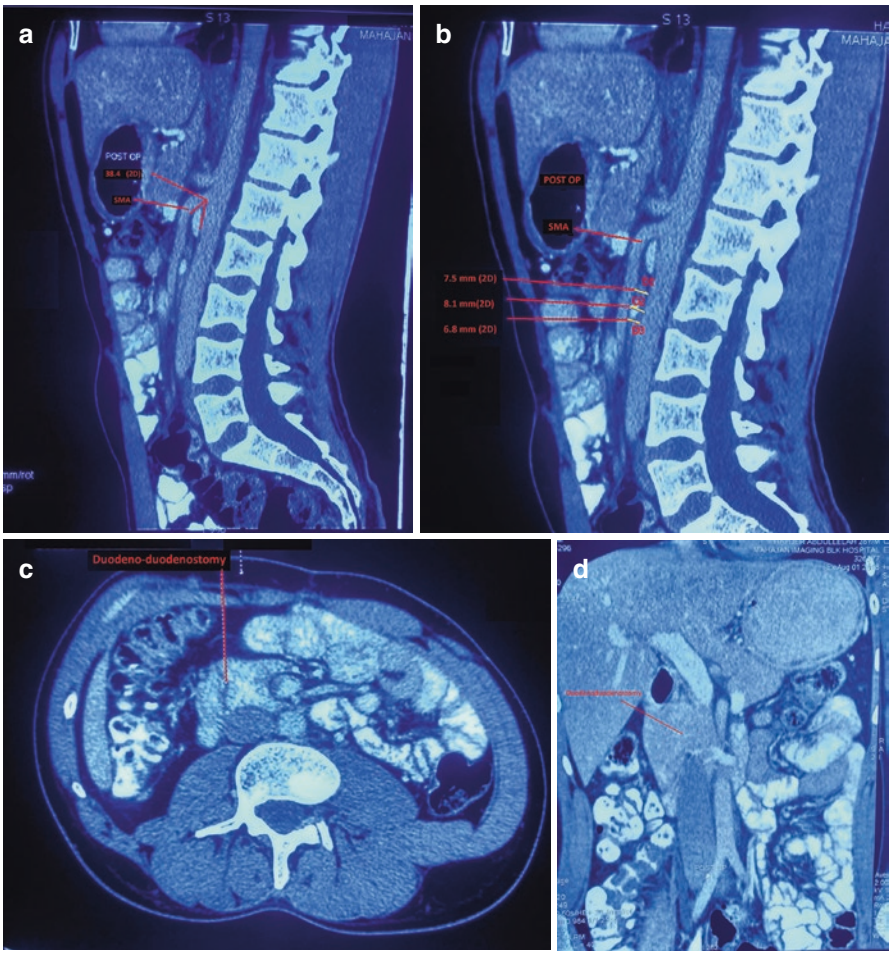


Fig. 2.14 (**a**–**d**) Post-op 4 years after duodenoduodenostomy

2.9.5.2 Strong's Procedure

Another less invasive surgical procedure known as Strong's procedure is also known as duodenal de-rotation procedure. This is also called de-rotation because the final position of the midgut is in direct opposition to the normal embryonic rotation of the midgut. Strong's procedure involves lysis of ligament of Treitz with mobilization of the duodenum. This operation has a failure rate of 25%. Strong's procedure is used rarely in some pediatric cases where there are associated congenital anomalies like incomplete rotation.

2.9.5.3 Gastrojejunostomy

Gastrojejunostomy has also been used for SMAS. However, it is an ill-conceived operation for SMAS. The intent to drain the duodenal obstruction retrogradely through a gastrojejunostomy is inherently not physiological with biliary gastritis and stomal ulceration in a non-vagotomized stomach being other areas of concern. The very ability of a chronically distended stomach to propel food across the gastrojejunostomy is also suspect [55].

2.9.5.4 Duodenoduodenostomy

Duodenoduodenostomy has been mentioned as a treatment for SMAS. Technically demanding it requires extensive duodenal mobilization with a generous Kocherization and release of the duodenojejunal flexure. It is usually indicated for the management of neonatal proximal duodenal atresia.

We have treated three patients with SMAS. One had a duodenoduodenostomy with good result. A 28-year-old male presented with upper abdominal pain and vomiting. A CECT abdomen during presentation in 2015 showed a classical narrowing of the aortomesenteric angle. He reported for review recently. He was asymptomatic and had put on 15 kg weight. A repeat CECT now shows a well-functioning duodenoduodenostomy and normalization of the aortomesenteric angle, even as the aortomesenteric distance has remained the same. This seems to suggest that an increase in the size of the pad of fat in the aortomesenteric angle may play an important role in widening the angle (Figs. 2.13 and 2.14).

2.9.5.5 Duodenojejunostomy

Duodenojejunostomy proximal to the point of obstruction with or without division of the ligament of Treitz is the currently favored surgical procedure for SMAS. Duodenojejunostomy is reported to have a success rate up to 90% [56]. It can be done by a traditional open approach, laparoscopically, or now even robotically.

The essential steps for performing duodenojejunostomy with a division of the ligament of Treitz start with mobilizing the duodenal jejunal (DJ) flexure by incising the peritoneum on the lateral aspect of the DJ flexure to the right of the inferior mesenteric vein and carrying the dissection along the upper border of the duodenum till the point at which pulsation of the SMA can be seen and palpated.

Attention is then drawn to identifying the dilated duodenum which can be easily done by holding up the transverse mesocolon, and the duodenal dilatation becomes easily visible. Varying lengths of the afferent jejunal limb for performing the anastomosis have been used. It is our practice to use a length which is short enough to

allow a tension-free side-to-side anastomosis. There are reports in literature of using a Roux limb. This would be useful if an anastomosis is planned with the second part of the duodenum. The most feasible physiologically sound procedure is a side-to-side duodenojejunostomy with a short afferent limb.

A laparoscopic approach to the SMAS has been used with good results. There are several case reports and series of laparoscopic and even robotic operations for SMAS [57, 58]. Gersin et al. [59] reported the first case of laparoscopic duodenojejunostomy in 1998. One of the largest series is by Munene et al. [60]. They did duodenojejunostomy with or without division of the duodenal ligament in 13 cases with good results. Currently laparoscopic duodenojejunostomy should be considered the treatment of choice for SMAS where facilities for the same are available [61].

A robotic procedure may be an overkill as a laparoscopic duodenojejunostomy is fairly simple to do.

2.10 Conclusion

SMAS is a rare condition and though the exact etiology is an enigma, it is reasonable to assume that it is precipitated by an acquired cause in patients who have a preexisting embryological predilection for developing the syndrome. The investigation of choice for diagnosing the condition is MDCT with sagittal and axial reconstruction. All patients need intensive resuscitation, and the best results for those patients who need an operation are achieved by a side-to-side duodenojejunostomy performed conventionally or laparoscopically.

Editorials Comments

The authors have provided a detailed description of the superior mesenteric artery (SMA) syndrome. This syndrome is commonly associated with severe debilitating diseases such as cancer, AIDS [62], abdominal trauma [63], burns [64], etc. A rapid and large amount of reduction in body weight as may occur in drug abusers and in those suffering from anorexia nervosa [65] can also cause SMA syndrome. Genetic predisposition has also been suggested as a possible factor in its occurrence as SMA syndrome has been reported in identical twins [66]. A number of patients with SMA syndrome have coexisting celiac axis compression [67]. The diagnosis is unlikely to be confused with chronic mesenteric ischemia and atherosclerosis [68]. In the chronic form of the disease, the duodenum and the stomach are dilated. This may result in ischemia of the stomach resulting in necrosis manifesting as perforation, gastric pneumatosis, and air in the portal venous system [69].

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Chapter 3
Biologics and Inflammatory Bowel Disease

V. Pratap Mouli and Vineet Ahuja

3.1 Background

Crohn's disease (CD) and ulcerative colitis (UC) are idiopathic inflammatory bowel diseases (IBD) which occur due to dysregulated immune response in genetically predisposed individuals [1, 2]. With advances in the understanding of the molecular pathways of pathogenesis of IBD, it is now known that innate immune cells secrete pro-inflammatory cytokines in response to certain gut bacteria or environmental agents which in turn activate adaptive immune system cells such a TH1 and TH17 cells, upregulate the expression of adhesion molecules on endothelial cells, lead to leukocyte migration to sites of inflammation, and cause uncontrolled inflammatory response and thereby result in tissue injury [3]. Anti-inflammatory and immunosuppressive therapies such as aminosalicylates, corticosteroids, and azathioprine remained the mainstay of therapy for IBD for a long duration. Over the last two decades, there has been an advent of biological drugs targeting specific cytokines and thereby blocking specific immune pathways, in the therapy of IBD as well as other immune-mediated diseases such as rheumatoid arthritis, psoriasis, etc. Tumor necrosis factor alpha (TNF-α) was found to be one of the major cytokines involved in the pathogenesis of IBD [3]. With the advent of anti-TNF-α agents, the treatment paradigm of IBD has changed with a favorable change in the overall natural history of the disease, decreasing the morbidity associated with these diseases [4]. In the current review, the various biologics currently available for the treatment of IBD, indications for their use in IBD, efficacy of biologics in the treatment of IBD, and adverse effects of these drugs are discussed.

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Table 3.1 Biologics commonly used for inflammatory bowel diseases

Drug class	Drug	Trade name	Induction regimen	Maintenance regimen
Anti-TNF-α antibodies	Infliximab	Remicade[a]	5 mg/kg IV at 0, 2, 6 weeks	5 mg/kg IV 8 weekly
	Adalimumab	Humira	160 mg at 0, 80 mg at 2 weeks SC	40 mg SC 2 weekly
	Certolizumab peg	Cimzia	400 mg SC at 0, 2, 4 weeks	400 mg SC 4 weekly
	Golimumab	Simponi	200 mg at 0, 100 mg at 2 weeks SC	100 mg SC 4 weekly
	Infliximab biosimilar	Infimab[a] Remsima Inflectra Renflexis Flixabi	5 mg/kg IV at 0, 2, 6 weeks	5 mg/kg IV 8 weekly
	Adalimumab biosimilar	Exemptia[a] Adfrar[a] Mabura[a] Amjevita	160 mg at 0, 80 mg at 2 weeks SC	40 mg SC 2 weekly
Anti-integrin antibodies	Natalizumab	Tysabri[a]	300 mg IV at 0 weeks	300 mg IV 4 weekly
	Vedolizumab	Entyvio	300 mg IV at 0, 2, 6 weeks	300 mg IV 8 weekly

[a]Marketed and available in India

3.2 Biologic Agents for the Treatment of IBD

The most commonly used biologics for the treatment of IBD are anti-TNF-α agents and anti-integrin agents (Table 3.1). There are various other agents which are under investigation which have been listed subsequently.

3.2.1 Anti-TNF-α Antibodies

The anti-TNF-α agents which were subjected to clinical research in patients with IBD include infliximab, adalimumab, certolizumab peg, golimumab, and etanercept (Fig. 3.1). Apart from these original products, biosimilars are available for infliximab and adalimumab.

Infliximab (trade name Remicade) is a chimeric (mouse/human) monoclonal IgG1 antibody which is administered as an intravenous (IV) infusion with the typical dosage being 5 mg/kg body weight at 0, 2, and 6 weeks as induction regimen and subsequently at 8 weekly intervals as maintenance regimen.

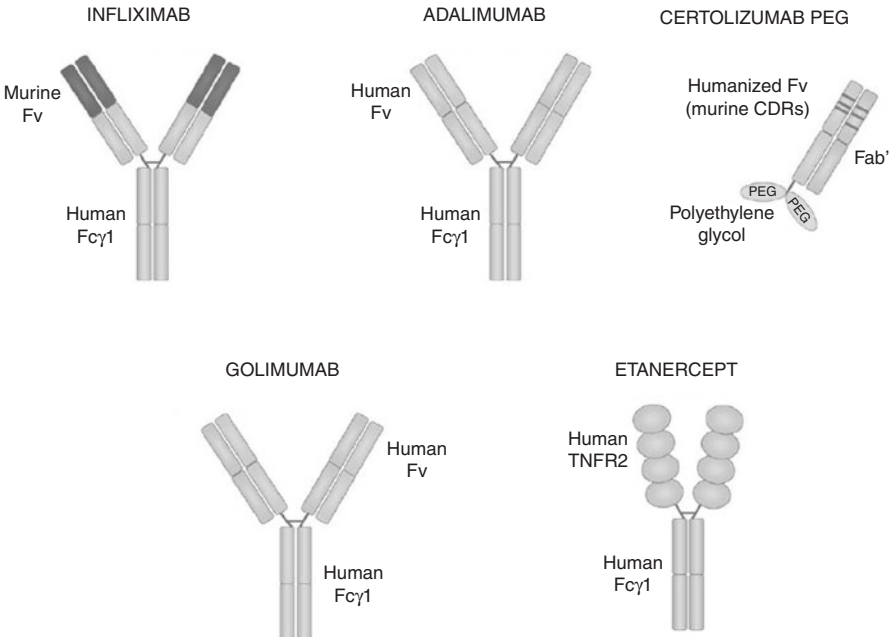

Fig. 3.1 Molecular structure of anti-tumor necrosis factor (anti-TNF) agents Fv–variable fragment; Fcγ1–immunoglobulin gamma 1 crystalline fragment; CDR–complementarity determining region; Fab'–antigen binding fragment; TNFR2–tumour necrosis factor receptor 2

Adalimumab (trade name Humira) is a fully human monoclonal IgG1 antibody which is administered subcutaneously (SC) with the typical adult dosage being 160 mg at initiation and 80 mg at 2 weeks as the induction regimen followed by 40 mg every 2 weeks as maintenance regimen.

Certolizumab peg (trade name Cimzia) is a pegylated Fab' fragment of a humanized anti-TNF monoclonal IgG4 antibody lacking the Fc portion. It is administered SC with the induction dosage being 400 mg at 0, 2, and 4 weeks followed by maintenance dosage of 400 mg every 4 weeks.

Golimumab (trade name Simponi) is a fully human monoclonal IgG1 antibody which is administered SC with the typical dosage being 200 mg at initiation and 100 mg at 2 weeks as the induction regimen followed by 100 mg every 4 weeks as maintenance regimen.

Etanercept (trade name Enbrel) is a chimeric fusion protein produced by the combination of two naturally occurring soluble human TNF receptors linked to an Fc portion of IgG1.

Biosimilars are biologic products which are nearly identical to the original biologic agent but are manufactured by a different company once the patent for the original product expires. Such biosimilars are available for infliximab and adalimumab.

Of all the anti-TNF-α agents mentioned above, etanercept was not found to be effective in IBD. This is because there could be various other effector mechanisms apart from neutralization of soluble TNF-α by which anti-TNF-α agents act to downgrade the inflammatory process in IBD. These include (1) induction of lamina propria T cell apoptosis and (2) triggering of differentiation of monocytes to M2-type wound-healing macrophages through a mechanism dependent on the Fc region on the biologic agent. Etanercept doesn't elicit the latter mentioned effector mechanisms which is likely because of its structure, which would explain the ineffectiveness of etanercept in IBD [5].

3.2.2 Anti-integrin Antibodies

Natalizumab (trade name Tysabri) is a humanized monoclonal IgG4 antibody directed against the α4 integrin chain. Natalizumab blocks both α4β1 and α4β7 integrins. It is given IV in a dosage of 300 mg every 4 weeks.

Vedolizumab (trade name Entyvio) is a humanized monoclonal IgG1 antibody which binds to integrin α4β7. It does not bind to α4β1 integrin; thus it has gut-specific anti-inflammatory action. It is administered as an IV infusion in a dosage of 300 mg at 0, 2, and 6 weeks as induction regimen and subsequently at 8 weekly intervals as maintenance regimen.

3.2.3 Newer Drugs

The newer drugs which are under research for treatment of IBD include anti-IL12/anti-IL23 antibodies (ustekinumab), anti-IL13 antibodies (tralokinumab, anrukinzumab), anti-eotaxin-1 antibodies (bertilimumab), anti-IL6 antibodies (tocilizumab), Janus kinase inhibitors (tofacitinib, filgotinib), SMAD7 antisense oligonucleotide (mongersen), tyrosine kinase inhibitor masitinib, anti-ICAM-1 antibodies (alicaforsen), and anti-sphingosine 1-phosphate 1 antibodies (fingolimod).

Anti-TNF-α agents and anti-integrin agents are widely approved drugs for the management of IBD; these are discussed in detail in the subsequent sections.

3.3 Indications of Biologics in the Treatment of IBD

Anti-TNF-α agents are recommended to be used in moderately severe, steroid-dependent, or steroid-refractory patients with UC; in steroid-refractory cases of severe acute colitis; in the management of luminal CD either as a top-down or step-up protocol; in perianal CD, fistulizing CD, to prevent postoperative recurrence of

Table 3.2 Indications of biologics in the management of inflammatory bowel diseases

• Steroid-dependent ulcerative colitis
• Steroid-refractory ulcerative colitis
• Rescue therapy in steroid-refractory acute severe colitis
• Refractory pouchitis post ileal pouch anal anastomosis surgery (IPAA)
• Moderate or severe cases of luminal Crohn's disease
• Crohn's disease with inflammatory strictures
• Fistulizing Crohn's disease (enterocutaneous or perianal)
• Prevention of postoperative recurrence of Crohn's disease
• Extra-intestinal manifestations
– Refractory spondyloarthropathy
– Pyoderma gangrenosum
– Erythema nodosum
– Sweet's syndrome
– Recurrent and refractory oral aphthae
– Refractory uveitis

CD; in the treatment of refractory pouchitis; and in the treatment of certain extra-intestinal manifestations of IBD (Table 3.2). The various aspects with regard to the clinical usage of anti-TNF-α agents are discussed in the following sections. Data pertaining to anti-adhesion agents is new and accrued in the last 4 years and is discussed subsequently.

3.4 Anti-TNF-α Agents in the Management of Ulcerative Colitis

3.4.1 Efficacy of Anti-TNF-α Agents in Inducing Remission in Moderate to Severe UC

Infliximab, adalimumab, and golimumab were shown to be superior to placebo in inducing remission as well as achieving clinical response in moderate to severe UC in randomized controlled trials. Infliximab in a dosage of 5 mg/kg IV at 0, 2, and 6 weeks was shown to induce remission in 38.8% and 33.9% of patients at 8 weeks in the ACT 1 and ACT 2 trials compared to remission rates of 14.9% ($p < 0.001$) and 5.7% ($p < 0.001$) with placebo [6]. Adalimumab in a dosage of 160/80/40/40 mg SC at 0, 2, 4, and 6 weeks was shown to induce remission in 18.5% and 16.5% of patients at 8 weeks in the ULTRA 1 [7] and ULTRA 2 [8] trials compared to remission rates of 9.2% ($p = 0.031$) and 9.3% ($p = 0.019$) with placebo. Golimumab in a dosage of 200/100 mg SC at 0 and 2 weeks was shown to induce remission in 17.8% of patients at 6 weeks in the PURSUIT-SC trial compared to remission rate of 6.4% ($p < 0.0001$) with placebo [9].

3.4.2 *Efficacy of Anti-TNF-α Agents in Maintaining Remission in Moderate to Severe UC*

Infliximab, adalimumab, and golimumab were shown to be superior to placebo in maintaining remission in patients with moderate to severe UC. In those patients who responded to the induction dosage of infliximab, 34.7% and 25.6% of patients who received infliximab in a dosage of 5 mg/kg IV every 8 weeks maintained clinical remission in the ACT 1 and ACT 2 clinical trials at 54 weeks and 30 weeks, respectively, compared to remission rates of 16.5% and 10.6% with placebo [6]. Patients who achieved benefit from infliximab in the ACT 1 and ACT 2 trials were followed up for an additional 3 years of therapy with infliximab given every 8 weeks. It was found that 30.6% of patients discontinued infliximab due to various reasons such as adverse effects, lack of efficacy, colectomy, etc. during the follow-up period, whereas infliximab was effective and well-tolerated in the rest of the patients [10]. In the ULTRA 2 trial, in those patients who received maintenance adalimumab in a dosage of 40 mg SC every 2 weekly after an induction regimen of 160/80 mg, the clinical remission rate at 52 weeks was 17.3% compared to 8.5% with placebo ($p = 0.004$) [8]. Patients who received adalimumab in the ULTRA 1 and 2 trials and patients in the placebo arm of these trials who subsequently received adalimumab were followed up in an open-label fashion, and the long-term remission rates at 4 years were studied, and among the patients who were in remission when they entered into the open-label study to continue adalimumab, 63.6% maintained remission at 4 years [11]. In the PURSUIT-M trial, among those patients who responded to golimumab induction therapy, 27.8% of patients who received golimumab 100 mg SC every 4 weekly maintained clinical remission at 54 weeks compared to 15.6% with placebo ($p = 0.004$) [12].

3.4.3 *Mucosal Healing in UC Patients with Anti-TNF-α Agents*

Mucosal healing was observed in 45.5% and 46.3% of patients who received 5 mg/kg infliximab in the ACT 1 and ACT 2 trials at 54 weeks and 30 weeks, respectively, compared to rates of 18.2% ($p < 0.001$) and 30.1% ($p = 0.009$) with placebo. Achievement of early mucosal healing at 8 weeks was associated with increased rates of symptomatic remission, corticosteroid-free symptomatic remission, mucosal healing, and colectomy-free survival at 54 weeks and 30 weeks, respectively, in the ACT 1 and ACT 2 trials [6]. Mucosal healing was observed in 41.1% of patients at 8 weeks and in 25% of patients at 52 weeks who received adalimumab compared to 31.7% ($p = 0.032$) and 15.7% ($p = 0.009$), respectively, among the patients who received placebo in the ULTRA 2 trial [8]. Among the

patients from ULTRA 1 and ULTRA 2 trials who were followed on long-term maintenance therapy with adalimumab, mucosal healing was observed in 27.7% at 4 years [11]. Mucosal healing was observed in 42.3% of patients who received 200/100 mg golimumab ($p = 0.0014$) as compared to 28.7% of patients who received placebo at 6 weeks in the PURSUIT-SC trial [9], while 42.4% of patients who received maintenance dosage of 100 mg golimumab showed mucosal healing compared to 26.6% of patients who received placebo ($p = 0.002$) at 54 weeks in the PURSUIT-M trial [12].

3.4.4 Efficacy of Anti-TNF-α Agents in the Management of Acute Severe Colitis

Infliximab is the only anti-TNF-α agent and the only biologic which has been studied in randomized controlled trials in the setting of severe acute colitis refractory to intravenous corticosteroids.

The CySIF trial is an explanatory trial wherein patients with severe acute colitis who failed to respond to 5 days of IV hydrocortisone therapy were randomized to receive either cyclosporine (in a dosage of 2 mg/kg/d IV for 7 days followed by oral cyclosporine in a dosage of 4 mg/kg/day) or infliximab (in a dosage of 5 mg/kg IV at 0, 2, and 6 weeks) as a rescue strategy [13]. All the patients received azathioprine from day 7. Significant and similar clinical response was obtained with both infliximab and cyclosporine at day 7 to the tune of 84% and 86%, respectively ($p = 0.76$). Treatment failure occurred in 54% of patients treated with infliximab compared to 60% of patients treated with cyclosporine at 98 days ($p = 0.52$). After 5 years of follow-up, it was found that the colectomy-free survival rate was 65.1% in the patients who received infliximab which was similar to the 61.5% colectomy-free survival rate in patients who received cyclosporine ($p = 0.97$). The cumulative incidence of first infliximab use at 5 years in the patients who were initially treated with cyclosporine was 57.1%, while very few patients who received infliximab switched over to cyclosporine [14].

The CONSTRUCT trial is a pragmatic trial wherein patients with severe acute colitis who failed to respond to IV hydrocortisone despite 2–5 days of therapy were randomized to receive either cyclosporine (in a dosage of 2 mg/kg/d IV for 7 days followed by oral cyclosporine in a dosage of 5.5 mg/kg/day for 12 weeks) or infliximab (in a dosage of 5 mg/kg IV at 0, 2, and 6 weeks) [15]. Azathioprine was started at the physician's discretion at 4 weeks and beyond 12 weeks; all the treatment was at the discretion of the patient's physician. The primary outcome was quality adjusted survival over 1–3 years which was similar with both infliximab and cyclosporine. The frequency of colectomy was also similar with infliximab and cyclosporine (41% and 48%, respectively, $p = 0.223$).

3.5 Anti-TNF-α Agents in the Management of Crohn's Disease

3.5.1 Efficacy of Anti-TNF-α Agents in Inducing Remission in Moderate to Severe CD

Targan et al. had shown that infliximab in dosage of 5 mg/kg or 10 mg/kg or 20 mg/kg IV induced remission in 33% of patients with moderate to severe CD resistant to conventional treatment as compared to 4% of patients who received placebo ($p = 0.005$) at 4 weeks in a multicenter, randomized clinical trial [16]. Lemann et al. showed that infliximab given in a dosage of 5 mg/kg IV at 0, 2, and 6 weeks in combination with azathioprine/6-mercaptopurine (6-MP) was better than azathioprine/6-MP alone in inducing remission in patients with corticosteroid-dependent CD [17]. Adalimumab in a dosage of 160/80 mg SC was shown to induce remission in 36% of anti-TNF-α-naïve moderate to severe CD patients as compared to 12% with placebo ($p = 0.001$) at 4 weeks in the CLASSIC-1 trial [18]. In another randomized controlled trial done in Japanese patients among whom 60% were anti-TNF-α experienced, patients who received 160/80 mg induction dosage of adalimumab had the highest rate of clinical remission at 4 weeks compared to 80 mg/40 mg adalimumab or placebo (33%, 18%, and 13%, respectively). Patients who were anti-TNF-α naïve had better outcomes with adalimumab compared to anti-TNF-α-experienced patients [19]. Certolizumab in a dosage of 400 mg SC at 0, 2, and 4 weeks was shown to elicit clinical response in 37% of patients as compared to 26% among patients who received placebo ($p = 0.04$) at 6 weeks in the PRECISE-I trial [20].

3.5.2 Efficacy of Anti-TNF-α Agents in Maintaining Remission in Moderate to Severe CD

Infliximab, adalimumab, and certolizumab were shown to be superior to placebo in maintaining remission in patients with moderate to severe CD. In the ACCENT 1 trial, the initial clinical response, remission rate, and discontinuation of steroids was superior with infliximab compared to placebo at 30 weeks and 54 weeks. The remission rate with 5 mg/kg infliximab was 39% compared to 21% with placebo ($p = 0.003$) at 30 weeks. Patients who received scheduled infliximab therapy had significantly higher clinical response rates from week 10 to 30 and also significantly lower CD-related hospitalizations and surgeries at 54 weeks compared to the patients who received episodic therapy [21]. In the CLASSIC II trial, in those patients who were in clinical remission at 4 weeks after induction regimen, remission was maintained in 79% of patients who received 40 mg alternate-week adalimumab compared to 44% of patients who received placebo ($p < 0.05$) at 56 weeks

[22]. In the CHARM trial, the remission rate at 56 weeks with alternate-week adalimumab was 36% compared to 12% with placebo ($p < 0.001$) [23]. In the PRECISE II trial, in those patients who had a successful induction with certolizumab, 48% maintained clinical remission on certolizumab at 26 weeks compared to 29% of patients who received placebo ($p < 0.001$) [24].

3.5.3 Mucosal Healing in CD Patients with Anti-TNF-α Agents

In a randomized controlled trial which examined the clinical efficacy of a single infusion of infliximab (dosage of 5 mg/kg or 10 mg/kg or 20 mg/kg IV) in CD, mucosal healing was evaluated in European patients participating in the trial. It was found that there was significant improvement of the ulcerations on endoscopy at 4 weeks in most of the patients treated with infliximab irrespective of the dosage used, whereas there was no improvement in the endoscopic findings in patients who received placebo [25]. Mucosal healing was observed in a higher proportion of patients at 54 weeks when they received scheduled infliximab therapy compared to those who received episodic infliximab therapy based on their clinical symptoms (44% vs. 18%, $p = 0.041$) [26]. In the SONIC trial, mucosal healing was noted in 43.9% with infliximab and azathioprine combination therapy ($p < 0.001$) and in 30.1% with infliximab alone ($p = 0.02$) which were significantly higher than the 16.5% mucosal healing rate observed with azathioprine alone [27]. In the EXTEND trial, among those patients who received maintenance adalimumab therapy, mucosal healing was noted in 24% of patients at 52 weeks compared to none who received placebo ($p < 0.001$) [28]. In the MUSIC trial, a significant decrease in the Crohn's disease index of severity (CDEIS) score of 5 points from baseline was noted at 10 weeks after treatment with certolizumab. Endoscopic remission as defined by a CDEIS score of <6 was seen in 27% of patients at 54 weeks after treatment with certolizumab [29].

3.5.4 Efficacy of Anti-TNF-α Agents in Fistulizing Crohn's Disease

Infliximab in dosages of 5 mg/kg and 10 mg/kg IV at 0, 2, and 6 weeks was shown to be better than placebo (68% and 56% vs. 26%, $p = 0.002$ and 0.02, respectively) in inducing closure of at least 50% of fistulae, perianal or enterocutaneous [30]. In patients with fistulizing CD who had response to induction therapy with infliximab, maintenance therapy with infliximab helped to sustain response with 36% of patients maintaining complete closure of fistulae which was significantly higher than the 19% rate of fistula closure noted with placebo at 54 weeks ($p = 0.009$).

The median duration of fistula closure was 40 weeks in these responders as compared to 23 weeks with placebo [31]. A combination of infliximab and ciprofloxacin was found to be better than infliximab alone in the treatment of perianal CD [32]. In a study which evaluated the long-term efficacy of infliximab for fistulizing perianal CD, it was found that the cumulative probability of fistula recurrence was 40.1% at 5 years [33]. Adalimumab resulted in complete closure of fistulas in 33% of patients at 56 weeks compared to 13% of patients on placebo ($p = 0.016$) in the CHARM trial [23]. Combination treatment with adalimumab and ciprofloxacin was found to be better than adalimumab alone in the treatment of perianal CD [34]. Combination treatment of infliximab and seton was found to be better than treatment with seton alone [35] or anti-TNF-α alone [36] in patients with perianal fistulizing CD; however, the decision to place a seton has to be individualized.

Majority of the patients who were analyzed for outcomes with regard to fistulizing disease in the above mentioned trials had perianal fistulae. Data regarding enterocutaneous fistulas is relatively scarce. In a retrospective study on the long-term outcome of enterocutaneous fistula in patients with CD who were treated with anti-TNF-α agents, it was found that complete closure of the fistula occurred in 33% of patients at 3 months, but half of them relapsed during the follow-up period. Abdominal abscess developed in 31% of the patients who received anti-TNF-α agents for enterocutaneous fistula. The presence of multiple enterocutaneous fistula tracts and the presence of intestinal stricture precluded the patients from having complete fistula closure despite anti-TNF-α therapy [37].

3.5.5 Efficacy of Anti-TNF-α Agents in Small Bowel Strictures in Crohn's Disease

Fibrostenosing disease is generally considered to be one of the predictors for loss of response to anti-TNF-α agents in CD. However, data regarding the efficacy of anti-TNF-α agents for stricturing disease is controversial, and one reason could be that it is not always easy to distinguish between predominantly inflammatory and predominantly fibrotic strictures. The CREOLE study was a multicentric, prospective, observational study which assessed the efficacy of adalimumab in the treatment of symptomatic small bowel strictures in 97 CD patients [38]. It was found that 64% of patients achieved success at 24 weeks without requiring corticosteroids or endoscopic dilatation or surgery. Nearly 29% of the patients had prolonged success at 4 years by remaining on adalimumab without requiring endoscopic dilatation or surgery. Predictors of successful therapy with adalimumab included usage of immunomodulators along with adalimumab, presence of obstructive symptoms for <5 weeks, Crohn's disease obstructive score >4, MR enterography findings of stricture length of <12 cm, maximum small bowel diameter proximal to stricture of 18–29 mm, marked enhancement on delayed phase, and absence of fistula. It was felt that these features could possibly represent reversible and non-severe strictures.

3.5.6 Step-Up vs. Top-Down Approach for the Treatment of Crohn's Disease

In the step-up approach, patients are initiated on steroids and then shifted to immunosuppressants and subsequently to biologics if these patients are steroid-dependent or steroid-refractory, whereas in the top-down approach biologics and immunosuppressants are started as the first-line therapy up front from the time of diagnosis. In a randomized controlled trial, it was found that patients who received treatment in a top-down fashion had significantly better clinical outcomes compared to treatment in a step-up manner at 24 weeks and 52 weeks; mucosal healing was also significantly more frequent among those patients who were treated with a top-down approach [39]. However, it is important to understand that in real-life scenario, a significant proportion of patients with CD may do well with just milder treatment [40]. So it is imperative to recognize those patients who are at a higher chance to have a complicated disease course, and these patients may benefit from a top-down approach.

3.5.7 Efficacy of Anti-TNF-α Agents in the Postoperative Prevention of Crohn's Disease

Regueiro et al. performed a single-center, randomized controlled trial to evaluate the efficacy of infliximab in the prevention of postoperative recurrence in 24 patients with CD who underwent ileocolonic resection with the treatment being initiated within 4 weeks of surgery [41]. Concomitant treatment with thiopurines was continued in 36.4% of patients who received infliximab and 53.8% of patients who received placebo. It was found that the rate of endoscopic recurrence in patients who received infliximab was only 9.1% which was significantly lower as compared to 84.6% who received placebo ($p = 0.0006$). The histologic recurrence rate and clinical recurrence rate (defined by a Crohn's disease activity index [CDAI] score of more than 200) at 1 year were also significantly lower with infliximab compared to placebo. After a further follow-up of at least 5 years, it was found that endoscopic recurrence occurred in only 22.2% of patients who received long-term infliximab compared to 93.9% of patients who did not receive infliximab ($p < 0.0001$); the rate of requirement of additional surgery was 20% in patients who received long-term infliximab compared to 64.3% who received it for only shorter periods ($p = 0.047$) [42].

In another randomized controlled trial by Rigueiro et al., 297 patients who underwent ileocolonic resection in the past 45 days were included from 104 centers [43]. Concomitant treatment with immunosuppressants was continued in 17% of patients who received infliximab and 18% of patients who received placebo. It was found that infliximab was not superior to placebo in preventing clinical recurrence at 76 weeks (defined by a 70-point increase of CDAI score from baseline along with a total CDAI score of ≥200), but infliximab was superior to placebo in preventing endoscopic recurrence (30.6% vs 60%, $p < 0.001$).

The POCER study was designed to identify the optimal strategy to prevent postoperative recurrence of CD [44]. In this randomized trial, thiopurines and adalimumab were the drugs administered to the patients who were eligible to receive drug therapy as per the study protocol. In this study it was shown that treatment according to clinical risk of recurrence, with early colonoscopy at 6 months after surgery and treatment step-up for recurrence, was better than conventional drug therapy alone, for prevention of postoperative recurrence of CD. In a subanalysis of this study, the relative efficacy of adalimumab in comparison to thiopurines was assessed in 101 CD patients who were at high risk for postoperative recurrence, and it was found that adalimumab was superior to thiopurines in preventing endoscopic recurrence at 6 months [45]. Endoscopic recurrence (defined as Rutgeerts score i2–i4) occurred in 21% of patients treated with adalimumab compared to 45% among patients treated with thiopurines ($p = 0.028$); complete endoscopic mucosal normality (Rutgeerts score i0) was seen in 54% of adalimumab-treated patients compared to 23% among thiopurine-treated patients ($p = 0.003$) at 6 months. The clinical recurrence rates were similar in both the groups at 6 months.

In a meta-analysis of six prospective studies evaluating the efficacy and safety of anti-TNF-α agents for the prevention of postoperative recurrence of CD, it was found that anti-TNF-α agents were superior to non-biologic treatment (which included mesalamine, thiopurines, or placebo) in preventing endoscopic and clinical recurrence of CD without causing more adverse events. The rate of endoscopic recurrence was 9.2% with anti-TNF-α agents compared to 61.5% in the non-biologics group ($p < 0.001$); the rate of severe endoscopic recurrence was 1.6% in the anti-TNF-α group compared to 32.7% in the non-biologics group ($p = 0.04$); clinical recurrence was 3.4% in the anti-TNF-α group compared to 41.1% in the non-biologics group ($p < 0.001$); clinical remission was noted in 86.5% of patients treated with anti-TNF-α agents compared to 58.1% of patients in the non-biologics group ($p < 0.01$) [46]. In a network meta-analysis of randomized controlled trials which estimated the comparative efficacy of various drugs for postoperative prevention of CD, it was found that anti-TNF-α monotherapy was the most effective treatment strategy for postoperative prevention [47].

3.6 Efficacy of Combination of Anti-TNF-α Agents with Immunomodulators

To increase the effectiveness of treatment of IBD, one of the strategies studied was combining anti-TNF-α therapy with immunomodulators. In the SONIC trial, it was found that the combination of infliximab and azathioprine was superior to infliximab alone as well as azathioprine alone in achieving corticosteroid-free remission and in achieving better clinical response at 26 weeks in patients with moderate to severe CD, but this superior efficacy of combination therapy over infliximab alone was not maintained in the long term at 50 weeks [27]. In the COMMIT trial, there was no difference in the outcomes in patients with moderate to severe CD who received infliximab in combination with methotrexate as compared to those who received

infliximab alone [48]. In the UC-SUCCESS trial, it was found that the combination of infliximab and azathioprine was superior to infliximab alone in inducing corticosteroid-free clinical remission at 16 weeks in patients with moderate to severe UC [49]. In a meta-analysis of placebo-controlled trials comparing the efficacy of combination therapy of anti-TNF-α agents and immunomodulator with anti-TNF-α monotherapy in patients with CD who failed immunomodulator therapy, it was found that combination therapy was not more effective than anti-TNF-α monotherapy in inducing or maintaining clinical response or remission [50]. In another meta-analysis, it was found that combination of adalimumab and immunomodulator was superior to adalimumab monotherapy in inducing clinical remission but not for maintaining remission or for curbing dose escalation [51]. In another meta-analysis, it was found that the formation of anti-drug antibodies was lower with combination of anti-TNF-α and immunomodulators compared to anti-TNF-α monotherapy, though the trough levels of the anti-TNF-α agents did not differ between the groups [52].

Thus, combination therapy with anti-TNF-α agents and immunomodulators is superior to monotherapy with anti-TNF-α agents or immunomodulators in some aspects. Immunomodulators appear to decrease immunogenicity against anti-TNF-α agents.

3.7 Efficacy of Anti-TNF-α Biosimilars in IBD

In a prospective, multicentric, nationwide study done in Italy, it was shown that the infliximab biosimilar CT-P13 resulted in clinical response in 92% of patients at 8 weeks [53]. In a prospective, multicentric, nationwide study done in Hungary, it was shown that CT-P13 induced clinical remission in 53.6% of patients with CD and 58.6% of patients with UC, and clinical response was noted in 81.4% of CD patients and 77.6% of UC patients at 14 weeks. Steroid-free clinical remission was achieved in 50% of CD patients and 56% of UC patients at 30 weeks. Adverse events occurred in 17% of patients at 30 weeks [54]. The outcomes with CT-P13 at 54 weeks were reported in another prospective study; among those patients who completed 54 weeks of therapy with CT-P13 continuous, clinical response was noted in 69.4% of CD patients and 57.6% of UC patients with the overall rate of loss of response being 30.4% in CD and 34.8% in UC patients at 54 weeks [55]. In another prospective study, it was found that in UC patients, CT-P13 led to steroid-free mucosal healing in 47.6% and complete mucosal healing in 27% at 14 weeks [56].

3.8 Switching of Anti-TNF-α Agents When the Disease Is Under Control

The choice of anti-TNF-α agents that is to be used is usually based on the patient and physician preference, and various factors such as cost, route of administration, ease of administration, and side effects do weigh in while making this choice. When

the initial anti-TNF-α agent has failed, there may be a necessity to change the anti-TNF-α agent. However, when the disease is well-controlled and the patient is doing well otherwise, it is important to know whether the anti-TNF-α agent can be changed.

Van Assche et al. studied the impact of elective switching of patients with CD who were well-maintained in remission with infliximab infusion to subcutaneous adalimumab in a randomized controlled trial named the SWITCH trial [57]. Dose intensification or early treatment termination (either due to loss of efficacy or due to intolerance) was observed in 47% of patients switched to adalimumab as compared to 16% of patients who were continued on infliximab ($p = 0.03$) at 54 weeks, implying that elective switching to adalimumab led to worse outcomes than maintaining on infliximab.

Smits et al. switched 83 adult IBD patients (69% CD, 29% UC) being treated with infliximab in their center to a biosimilar agent CT-P13, and among the patients who were in clinical remission at baseline, over 80% of patients maintained remission till at 16 weeks, thus showing that switching did not result in significant changes of disease activity in the short term [58]. Buer et al. switched 143 adult IBD patients (69% CD, 31% UC) being treated with infliximab in their center to the biosimilar agent CT-P13, and found that 97% of the patients who switched over to CT-P13 remained on this biosimilar at 6 months follow-up; only 23% of patients needed treatment intensification during this period [59].

Thus to summarize, as per the current available evidence, switching from infliximab to adalimumab in well-controlled CD patients is not recommended as it leads to loss of efficacy and intolerance, while switching of infliximab to its biosimilars appears to be a feasible strategy in patients with CD and UC.

3.8.1 Withdrawal of Anti-TNF-α Agents in Patients with Disease Remission

Treatment with biologics is costly and associated with concerns regarding safety in the long term especially in India where tuberculosis is a major concern. Hence, it is important to know whether biologics can be stopped in patients who attained remission.

In the STORI trial, 115 patients with CD who were on a combination of infliximab and antimetabolite for at least 1 year with them being in steroid-free remission for at least 6 months were followed up for at least 1 year after stopping infliximab [60]. The 1 year relapse rate was 43.9%. On multivariate analysis, the predictive factors for relapse were male sex, absence of surgical resection, leukocyte count >6000/mm^3, hemoglobin ≤14.5 g/dL, CRP ≥ 5 mg/L, and fecal calprotectin ≥300 μg/g. When there were only two (or less) of these risk factors, the relapse rate was only 15% at 1 year. Majority of the patients who relapsed could be successfully retreated in the short term with restarting infliximab. A sudden and pronounced

increase in CRP and calprotectin levels usually occurred within 4 months prior to the relapse. After a long-term follow-up of median of 8 years, only 15% of the patients remained without experiencing failure, suggesting that relapse rates increased with time.

Gisbert et al. performed a meta-analysis of 27 studies which reported the risk of relapse after discontinuation of anti-TNF-α agents in patients with CD and UC [61]. The overall risk of relapse after discontinuation of anti-TNF-α therapy was 44% for patients with CD (follow-up range, 6–125 months) and 38% for patients with UC (follow up range, 6–24 months). In patients with CD, the relapse rate after 1 year was 42% when the only criterion to stop anti-TNF-α therapy was clinical remission, whereas the relapse rate was 26% when endoscopic remission was taken as a necessary criterion to stop anti-TNF-α therapy. Retreatment with the same anti-TNF-α agent gave favorable results with an 80% possibility of re-inducing remission.

3.8.2 Anti-TNF-α Agents in the Management of Extra-Intestinal Manifestations of IBD

There are reports of beneficial effects of anti-TNF-α agents, mainly with infliximab and adalimumab, in certain extra-intestinal manifestations in patients with IBD. Anti-TNF-α agents are a therapeutic option in refractory cases of peripheral arthritis, sacroileitis, pyoderma gangrenosum, erythema nodosum, Sweet's syndrome, recurrent oral aphthae, and uveitis [62, 63].

3.9 Anti-integrin Agents in the Management of IBD

3.9.1 Efficacy of Natalizumab in IBD

The efficacy of natalizumab was studied in patients with moderate to severe CD in clinical trials. In the ENCORE trial, clinical response was achieved in 48% of patients who received natalizumab at 12 weeks compared to 32% among those who received placebo ($p < 0.001$); sustained remission was seen in 26% of patients who received natalizumab at 12 weeks compared to 16% among those who received placebo ($p = 0.002$) [64]. In a meta-analysis, natalizumab was shown to be significantly superior compared to placebo in inducing clinical remission (RR 0.86, 95% confidence interval [CI] 0.80–0.93) [65]. In the ENACT-2 trial, among those patients who received maintenance therapy with natalizumab, clinical response was achieved in 61% of patients at 36 weeks compared to 28% of those who received placebo ($p < 0.001$); clinical remission was maintained in 44% of patients who were on natalizumab at 36 weeks compared to 26% among those who received placebo ($p = 0.003$) [66].

3.9.2 Efficacy of Vedolizumab in IBD

In patients with moderate to severe UC, vedolizumab was found to induce clinical response in 47.1% of patients at 6 weeks as compared to 25.5% with placebo ($p < 0.001$) in the GEMINI I trial whereas clinical remission was seen in 16.9% of patients who received vedolizumab compared to 5.4% who received placebo ($p = 0.001$) at 6 weeks. Maintenance therapy with vedolizumab was found to be superior to placebo at 52 weeks in maintaining clinical remission, corticosteroid-free clinical remission, and mucosal healing. Among the patients included in the GEMINI I trial, 41% had prior anti-TNF-α failure [67]. In a meta-analysis of 4 studies including 606 patients, it was found that vedolizumab was significantly superior to placebo for induction of clinical remission, clinical response, and endoscopic remission and for maintaining remission at 52 weeks in those patients who had clinical response at 6 weeks [68].

In the GEMINI II trial, vedolizumab was found to be superior to placebo in inducing clinical remission at 6 weeks in patients with moderate to severe CD (14.5% vs. 6.8%, $p = 0.02$), though there was no difference in improvement of CDAI scores by at least 100 points as well as in CRP levels. Vedolizumab was found to be significantly superior to placebo in maintaining clinical remission, corticosteroid-free clinical remission, and improvement of CDAI score by at least 100 points at 52 weeks in patients with moderate to severe CD, though there was no difference in the rate of durable clinical remission between the two groups. Among the patients included in the GEMINI II trial, 57.8% had prior anti-TNF-α failure [69]. In the GEMINI III trial, patients with ileal or colonic CD with moderate to severe activity were included, and 75.7% of patients had prior anti-TNF-α failure. Among the patients with prior anti-TNF-α failure, vedolizumab induced clinical remission in 26.6% of patients at 10 weeks compared to 12.1% with placebo ($p = 0.001$), whereas the overall clinical remission in all the patients was 28.7% with vedolizumab at 10 weeks compared to 13% with placebo ($p < 0.001$) [70].

3.10 Head to Head Comparison of Biologics

There are no trials with head to head comparison of biologics in IBD patients. The choice of biologics is usually based on the patient and physician preference, and various factors such as cost, route of administration, ease of administration, side effects, and anecdotal experience play a role while making this choice. As there is no direct evidence from comparative efficacy trials, the best evidence as of today regarding the comparative efficacy of biologics in IBD comes from network meta-analyses which indirectly assessed the comparative efficacy of various biologics across a network of RCTs.

In a network meta-analysis, it was found that infliximab had significantly better efficacy compared to certolizumab peg, natalizumab, vedolizumab, and ustekinumab for induction of remission in biologic naïve adult patients with moderate to severe luminal CD [71]. Infliximab had an 86% probability and adalimumab a 16% probability of being ranked as the most efficacious biologic for inducing remission in biologic naïve, moderate to severe adult CD patients. After responding favorably to induction regimen of the index biologic agent, there were no significant differences between the individual biologic drugs in maintaining remission. Adalimumab had a 48% probability, natalizumab a 29% probability, and infliximab a 11% probability of being ranked as the most efficacious biologic for maintaining remission in moderate to severe adult CD patients who responded to an induction regimen of the index biologic agent.

Infliximab was found to be superior to adalimumab in a network meta-analysis in inducing clinical remission, clinical response, and mucosal healing in patients with moderate to severe UC, but there were no significant differences in head to head comparison of other biologics in network meta-analysis [72]. With regard to the network meta-analysis indirectly comparing the efficacy of various biologics during the maintenance phase, it was found that vedolizumab had significantly better clinical remission compared to infliximab; vedolizumab had significantly better durable clinical response compared to adalimumab, infliximab, and golimumab; and vedolizumab had significant improvement in mucosal healing compared to adalimumab.

3.11 Status of Biologics in Pregnancy (Table 3.3)

Active disease in IBD patients is associated with adverse outcomes in pregnancy. The impact of the safety profile of biologics on conception, pregnancy, fetus, and newborn and the risk of stopping biologics in pregnancy leading to disease flare are two diverse aspects which affect the decision-making regarding treatment with biologics in women who are in the reproductive age and who are pregnant.

Table 3.3 Biologics and pregnancy

• Anti-TNF-α agents are category B risk drugs in pregnancy
• Anti-TNF-α agents are not associated with adverse pregnancy outcomes
• Anti-TNF-α agents apart from certolizumab peg have transplacental transmission
• Anti-TNF-α agents can be continued in the first two trimesters of pregnancy
• Significant levels of anti-TNF-α agents can be detected in the blood of infants whose mothers received anti-TNF-α agents in the third trimester
• Anti-TNF-α agents can be safely discontinued in the third trimester of pregnancy
• Infants whose mothers received combination of anti-TNF-α and thiopurines are at a higher risk of infections compared to those whose mothers received monotherapy
• Breast feeding can be continued by mothers who are on anti-TNF-α therapy
• Data regarding anti-integrin agents with respect to pregnancy is limited

Anti-TNF-α agents are stratified by US FDA as pregnancy risk category B drugs. The pregnancy outcomes of IBD patients who were on anti-TNF-α agents or thiopurines were prospectively studied in a cohort of 1052 women in the PIANO registry. It was found that among the infants who had intrauterine exposure to anti-TNF-α agents, there was no increased risk of congenital anomalies and abnormal newborn growth and development compared to the infants of mothers who were not exposed to these medications during conception or pregnancy [73]. In a meta-analysis of studies assessing the pregnancy outcomes in women with IBD who were exposed to anti-TNF-α agents, it was found that there was no increased risk of congenital anomalies in the newborns and there was no increase in adverse pregnancy outcomes among those who were exposed to anti-TNF agents during pregnancy except for a decrease in gestational age of newborns of women exposed to anti-TNF agents as shown in one study [74].

IgG is transferred transplacentally from mother to fetus starting at 22 weeks of gestation peaking in the third trimester. The Fc portion in the IgG/anti-TNF-α agent is the mediator for crossing the placental barrier by binding the neonatal Fc receptor expressed on the syncitiotrophoblasts of the placenta [75]. Certolizumab doesn't have the Fc moiety within its structure; hence, it is not transmitted transplacentally. It was shown that the transplacental transfer of infliximab and adalimumab was higher in the third trimester of pregnancy [76, 77]. In a study of 80 mother-baby pairs, where the mothers were exposed to either infliximab or adalimumab during pregnancy were followed prospectively, and it was found that the cord blood concentration and maternal blood concentration at birth of anti-TNF-α agents correlated inversely with the duration since the last exposure of the anti-TNF-α agent, with the anti-TNF-α concentration in cord blood and maternal blood at delivery being significantly lower when the drug was stopped before 30 weeks of gestation [78]. Bacterial infections were noticed in 5% of infants, and viral infections occurred in 20% of infants; all of them had a benign course. The relative risk of infection was significantly higher in infants whose mothers received combination therapy of anti-TNF-α and thiopurines during pregnancy compared to monotherapy (RR 2.7, 95% CI 1.09–6.78, $p = 0.02$). Continuing anti-TNF-α therapy after 30 weeks of gestation did not increase the likelihood of infection in infants compared to discontinuing anti-TNF-α therapy before 30 weeks, and the median levels of anti-TNF-α were similar between the infants who had infection and who did not have infection. The mean time to clearance was 4 months for adalimumab-exposed infants compared to 7.3 months for infliximab-exposed infants. While none of the adalimumab-exposed infants had detectable drug levels by 9 months, 11% of the infliximab-exposed infants still had detectable drug levels at 9 months. Hence, live vaccines should be withheld till 1 year of age. Breast feeding did not affect the anti-TNF-α levels in the infants.

In a prospective study by de Lima et al. evaluating the outcomes of pregnant women on anti-TNF-α agents, 106 patients with 83 completed pregnancies were included [79]. Women in sustained remission stopped anti-TNF-α agents before week 25, and those who were not in sustained remission continued anti-TNF-α

agents, and they received the last dose of the anti-TNF-α agent in pregnancy at 30 weeks of gestation or beyond. It was found that there was no significant difference in the relapse rates in both the groups. Also there was no significant difference in allergic reactions and loss of response in the postpartum period. This data showed that anti-TNF-α agents could be safely withheld in the third trimester in pregnant women who were in sustained remission.

Data with regard to the pregnancy outcomes pertaining to anti-integrin agents is limited. The Tysabri pregnancy exposure registry evaluated the pregnancy outcomes of women with multiple sclerosis or CD who were exposed to natalizumab any time during the period of 3 months pre-conception or pregnancy [80]. This cohort had 355 women with known pregnancy outcomes, majority of whom (99.4%) had multiple sclerosis. It was found that the overall rate of major birth defects was higher in natalizumab-exposed women compared to the background rate in the general population, while the rate of spontaneous abortions was similar to that of the general population. With regard to vedolizumab, limited data of only 24 vedolizumab-treated pregnant women was available, without any concrete safety concerns identified [81].

3.12 Strategies to Optimize Response When Therapy with Anti-TNF-α Agents Has Failed

Treatment failure with anti-TNF-α agents can occur due to primary non-response to the drug or a secondary loss of response to the drug to which there was an initial response. Primary non-response to anti-TNF-α agents occurs in 13–40% of patients [21, 82, 83], whereas secondary loss of response occurs at a rate of 13% per year in infliximab-treated patients [84] and at a rate of about 20% per year in adalimumab-treated patients [85]. The following strategies are used to recapture response when there is loss of response to anti-TNF-α agents:

1. Dose escalation by increasing the dose, shortening the interval between the dosages, or using induction regimen dosage again [22, 23, 86, 87]
2. Addition of an immunomodulator [88, 89]
3. Switching anti-TNF-α agent to a different anti-TNF-α agent [90] or to a different biologic class such as anti-integrins [70, 91]

3.12.1 Therapeutic Drug Monitoring-Based Approach

Therapeutic drug monitoring of anti-TNF-α therapy includes estimation of the serum levels of the anti-TNF-α agent and anti-drug antibodies. When there is a loss of response to an anti-TNF-α agent, therapeutic drug monitoring helps in decision-making in the following ways [92]:

1. In case of low or undetectable serum anti-TNF-α levels along with undetectable anti-drug antibodies, there will be benefit from dose escalation.
2. In case of high titers of anti-drug antibodies, there will be benefit from switching to a different anti-TNF-α agent.
3. In case of adequate levels of anti-TNF-α concentration, there will be benefit from changing therapy to a drug of different mechanism of action (as the disease may no longer be predominantly TNF-α driven).

3.13 Adverse Effects

3.13.1 Anti-TNF-α Agents (Table 3.4)

3.13.1.1 Infections

TNF-α and IFN gamma play an important role in the formation of granulomas containing *Mycobacterium tuberculosis*. Anti-TNF-α agents suppress TNF-α and IFN gamma, thus leading to reactivation of latent TB or even occurrence of de novo TB in patients exposed to these agents. The relative risk of development of tuberculosis (TB) was 29.3 with adalimumab and 18.6 with infliximab [93]. In a retrospective analysis from 3 IBD referral centers from India, it was found that among 79 patients with UC treated with infliximab, 8.8% (7 patients) developed TB after a median period of 8 weeks after initiation of infliximab, and among these 7 patients, 4 patients had disseminated TB, whereas 3 patients had pulmonary TB and all of them were successfully treated with antitubercular therapy [94]. In a study from the USA, the crude incidence rate of TB among anti-TNF-α users was 49 per 100,000 person-years as compared to a background rate of 2.8 per 100,000 person-years among the general population [95]. All the

Table 3.4 Adverse effects of anti-TNF-α agents

• Tuberculosis
• Non-tuberculous mycobacterial infections
• Reactivation of hepatitis B
• Other infections including bacterial, fungal, and viral
• Dermatologic side effects (psoriasis, Stevens-Johnson syndrome, erythema multiforme, toxic epidermal necrolysis)
• Nonmelanoma skin cancer
• Hepatosplenic T-cell lymphoma
• Lupus-like syndrome
• CNS demyelination
• Inflammatory neuropathies
• Worsening of heart failure
• Infusion reactions with infliximab

patients who are being started on anti-TNF-α agents should be screened for latent tuberculosis by taking a thorough medical history for prior TB and any antitubercular therapy (ATT) received in the past including the regimen and duration, and chest X-ray, Mantoux, and interferon-gamma release assay testing. It is standard practice to even do a HRCT chest in patients being started on anti-TNF-α agents at the IBD clinic in our center. In patients with latent TB, 6–9 months of therapy with isoniazid is recommended. In patients with active IBD, anti-TNF-α agents should be delayed for at least 3 weeks after starting ATT in patients with latent TB. In patients with active TB, anti-TNF-α agents should preferably be started after completion of ATT, and in case of pressing need, anti-TNF-α agents should be avoided until at least 2 months after initiation of ATT [96].

The crude incidence rate of nontuberculous mycobacterial infection was 74 per 100,000 person-years among anti-TNF-α users as compared to a background rate of 4.1 per 100,000 person-years among the general population in a study from the USA [93]. The risk of various other bacterial infections such as listeriosis and legionellosis and serious respiratory infections was found to be increased with usage of anti-TNF agents. Fungal infections due to *Pneumocystis jirovecii*, *Histoplasma*, *Aspergillus*, *Cryptococcus*, *Candida*, *Coccidioides*, and *Actinomyces* were reported with anti-TNF-α agents. Reactivation of hepatitis B was reported to occur with anti-TNF-α therapy; hence, screening of chronic hepatitis B infection with HBsAg and total anti-HBc Ab testing is recommended prior to initiation of anti-TNF-α therapy. Anti-TNF-α therapy is considered to be safe in patients with chronic hepatitis C as well as in patients with HIV with higher CD4 counts especially when they are on antiretroviral therapy. CMV reactivation can occur while patients with IBD are on immunosuppressive therapy including anti-TNF-α agents; hence, in cases with exacerbation of disease symptoms while on anti-TNF-α therapy, CMV infection has to be ruled out. Reactivation of varicella zoster and herpes simplex viral infections has been reported with anti-TNF-α agents [97].

3.13.1.2 Dermatologic Side Effects

Various dermatologic side effects occur with anti-TNF-α therapy which include injection site reactions, cutaneous manifestations of infusion reactions, cutaneous infections, non-melanoma skin cancer, psoriasis, lupus-like syndrome, Stevens-Johnson syndrome, erythema multiforme, and toxic epidermal necrolysis [98].

3.13.1.3 Malignancies

Patients treated with a combination of anti-TNF-α agents and thiopurines may have a higher risk of developing hepatosplenic T-cell lymphoma and non-melanoma skin cancer [99].

3.13.1.4 Autoimmune Manifestations

Anti-TNF-α therapies have been reported to cause autoimmune like syndromes such as lupus-like syndrome, CNS demyelination, and inflammatory neuropathies [100].

3.13.1.5 Infusion Reactions

Infliximab infusion can lead to immediate reactions such as pruritus, flushing, dyspnea, chest discomfort, hypertension, myalgia, nausea, urticaria, headache, skin rash, and dizziness and late reactions of serum sickness type with pruritic skin eruptions, fever, malaise, polyarthralgia, and jaw pain. Immediate reactions usually occur 1–2 hours after infusion, and late reactions usually occur 1–3 weeks after administration [101].

3.13.1.6 Cardiovascular

Worsening of heart failure can occur with anti-TNF-α therapy. Patients with mild heart failure and symptoms of NYHA class I and II should be closely monitored while on anti-TNF-α therapy, whereas anti-TNF-α therapy is a contraindication when symptoms are of NYHA class III and IV [102].

3.13.2 Anti-integrin Agents

The side effects associated with vedolizumab are gastrointestinal related such as gastroenteritis, abdominal abscesses, clostridial infections, etc. The overall increase in risk of any infection or serious infection with vedolizumab was found to be similar to that of placebo in pooled data of various clinical trials. The risk of TB with vedolizumab was found to be very limited in this pooled analysis [103]. Progressive multifocal leukoencephalopathy (PML) is a potentially life-threatening CNS infection caused by JC virus, and treatment with natalizumab [104, 105] but not vedolizumab [65] is associated with an increased risk of development of PML. Infusion reactions can occur with natalizumab as well as vedolizumab.

3.14 Experience at Our Center

3.14.1 Infliximab

There were 69 patients who received infliximab at the IBD clinic in our center [106]. Of these 69 patients, 31.9% had UC and 68.1% had CD; 50.7% of them were males. Infliximab was started after a median duration of 45 months in UC

patients and 36 months in CD patients, and the median duration of follow-up was 24 months in patients with UC and 19 months in patients with CD after the initiation of infliximab. Among the UC patients, 59.1% had pancolitis, whereas among the CD patients, 36.2% had stricturing disease, 25.5% had fistulizing disease, and 36.2% had perianal disease. The median number of doses of infliximab received was 6.7 (range, 2-35) in UC patients and 9.9 (range, 2-52) in CD patients with the median duration of treatment being 36.5 weeks (range, 2-262 weeks) in UC patients and 61 weeks (range, 2-398 weeks) in CD patients. Clinical remission was seen in 77.3% of UC patients and 80.8% of CD patients after the induction regimen. Infliximab was discontinued in 59.1% of UC patients and 55.3% of CD patients. The reasons for discontinuation were non-affordability of the medication in 28.2%, primary non-response to the medication in 25.6%, secondary loss of response in 20.5%, and adverse events in 23.1% among all the IBD patients who discontinued these medications. Tuberculosis occurred in 11.6% of patients after a median period of 19 weeks after initiation of infliximab.

3.14.2 Adalimumab

A multicenter audit of patients receiving biosimilar of adalimumab from four centers in India including AIIMS was done [107]. Seventy patients (49 UC; 21 CD) with a median age of 39 (range 13–73) years, male predominance (64.3%), and median (IQR) disease duration of 72 months were included. ADA biosimilar was effective in inducing remission (at 8 weeks) in 46.9% and 52.4% patients with CD and UC, respectively, of which 32.7% and 33.3% patients (3/4th of remitters) maintained remission over 1 year, respectively. Twenty (28.6%) patients experienced adverse events and 8 (11.4%) were serious, out of which three developed tuberculosis. Adalimumab biosimilar was found to be safe and effective in inducing and maintaining remission in Indian patients with IBD. Steroid-free clinical remission was observed in one-third of UC and CD cases at 1 year of therapy.

Key Points

1. Anti-TNF-α agents and anti-integrin agents are commonly used biologics in patients with IBD.
2. Biologics are indicated in cases of steroid-dependent and steroid-refractory UC; as rescue therapy in steroid-refractory acute severe colitis, moderate to severe luminal CD, stricturing and fistulizing CD, and refractory extra-intestinal manifestations of IBD; and in the postoperative prevention of CD.
3. Cost and side effects such as reactivation of tuberculosis (with anti-TNF-α agents) are major concerns while using biologics.

Editorial Comments

The exact mechanism of the development of inflammatory bowel disease (IBD) is not yet clear. However, it does appear to be immune mediated. Our understanding of the pathogenesis has improved and associated with it has been the use of various biological agents that target molecules involved in its causation. There has been substantial increase in the use of biological agents. These drugs are successful in causing mucosal healing and clinical remission. Some patients do not respond to biological agents suggesting that we do not understand all about the pathogenesis of the disease. We also need to identify patients who will not respond to a particular kind of treatment. Development of suitable biomarkers may help treat the right patient with a given drug, avoiding or minimizing its use in those who are unlikely to respond. This would also possibly help decrease the adverse effects of various drugs.

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Chapter 4
New Surgical Modalities in the Management of Rectal Cancer

Deeksha Kapoor, Amanjeet Singh, and Adarsh Chaudhary

4.1 Introduction

Colorectal cancer is the third most commonly diagnosed cancer worldwide. It accounts for over 8% of all cancer deaths, making it the fourth most common cause of cancer-related deaths. Professor Bill Heald was the first to describe the technique of total mesorectal excision (TME) in 1982. His landmark publication in 1986, revolutionized surgery for rectal cancer and TME became the gold standard surgical technique for rectal cancer [1]. A complete TME, with intact mesorectal fascia and no invasion into the muscular coat, is the desired endpoint of any oncological procedure for carcinoma rectum. It is associated with decreased local recurrence and improved cancer-specific survival which is an important positive prognostic factor against local tumour recurrence and also for cancer-specific survival [2–4]. This era of TME has evolved from the traditional "open" approach to minimal access surgeries, such as laparoscopy, robotics and more recently the transanal approach.

Modern times have moved towards rectal preservation and minimal access surgery, at the same time trying to maintain oncological adequacy. The adequacy and equivalence of one technique over the other remains a matter of debate and depends on case selection, histopathology of the tumour, functional outcomes and costs. Although neoadjuvant and adjuvant chemotherapy serve as an adjunct to improve outcomes following rectal cancer surgery, they cannot compensate for a poor TME. A poorly performed TME yields a poor surgical specimen, compromising the quality and oncological adequacy of rectal resection. Testimony to this is born by the evidence from Medical Research Council of UK CR07 and National Cancer Institute of Canada CTG CO16 trials, which emphasized on the need of a well-conducted surgery [4].

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In this chapter, we discuss the two ongoing developments which hold the potential to metamorphose the face of surgery for rectal cancer in the near future.

4.2 Need for a New Technique

Laparoscopy has made inroads into the surgical management of colorectal cancers. The COST trial was one of the first trials to establish laparoscopic colectomy as a safe and oncologically adequate operation, with clinical benefits over open surgery. However, until a few years ago, laparoscopy for rectal cancers was less well established. There is already data available regarding the use of laparoscopy for rectal cancer surgery. Initial trials showed the short-term benefits and technical superiority, but recent few trials have questioned the role.

The two most recent studies, ALaCaRT and ACOSOG Z6051, looking into laparoscopic resections for rectal cancers, have failed to establish non-inferiority of laparoscopy compared to open rectal resections.

However, challenge remains in the surgery for low rectal cancers. Working in the confines of a deep and narrow pelvis, with inflexible and straight laparoscopic instruments, trying to negotiate difficult angles can be a challenging and formidable task for a rectal surgeon. The traction given to pull the rectum out of a deep pelvis leads to tears in the mesorectal fascia, thereby decreasing the quality of TME specimen. Precise articulation of staplers to achieve an adequate distal margin for a low rectal tumour is a challenge even in the hands of a veteran rectal surgeon. These challenges become further exaggerated, in a previously irradiated, narrow deep pelvis of an obese male patient. These limitations heightened the need to formulate other techniques to improve outcomes following surgery for low rectal tumours.

Two ways to address these limitations are to first start dissection from below—as described in transanal TME. Second is the use of robotics to overcome the limitations of laparoscopy, like restricted movements in the pelvis and difficult articulation with rigid laparoscopic instruments.

4.3 Transanal TME

Transanal TME (TaTME) was first described by Sylla and Lacy in 2010 [5, 6]. It adopts the "bottom-to-top" dissection approach, as against the "top-to-bottom" approach undertaken by open and other minimally invasive techniques. By adopting this approach, the most difficult part of the dissection is completed first from the caudal end [7].

Lacy et al. initially published a short case series of 20 patients and then further validated the technique with a series of 140 patients, published in 2015. The hope was to improve the oncological outcomes following surgery for low rectal cancers. An additional desire would be to improve functional outcomes and quality of life measures.

4.3.1 Concept of TaTME

The anatomical challenges in approaching a tumour placed in mid to low rectum, during open surgery, have been difficult to overcome in the laparoscopic approach. The reasons for this are mainly anatomic. Laparoscopy has not been able to overcome the disadvantages of a narrow pelvis, with no place to manipulate instruments. This leads to poor surgical specimens with irregular mesorectal sections and chances of increased circumferential margin positivity. Often, it is difficult to assess the lower end of the tumour, with poor ergonomics for manipulating the endostapler distally, leading to poor margins and multiple firings at the distal end [8]. These factors compromise the oncological adequacy of the surgery and create technical problems, predisposing to an increased chance of anastomotic leak. These challenges have been highlighted by the results of a recent randomized controlled trial, which showed circumferential radial margin (CRM) positivity rate of 10% in laparoscopic and open TME with a particularly high CRM positivity of 22% in lower rectal cases, in the open arm of the trial [9]. TaTME tries to overcome these issues, by approaching the rectum from "below".

4.3.2 Evolution of TaTME

The development of techniques like transanal endoscopic microsurgery by Buess in 1983, followed by transanal minimally invasive surgery and, finally, natural orifice transluminal endoscopic surgery (NOTES), has facilitated and set the stage for the development of TaTME in Barcelona [5, 10–12]. Transanal endoscopic surgery uses a rigid resectoscope fixed transanally, which allows performance of an intra-luminal excision of the lesion under high-definition optical vision. This technique requires specific instruments, which help in maintaining a stable pneumorectum and allows high precision dissection in one quadrant of the bowel at a time. Instruments are angulated at their end and require a more wrist-dependent dissection as against the criss-crossing movements of laparoscopy. Although this technique has distinct advantages over other transanal resection methods, its acceptance in the clinical field has been slow, because of two main reasons. It has a steep learning curve as the instrumentation takes time getting used to and a high initial cost of the operating system.

With the development of single-incision laparoscopy and improved laparoscopic skills, the disadvantages of transanal endoscopic surgery were overcome by TAMIS—transanal minimally invasive surgery. This modality was described by Dr. Sam Atallah in 2010. It uses the single-incision laparoscopy equipment as a transanal access platform, with use of routine laparoscopic instruments for dissection. It overcomes the disadvantages of TES (transanal endoscopic surgery)—by lowering the learning curve and the upfront cost of performing this procedure. Although both these techniques had limitations in patient selection, they paved the path for development of TaTME.

Simultaneously, in 1984, Dr. Gerald Marks developed a procedure called TATA—transanal abdominal transanal proctosigmoidectomy with coloanal anastomosis. TATA introduced the concept of bottom-up approach to the traditional top-down approach of abdominal surgery. Dr. Marks proposed that by starting the surgery distally, a known distal margin could safely be achieved even for cancers of distal one third of rectum, provided the cancer was not growing into the levators. These concepts may help improve the quality of specimens, leading to good CRM and distal margins. There may be a potential benefit of doing proctectomy from "bottom to top"; it may be technically easier and safely performed. The first step in this technique is to identify the distal extent of the tumour endoluminally, followed by a purse-string occlusion of the lumen, under direct vision, thereby ensuring an adequate margin distal to the tumour.

The challenges and limitations of a purely transanal approach were also duly identified and subsequently confirmed by many other teams in bovine, swine and cadaver models. The entire dissection is difficult to accomplish transanally, and if an incorrect retroperitoneal plane is entered, progression of surgery becomes technically difficult. A trans-abdominal surgical component was thereby added to the procedure, which seemed inevitable for a safe and accurate mobilization of the splenic flexure and adequate ligation of the inferior mesenteric artery pedicle [13].

4.3.3 Indications of TaTME

Malignant tumours of the mid and lower third of the rectum are the main benefactors of the TaTME approach [14]. Along with a composite surgical technique, the patient's anatomy, tumour characteristics and response to neoadjuvant therapy have bearing in a well-conducted total mesorectal excision. The procedure can be particularly difficult in the confines of narrow, deep pelvis of an obese male patient. The technical demands of the surgery increase manifold, threatening the fulfilment of complete TME, with negative circumferential resection margins. It was postulated that approaching the same tumour transanally would possibly be a little less challenging, as against a total abdominal approach [15].

TaTME has also been found useful for certain benign conditions of the rectum especially inflammatory bowel disease. This technique may prove helpful during Hartmann's reversal, completion proctectomy or restorative proctocolectomy with ileal pouch-anal anastomosis.

4.3.4 TaTME for Rectal Cancer

Certain local and pathological factors make TaTME a preferred approach for rectal cancer surgery [16]. TaTME has been utilized in male patients with narrow and deep pelvis, with tumours less than 12 cm from the anal verge (preferably low rectal cancers).

This technique is also useful in patients with visceral obesity or a body mass index >30 kg/m^2. Obtaining an adequate distal margin has been found to be more feasible with TaTME in patients who are post-neoadjuvant therapy and those with a low primary tumour which may be difficult to assess trans-abdominally. Failure to proceed during a traditional abdominal approach may be considered an additional indication for the transanal approach while operating on a low rectal tumour.

In these situations, TaTME allows early and accurate identification of the lower extent of tumour, with precise definition of the distal transection line. A purse-string suture at the distal end facilitates an end-to-end stapled anastomosis, eliminating the need of multiple firings on the distal rectal stump [17–19]. Since multiple firings at the distal stump have been associated with increase in colorectal anastomotic leaks, TaTME may be associated with a low anastomotic leak rate.

4.3.5 TaTME in Benign Disease [16]

This approach has been proven to be helpful in certain benign diseases as well, which includes rectal strictures, proctectomy for Crohn's disease, ulcerative colitis or familial adenomatous polyposis and radiation proctitis.

4.3.6 Contraindications

It would be prudent to consider emergency procedures, T4 tumours and obstructing rectal tumours as contraindications to the use of this approach.

4.3.7 Technique of TaTME

The procedure is performed in the modified lithotomy (Lloyd Davies) position. A single- or a two-team approach can be adopted. Single-team approach was originally described by Lacy et al. and later modified to a two-team approach (Cecil approach). The two-team approach allows better traction and counter-traction, improves visualization and allows for shorter operative times.

Depending on the tumour location and proposed operation, TaTME can be performed with three variations: complete TME, partial mesorectal excision or intersphincteric resection.

The greatest experience of this approach is reported with flexible transanal access devices: the GelPOINT path™ transanal platform (Applied Medical, Inc., Rancho Santa Margarita, California, USA) and the SILS port™ (Covidien, Medtronic, Dublin, Ireland). The use of these transanal access devices is an extension of their use in TAMIS.

4.3.8 Technical Description of a Two-Team Approach [5, 6]

This technique can be described in two parts—transanal and trans-abdominal parts.

4.3.8.1 Trans-abdominal Phase

The agenda in the trans-abdominal approach is to adequately mobilize the sigmoid, left colon and splenic flexure if needed. Division of inferior mesenteric vessels, with high ligation, is undertaken, as in a routine laparoscopic anterior resection. However, the TME is undertaken from below using the transanal approach.

4.3.8.2 Transanal Phase

The aim of the transanal phase is to accomplish rectal mobilization with safety, maintaining oncological adequacy. It can be divided into ten steps.

With the patient in lithotomy position, the anus is dilated, and a self-retaining retractor (Lone Star, CooperSurgical) is applied to obtain adequate exposure of the anal canal and lower rectum. At this point, the dentate line should be clearly identified.

Next, a disposable single-port device is inserted into the anal canal (GelPOINT path transanal access) and secured to the buttocks with silk sutures. Three trocars are generally used which are inserted in an inverted triangular fashion. Pneumorectum up to 10–12 mmHg is established. A 10 mm laparoscopic camera, with a flexible tip, can be used, which provides good spatial orientation and better perception of depth. Alternatively a conventional 30 degree laparoscopic camera can be used.

A purse-string suture is taken to close the rectal lumen, at least 2 cm distal to the lower extent of tumour. An air-tight closure should be attempted to avoid seepage of colonic contents into the surgical field. At this point, it is advised to irrigate the rectum with iodine solution to limit contamination of the field.

The rectal mucosa is marked circumferentially, just distal to the purse-string suture, which would be the level of rectal division. A hook cautery is used to open the rectal wall layer by layer, until the perirectal avascular plane is encountered. Care should be taken to maintain a perpendicular line of transection. This avoids specimen coning and inadvertent dissection into the proximal mesorectum. Dissection is continued caudo-cranially in the perirectal space, avoiding breaches in the mesorectal or endopelvic fascia. Overzealous lateral dissection may cause severe bleeding or cause damage to surrounding structures. During posterior dissection, the surgeon must respect the presacral fascia and carefully negotiate the curve of the sacrum. On breaching the presacral fascia, unforgiving bleeding can be

encountered which obscures the surgical field and leads to the creation of a pneumoretroperitoneum, which bothers the abdominal surgeon as well.

Circumferentially dissection is done in the same avascular plane, which releases the rectum on all sides, to obtain a symmetrical cylindrical specimen. During anterior dissection, one must be vary of the vagina in females and seminal vesicles and prostate in male patients.

As the transanal surgeon continues dissection in the cephalad direction, he/she will meet the abdominal surgeon—obtention of a "rendezvous". Dissection from both sides finally releases the specimen.

After completion of transanal dissection, Prolene purse-string sutures are placed on the open anorectal stump.

At this point, one needs to decide if the specimen has to be extracted transanally or an abdominal incision needs to be given for specimen removal. If the tumour is small, and the mesorectum is not bulky, a transanal extraction can be undertaken. The colon is delivered transanally and a colotomy done. The anvil of the circular stapler is introduced along the ante-mesenteric border before dividing the specimen with a linear cutter stapler. Alternatively, the specimen can be delivered via a small abdominal incision. The specimen is removed, and the anvil of the stapler is fixed to the open end of proximal colon. Accordingly, an end-to-end or side-to-end colorectal anastomosis is accomplished.

During one-team approach, the procedure is accomplished sequentially, with the surgeon moving from the abdominal part to the transanal part. It may be advisable to perform the abdominal part initially because there is a risk of pneumoretroperitoneum if the transanal dissection is started first. Once the retroperitoneal planes get distorted, it may become difficult to identify the planes of dissection trans-abdominally.

In case of a low rectal anastomosis or a previously irradiated pelvis, a temporary diversion stoma may be added.

4.3.9 Safe Implementation of TaTME

With enhanced access and visualization to the distal rectum, TaTME allows for adequate margins, optimal lymph node harvest and good-quality resection [20–22]. As demonstrated by Denost et al. in a recent randomized trial, chances of CRM positivity may decrease with a perineal approach as against an abdominal one [23]. TaTME may even be oncologically superior for low rectal tumours.

An online registry exists for reporting TaTME cases, which is a secure online database funded by Pelican Cancer Foundation and accessed via Low Rectal Cancer Development (LOREC) website. It is a voluntary forum, and any surgeon performing TaTME can join. Data is collected under nine sections: patient

demographics, staging and neoadjuvant treatment, operative details, postoperative clinical and histological outcomes, readmissions details, late morbidity and long-term oncologic follow-up. In a recent report of this registry, data was analysed from 66 registered units in 23 countries, with the primary endpoint of "good quality TME surgery" [24]. TaTME was found to be a safe and oncologically effective approach with acceptable short-term outcomes. They reported postoperative morbidity up to 32.6%, anastomotic leak rates up to 6.7% and mortality up to 2.6%. However, the usefulness of this technique needs to be proved in larger controlled trials, and a longer follow-up is needed to prove oncological non-inferiority. It has been recommended that surgeons undergo formal hands-on training, with active proctoring during the first year. Participation in multicentre registries will improve quality control and facilitate long-term follow-up [25]. The technique and training needs to be standardized to allow safe implementation in clinical practice.

4.3.10 Benefits of TaTME

- *Oncological outcomes*: The technique was formulated with the hope of obtaining a higher quality of surgical specimen. Complete or almost complete mesorectal excision rates of up to 96% have been reported in the international TaTME registry [24].

  A meta-analysis by Xu et al. reported superior results with TaTME than laparoscopic TME [26]. TaTME gives the advantage of a longer CRM (95% CI 0.61–1.29; I2 = 5%) and lower CRM positivity rate (OR 0.34; 95% CI 0.12–0.93) when compared with laparoscopic TME. It was also associated with lower operating time (95% CI −37.45 to −1.96).

  In another meta-analysis by Ma et al., TaTME was associated with better quality of TME specimen. The rates of complete and near-complete TME were found to be higher than with laparoscopic TME. CRM positivity was also significantly lower in the TaTME group (OR: 0.39, $p = 0.02$) [27].

  In general, there is better visualization of distal rectal margin. The traction needed for laparoscopic rectal resection is minimized in the transanal approach, thereby decreasing the possibility of breach of mesorectal fascia.

  In the international registry report by Penna et al., a factor found to be associated with positive CRM was tumour height less than 2 cm from anal verge. They reported R1 rate of 7.4%, other statistically significant factors being CRM positivity on preoperative MRI and if the posterior pelvic dissection performed by top-down approach reached less than 4 cm from anal verge. However, patient-related factors like narrow deep pelvis, male sex and obesity were not associated with a poor specimen.
- *Functional benefits*: TaTME has a potential benefit of decreasing the number of permanent stomas, by being a rescue technique in patients with a deep and narrow pelvis. However, there is an associated increase in the rate of coloanal

anastomosis. This has an impact on functional outcomes and continence rates. In the unfortunate scenario of a leak, there is a risk of impaired continence and functional outcomes. The international TaTME registry has reported an anastomotic leak rate of 6.7%.

Initial results suggest similar postoperative function, when compared with laparoscopic or open TME [28, 29]. However, studies with a longer follow-up and larger sample size are required to assess the functional outcomes following TaTME. Urinary dysfunction has been reported to be lower with TaTME, possibly because of enhanced visualization which allows meticulous dissection in the presacral plane, sparing the autonomic nerves [30]. In the same study, quality of life scores dipped at 1 month postoperatively. Patients reported an initial poor quality in social life; however, this difference disappeared after 6 months. Similar results were reported for perianal pain—initial worsening at 1 month postoperatively, with improvement in pain scores after 6 months. Anorectal function, after stoma closure, also follows a similar pattern. Worse scores were observed at 1 month with LARS score, with improvement at 6 months. The mean difference between preoperative and 6-month values was not significant ($p = 0.339$).

A lower rate of urinary dysfunction has been observed after TaTME. Enhanced visualization of anatomic landmarks allows nerve-sparing dissection in the presacral planes. This may possibly attribute to low rates of urinary dysfunction.

However, urethral injury has emerged as a unique complication following this procedure, with some studies reporting an incidence as high as 10%. During anterior dissection, an inadvertent breach of posterior prostatic capsule increases the chance of injury to the membranous urethra. Therefore, it is paramount to ensure meticulous dissection in the anterior plane. It has been suggested that with adequate training, incidence of urethral injury may decrease [31].

- *Technical benefits:* Dissection of the lower-most rectum is accomplished with ease because of adequate visualization. The technical shortcomings of laparoscopic TME may be overcome by a bottom-to-top approach, enabling surgeons to proceed with an increased ease and efficiency. With the use of two-team approach, shorter operating times have been reported. Decreased conversion rates have been reported with this technique, in comparison to laparoscopic TME (2.6% vs 8.6%) [27]. A higher conversion rate in the laparoscopic group was associated with high BMI and a narrow pelvis.

4.3.11 Shortcomings of TaTME

TaTME has definitely found a place for itself in the surgical armamentarium for rectal cancer, with promising oncological and functional results. Nevertheless, any new technique brings with it new complications and hurdles to overcome.

- *New complications:* Since rectal division is undertaken at the very start of the procedure, leading to bacterial contamination, an increased incidence of local collections and abscesses has been reported following TaTME [32].

  Injury to the membranous urethra is a real and unique complication of TaTME, compared to trans-abdominal rectal cancer surgery, with a reported incidence of up to 10%.

  Improper lateral and posterior dissection can expose deeper planes, leading to bleeding from presacral venous plexus, and pose a significant risk of autonomic nerve injury [22, 33].

  Additionally, rectal perforations have been reported in about 2% specimens on histological analysis which are difficult to identify intraoperatively.
- *Learning curve:* It is important to realize that TaTME has a significant learning curve. At the outset, the surgical approach of bottom to top can be spatially disorientating as the abdominal surgeon is not trained in dissection in the reverse sequence.

  The transanal surgeon must learn to negotiate the sacral curve in the reverse direction to prevent autonomic nerve injury and bleeding from presacral venous plexus. Therefore, adequate training is required before undertaking this procedure in clinical surgical practice.
- *Technological hiccups:* In the report of international registry of TaTME, Penna et al. reported adverse events from a case series of 720 TaTMEs. About 16% surgeons had a difficulty in maintaining pneumorectum; another 22% complained of excessive smoke obscuring vision. Entering an incorrect plane and excessive bleeding were some other adverse events reported.

4.3.12 TaTME: Its True Role?

- The new approach has been welcomed with a lot of enthusiasm as a potential solution to the problems of a narrow deep pelvis in an obese male patient. These are the patients in whom an abdominal approach for TME becomes difficult. However, a significant number of successfully reported cases have been attempted in a more favourable pelvis, raising a question about the "true" role of this procedure. There is a reporting bias, in which stories of only successful cases have seen the light of day. It would be prudent to assess the technical failure rates of this procedure and their patient and tumour profile.
- TaTME being a complex and challenging procedure has an inherent learning curve, even for the experienced colorectal surgeon. The pelvic anatomy needs to be relearnt with a bottom-to-top vision and surgical plan. Initial attempts in a broad female pelvis with small tumours have been recommended, to familiarize the surgeon with the reverse anatomy.
- Although a partial TME can be undertaken transanally, most authorities would not consider a high rectal tumour as a true indication of TaTME. The most important indications remain low rectal tumours in a narrow deep pelvis of an obese male.

- The oncological adequacy of TaTME needs to be proved in well-designed controlled trials. COLOR III and TaTME trial in the USA are currently recruiting patients with the primary outcome of non-inferiority for local recurrence.

4.4 Robotics in Rectal Cancer Surgery

4.4.1 Introduction

Development of robotics in surgery for rectal cancer seems to be a natural evolution, with the hope of avoiding the physiological stress of a laparotomy while maintaining or, hopefully, improving oncological outcomes.

Robotics circumvents the obvious limitations of laparoscopy, like 2D vision, limited range of movements and use of rigid long instruments, but definitely increases the cost of surgery.

The key elements and obvious benefits of robotics include high-definition 3D vision, EndoWrist instruments and greater degrees of freedom with absence of tremors of the human hand. Advances of tremors in robotic colorectal surgery have widened the scope of minimal access surgery, but uptake has been slower because of increased costs and limited evidence of improved outcomes [34].

4.4.2 Robotic TME: Technique [35]

Robotic TME can be performed either by fully robotic dissection or by a hybrid approach.

In the fully robotic approach, both colon mobilization and rectal dissection are performed robotically. This approach has been found to be more challenging as the procedure can rarely be completed with single docking. Dual docking is usually required, left colonic and splenic flexure mobilization, followed by redocking for rectal dissection. Choi et al. suggested a left hip position, in which two sets of ports were used with overlap between the ports. One was used for colonic mobilization and another for rectal dissection. However, the latest X1 version of da Vinci has been designed for multiquadrant surgery and decreased the need for cart repositioning and redocking.

Fully robotic approach has been found to be cumbersome in obese with an increase in minor complications as compared to a hybrid approach.

In the hybrid approach, colonic mobilization is completed laparoscopically and the TME robotically. The cart is docked at the left hip or between the legs. The most ergonomic position for the surgeon for rectal dissection is to keep the cart between the legs. But repeated rectal examination to assess the distal tumour margin becomes difficult. A reverse hybrid approach can also be used in which the rectal TME is completed first followed by laparoscopic colon mobilization, lymphadenectomy and anastomosis.

4.4.3 Robotic Instrumentation

For adequate TME to proceed robotically, macro- and micro-retraction are required. Macro-retraction refers to the retraction of macrostructures, such as the rectosigmoid while opening the posterior sacral plane, or retraction of the anterior pelvic structures for anterior dissection. Tissue tension may be used to perform cautery dissection which is referred to as micro-retraction.

The bedside assistant provides adequate tension and exposure for the robotic surgeon. Right arm is used for cautery dissection, middle arm for micro-retraction and bipolar cautery and the third arm for macro-retraction.

4.4.4 Robotic TME

Dissection is started posteriorly, entering the avascular plane, and proceeds caudally to the pelvic floor and coccyx, followed by lateral dissection. Once the rectovesical/rectovaginal peritoneal fold is incised to expose the Denonvilliers' fascia, anterior rectal dissection is started. Anterior rectal dissection is facilitated by retraction on the bladder or vagina, by using the third robotic arm.

Various techniques have been described for distal rectal transection. After undocking the robot, the left lower quadrant or suprapubic ports can be upsized for the use of a laparoscopic stapler. Robotic staplers are also available now, which can be used via the right arm. Specimen can be extracted from a suprapubic incision or from the ileostomy site or per anus.

In patients for whom an abdominal perineal excision is undertaken, transection of levators can be done intra-abdominally using the robot, along with the TME. This minimizes the perineal wound while facilitating a cylindrical specimen.

4.4.5 Outcomes Following Robotic TME

Outcomes can be studied under three broad headings:

1. Perioperative outcomes: Outcomes such as length of hospital stay, return of bowel function and blood loss are comparable between laparoscopic and robotic surgery. Conversion rates, however, have been found to be lower in robotic series, varying from 0 to 4.9%, as against 7.3–34% in laparoscopic series. This favours robotic approach for rectal resections and has been validated in a meta-analysis conducted by Trastulli et al. They reported a conversion rate of 2% in robotic approach as opposed to 7.5% for laparoscopy ($p = 0.0007$). Short-term complications, like anastomotic leak rates, have also been found to be similar to laparoscopic series, 1.8–12.1% [36].

2. Oncological outcomes: Adequacy of TME is determined by the completeness of the resected specimen. Therefore, pathological outcomes are studied as CRM positivity, negative distal margin and lymph node yield. CRM rates have been found to be comparable with open surgery and possibly better than laparoscopic surgery. Various series have reported a CRM positivity rate of 0–7.1%. In 2014, a meta-analysis by Xiong et al. reported a positive CRM in 5.78% patients in laparoscopic group, vs 2.74% for robotics ($p = 0.04$). Distal margin positivity rates are reported at 0–1.9% and a lymph node harvest of 13–20 nodes, both of which are comparable with open surgery [38].

   Studies assessing long-term outcomes are limited, but available data suggests results similar to laparoscopic and open groups. Park et al. have reported outcomes with a median follow-up of 58 months. Five-year overall survival, disease-free survival and local recurrence rates were found to be similar between laparoscopic and robotic groups [39].

   In another large series of consecutive robotic rectal resections of 200 cases, Hara et al. have reported disease-free survival for stage 3 rectal cancer of 76.6%, at 5 years of follow-up. They also reported local pelvic control and overall survival at 5 years as 93.0% and 88.6%, respectively [40].
3. Functional outcomes: Genitourinary and sexual functions get affected following pelvic dissection in these patients. Both robotic surgery and laparoscopic surgery lead to decreased sexual function and libido, but recovery has been found to be earlier following robotic approach, by 6 months, as compared to 1 year following laparoscopic approach. Bladder function also deteriorates in the immediate post-operative period but improves within 3 months following robotic versus 6 months in laparoscopy. This may be explained by better visualization in robotic surgery and possibly decreased trauma to the nerves.

4.4.6 Current Evidence

Robotic versus Laparoscopic Resection for Rectal Cancer (ROLARR) trial is an international, multicentre, prospective randomized controlled trial comparing robotic-assisted vs conventional laparoscopic surgery [37]. The primary endpoint studied was conversion to open laparotomy, and secondary endpoints included pathological outcomes and quality of life measures. They found that conversion rates to open laparotomy were not significantly reduced following robotic-assisted surgery as compared to conventional laparoscopy. CRM positivity rate was 6.3% in conventional laparoscopy group, as compared to 5.1% in robotic-assisted group ($p = 0.56$).

This trial also did a health economic analysis. Health-care costs incurred in robotic-assisted surgery were significantly higher than conventional laparoscopy. They analysed that the main drivers of higher operative costs were longer operating time (difference = 50.88 min, p value = 0.001) and mean cost of instruments (difference = £ 513 or $ 593, $p < 0.001$).

4.4.7 New Frontiers

The field of minimally invasive colorectal surgery continues to evolve, with robotics making inroads into various procedures. Transanal TME, a novel bottom-to-top approach for rectal dissection, can be achieved robotically as well. The first robotic-assisted TME was reported as a part of proctocolectomy for familial adenomatous polyposis by Larach et al. [41].

The da Vinci Xi system is a fourth-generation, highly advanced surgical robot and is the most sophisticated system available. The docking procedure and system setup stands simplified, thereby enhancing surgeon's performance. With a decreased size and extended range of motions, it improves ergonomics and reach of instruments. It provides access to all quadrants of the abdomen without the need of re-docking the system.

4.4.8 Robotic Rectal Surgery: Current Status

Robotic surgery has been found to be safe regarding oncological outcomes. However, it has not surpassed laparoscopy in head-to-head comparisons. Robotic-assisted rectal resections can be considered in obese male patients with a low rectal tumour and narrow deep pelvis; however, there is as yet no level 1 evidence to support this concept. New robotic technology surpasses the old systems and provides better visualization and improved ergonomics and control. Possibly, the surgeon benefits more than the patient. The real value of robotic rectal surgery needs to be proved in large controlled trials.

Editorial Comments

More than 100 years have passed since Ernest Miles introduced abdomino-perineal resection for rectal cancer. Surgical treatment has been evolving since then. Various techniques have been added in the past few decades. What has not changed though are the principles of oncological clearance. New innovations are always useful as these help address various facets of surgical outcome, be it oncological or related to quality of life. However, one should be cautious while adopting these techniques. An example is the minimally invasive route for rectal cancer. While it does decrease morbidity and improve quality of life, it has not been shown to provide a better oncological outcome. Robotic surgery and transanal procedures are new, and their role needs to be established through well-designed multi-institutional studies, and till then the widespread adoption of these methods should be avoided. This reminds me of the age-old surgical aphorism: "Too much zeal about the new and contempt for the old should be avoided if not condemned all together!"

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Chapter 5
Tumor Markers in GI and HPB Cancers

Anand Bharathan and V. Sitaram

Tumor markers are substances produced in large quantities by cancer cells or by normal cells in response to the presence of a cancer. They may also be produced in small quantities by normal cells. These substances are usually proteins (enzymes, hormones, DNA, RNA, mRNA, metabolites, receptors, carcinoembryonic proteins, and oncoproteins) or carbohydrates. They may be elevated when there is no cancer (false positive) or may be normal or low when there is a cancer (false negative). They are usually measured in blood, urine, and other body fluids or identified in tumor tissue.

Tumor markers can be used to:

- Help in making a diagnosis
- Assess prognosis
- Predict/monitor response to therapy
- Follow up patients after completion of treatment

There is as yet no consensus regarding the use of a tumor marker in the screening of a population for a GI/HPB cancer [1, 2].

This article will deal with commonly used tumor markers. Circulating tumor cells (CTC), circulating tumor-associated DNA/RNA/mRNA, tumor markers identified in tumor tissue, gene mutations, and patterns of gene expression associated with cancers will not be discussed [3].

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Advantages of understanding the physiology and pathology of tumor markers are:

- Prevention of escalation of cost of treatment by judicious use of these tests
- Improving quality of care by understanding false-positive and false-negative test results

Renal dysfunction, dialysis, and immunosuppression after kidney transplantation affect levels of tumor markers and must be viewed with caution in these settings [4].

The "ideal" tumor marker is economical, easy to estimate in easily accessible body fluids like blood or urine, has high sensitivity and specificity, can be used to screen for a cancer, has prognostic and predictive value at diagnosis, and is reliable during treatment and follow-up. It does not exist as of now [5].

Commonly used tumor markers in gastrointestinal, liver, biliary tract, and pancreatic cancers are alpha fetoprotein (AFP), CA19.9, carcinoembryonic antigen (CEA), and chromogranin A (CgA).

5.1 Alpha Fetoprotein (AFP)

Alpha fetoprotein (AFP) is a glycoprotein that is produced in the yolk sac and the fetal liver. It is the most commonly used tumor marker for hepatocellular carcinoma (HCC). AFP-L3 which is a sub-type of AFP (please see below) and PIVKA-II (prothrombin in the absence of vitamin K) syn. des-gamma-carboxy prothrombin (DCP) are less frequently used tumor markers [6].

AFP may be raised in gonadal tumors, gastric cancer, and benign states like pregnancy, viral hepatitis, and cirrhosis caused by hepatitis C.

The normal range is 10–20 ng/ml. Values above 400 ng/ml or a steady rise in serial estimation (even if lower than 400 ng/ml) is highly suggestive of HCC in a patient at risk of developing HCC [7]. Persistent elevation of AFP is more significant than fluctuating levels [8]. AFP levels are usually normal in the fibrolamellar variety of HCC [9, 10].

AFP is a heterogeneous molecule with respect to the carbohydrate moiety. Different AFP glycoforms can be separated and characterized by their affinity for lectins. Lectins are carbohydrate-binding proteins. Examples of lectins include Concanavalin A (Con A) and *Lens culinaris* agglutinin (LCA). AFP can be divided into three fractions according to LCA reactivity on affinity electrophoresis.

- AFP-L1 that does not react with LCA is seen in nonmalignant liver diseases.
- AFP-L2 (intermediate reactive) is seen in maternal serum during pregnancy and patients with yolk sac tumors.
- The highly LCA-reactive AFP-L3 is seen in malignant liver tumors.

AFP-L3 is perhaps more useful than AFP in the screening of patients for HCC in susceptible populations [11].

Although stating the obvious, screening for HCC should be done only in patients who are at high risk for HCC (HBV/HCV infection, high viral load, raised ALT) and who would be candidates for further treatment like resection/liver transplantation/radiofrequency ablation/transarterial chemo- or radio-embolization.

AFP alone should not be used to screen for HCC [12]. The use of AFP as a screening tool along with ultrasound liver is debatable. Many factors play a part in this setting. Changes in the cutoff value used will change the sensitivity and specificity of the test. Generally speaking, if you raise the cutoff value, it will decrease the sensitivity and increase the specificity. The cause of the cirrhosis (useful in HBV- and HCV-related cirrhosis, not useful in alcohol-related cirrhosis) and the prevalence of HCC in the study population are also important in determining the efficacy of AFP in detecting HCC. A combination of AFP, AFP-L3, and DCP may be more useful than AFP alone [13].

In the setting of liver resection for HCC, opinion is divided whether pre-resection AFP has prognostic and predictive value [14–17]. Multiple publications contest any value for pre-resection AFP [18, 19]. Posttreatment elevation carries poor prognosis [19, 20].

AFP level >500 ng/ml predicts high recurrence rate after transplantation, and such patients are not listed in the USA [12]. Rise of AFP while on the wait list is also a poor prognostic factor [21]. AFP >1000 ng/ml appears to be related to poor prognostic factors like microvascular invasion, portal vein invasion, bile duct invasion, and intrahepatic metastasis. In 2012 a French paper reported a model that added AFP to Milan criteria which improved prediction of recurrence and survival after liver transplantation for HCC [22]. This has since been validated by an Italian study [23] and by a Korean study [24]. An online calculator, based on size of largest tumor, number of tumors >1 cm, and AFP, is available at http://www.hcc-oltmetroticket.org/ [25].

5.1.1 CA 19-9

CA 19-9 is the abbreviation for carbohydrate antigen or cancer antigen 19-9. This tumor marker belongs to the family of mucinous markers. These have a transmembrane protein skeleton and an extracellular side that has glycosylated oligosaccharides. It is a sialylated Lewis blood group antigen [26]. Lewis blood group antigens are synthesized by intestinal epithelial cells, secreted into blood, and adsorbed on the surface of erythrocytes. These antigens reach adult levels only by 6 years of age [11]. Up to 22% of Afro-Americans and 10% of Caucasians are Lewis blood group antigen negative and will not have circulating CA 19-9, both physiologically and in disease states [11, 27, 28].

Mucus glands in the pancreas, biliary tree, salivary glands, stomach, colon, and endometrium physiologically secrete CA 19-9, and this is present in small quantities in serum [11]. Higher levels are observed in inflammatory conditions of the pancreas and biliary tree like acute pancreatitis, biliary obstruction, and cholangitis.

Malignancies of the pancreas, biliary tree, liver cells, stomach, colon, and breast result in high serum CA 19-9 level. Hashimoto's thyroiditis, heart failure, rheumatoid arthritis, diverticulitis, and ovarian cyst have also been reported to cause elevated CA 19-9 level [11]. It is evident that CA 19-9 is not very sensitive or specific for diagnosis of GI malignancy. Sensitivity is lost as it is absent in a significant proportion of population. Specificity is lost, as numerous benign conditions have been reported to be associated with high CA 19-9 level.

Two commercial versions of CA 19-9 assay are available. While both are accurate by themselves, the results obtained by each could vary. For follow-up, it is recommended that the same assay method is used for any given patient [29].

Overall mean sensitivity and specificity of serum CA 19-9 for diagnosis of pancreatic cancer are 81% and 90% according to one recent review [30]. This study reported these results using 37 KU/l as cutoff of CA 19-9. Serum CA 19-9 seems to fare very poorly and is unsuitable as a screening modality for pancreatic cancer. In one of the largest reviews of data, positive predictive value for diagnosis of pancreatic cancer was only 0.9%. In this study, over 70,000 asymptomatic individuals were screened, 4 patients were diagnosed to have pancreatic cancer, and 1059 patients were false positive for pancreatic cancer [31]. In symptomatic individuals, CA 19-9 may be useful to differentiate benign from malignant pancreatic lesions. One study reported positive and negative predictive values of 72% and 81%, respectively. However, when the pancreatic cancer is less than 3 cm in diameter, only 50% of patients had elevated levels of CA 19-9 [32]. Premalignant lesions may not be accompanied by increase in CA 19-9. Considering these facts, European guidelines suggest that this tumor marker could aid diagnosis but by itself has only limited value in the diagnosis of pancreatic cancer, particularly in its early stages [30].

Two small, but noteworthy, Indian studies addressed the role of CA 19-9 in clinical practice. The study from Kochi reported that CA 19-9 at a cutoff of 37 U/l had sensitivity of 68% to diagnose malignancy in 84 patients with chronic pancreatitis. Overall specificity was 70% for pancreatic cancer. Specificity increased to 100% when cutoff was 300 U/ml. The study concluded that CA 19-9 level of 300 U/ml was always indicative of malignancy in patients with chronic pancreatitis and focal mass in the pancreas. But the latter criteria were present only in 5/34 patients with malignant lesions of pancreas and could be a Type II error [33]. Another study from Mumbai used CA 19-9 to predict operability in 49 patients with pancreatic cancer. When CA 19-9 was more than twice the normal (37 U/l), 88% were unresectable. Out of the 29 patients considered resectable after contrast-enhanced CT scan of abdomen, 5 patients were found unresectable at operation due to subcentimeter liver or peritoneal metastasis. All these five patients had CA 19-9 level more than three times the normal limit. These investigators suggest that diagnostic/ staging laparoscopy should be used to avoid a non-therapeutic laparotomy if CA 19-9 is more than thrice the normal limit [34].

A study from New York reported that both postoperative decrease in CA 19-9 and postoperative level less than 200 U/ml were strong independent factors for survival, even after adjusting for stage of disease [35]. Multiple other small studies derived similar conclusions [11].

A study from Germany of 43 patients with metastatic or locally advanced pancreatic cancer found that decrease of CA 19-9 by more than 20% at 8 weeks following start of gemcitabine based chemotherapy predicted better median survival (268 vs. 110 days) [36]. NACB panel recommends that CA 19-9 level should be checked along with imaging, to follow up patients on palliative chemotherapy and after potentially curative resection. ASCO recommendations 2006 state that high CA 19-9 should not be used to define recurrence if not supported by imaging [11].

5.1.2 Carcinoembryonic Antigen (CEA)

CEA is an oncofetal glycoprotein that is seen in the fetus. Levels are low in adult life but may be elevated in epithelial tumors, chiefly colorectal cancer (CRC) [37]. It has long been known that CEA is elevated in smokers [38, 39]. CEA can be elevated in patients with gastritis, peptic ulcer disease, diverticulitis, liver disease, chronic obstructive pulmonary disease, and diabetes and in inflammatory states. The optimum cutoff value for CEA is being debated.

Preoperative CEA should be measured in all patients with CRC. Elevated preoperative level carries poor prognosis (more than node positivity) [40, 41], and persistent elevation after excision of the tumor is worse [41]. Whether patients with node negative disease and elevated CEA will benefit from adjuvant chemotherapy is yet to be determined.

Postoperative CEA should be obtained every 3 months for 3 years in patients with stage 2 and stage 3 disease if they are candidates for treatment with curative intent (surgery/chemotherapy) if recurrence is detected [1]. Elevation of serial postoperative CEA is likely to indicate recurrent disease. However, normal values do not mean that patient is disease-free [42–44]. Whether intensive postoperative CEA monitoring improves survival is hotly debated. Cost-effectiveness in a resource poor environment like ours is also an issue [45–47].

5.1.3 Chromogranin A (CgA)

CgA is an acidic glycoprotein that is ubiquitously present in almost all endocrine and neuroendocrine cells of the human body. They are synthesized in these cells, stored along with other hormones/neurotransmitters in vesicles and released from the cells by exocytosis along with other hormones [48]. The granin family consists of eight different substances of which chromogranin A is the best known and the one in clinical use for several decades now [49]. Gene encoding chromogranin A is in chromosome 14 and is named CHGA/CgA. It is a precursor protein and could be cleaved by proteases into various other biologically active peptides.

CgA is thus a universal marker for neuroendocrine cell differentiation and activity. Testing its serum level is a marker of neuroendocrine secretory activity in the body. There are numerous limitations for the use of serum chromogranin A for diagnosis or follow-up of gastroenteropancreatic neuroendocrine tumors (GEP-NETs). However, it still remains the preferred tumor marker in these conditions, as it is widely available and less cumbersome to perform and retains a reasonable sensitivity and specificity provided the clinician applies all necessary recommended precautions in performance of the test and interpretation of the results.

Three different methods are available commercially for measuring CgA level. These are ELISA, immunoradiometric assay (IRMA), and radioimmunoassay (RIA). RIA seems to have the best outcomes with reported sensitivity and specificity of 93% and 85% [50]. Plasma level of CgA has been reported to be much higher than simultaneous serum estimation [49, 51]. Clinicians should read a report of CgA with great diligence (what sample and what assay).

The list of non-neuroendocrine disorders in which CgA is elevated is very long. The most common of such conditions is the use of proton pump inhibitors (PPI), H2 receptor blockers, and atrophic gastritis, which decrease gastric acid secretion and so result in elevation of serum gastrin level. CgA is co-secreted with gastrin too, and so these conditions result in very high levels. Even 5 days of PPI intake could result in significant increase in serum CgA level. It is recommended that PPIs and H2 receptor blockers be stopped for at least 7 days and 1 day, respectively, before the test [49]. If levels are unexpectedly elevated, the test could be repeated 2 weeks after stopping PPI [52].

Impaired kidney function leads to decreased renal clearance of CgA, thus preventing the use of the test in renal failure. Elevated CgA has also been reported in heart failure, acute coronary syndrome, untreated systemic hypertension, rheumatoid arthritis, inflammatory bowel disease, and postprandial state and after strenuous exercise. It is imperative that patients are fasting and have taken adequate rest before testing for CgA [49, 52].

Important Precautions for Performance/Interpretation of CgA Level

1. Do it in fasting state.
2. Adequate rest and no strenuous exercise before sampling.
3. Stop PPIs for at least 1 week. High CgA levels could persist till 2 weeks.
4. Stop H2 receptor blockers for at least 1 day.
5. Use either plasma or serum levels. They are not interchangeable.
6. Radioimmunoassay is preferred. Use the same assay method every time.
7. Have a list of all comorbid conditions while interpreting results.
8. Somatostatin analogue therapy dose changes could affect serum levels.

A meta-analysis of 13 studies that analyzed 1260 patients with NETs and 967 healthy subjects reported overall sensitivity, specificity, and diagnostic odds ratio of 0.73, 0.95, and 56.29, respectively. Area under curve (AUC) for diagnosis of NET was 0.89 [53]. This positive outlook of performance of CgA is offset by many small studies that show that it lacks sensitivity and specificity.

Highest levels of CgA in GEP-NETs are obtained in midgut neuroendocrine tumors, previously termed as "carcinoid tumors." In ileal carcinoids with liver metastasis, level as high as 200 times upper normal limit is reported. GEP-NETs in MEN-1 syndrome could result in chromogranin A values of about 150 times the upper normal limit [52]. CgA levels in pancreatic NETs are about 60–80 times upper normal limit [49]. CgA is elevated in 100% of gastrinomas and 70% of pancreatic NETs. In gastrinoma, very high levels are reported even in the absence of liver metastasis [49].

CgA level of more than 5000 μg/l was found to be an independent prognostic factor for midgut NETs. Median survival was 33 and 57 months below and above the 5000 μg/l cutoff, respectively [54]. This interpretation of CgA level cannot be generalized to all GEP-NETs. Typical exception of high level without any metastatic disease is gastrinoma as mentioned earlier. CgA level does not correlate with the degree of differentiation of GEP-NETs. Diagnostic accuracy of CgA was 73% in well-differentiated NETs and 50% in poorly differentiated NETs. This is probably related to loss of secretory function of poorly differentiated NETs, where this tumor marker is less reliable [52].

CgA level has been reported to fall after all forms of therapy for GEP-NETs. This could be resection of the tumor, liver transplantation for metastatic disease, radionuclide therapy, or treatment with receptor blockade like everolimus [55–57]. RADIANT trials which evaluated use of everolimus for pancreatic NETs which showed progression despite conventional chemotherapy used CgA normalization or fall in level more than or equal to 50% as one of the criteria for response to medication. An early CgA response was defined as normalization or 30% decrease at 4 weeks. RADIANT 2 trial reported that median progression free survival was 13.3 months in early response versus 7.5 months otherwise ($p = 0.00004$) [58].

In a study of 56 patients who underwent resection of midgut NETs, follow-up was performed using a combination of CgA and imaging. It was found that in 85%, CgA elevation preceded radiologic evidence of recurrence [59]. Based on these findings, the study recommended 6-month monitoring of CgA after resection of GEP-NETs.

5.2 Summary

Understanding the pathophysiology, sensitivity and specificity of tumor markers will improve quality of care and reduce cost of treatment by avoiding inappropriate use of these tests.

Editorial Comments

Tumor markers are biological substances produced by a specific cancer. When the tumor marker level is high, it may indicate the presence of cancer. However, this alone is not enough to diagnose cancer as even non-cancerous conditions can cause an increase in levels of tumor markers. Tumor markers can be used to (1) assist in arriving at a diagnosis, (2) ascertain prognosis, (3) evaluate treatment response, and (4) detect recurrence during follow-up. A number of these tumor markers are used in gastrointestinal (GI) oncology and are discussed below.

Gastric cancer

The biomarkers used in gastric cancer are carcinoembryonic antigen (CEA), carbohydrate antigen 19-9 (CA 19-9), carbohydrate antigen 72-4 (CA 72-4), and alphafoetoprotein (AFP).

CEA is the most investigated tumor marker in GI malignancy including gastric cancer. A high preoperative CEA level in gastric cancer indicates an advanced stage of disease, possibly with peritoneal involvement [60]. Peritoneal fluid CEA levels correlate well in such situations [61, 62]. An elevated CEA following therapy indicates locoregional relapse and thus is considered a predictor of recurrence. CEA levels rise nearly 3 months before liver metastasis can be detected [63, 64]. Patients with gastric cancer often have normal pretreatment CEA levels. These patients have a better survival especially if they receive preoperative chemotherapy [65]. Normal postoperative CEA levels are also associated with better survival [66].

CA 72-4 is another marker used in gastric cancer. Elevated serum CA 72-4 levels correlate well with lymph nodal disease. Akin to CEA, CA 72-4 can be high in peritoneal fluid. High peritoneal fluid CA 72-4 correlates with a higher T and N stage and worse prognosis [67, 68]. A meta-analysis of 33 studies has shown that CA 72-4 is more accurate than any other tumor marker in gastric cancer [69].

CA 19-9 can also be measured in the peritoneal fluid. The higher the CA 19-9 level, the higher the preoperative stage of the disease. Its greatest advantage is that it indicates recurrence even before imaging detects it [64]. An elevated AFP is more commonly seen in patients with gastric cancer and liver metastases. Raised AFP has not been noted with serosal or peritoneal disease [70]. However, Nakajima et al. found no correlation between raised AFP levels and pathological features such as lymph node involvement, vascular invasion, and liver metastasis [71].

Colorectal cancer

The main tumor marker used in colorectal cancer is CEA. Early colorectal cancer rarely has elevated CEA levels. Also, because of its inability to differentiate benign from malignant lesions (e.g., a polyp), it is not recommended for screening purposes. Based on CEA values a staging has been proposed—"c" stage [72]. There are three "c" stages: Cx CEA not detected; Co CEA

<5 ng/ml and C1 CEA >5 ng/ml. The prognostic value of CEA has been confirmed again in a study with a large number of patients with a median follow-up of 27 months. Low levels of CEA across various stages have been shown to have a longer survival [73]. CEA returns to normal after a curative resection (R0) in 4–6 weeks. If it remains elevated, it is a strong indicator that the patient has metastatic disease, often in the liver [74]. A slow increase in CEA level following surgery indicates local recurrence. A progressively rising CEA level is an indicator of metastatic disease [62]. CEA levels should be done every 3 months for the first 3 years after surgery and every 6 months thereafter until 5 years after surgery. If the CEA level is elevated in the postoperative period, patients should be given chemotherapy, even if they are asymptomatic as it improves survival. It is also used to monitor patients with widespread disease. If the CEA level rises in patients on chemotherapy, metastasis is suspected even if the imaging is negative [75]. Other markers used in colorectal cancer are CA 19-9 and CA 72-4. The sensitivity of both of these is inferior to CEA and is not suitable for diagnosis or post-therapy follow-up [74]. Two protein markers have also been extensively investigated. These are (1) tumor-specific M2 isoform of pyruvate kinase (M2-PK) and (2) tissue inhibitor matrix metalloproteinase 1 (T1MP1). M2-PK is estimated in the stool and is highly sensitive (91%) for colorectal cancer [76]. T1MP1, on the other hand, has not been found to be useful [77].

Hepatocellular carcinoma (HCC)

A large number of tumor markers have been explored both for the diagnosis and prognosis of HCC. Of these, AFP, AFP-L3 (*Lens culinaris* agglutinin reactive fraction of AFP), PIVKA (protein induced by vitamin K absence/antagonist II), and Glycipan-3 are widely used in clinical practice.

AFP is the most commonly used tumor marker. With a cutoff value of 20 ng/ml, it has 40–60% sensitivity and 60–80% specificity [78]. Its main limitation is that it may be normal in 40% of patients. It may also be increased in pregnancy, active liver disease, and other tumors. Moreover, small HCCs can secrete so little AFP that it is not detectable by the present methods of measurement. The reverse is also true, i.e., in large tumors, AFP may be higher than the upper limit of measurement [79]. AFP L3 is secreted only in HCCs and has sensitivity and specificity above 90% [61]. Kobayashi et al. [80] have reported superior diagnostic accuracy of AFP L3 than AFP.

Glypican-3 (GPC-3) is related to all growth regulation, its differentiation, and migration. It is expressed in HCC, and it promotes growth of HCC stimulating Wnt signaling [81]. Its sensitivity and specificity have been reported to be 77% and 96%, respectively [82].

Des-gamma-carboxy prothrombin (DCP) or PIVKA is secreted by HCC. The size of an HCC is related to the serum level of DCP (PIVKA). Thus, smaller tumors (<3 cm) have poor DCP sensitivity as compared to AFP,

and large tumors (>5 cm) have stronger DCP sensitivity than AFP [83]. Measurement of DCP and AFP has been shown to have a better diagnostic and predictive value of recurrence of HCC after surgery. Overall, the DCP level is associated with a large tumor often with vascular involvement and seems to be more accurate than AFP or AFP-L3. However, a recent study has suggested measurement of all three markers for assessment of progression of HCC [84], while another study had suggested that combined measurement improves their diagnostic value [85].

Pancreatic cancer

Development of tumor markers for the management of pancreatic cancer has been slow. Only CA 19-9 is used routinely for diagnostic screening, prognosis, and predictive purposes. For screening, CA 19-9 has been found to be effective in a Japanese study [86]. Its accuracy was reported to be 84% [87]. The main problem with CA 19-9 is that the levels are raised in biliary obstruction (the commonest presentation of pancreatic cancer), benign as well as malignant. Therefore, CA 19-9 levels should be done after relief of biliary obstruction, and if elevated it is suggestive of cancer [88]. Resectability of pancreatic cancer can also be assessed by the preoperative CA 19-9 value. A value >300 U/ml suggests advanced disease and hence is likely to be unresectable [89]. A study has suggested that CA 19-9 level >300 U/ml is seen in one-third of patients with pancreatic adenocarcinoma. Based on this study, it was suggested that staging laparoscopy should be done when the CA 19-9 level is above 130 U/ml [90]. Following surgical resection if the CA 19-9 level comes down below the preoperative value, it indicates a good prognosis. A low serum CA 19-9 level after resection has been shown to be associated with better overall survival [91]. An elevated postoperative CA 19-9 level indicates poor survival with a median survival of less than a year. It appears from the literature that if the postoperative level of CA 19-9 becomes normal irrespective of the preoperative CA 19-9 level, the survival is longer [91]. A reduction after treatment of the preoperative value to >75% overall has been shown to be associated with improved survival [92].

CA 125 and CEA are the other tumor markers used in pancreatic cancer. However, both are inferior to CA 19-9 with a sensitivity and specificity of about 50% and 80% compared with a sensitivity of 70% and specificity of 90% for CA 19-9 [91].

Gallbladder and biliary cancer

As with pancreatic cancer, tumor markers for gallbladder and biliary cancer are also not adequately studied. Older studies primarily dealt with CEA and later CA 19-9. Recent studies have also included CA 125 and CA 242. When a single marker is used, CA 19-9 has the highest sensitivity (71.7%) and CA 242 the highest specificity (98.7%). In a study from China, a combination of CA 19-9, CA 242, and CA 125 had a diagnostic accuracy of 69.2% for gallbladder cancer [93]. CA 19-9 and CA 242 increase with progression of the disease, and a high CA 242 has been found to indicate an advanced

gallbladder cancer. This along with increased CA 19-9 has been correlated with lymph nodal metastases in gallbladder cancer. All the three (CA 125, CA 19-9, CA 242) are elevated more often in recurrent disease than primary disease. For cancer of the gallbladder neck, CA 19-9 has an independent prognostic value. For other biliary cancers, CA 19-9 seem to correlate well with the clinical status, becoming normal following curative surgery, only to get elevated with recurrence of disease [94].

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Chapter 6
IgG4 HPB Disease

Jimil Shah and Usha Dutta

6.1 Historical Perspective

Mickulicz disease was first described in 1892 which was followed by the description of sclerosing cholangitis and autoimmune pancreatitis in 1995 (Table 6.1) [1, 2]. Later evidences showed association between these diseases and elevated IgG4 values [3]. Recently these and many other diseases have been included in a larger spectrum of multi-organ diseases called IgG4-related diseases (IgG4 RD) [4] (Fig. 6.1).

6.2 Epidemiology

The epidemiology of IgG4 HPB disease is poorly defined across the globe due to variations in the presentation, absence of well-defined criteria, or a single diagnostic test. In Japan, the incidence and prevalence of IgG4 RD are gradually increasing with the annual incidence of 1.4 per 100,000 and prevalence of 4.6 per 100,000 of the population in 2011 [5]. About 10.3% of AIP-1 have associated IgG4 sclerosing cholangitis (SC) making it the commonest extra-pancreatic site of involvement [5]. However, isolated IgG4 SC is a rarer phenomenon with incidence that varies from

Table 6.1 Historical landmarks

1892	Mickulicz disease
1995	Yoshida et al. (autoimmune pancreatitis)
2001	H. Hamano et al. (elevated IgG4 in AIP)
2002	H. Hamano et al. (infiltration of IgG4 plasma cells in tissue samples)

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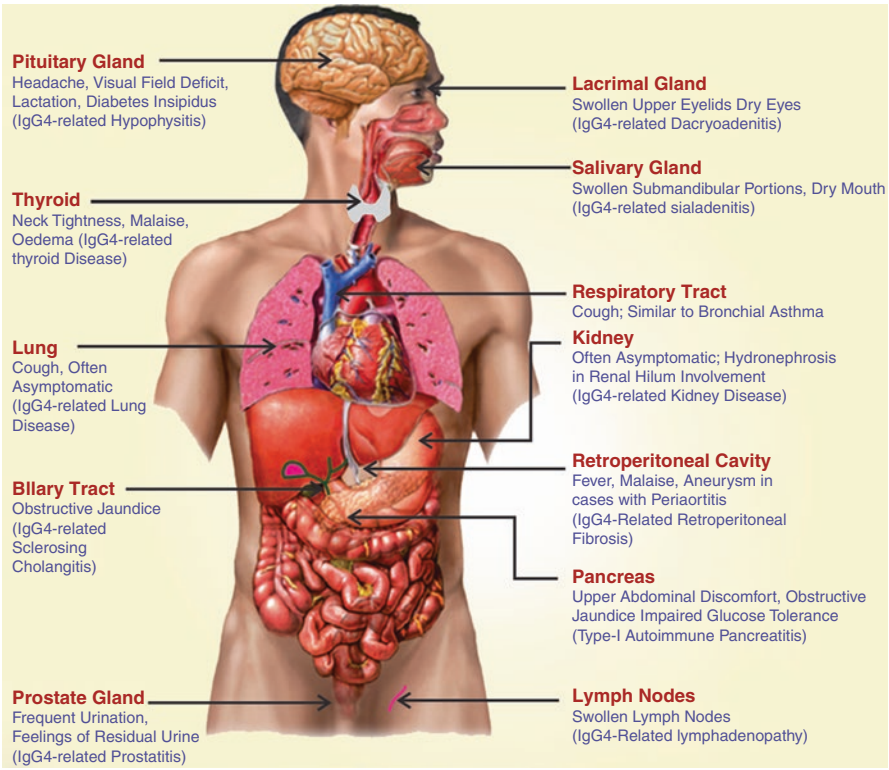


Fig. 6.1 Showing spectrum of IgG4-related diseases

1.5% in Japan to 8% in US cohort [6–8]. Incidence and prevalence of IgG4-related hepatopathy are not known due to scanty literature on this entity [9].

IgG4-related disease is more common in middle to elderly males. Mean age of patients with IgG4 SC at diagnosis is 66 years with male preponderance (male/female—4.7:1) [10] which is almost similar to that of AIP-1 (mean age 67 years; male/female—3:1). This disease is more common in men in the seventh decade which is sharply in contrast with other autoimmune diseases in which female predominance is usually observed. Though various genetic risk factors have been observed, no case of familial IgG4 RD has been reported yet.

6.3 Pathogenesis and Risk Factors

Multiple pathways including autoimmune pathway, genetic pathway, and molecular mimicry have been postulated to be involved in the pathogenesis of IgG4-related diseases. However, it is now understood that the pathogenesis is more likely to be an interplay of various pathways rather than a single etiology.

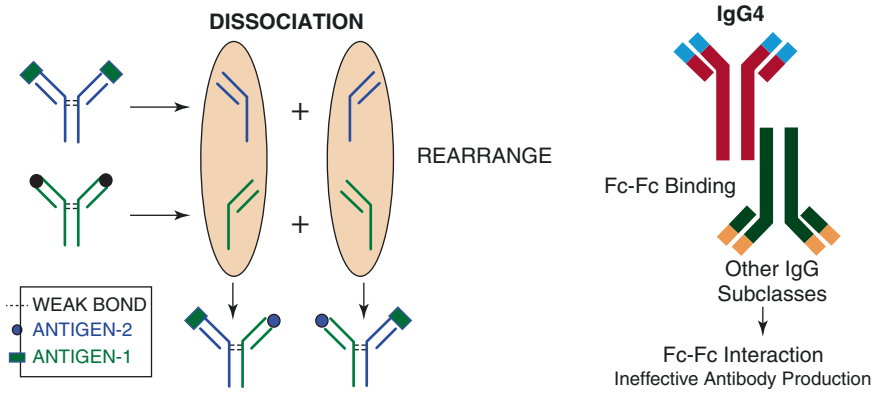


Fig. 6.2 Showing weak disulfide bond between heavy chain of IgG4 molecule resulting in Fab-arm exchange and Fc–Fc interaction making them ineffective antibody to bind with antigen or complement factors

6.3.1 IgG4 Antibody

Serum IgG4 antibody is elevated in patients with IgG4-RD. Normally it constitutes <5% of total IgG antibodies. IgG4 has an unstable disulfide bond between its heavy chains which results in dissociation of the heavy chain and joining with other dissociated chains [11]. This makes IgG4 molecule ineffective for action against one specific antigen (Fig. 6.2). Fragment antigen-binding (Fab)-arm exchange also takes place between IgG4 molecules making them asymmetric, bispecific antibody preventing effective participation in various inflammatory reactions [12]. If this theory is true, then the elevated IgG4 level is just secondary to some other primary inflammatory stimulus without itself being primarily responsible for pathogenesis of disease.

6.3.2 Genetic Risk Factors

Various HLA and non-HLA risk factors have shown to increase genetic susceptibility of acquiring IgG4 RD. HLA DRB1*0405 and DQB1*0401 and DQβ1-57 without aspartic acid have been found to increase susceptibility of IgG4-RD in Japanese and Korean populations, respectively [13, 14]. Similarly, single nucleotide polymorphism involving TNF-α and CTLA-4 has also been associated with increased susceptibility of IgG4-RD [15].

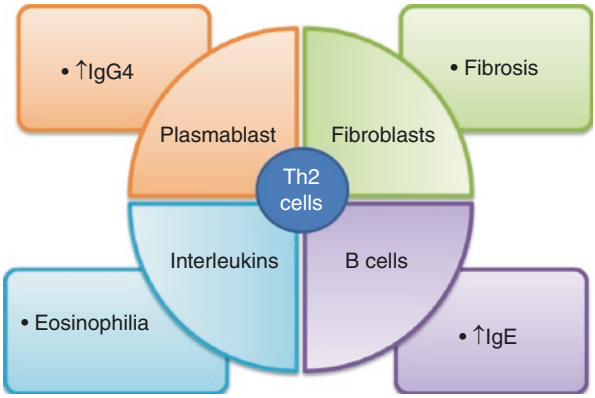


Fig. 6.3 Showing interplay between various pathways in pathogenesis of IgG4-related diseases. Th2 cells appear to play the most important role in pathogenesis of IgG4-related diseases. Th2 cells cause increase in B cells, plasma cells, and fibroblasts which are responsible for lymphoplasmacytic infiltration with fibrosis in various organs

6.3.3 Bacterial Infection and Molecular Mimicry

Substantial homology exists between plasminogen-binding protein moiety of *H. pylori* and n-recognin 2 expressed in pancreatic acinar cells [16, 17]. This bacterial infection can trigger auto-inflammatory reaction and IgG4 molecule production. Autoimmune pathway can cause damage to the pancreas, bile ducts, and salivary gland epithelium.

6.3.4 Immune Pathway

Th2 is the predominant inflammatory pathway involved in the pathogenesis of disease [18–20]. Th2-cell activation results in increased production of IL-4, IL-5, and IL-13. T cells stimulate plasma cells to produce more IgG4 molecules. Eosinophilia and elevated IgE levels found in half of the patients with IgG4 RD is also mediated by Th2 pathway. In contrast to other autoimmune diseases, IgG4 RD is associated with activation of Treg cells and increases expression of FOXP3 [21]. Activation of Treg cells is associated with increased secretion of TGF-β which is responsible for increased fibrosis in various IgG4-related diseases [22].

Thus, pathogenesis of IgG4-RD involves interplay between multiple pathways resulting in increased IgG4 levels, lymphoplasmacytic infiltration, and fibrosis causing organ dysfunction (Fig. 6.3).

6.4 Clinical Presentation

IgG4-related hepato-pancreato-biliary diseases can present with a wide array of symptoms mimicking malignancy, infections, and various autoimmune diseases requiring high index of clinical suspicion for early diagnosis and effective treatment. These diseases typically present in the seventh decade of life with male predominance [5, 10]. Most common presentations include painless jaundice (60–70%), pancreatic mass lesion, and pancreatic insufficiency [23]. Presentation with acute pancreatitis or signs of secondary biliary cirrhosis is rarely documented [10]. Patients with IgG4-related hepatopathy may present with transaminitis and symptoms resembling autoimmune hepatitis [9, 24]. Patients may present initially with extra-pancreatic organ involvement in the form of salivary or lacrimal gland involvement, mediastinal or retroperitoneal lymph node involvement followed by pancreatic involvement which may be found incidentally. Abnormal liver function tests or cross-sectional images may also incidentally alert the physician to its presence.

6.5 Diagnosis

There are four cornerstones in establishing the diagnosis of IgG4 HPB: laboratory evaluation, radiological evaluation, endoscopic evaluation, and histological evaluation.

6.5.1 Laboratory Evaluation

- *Liver function test*: Liver function test abnormality commonly involves either abnormal transaminase levels in IgG4 hepatopathy or abnormal alkaline phosphatase levels due to IgG4 SC. Half of the patients with IgG RD have abnormally elevated IgE levels and eosinophils [25]. Thirty to forty percent of patients have increased levels of antinuclear antibody titer and rheumatoid factor [26].
- *Serum IgG4 levels*: Serum IgG4 levels of more than 1.4 g/L are found in 65–80% of patients and considered the most useful marker of this disease [7, 8]. Levels more than 2.5 g/L have a sensitivity of 67–89% and specificity of 95% to differentiate IgG4 SC from primary sclerosing cholangitis (PSC) [27]. However, 5–25% of patients with various autoimmune and inflammatory diseases and even pancreatic carcinoma may also have elevated levels, adding further diagnostic dilemma [28–30]. Similarly IgG1/IgG4 ratio >0.24 also have a high sensitivity and specificity of 86% and 95%, respectively, to differentiate PSC from

IgG4 SC [27]. IgG4 levels of >5.6 g/L can also differentiate IgG4 SC from PSC and cholangiocarcinoma with specificity and positive predictive value of 100% [27]. Similarly, levels more than two times increase specificity for diagnosis of AIP-1 compared to pancreatic carcinoma.

A subset of patients with normal IgG4 levels (20–25%) pose a difficult diagnostic challenge [7]. This subgroup has distinct phenotype with fewer relapses and less organ involvement. In this group of patients, IgG4/IgG RNA ratio has shown promise to differentiate IgG4 SC from PSC and cholangiocarcinoma [31]. Similarly, peripheral plasmablast levels have also been found to be increased in patients with IgG4 RD [32, 33]. Increased IgE levels of >408kU/L have also shown to differentiate IgG RD from non-IgG4 RD with elevated IgG4 levels [34]. One small study has identified the use of anti-plasminogen-binding peptide antibody which was elevated in 94% of AIP patients [16]. However, due to small sample size, this finding requires further validation.

6.5.2 Radiological Investigations

6.5.2.1 Imaging of Autoimmune Pancreatitis Type-1 (AIP-1)

Pancreatic involvement can be either in the form of diffuse, focal, or multifocal involvement with diffuse involvement being the commonest form. Diffuse enlargement of the pancreas appears as loss of normal lobulated contour called "sausage-shaped pancreas" [35, 36]. The presence of low-attenuating rim of pancreas "halo sign" is highly specific but seen only in 30–40% of patients. Rarely, it may present with focal mass or multifocal disease resulting in difficulty in differentiating it from pancreatic carcinoma. The presence of low-density mass, dilatation of main pancreatic duct, and distal atrophy is not typically seen in AIP-1 and should suggest pancreatic carcinoma [37]. On MRI the pancreas shows hypo-intensity of parenchyma on T1W images and slight hyperintensity on T2W images with delayed enhancement during the late phase [38]. Classically the main pancreatic duct shows long-segment stricture (>1/3 of the main pancreatic duct) without upstream duct dilatation (<5 mm) in patient with AIP-1 [39]. However, multifocal or short-segment stricture may also be present. Associated biliary system involvement also points toward the presence of AIP-1.

6.5.2.2 Imaging of IgG4-Related Sclerosing Cholangitis (IgG4 SC)

Ultrasound has a limited role in diagnosis of IgG4 HPB disease except to show the presence of bile duct stricture or pancreatic mass lesion. MRCP usually shows symmetrical biliary wall thickening, biliary strictures, and associated involvement of the pancreas or gall bladder. The presence of continuous bile

duct involvement and common bile duct wall thickness of more than 2.5 mm and presence of gallbladder, pancreatic, or renal involvement favor the diagnosis of IgG4-RD over PSC [40].

Apart from these imaging, we have found that PET-CT scan can be used in the presence of diagnostic dilemma to demonstrate clinically silent extra-pancreatic organ involvement (salivary glands, renal parenchyma or retroperitoneal fibrosis, etc.), though its routine use is yet to be defined [41].

6.5.3 Role of Endoscopy

- *Role of ERCP*: Endoscopic retrograde cholangiopancreatography (ERCP) plays a very crucial role in diagnosis and management of IgG4-related diseases. Cholangiogram can show the presence of long-segment stricture (more than one third of the length of the bile duct), multifocal stricture, and associated pancreatic involvement [42]. It can also be useful to obtain endoscopic brushings, bile fluid sampling, and intrabiliary or ampullary biopsy to differentiate it from cholangiocarcinoma. Pancreatogram can show thin, diffusely narrowed pancreatic duct. ERCP can also be helpful for biliary drainage in the presence of cholangitis.
- *Role of EUS*: Endoscopic ultrasound (EUS) can also be helpful in the diagnosis of IgG4-related HPB disease. The pancreas may appear as diffusely enlarged with hypoechoic and heterogenous parenchyma. It may also show focal pancreatic mass involving the head of the pancreas with pancreatic duct wall thickening and peripancreatic lymphadenopathy mimicking pancreatic carcinoma [43, 44]. EUS-elastography and contrast-enhanced EUS have also shown promising results to differentiate between AIP-1 and pancreatic carcinoma [45, 46]. EUS-guided FNA and Tru-cut biopsy are very useful to obtain tissue for histopathological diagnosis with sensitivity of more than 70% [47]. Biliary system involvement in EUS shows symmetrical, homogenous biliary wall thickening with smooth inner and outer margins [48].
- *Cholangioscopy*: It can also be used for evaluating strictures and targeted biopsies. It is especially useful to differentiate IgG4 SC from cholangiocarcinoma [49].

6.5.4 Histology

Histology remains the mainstay for the final diagnosis of IgG4-RD. Histological sample may be acquired by either biliary brushings, intraductal or ampullary biopsy, EUS, or USG-guided FNA or Tru-cut biopsy of pancreatic mass. Three major histological features associated with IgG4 RD are (1) dense lymphoplasmacytic infiltrate in which small lymphocytes (predominantly T cells) are diffusely infiltrated throughout the pancreatic parenchyma interspersed with plasma cells, (2) storiform

fibrosis resembling spokes of a cartwheel with spindle cells radiating from the center, and (3) obliterative phlebitis where venous channels are obliterated by lymphoplasmacytic infiltrate [50]. Appropriate cutoff of IgG4+ plasma cell required for diagnosis is >10 cells/hpf in the biopsy specimen and >50 cells/hpf in the resection specimen [50]. In the presence of advanced disease with predominant fibrosis, infiltration with IgG4+ plasma cells might not be predominant in which using IgG4/IgG plasma cell ratio >40% can be useful [51]. Similarly newer marker like FOXP3+ lymphocyte in ampullary biopsy is also under evaluation [52].

Liver involvement in AIP-1 is histologically described in five patterns: portal inflammation with or without interface hepatitis, canalicular cholestasis, portal sclerosis, lobular hepatitis, and large bile duct obstructive features [9]. Rarely it may present as hepatic pseudotumor due to aggregation of IgG4 plasma cells, obliterative phlebitis, and fibrosis mimicking hepatic malignancy.

6.6 Classification of IgG4-Associated Sclerosing Cholangitis

IgG4 SC can be classified into four types based on the presence of stricture on cholangiography. Type 1 shows stricture in lower part of common bile duct and should be differentiated from cholangiocarcinoma, chronic pancreatitis, and pancreatic carcinoma. Type 2 shows multifocal stenosis involving intra- and extrahepatic bile ducts, and PSC is the most important differential diagnosis in this type of stricture. Type 2a involves narrowing of bile ducts with pre-stenotic dilatation, while type 2b involves narrowing of bile ducts without pre-stenotic dilatation and reduced bile duct branches. Type 3 involves stricture at both the hilum and lower part of the common bile duct, and type 4 involves stricture only at the hilar bile duct. Cholangiocarcinoma is the most important differential diagnosis with these types of strictures (Fig. 6.4) [53, 54].

6.7 Diagnostic Criteria

The diagnosis of IgG4 HPB disease is based on the combination of clinical, laboratory, and radiological investigations.

6.7.1 Diagnostic Criteria for Autoimmune Pancreatitis

Mayo Clinic HISORt (histology, imaging, serology, other organ involvement, and response to steroid treatment) criteria is the frequently used criteria for the diagnosis of both AIP and IgG4 SC [55]. Other criteria like the Japanese criteria and International Association of Pancreatology (IAP) criteria are being frequently used in current practice (Tables 6.2 and 6.3) [56].

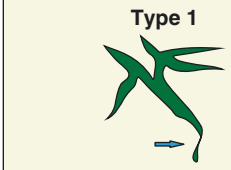
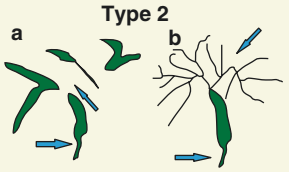
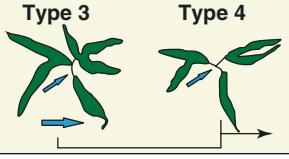
	Differential Diagnosis	Useful Modalities
	Pancreatic Cancer Bile Duct Cancer Chronic Pancreatitis	IDUS (Bile Duct) EUS-FNA (Pancreas) Biopsy (Bile Duct)
	Primary Sclerosing Cholangitis	Liver Biopsy Colonoscopy (R/O coexistence of IBD)
	Bile Duct Cancer Gallbladder Cancer	EUS (Bile Duct, Pancreas) IDUS (Bile Duct) Biopsy (Bile Duct)

Fig. 6.4 Showing types of IgG4-related sclerosing cholangitis and their respective differential diagnosis IDUS–Intraductal ultrasound; IBD–Inflammatory bowel disease

Table 6.2 International consensus diagnostic criteria for type 1 autoimmune pancreatitis [56]

Criterion	Level 1	Level 2
Parenchymal imaging (P)	Typical: Diffuse enlargement with delayed enhancement	Intermediate: Focal enlargement with delayed enhancement
Ductal imaging (ERP) (D)	Long or multiple strictures (>1/3 duct length) without upstream dilatation	Focal narrowing without upstream dilatation (<5 mm)
Serology (S)	IgG4 >2× upper limit	IgG4 1–2× upper limit
Other organ involvement (OOI)	Extra-pancreatic organ histology. Any three of: 1. Lymphoplasmacytic infiltration with fibrosis and without granulocytic infiltration 2. Storiform fibrosis 3. Obliterative phlebitis 4. >10 cells/HPF IgG4-positive cells Or Typical radiology. Any one of: 1. Segmental/multiple proximal or distal biliary stricture 2. Retroperitoneal fibrosis	Extra-pancreatic organ histology including bile duct biopsies. Both of: 1. Marked lymphoplasmacytic infiltration without granulocytic infiltration 2. 10 cells/HPF IgG4-positive cells Or Physical or radiological evidence of at least one of: 1. Enlarged salivary/lacrimal glands 2. Renal involvement

(continued)

Table 6.2. (continued)

Criterion	Level 1	Level 2
Histology of pancreas (H)	LPSP[a]—any three of the following: 1. Periductal lymphoplasmacytic infiltrate without granulocytic infiltration 2. Obliterative phlebitis 3. Storiform fibrosis 4. >10 cells/HPF IgG4-positive cells	LPSP[a]—any two of the following: 1. Periductal lymphoplasmacytic infiltrate without granulocytic infiltration 2. Obliterative phlebitis 3. Storiform fibrosis 4. >10 cells/HPF IgG4-positive cells
Response to steroids (Rt)	Rapid (<2 weeks) radiological demonstration of marked improvement in pancreatic/extra-pancreatic manifestations	

[a]Lymphoplasmacytic sclerosing pancreatitis

Table 6.3 International consensus diagnostic criteria for type 1 autoimmune pancreatitis [56]

Diagnosis of type 1 AIP			
Diagnosis	Primary basis for diagnosis	Imaging evidence	Collateral evidence
Definitive	Histology	Typical/ indeterminate	Histologically confirmed LPSP (level 1H)
	Imaging	Typical	Any non-D level 1/level 2
		Indeterminate	Two or more from level 1 (+level 2 D*)
	Steroid response	Indeterminate	Level 1S/OOI and Rt or level 1D + level 2S/OOI/H + Rt
Probable		Indeterminate	Level 2S/OOI/H + Rt

*Level 2 D is considered as Level 1 in this setting

6.7.2 Diagnostic Criteria for IgG4-Related Sclerosing Cholangitis

Mayo Clinic HISORt criteria can also be used for diagnosis of IgG4-SC. In 2012 the Japanese Association developed criteria for diagnosis of IgG4-SC which is routinely used in clinical practice (Table 6.4) [54].

6.8 Differential Diagnosis

Differentiating IgG4 RD from other diseases remains the most important aspect considering its wide array of presentations. Pancreatic carcinoma and chronic pancreatitis remain the most important differential diagnoses in patients with suspected AIP-1. Similarly, IgG4-related cholangiopathy needs to be differentiated from cholangiocarcinoma, PSC, and chronic pancreatitis-induced benign stricture. Autoimmune hepatitis and benign and malignant tumors need to be differentiated from IgG4-related hepatopathy (Tables 6.5 and 6.6; Fig. 6.5).

Table 6.4 Japanese Association criteria for IgG4-related sclerosing cholangitis [54]

Diagnostic items
1. Biliary tract imaging reveals diffuse or segmental narrowing of the intrahepatic and/or extrahepatic bile duct associated with thickening of bile duct wall
2. Hematological examination shows elevated serum IgG4 concentrations (≥135 mg/dL)
3. Coexistence of autoimmune pancreatitis, IgG4-related dacryoadenitis/sialadenitis, or IgG4-related retroperitoneal fibrosis
4. Histopathological examination shows:
a. Marked lymphocytic and plasmacyte infiltration and fibrosis
b. Infiltration of IgG4-positive plasma cells: >10 IgG4-positive plasma cells/HPF
c. Storiform fibrosis
d. Obliterative phlebitis
Option: effectiveness of steroid therapy
Diagnosis
Definitive diagnosis
(1) + (3)
(1) + (2) + (4) a, b
(4) a, b, c
(4) a, b, d
Probable diagnosis
(1) + (2) + option
Possible diagnosis
(1) + (2)

Table 6.5 Differential diagnosis of IgG4 HPB diseases

• Chronic pancreatitis
• Pancreatic carcinoma
• Primary sclerosing cholangitis
• Secondary sclerosing cholangitis
• Cholangiocarcinoma
• Carcinoma gall bladder
• Vasculitis
• Benign and malignant liver tumors

Table 6.6 Differentiating points between IgG4 SC, PSC, and cholangiocarcinoma

Character	IgG4 SC	PSC	Cholangiocarcinoma
Age (years)	40–70	30–40	>60
Gender	M	M	M
Associated disease	Pancreas	IBD	–
Stricture characteristics	Long segment	Multiple	Short segment
Serum markers	IgG4	p-ANCA	CA-19-9
Hilar mass	+	–	+
Response to steroids	++++	+	–

IBD Inflammatory bowel disease

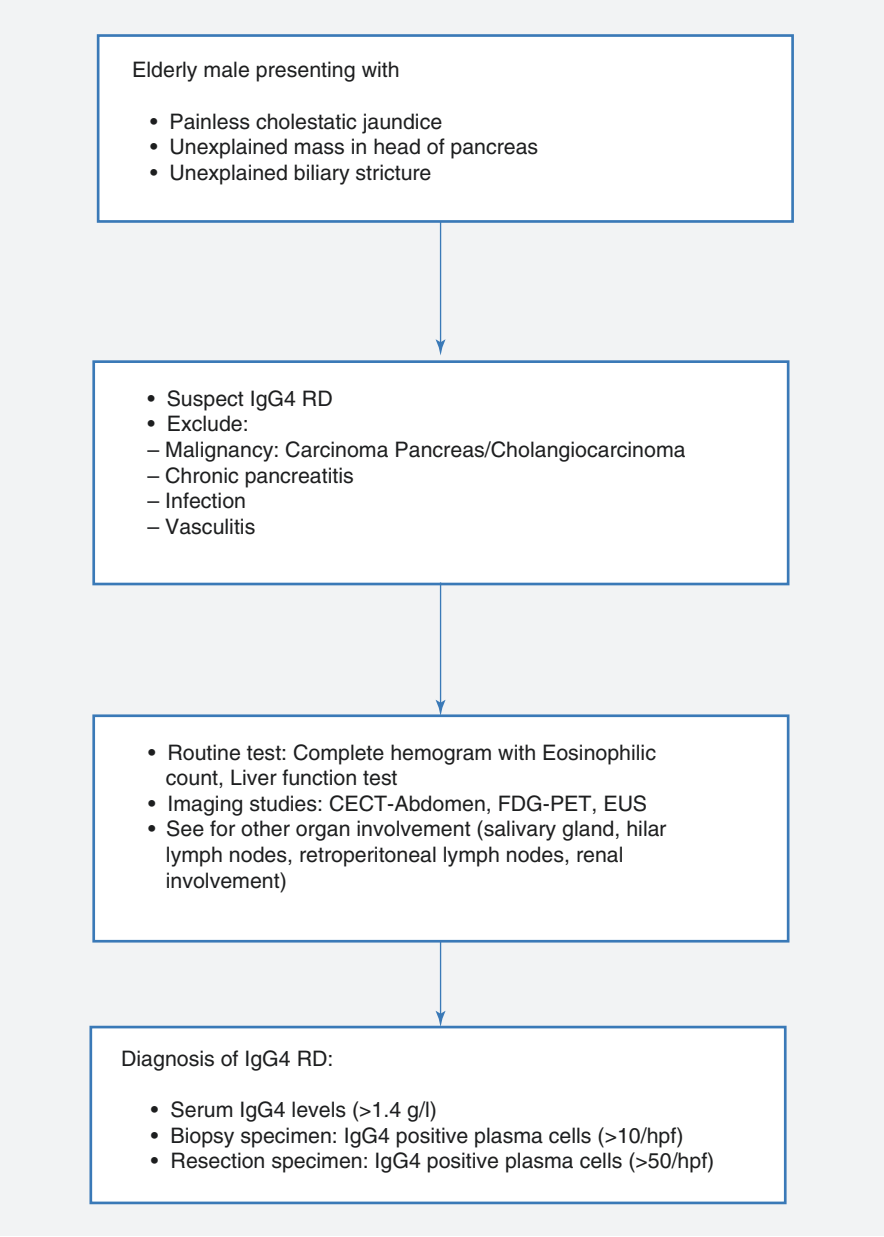


Fig. 6.5 Approach to patient with suspected IgG4-related diseases (RD)

6.9 Treatment

IgG4 RD are fibroinflammatory diseases in which the early stage is characterized by robust inflammation which easily and rapidly responds to the steroid therapy, while the later phase involves fibrosis in which response to treatment is limited. So, early diagnosis and prompt treatment are keys to prevent further progressive damage (Fig. 6.6).

6.9.1 Indication of Treatment

All symptomatic patients with IgG4 HPB disease require treatment. In recently published management consensus, IgG4 HPB disease has been classified as a disease group which requires *urgent* treatment considering the grave consequences [57]. Moreover, even asymptomatic patients of IgG4 HPB diseases may require initial treatment in view of the risk of cholangitis and biliary cirrhosis in the presence of IgG4-related cholangiopathy and the risk of exocrine and endocrine insufficiency in AIP [58, 59]. Patients with IgG4 SC who present with cholangitis may require treatment with short-term biliary stenting. Only in the presence of dense fibrosis and "burn-out" disease, treatment might not be warranted due to a higher risk of complications and poorer response to therapy.

6.9.2 Induction of Remission

Glucocorticoids are the usual first-line agent for induction of remission in patients with IgG4 HPB diseases. Typical dose of glucocorticoid used for induction of remission is 30–40 mg (0.67 mg/kg) which is maintained for 2–3 weeks followed by gradual taper over the next 3–6 months. Improvement is assessed in two of the three parameters: improvement in clinical status, normalization of IgG4 values, and improvement in radiological abnormalities. Different studies have reported success rate >80% with glucocorticoid therapy (Tables 6.7 and 6.8) [60, 61].

Few centers have used steroid-sparing agents like azathioprine, mycophenolate mofetil, and cyclophosphamide in the induction regimen in certain difficult situations. Failure to taper steroids without relapse or development of serious side effects during induction with steroids is the typical indication for using steroid-sparing agents [62, 63]. Recent trials have even used rituximab (anti-CD 20, B-cell-depleting agent) with encouraging results [64, 65].

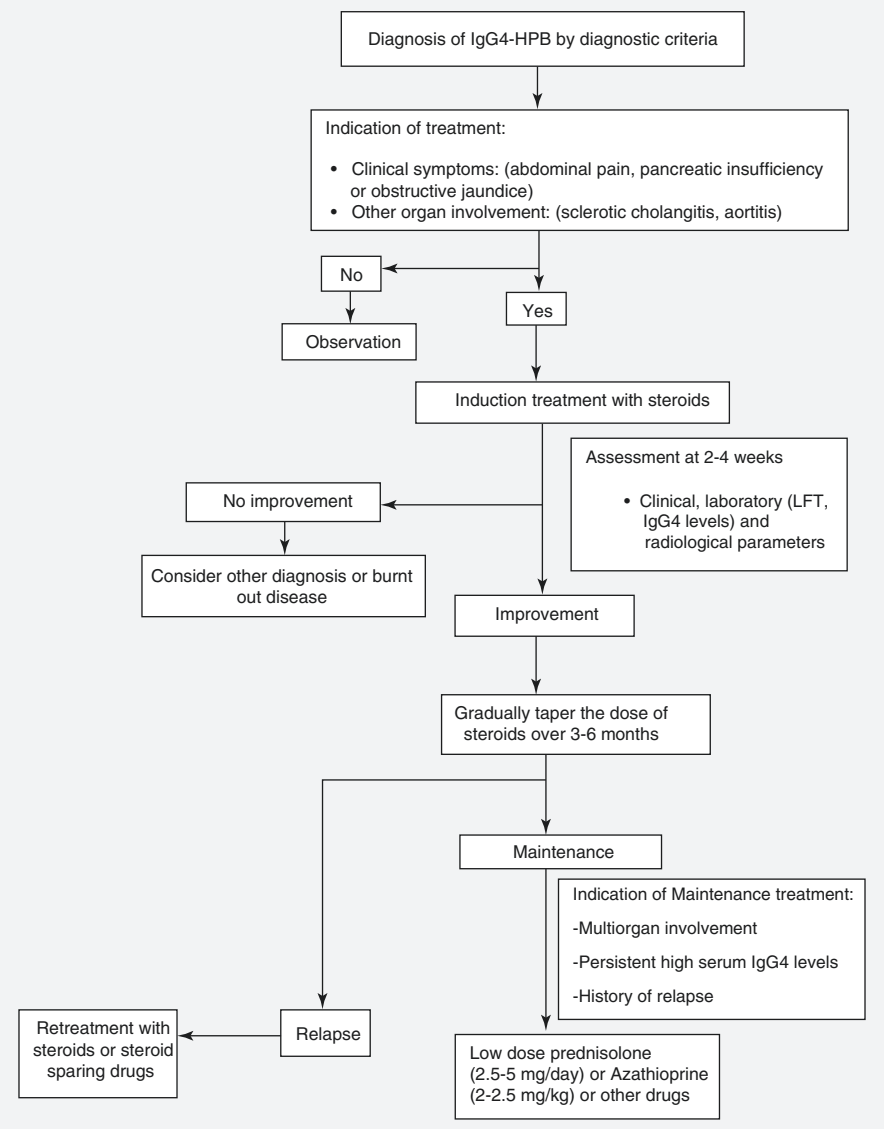


Fig. 6.6 Management algorithm in IgG4 HPB diseases

Therapy with glucocorticoids is also helpful in patients with relapse of disease. However, these patients usually require long-term maintenance treatment also apart from induction therapy.

Table 6.7 Drugs useful in IgG4 HPB diseases

• Glucocorticoids
• Azathioprine
• Mercaptopurine
• Methotrexate
• Mycophenolate mofetil
• Cyclosporine
• Cyclophosphamide
• Rituximab

Table 6.8 Response evaluation in patients on treatment

• Clinical assessment
• Liver function test
• Serum IgG4 levels
• Serum IgG4 plasmablasts
• Imaging follow-up: PET-CT

Table 6.9 Indication of maintenance treatment

• Multi organ involvement or proximal bile duct involvement
• Significantly elevated IgG4 levels
• Prior history of disease relapse

6.9.3 Maintenance of Remission

Although controversies still exist regarding the need for maintenance treatment in patients with IgG4 HPB diseases, few studies have identified certain risk factors for early disease relapse and progressive organ damage. Patients with multi-organ involvement, significantly elevated serum IgG4 concentration, involvement of proximal bile ducts, or a history of prior relapse form a group which will benefit from maintenance treatment (Table 6.9) [66]. Low-dose steroids or any of the above mentioned steroid-sparing agents can be used for maintenance treatment. Rituximab at every 6 months has also been found to be useful as maintenance treatment. Though these agents have been suggested as effective options for maintenance treatment, the exact duration of therapy is yet to be defined.

To conclude, though IgG4 HPB diseases present with a myriad of presentations and are difficult to diagnose, early therapy is associated with good outcome (Table 6.10).

Table 6.10 Key points

Clinical scenario
• Elderly male (seventh decade)
• Painless jaundice
• Pancreatic head mass
• Biliary stricture
Investigation
• IgG4 levels, IgG/IgG4 ratio, circulating plasmablasts
• Imaging (CT, MRI, PET, EUS): Enlarged sausage-shaped pancreas without MPD dilatation with or without stricture. Associated with biliary stricture
• Histopathology: Storiform fibrosis, obliterative phlebitis, IgG4 staining positive cells
Differential diagnosis
• Differentiate IgG4 SC from PSC, cholangiocarcinoma
• Differentiate AIP-1 from chronic pancreatitis, pancreatic carcinoma
Treatment
• First-line therapy for induction of remission: Glucocorticoids
• Second-line therapy for induction of remission: Immunosuppressant
• Maintenance therapy: In selected patients

Editorial Comments

IgG4-RD is a systemic disease and can affect any organ of the body. The disease is believed to be an immune-mediated inflammatory disease. It often resembles a neoplastic disease of the affected organ. While a number of things related to the disease are not clear, it has been established to be associated with IgG4 and is of B-cell origin [67] (though T cells have also been implicated [68]). In addition, plasma cells too are likely to be involved. The result is abundance of IgG4 in the serum, which is considered a biomarker of the disease [69]. IgG4 disease commonly affects the pancreas, the bile duct, and the liver in decreasing order of frequency, and the conditions are called autoimmune pancreatitis, IgG4-related sclerosing cholangitis, and inflammatory pseudotumor of the liver and bile duct.

IgG4-Related Pancreatitis (Autoimmune Pancreatitis): Two distinct forms of the disease have been described—type 1 and type 2. Type 2 disease is not related to IgG4. However, both have similar imaging features and response to steroid therapy. Type 1 disease typically affects an elderly male, the gland is diffusely enlarged on imaging, and the serum IgG4 level is grossly elevated. When all these features are present, a diagnosis of autoimmune pancreatitis can be made clinically. A histological diagnosis is necessary only in patients with atypical features such as normal IgG4 level (occurs in 20% of patients), focal pancreatitis, or any abnormal imaging feature suggesting malignancy [70]. The histological characteristics include storiform fibrosis, lymphoplasmacytic infiltrate, and obliterative phlebitis (and sometimes arteritis). A definite diagnosis can be made if these features are present with at least ten IgG4 plasma cells. The diagnosis is nearly 100% correct if the IgG4/IgG ratio exceeds 40% [50].

When a diagnosis is based on IgG4 plasma cells, one needs to be aware that even pancreatic cancer can have dense fibrosis around the tumor and IgG4 plasma cells. If the tissue is obtained from areas consisting of these, an erroneous diagnosis of autoimmune pancreatitis can be made [71]. Hence, all the features must be taken into consideration while making a diagnosis—imaging, serum IgG4 level, and involvement of other organs (known to occur in IgG4-RD). In case of doubt, a trial of steroids can be given. If the response is good, then the diagnosis is likely. However, the aim should be to not miss a malignancy.

IgG4-Related Sclerosing Cholangitis (IgG4 SC): The next common IgG4 disease affecting the hepato-pancreato-biliary (HPB) system is sclerosing cholangitis. This is a definite entity that used to be diagnosed as primary sclerosing cholangitis or bile duct cancer. However, despite increasing awareness diagnosing the condition is difficult. This is due to the non-specific nature of symptoms and the imaging. Even histological features that are pathognomonic are not always present in biopsy samples. Sclerosing cholangitis on imaging can have multiple strictures, dilatation of both the intra- and extrahepatic bile ducts resembling primary sclerosing cholangitis, mass-forming lesions with or without bile duct dilatation, and a solitary stricture of the bile duct [71]. The overwhelming majority of IgG4-SC have associated autoimmune pancreatitis. Thus, if both are present together, the sclerosing cholangitis can be labeled as IgG4 related [72]. If it is associated with high IgG level, the diagnosis is almost certain, and an invasive biopsy for histological confirmation is not necessary. In the absence of autoimmune pancreatitis, the diagnosis is based on the IgG4 level. Imaging suggesting an isolated bile duct stricture may suggest a malignancy, which then necessitates surgical exploration [70].

Histologically, involvement of the entire thickness of the bile duct in its entire course is characteristic of IgG4 SC. The lining epithelium in this disease is intact unlike in patients with PSC. The fibrosis seen in IgG4 SC is limited to the outer half of the bile duct again unlike PSC in which fibrosis starts immediately beneath the lining epithelium [70]. Both these features make histological diagnosis (on the basis of a tiny biopsy) extremely difficult.

IgG4-Related Inflammatory Pseudotumor of the Liver: The liver is also involved in IgG4-RD. In addition to PSC, a mass-forming lesion can occur in the liver in IgG4-RD—inflammatory pseudotumor. This is not a true tumor as the name suggests. It is a mass-forming lesion with dense lymphoplasmacytic infiltrate with characteristic storiform fibrosis. Other forms of pseudotumor are also known which are not IgG4 related, e.g., tuberculosis, sarcoidosis, and inflammatory myofibroblastic tumor. On imaging pseudotumors of the liver can mimic intrahepatic cholangiocarcinoma and, in the region of the hepatic hilum, a Klatskin-like tumor. In an appropriate setting, a trial of steroids may be useful.

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Chapter 7
ERCP-Induced Perforations

S. Soundappan, R. Pradeep, G. V. Rao, and D. N. Reddy

7.1 Introduction

In the epoch of minimally invasive management of biliary and pancreatic disorders, endoscopic retrograde cholangiopancreatography (ERCP) combined with endoscopic sphincterotomy (ES) has become a prevalent procedure all over the world. Even though ES is a safe procedure, it carries a small but significant number of serious complications which include pancreatitis, bleeding, cholangitis and perforation.

As per old literature, ERCP-related perforations were reported in 0.5–2.1% of sphincterotomies with a mortality rate of 16–18%. However, the improvement in the experience and skill of the endoscopy specialists combined with advancements in technology have reduced the incidence of perforation to <0.5% over the years [1].

Sphincterotomy (56%) and guidewire manipulation (23%) are widespread causes of perforations related to endoscopic retrograde cholangiopancreatography (ERCP) [2].

There is a dearth of evidence-based strategies with respect to the proper management of ERCP perforations. While one set of investigators promote on-demand conservative and surgical management, based on a clinical course, the others support operative repair in all cases on account of the complications associated with the delayed operative intervention.

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The two major factors to be considered while making the above-mentioned decision include:

1. The method of the procedure which would provide information about the exact site of perforation which include the duodenum, the common bile duct (CBD) and the pancreatic duct. Duodenal perforation requires surgical exploration, but CBD and pancreatic duct perforations can be conservatively managed.
2. The clinical status of a patient who is in generalized peritonitis should be explored [3].

ERCP can injure the oesophagus, stomach, duodenum, pancreas, bile duct and even small bowel [4–7].

7.2 Types of Injury

Stapfer proposed a classification of ERCP- and sphincterotomy-induced injuries [8]:

1. Duodenal wall
2. Sphincter of Oddi
3. Common duct injury
4. Retroperitoneal air alone

Of these, retroperitoneal duodenal perforations are the most prevalent (Fig. 7.1).

The CBD, in the upper part, lies in the free border within the lesser omentum; in the middle part, it descends behind the first part of the duodenum; and then the lower part of CBD enters the pancreas, thus forming a retroperitoneal structure. So perforation in CBD can lead to air in the retroperitoneum [9, 10].

Distal bile duct injuries, which are caused either by guidewire or by instrumentation to relieve obstruction, are often small.

Type IV injury, which has retroperitoneal air without evident site of injury, is usually due to compressed air used during ERCP, to maintain the patency of the lumen. This is not a true perforation.

7.3 Risk Factors of ERCP Perforation [11–13]

- Performance of a sphincterotomy, outside the recommended landmarks (11 to 1 o'clock)
- Pre-cut access
- Billroth II anatomy
- The intramural injection of contrast
- Prolonged duration of procedure
- Presence of periampullary diverticulum

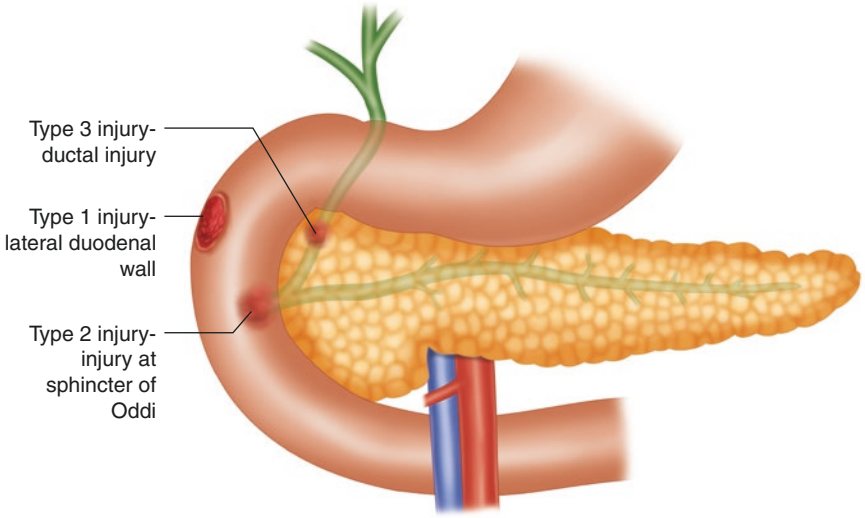


Fig. 7.1 Sites of ERCP-induced perforation as per Stapfer classification (type 4 not shown, only retroperitoneal air)

- Biliary stricture dilation
- Malignancy

7.4 Management

7.4.1 Grading

1. Mild—minimal contrast leak only which can be medically managed in a short duration of around 3 days or less.
2. Moderate—imaging-wise confirmed perforation but a more protracted course than mild category. It can also be medically managed but takes 4–10 days for recovery.
3. Severe—treatment for more than 10 days or intervention (percutaneous or surgical) [14].

7.4.2 Medical Management

Any case that is suspected to have ERCP-induced perforation is kept nil by mouth, and the gastric contents are decompressed by Ryles tube and intravenous antibiotics.

If it is predicted that a patient needs to be kept nil by mouth for a period of 5–7 days, the nutrition of the patient should be taken care by providing total parenteral nutrition in a parallel manner. In case of patients who are already malnourished, total parenteral nutrition has to be started much earlier [15–17].

When comparing the different types of perforations mentioned above, the type 1 perforation presents itself to be the most serious one and requires an early invasive treatment. This is caused by the endoscope itself and could lead to significant spillage of gastric and pancreatic juice and bile into the retroperitoneum and intraperitoneum which could result in severe necrosis of the cavities, thereby triggering sepsis and eventual death, if left undrained. These injuries usually get detected on the ERCP table either by witnessing the large gut perforation on endoscopy or by large contrast extravasation [18, 19].

The type 2 and type 3 injuries, unlike type 1 injuries, are less severe and have the tendency to heal by themselves with proper conservative management. During ERCP if there is only minimal contrast extravasation, a conservative method of treatment is followed either by checking through UGI endoscopy or by doing a double-contrast CT, after 8 h. These tests are repeated again after 48 h of the index injury. If either of these tests confirm sealing of the perforation and also if the patient is free of sepsis or any collection, then conservative management can be done. However if there is a deterioration in the clinical status of the patient or if there is a large contrast extravasation, then the patient must be taken up for surgery [20].

Type 4 injuries are usually diagnosis of exclusion. If the patient remains clinically stable with no collection or contrast leak, then conservative management can be followed. The amount of retroperitoneal air cannot be used as an indicator to predict the clinical outcome, but it only correlates with the amount of air used during the ERCP procedure [21, 22].

The management of ERCP perforation is a continuous process, and it should be upscaled whenever there is deterioration in the clinical status of the patient. The patient in this case may require surgery, until it is declared that he/she has healed, probably after 7–10 days of index injury, and evidence has been obtained that there is no leak or collection before discharge.

7.4.3 Endoscopic Methods

ESGE (European Society of Gastrointestinal Endoscopy) recommends initial endoscopic treatment when the index injury has been detected on the table [23–28]. It is because of the fact that this procedure is less invasive than surgery, and it has a good success rate [29–31]. However the success rate decreases as the time of intervention of the endoscopic procedure increases. This is because the edges of the perforation become very inflamed. The treatment advocated by ESGE is as follows.

Oesophageal perforation	
Perforation size <1 cm	TTS clips
Perforation size 1–3 cm	OTSC/stents
Gastric/duodenal	
Perforation size <1 cm	TTS clips
Perforation size 1–3 cm	OTSC with or without omental patching Or endoloop and through the scope clips used in combination

TTS through the scope, *OTSC* over-the-scope clips

If perforation is either suspected or confirmed during an ERCP procedure, it is advised to switch to carbon dioxide insufflation as it would prevent tension pneumothorax and pneumoperitoneum. It would also prevent abdominal compartment syndrome, though there is no conclusive proof for the same [32, 33].

With advances in the field of endoscope, new suturing devices are being used to suture the perforation.

Other than managing perforations, endoscopy is also being used widely to drain bile. As mentioned earlier, the gastric, pancreatic and biliary juice can escape through the perforation and cause peritonitis and sepsis. So if a type 3 (CBD) perforation is suspected, repeat ERCP with biliary stenting can be done which will divert bile into the duodenum. At the same time, the stone can also be retrieved, thereby treating the index disease and avoiding surgery. When there is a small duodenal perforation, repeat ERCP is done, and nasobiliary tube is placed so as to decrease the bile load passing across the perforation into the duodenum [23, 34–37].

7.4.4 Other Non-surgical Interventional Procedures

Fluid collections can be drained (1) percutaneously or (2) through EUS-guided enteral drainage by stenting or (3) by percutaneous transhepatic drainage [38].

Endoscopic vacuum therapy is also being used as a newer method of treatment [39]. Fibrin glue is used to close small duodenal and paravaterian perforations after the collection is managed by other means [40, 41].

7.5 Surgical Indications After ERCP-Related Perforation [42–47]

1. Large extravasation of contrast at the time of ERCP defined as incomplete dissipation of contrast after 1 min on follow-up plain film.
2. If there is only a small amount of contrast extravasation, where there is complete dissipation after 1 min of ERCP, on follow-up plain film, then a UGI with contrast injection on fluoroscopy is performed in 2–8 h. If this shows extravasation, we recommend surgical exploration.

3. Follow-up CT scan showing a collection due to perforation in the retroperitoneum or intraperitoneum.
4. Retained hardware unable to be removed by endoscopy along with perforation.
5. Massive subcutaneous emphysema.
6. Failure of conservative management.

A delay in diagnosis or in surgery will lead to death. The reason is that there is a massive autodigestion of body tissues which is due to a constant release of enzymes, and this eventually leads to sepsis.

The principle of treatment by surgery is the same as endoscopic treatment. This is done by diverting bile, enteric and pancreatic juices away from the site of perforation. However simple drainage will also cause the juices to flow through the perforation site and body cavities before draining out of the tubes [48, 49]. This could be avoided by diverting the juices through well-controlled different paths which could be done by the following procedures:

1. T-tube in CBD
2. Placement of duodenostomy tube—lateral/end duodenostomy
3. Duodenal diverticulization
4. Pyloric exclusion
5. Roux-en-Y duodenojejunostomy [50]

The disadvantage of using Roux-en-Y duodenojejunostomy is that if the edges are inflamed, then the sutures will not hold properly. However other procedures can be used even when the edges are inflamed. Even though duodenostomy appears to be simple, a part of gastric and duodenal contents pass across the perforation site. Duodenal diverticulization involves three things: (1) tube to divert duodenal and pancreatic juice, (2) T-tube in CBD to divert bile and (3) distal gastrectomy and Billroth II anastomosis to provide an alternate pathway for food and gastric juice, thereby preventing these from passing through the site of perforation. Although this procedure has been proved to be successful, it is less widely used due to its complex nature (Fig. 7.2).

Pyloric exclusion is a simpler form in which the pylorus is closed by purse string by long-standing absorbing sutures like PDS 2.0 instead of distal gastrectomy. Similar to duodenal diverticulization, T-tube drainage of the CBD and loop gastrojejunostomy are done. The duodenal perforation is closed over a duodenostomy tube (Fig. 7.3).

Whenever there is collection which is localized to the retroperitoneum, retroperitoneal surgical approach can be carried out. Advantages of this procedure are (1) it permits gravitational drainage, (2) avoids septic complication of the peritoneal cavity, (3) directs retroperitoneal necrosectomy with post-operative washes and (4) avoids complex intra-abdominal surgeries. However the disadvantage of this procedure is that it can be used only for retroperitoneal-contained perforations [51, 52].

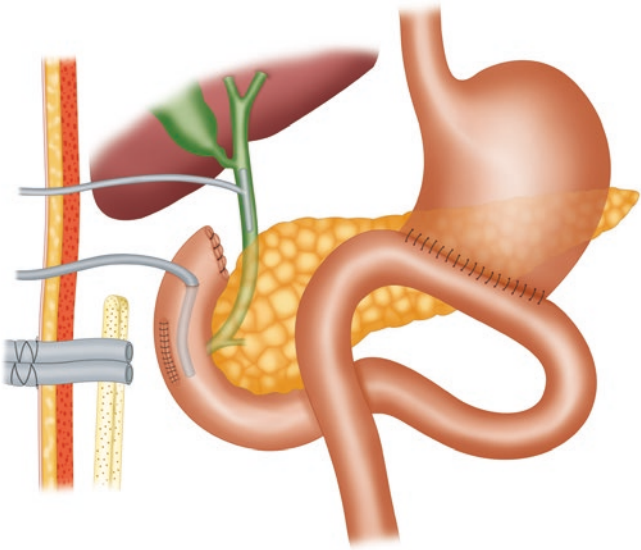


Fig. 7.2 Duodenal diverticulization

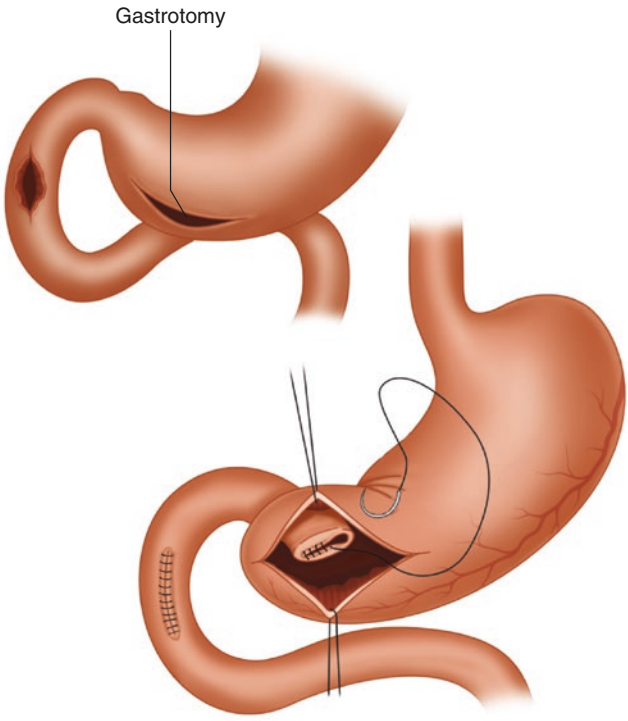
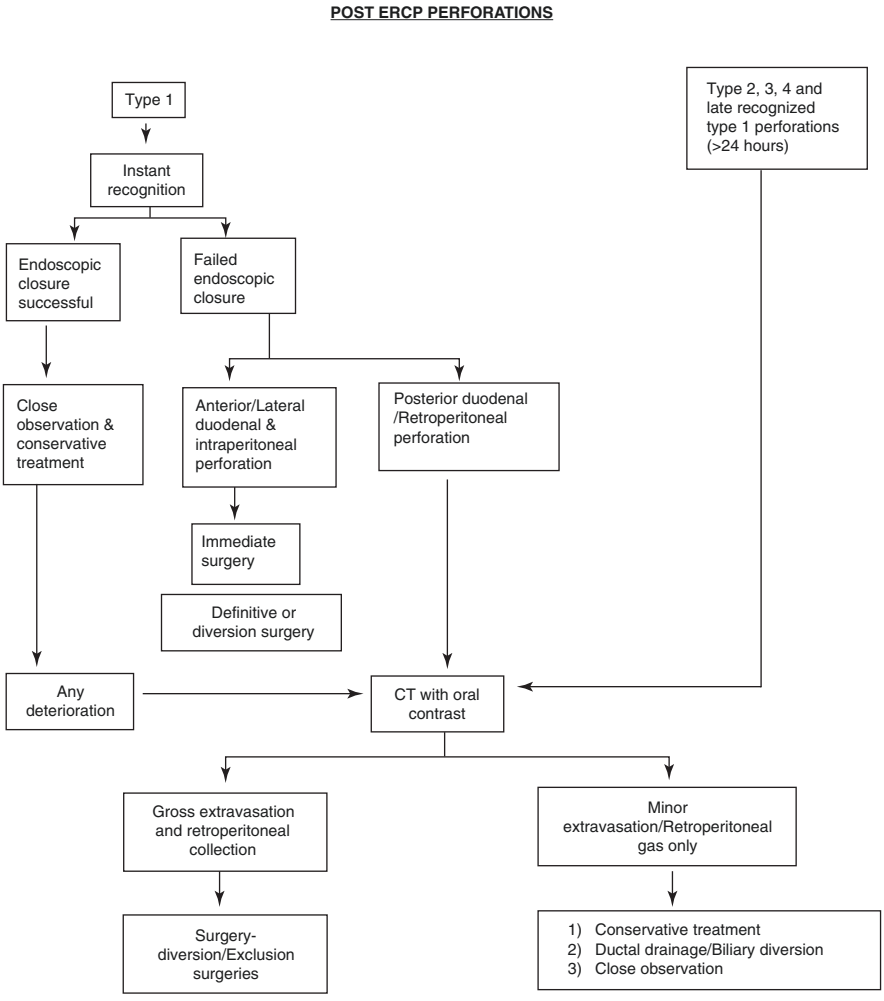


Fig. 7.3 Pyloric exclusion

7.6 Prevention

By ensuring correct ERCP technique like:

- Proper orientation of the sphincterotome and the cut is made between 11 and 1 o'clock.
- Step-by-step graded incision.
- Sphincterotomy length tailored to the pathology—size of stone in relation to the papilla and bile duct.
- Correct use of pre-cut papillotomy.
- Respect the presence of anatomical variants such as juxtapapillary diverticula and Billroth II gastrectomy.
- Use of balloon dilatation along with limited sphincterotomy will decrease the incidence of perforation [30, 53].



7.7 Conclusion

ERCP perforation is best prevented by adhering to strict protocols and techniques of ERCP. However in case a perforation occurs, guidance can be taken from clinical and radiological features regarding the type of treatment to be given to the patients. For type 1 perforations, surgical treatment is the best option, if advanced endoscopic clipping is either unavailable or unsuccessful. For type 2 and type 3 perforations, non-surgical conservative methods can be attempted. Nevertheless, the patient should be on constant observation until there is complete recovery, and surgery should be done only if there is no symptomatic improvement observed in the patient.

This also implies that not all patients with perforations post ERCP need to be explored. An initial conservative option can be tried if the site of perforation is CBD, pancreatic duct or a contained posterior duodenal wall and if the patient is stable. Initial surgery or endoscopic clipping is advocated for lateral/anterior wall of duodenal perforation depending on expertise.

Prompt surgery without delay and the intraoperative findings will determine the final outcome and morbidity as well as mortality. Delay in surgery for a patient with sepsis will increase the patient's morbidity and mortality rate.

7.8 Case Scenarios

7.8.1 Case 1

An 18-year-old female with history of laparoscopic cholecystectomy came with jaundice and fever after 3 months. MRCP was suggestive of Bismuth type 3 stricture involving confluence. A diagnosis of cholangitis was made and managed with antibiotics, and ERCP was tried to drain the system by negotiating with guidewire through the stricturous segment several times, but all attempts were in vain. PTBD of both the right and left biliary systems was done later to drain the infected bile the next day. That evening the patient complained of abdominal pain and was vomiting and had fever and tachycardia, and the abdomen was tender with guarding and no rigidity with lipase of 1800. Though pancreatitis was the first differential diagnosis, investigations were done to rule out perforation peritonitis.

CT abdomen was also done and showed retroperitoneal gas suggesting ERCP-induced perforation. So emergency exploration was done but did not reveal any perforation even after a complete search. So a drain was placed and the abdomen closed. Post-operative follow-up drains were clear and the patient improved. Retrospectively a diagnosis was made that the origin of the air was due to the entry of air through the perforation in CBD made by the guidewire which was introduced several times trying to pass through the stricturous segment during ERCP.

7.8.2 Case 2

A 45-year-old male underwent ERCP for clearance of CBD stone. The scope was passed through a duodenal peptic stricture and entered the peritoneal cavity, and significant contrast extravasation was found on fluoroscopy. The case was taken up for emergency laparotomy and CBD exploration, and primary lateral duodenal wall perforation closure with gastrojejunostomy, feeding jejunostomy and Ryles tube decompression was done. The patient recovered eventually.

Case 1 with only retroperitoneal perforation probably could have been managed by aggressive conservative treatment. Case 2 with intraperitoneal perforation could be salvaged with prompt early surgery or possibly endoscopic closure. Prompt and proper selection of treatment modality is important for better outcome.

Editorial Comments

Every intervention has some complication with its use. Endoscopic retrograde cholangiopancreatography (ERCP) is no exception, and it can be associated with significant morbidity and even mortality. The most common complications of ERCP are bleeding, pancreatitis and perforation. The last one is the focus of this article. I will restrict myself to the risk factors related to this complication and discuss measures to reduce the risks.

Perforation after ERCP is a dreaded complication as its effects can be devastating. Most perforations occur due to trauma at the time of manipulation of the endoscope or the guidewire or at the time of doing a sphincterotomy.

The incidence of ERCP-related perforations has been reported to be <1% with a mortality of approximately 10% [54]. Different types of perforations have been described based on the mechanism causing the injury. These are:

1. Type 1 perforations (duodenal wall): occur due to the shearing force or angulation of the tip of the endoscope
2. Type 2 perforations (periampullary): occur due to sphincterotomy incision extending beyond the intra-duodenal part of the duct
3. Type 3 perforations (ductal origin—bile or pancreatic duct): occur due to extra-advancement of wires into the duct(s)
4. Type 4 perforations (retroperitoneal air): are usually related to sphincterotomy when a minute leak allows air to escape into the retroperitoneum

Vezakis et al. [55] in a systemic review of 142,000 ERCPs reported type 1 perforations in 25%, type 2 perforations in 46% and type 3 perforations in 22%. The risk factors related to ERCP perforations have been mentioned by the authors. One should keep these in mind and take suitable measures so that the risk of perforation is minimized if not avoided all together. In addition it is important to get an informed consent after a detailed discussion with the patient before the procedure, especially if one or more of the risk factors are present.

Minimizing the Risk of a Perforation: Type 1 perforations are common in patients of Billroth II gastrectomy and in elderly people. This is due to the absence of a normal gastroduodenal axis following a Billroth II gastrectomy. In elderly patients, the bowel wall is more fragile and immobile. In patients who have undergone a previous Billroth II gastrectomy, it is useful for the endoscopist to orient oneself with the biliopancreatic limb of the anastomosis using a forward-viewing endoscope before inserting the side-viewing endoscope. For elderly patients, it is necessary to be extremely gentle during each manoeuvre of endoscopy [54]. Type 2 perforations can be prevented by a controlled sphincterotomy. The length of the cutting wire in contact with the ampulla should be minimal, and the incision should be made in a stepwise manner [56]. The force and direction of the cut should be guided by the right hand of the endoscopist using counterclockwise manoeuvres. Also cutting devices that use alternating current have been shown to reduce type 2 injuries [57].

Type 3 injuries are presumed to be due to poor understanding or concentration of the operator while using a wire in the pancreatobiliary ductal system. Therefore it is essential for the endoscopist to be familiar with the anatomy of the ductal system. It is best to keep track of the position of the wire. When resistance is encountered, it is best to not advance the wire blindly.

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Chapter 8
Bridging Therapy for HCC

Shailesh Sable and Vinay Kumaran

8.1 Introduction

Liver transplantation (LT) for hepatocellular carcinoma (HCC) has evolved from contraindication in the early 1990s to one of the common indications in today's era. A lot of credit goes to the Milan criteria (1 lesion up to 5 cm, 2–3 lesions up to 3 cm) for setting up this bench mark based on the seminal publication by Mazzaferro et al. nearly two decades ago [1]. LT provides good 4-year survival rates (actuarial rate 74%) with low recurrence rates (recurrence-free survival rate of 83%) if performed for HCC within these criteria [1]. Liver transplant (LT) has a dual advantage as treatment; it is not only oncologically the best operation but it also cures the underlying cirrhosis. In view of long wait times (due to shortage of organs) and high dropout rates (tumour progression/death), the practice of bridging (loco-regional) therapy is becoming an essential part of HCC treatment. In this chapter we will discuss available evidence on the efficacy of bridging therapy for HCC. We will also discuss the current role of downstaging in the management of HCC. Towards the end we would like to highlight the role of bridging therapy in the Indian scenario and also touch upon guidelines from Asian countries.

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8.1.1 Definition of Bridging Therapy for HCC

The use of locoregional therapy (LRT) (on DDLT [deceased donor liver transplant] wait-listed patient) either in isolation or in combination is used to induce tumour necrosis and inhibit tumour progression beyond the standard criteria for liver transplant (Milan criteria) [2]. On the other hand, downstaging is defined as use of LRT to bring patients whose tumour burden is outside standard (accepted) criteria to within acceptable criteria [3].

8.1.2 Aim of Bridging Therapy

The primary aim is to reduce the dropout rates due to tumour progression. The secondary aim is to improve post-transplant overall survival (OS) and disease-free survival (DFS). It can also serve as a valuable tool for assessing tumour biology before liver transplant.

8.1.3 Types of Bridging Therapy

Radio-frequency ablation (RFA), transarterial chemoembolisation (TACE), transarterial radioembolisation (TARE), liver resection (LR), microwave ablation (MWA), percutaneous ethanol injection (PEI), irreversible electroporation (IRE) and high-intensity focused ultrasound (HIFU).

8.2 Locoregional Therapy as Bridge to Liver Transplantation

An international consensus report recommends LRT for patients with HCC (T2, Milan criteria) awaiting LT for more than 6 months [4]. However in clinical practice due to unpredictable waiting time and risk of tumour progression, most patients will be subjected to some form of LRT based on the tumour characteristics, patient fitness, stage of liver disease (Child scores/MELD scores) and centre experience.

8.3 T1 HCC (1 lesion <2 cm)

Patients with T1 HCC on wait list (for other indications, listing not based on priority points and unresectable) pose a major dilemma over addition of LRT while waiting. As per AASLD (American Association for Study of Liver Disease) guidelines,

patients who develop T1 HCC who are already on wait list should be managed with observation only [2]. This recommendation was based on the retrospective study by Mehta et al., who proposed "wait and not ablate" policy [5]. This was based on the principle of acquiring bonus MELD points by allowing T1 HCC to progress to T2 HCC (Milan criteria). In addition to the above, approximately 31% of the patients transplanted for T1 HCC turn out to be non-HCC on explant histology [6]. During the observation period (median follow-up 2.4 years), 87% progressed from T1 to T2, 5.3% remained at T1 and 5.3% progressed from T1 to beyond T2 HCC. The wait list dropout rates were 4.5%, 7.1% and 15.6% within 6 months, 1 year and 2 years, respectively. The 1- and 3-year survival was 94.5% and 74.5%, respectively. The authors concluded that "wait and not ablate" approach is acceptable strategy as the chance of tumour progression beyond T2 HCC is <10%. However they recommended LRT for patients with high AFP (>500 mg/dL) or rapidly growing HCC (defined arbitrarily as increase in size by >1 cm within 3 months). On the other hand, if the patient has T1 HCC without any decompensation (low MELD score, unresectable), it would be worthwhile to consider LRT as it will not only prevent disease progression but it may even be curative in some (smaller lesions <2 cm). Huo et al. reported lowest dropout rates with RFA; the tumour progression rates were lowest in the RFA group (5.3% for T1 and 6.8% for T2 at 6 months). Since most of the patients in this group were hepatitis B-related cirrhosis, the risk of HCC (recurrence) remains to be high suggesting probability of requiring LT in the future [7]. In the Indian scenario, considering the limited number of organ donations and non-availability of priority points for HCC (unresectable), it appears wiser to bridge these patients with LRT while awaiting a liver.

8.4 T2 HCC (1 lesion ≤5 cm or 2–3 lesion none >3 cm; Milan Criteria)

The AASLD guidelines recommend bridging therapy for T2 HCC (Milan criteria) to reduce disease progression and hence reduce the dropout rates [2]. The idea here is to prevent disease progression (or wait list dropout) beyond T2 in order to keep patient on waiting list for LT and avail extra points (every 3 months). Now without LRT the reported dropout rates could be as high as 25% (6 months) and 38% (1 year) [8–10]. There are no randomised clinical trials available to answer this question. However there are comparative and non-comparative studies available to address this issue albeit with lot of heterogeneity (significant risk of bias). As per the analysis of comparative studies (transplant alone versus transplant with bridge therapy), there were lower dropout rates due to progression and all cause in the bridging group (relative risk [RR] 0.32 and 0.38), but the difference was non-significant statistically [11–14]. The post-transplant 1-, 3- and 5-year survival rates were also statistically not significant between the two groups (RR 1.01, 0.88 and 1.01) [11, 15–18]. The post-transplant 1-, 3- and 5-year recurrence and recurrence-free survival rates were also statistically non-significant between the two groups (RR 1.01, 1.07 and 0.92) [11, 15–18]. Based on the above results, it would

be safe to presume that patient chosen for LRT group (no randomisation prone for selection bias) with probably more advanced tumours, longer wait times and potentially bad tumour biology did as well as non-LRT group (tumours with no high-risk factors). The UCSF (University of California, San Francisco) group published their non-comparative data in 2012 using LRT in 96.1% of recipients on wait list. They showed use of bridge therapy (LRT) is associated with low dropout rates at 6 months (8.7%) and 12 months (22.9%), respectively [19]. As per the older SRTR (Scientific Registry of Transplant Recipients) data reported by Freeman et al., the post-transplant survival rates were 79% versus 75% ($P = 0.03$) for those who underwent LT with LRT versus LT alone. The main limitations of this study were small sample size, and it reported only 3-year survival rates (post MELD era recipients only) [20]. In summary, it can be safely concluded that the data available on bridging in T2HCC remains to be of low quality with a trend towards non-significant improved wait list and post-LT outcomes. Based on the available evidence, it appears reasonable to offer bridge therapy to patients with projected wait times of ≥6 months [4].

8.5 Downstaging Before Liver Transplant (Beyond Milan Criteria but Within UCSF [21])

An international consensus report recommends modest expansion of Milan criteria based on several studies showing comparable results [4]. The idea was to include more patients with HCC to have LT without compromising outcomes and affecting the wait list dynamic. UCSF criteria [21] (University of California, San Francisco) provide good post-LT outcomes, but could only benefit an extra 2.9% cases of HCC [22]. The consensus also recommends considering transplant for patients with worse prognosis outside Milan criteria provided the wait list dynamics allow it without undue prejudice to other recipients with better prognosis [4]. So in order to keep our bench mark high and at the same time allowing more HCC patients to benefit from LT, downstaging has evolved as an option. Although a controversial idea, the main principle of downstaging is to select a subset of HCCs with favourable biology that are likely to remain stable for a longer time and provide good post-transplant outcomes. At this stage there are several key questions that remain unanswered. (1) What should be the entry criteria (number of tumours, size of tumours, level of AFP, etc.) and exit criteria? (2) How to define an optimum response to therapy? (3) Ideal observation period after downstaging? (4) Should they even be transplanted when they are beyond standard criteria? In one of the first prospective studies on downstaging, the UCSF group defined entry criteria (1 lesion >5 cm and ≤8 cm, 2 or 3 lesions at least 1 >3 cm but ≤5 cm with total tumour diameter of ≤8 cm or 4 or 5 nodules all ≤3 cm with total tumour diameter ≤8 cm), response criteria (downstage within Milan criteria) and minimal observation period of 3 months. Using LRT (TACE, RFA or combination), 70% were successfully downstaged, and 53% underwent transplant (DDLT). The intention-to-treat (ITT)

survival rates were 89.3% and 81.3% at 1 and 2 years, respectively [23]. There was no recurrence at median follow-up of 16 months. Subsequently in 2015, the UCSF group came up with long-term ITT outcomes in 118 patients downstaged within Milan criteria (compared to 488 patients meeting Milan criteria without LRT) [24]. In the downstaging group, 54.2% underwent LT, and 7.5% developed recurrence. The dropout rates were higher in the downstaging group (35% at median of 8.2 months) compared to T2 group ($P = 0.04$). The Kaplan-Meier's 5-year post-transplant survival and recurrence-free probabilities were 77.8% and 90.8% versus 81% and 88%, respectively, in the downstaging group versus the T2 group ($P = 0.69$ and $P = 0.66$) [24]. The authors concluded that comparable outcomes can be achieved with downstaging for tumours beyond Milan criteria compared to no therapy in Milan criteria. High AFP (>1000 mg/dL) (HR 3.3, $P < 0.001$) and Child's B/C (HR 1.6, $P = 0.04$) liver disease was associated with higher dropout rates. The following two comparative studies have significant heterogeneity and high risk for bias but are worth mentioning in view of paucity of data. In a comparative study by Heckman et al. [25] which included 123 patients undergoing LT over 6 years, 50 patients received LRT before LT, and 73 underwent LT without LRT. Twelve patients (>T2, 24%) were successfully downstaged and underwent LT. The overall survival in this study at 1, 3 and 5 years were 81%, 74% and 74%, respectively. The downstaged patients did not have significant survival difference compared to non-responders and no therapy patients [25]. A retrospective study by Holwoko et al. [26] compared patients with or without TACE who exceeded Milan criteria on explants in 143 HCC cases [26]. The reported post-transplant outcomes were similar in both groups. In a recent multicentre study (2017) [27], Mehta et al. looked at 187 consecutive HCC patients enrolled for downstaging (3 centres in region 5 of the USA). LT was performed in 58% patients after successful downstaging with 32% dropout rate (due to progression). Based on Kaplan-Meier analysis (median follow-up of 4.3 years), 95% and 80% of patients would survive at 1 and 5 years, respectively. The recurrence-free survival probabilities at 1 and 5 years were 95% and 87%, respectively. There were no centre-specific differences in survival rates on ITT ($P = 0.62$), indicating replication of the UCSF experience to other centres as well [27]. In a systematic review and pooled analysis by Parikh et al. [28] in 2015, the success rate of downstaging protocols was more than 40% with post-LT recurrence rates at 16%. Just to highlight a few issues discussed in this analysis, (1) the baseline tumour burden varied from within UCSF to cases with tumour thrombus, (2) response assessment reporting varied from using entire lesion size to viable tumour size, (3) variable mandatory wait times to no report on wait times and (4) lastly tumour burden (at entry), liver function and wait times were not consistently reported in studies. Another important finding of this analysis was that they found no difference in the outcomes based on modality used (TACE versus TARE) [28]. In a recent AASLD guideline [2] on HCC, nearly two-third of non-comparative studies reported post-LT average recurrence rates of 20.4% (CI 0.15–27.7) and 5-year overall survival rates (OS) of 77.6% post-LT [2]. In summary, patients with HCC successfully downstaged had post-transplant survival comparable to those meeting Milan criteria without downstaging. Downstaging allows selection of

subgroups of tumours with favourable biology which do well after LT. It appears that the available evidence can be safely extrapolated to countries with predominant living donor programmes or programmes with scarce deceased donors in order to recruit more HCC patients for LT.

8.6 LRT for Tumours Beyond Milan and UCSF Criteria (Defining Upper Limits)

Tumour size and number are surrogate markers of tumour biology. Not all HCCs within Milan criteria have good biology, likewise not all HCCs outside UCSF criteria have bad biology. So, it would always be worth exploring the ideal criteria, which allows more HCCs to get curative therapy. After the success of their downstaging protocol, the UCSF group further stretched their indication for downstaging to beyond UCSF criteria (all-comers group). Rassiwala et al. [29] compared the ITT and post-LT outcomes between the all-comers group ($n = 74$) and the UCSF downstaged (DS) group ($n = 133$). A minimum 6-month observation period was mandatory post downstaging. The rate of successful downstaging to Milan criteria was 65% and 84%, respectively, for all comers versus UCSF ($P = 0.002$). The success of downstaging (all-comers group) was negatively influenced by increasing sum of largest tumour and number of tumours (HR 0.87, $P = 0.04$). The cumulative probability for dropout was higher in all-comers group 80% versus 36% at 3 years. ($P < 0.001$). The 5-year ITT survival rates were lower in the all-comers group (21% versus 56%, $P < 0.001$). The post-LT survival for all-comers group was 50% versus 79% in UCSF-DS group ($P = 0.51$) [29]. Although the idea may be controversial in the setting of cadaveric donor LT, it might work well in the LDLT scenario provided the principle of double equipoise is fulfilled. In summary, baseline tumour burden has an optimum limit beyond which downstaging doesn't work, and LT may not be justifiable. However while making decisions, it should be kept in mind that tumour biology is the criterion rather than size and number when it comes to recurrence and overall survival. Some single large tumours represent good tumour biology in that they have not metastasised despite reaching a large size.

8.7 Response to LRT as a Prognostic marker (and Selection Criterion)

The concept of response to therapy translating into good prognosis is very appealing in culling out patients from unnecessary resource utilisation, especially in resource-limited countries where organ donation rates are low. In a study by Otto et al. [30], the role of TACE was evaluated in selecting HCCs suitable for LT. RECIST (response evaluation criteria in solid tumours) criteria were used to define response and progression. Response was defined as 30% reduction in sum of the largest diameter of

the tumour nodules. And those who developed 20% increase in the sum of largest tumour diameter or developed new lesions were excluded from LT. A total of 96 patients underwent TACE, out of which 34 (35%) were within MILAN and 62 (65%) patients exceeded Milan criteria. Of the 50 patients who underwent LT, 34 exceeded Milan criteria with 5-year OS of 80%. Recurrence-free survival was 94.4% in recipients who had progress-free TACE (n = 39; P = 0.006) during waiting. Recurrence rates were higher in those who after initial response had progressed before LT (freedom from recurrence 35.4%; P = 0.001). Authors concluded, sustained response to TACE is a better selection criterion for LT than initial tumour size and number [30]. Subsequently Millonig et al. [31] in 2007 published a prospective study investigating the role of pre-LT-TACE on long-term survival of 116 patients. Again RECIST criteria were used to define and grade the response (CR [complete response]. no viable tumour; PR [partial response], devascularisation of ≥30%). Based on ITT analysis, 1-, 2- and 5-year survival rates for CR and PR were 100%, 93.2% and 85.7% and 93.8%, 83.6% and 66.2%, respectively. Whereas in the no-response or the progression group, the 1-, 2- and 5-year survival rates were 82.4%, 50.7% and 19.3%. Based on post-LT survival analysis, 1-, 2- and 5-year survival rates in the CR and PR groups were 89.1%, 85.1% and 85.1% and 88.6%, 77.4% and 63.9%, respectively, whereas in the no-response or progression group, the 1-, 2- and 5-year survival rates were 68.6%, 51.4% and 51.4%. On further subgroup analysis, the benefits of TACE were only noticed in patients within Milan criteria [31]. In summary, response to LRT for HCC within or outside Milan criteria may serve as a prognostic marker for improved post-LT outcomes and as a selection criterion for LT.

8.8 Ideal Bridge Therapy (No Consensus)

Based on the available evidence on LRT, no consensus can be made over preference of one LRT over other [2, 4]. Since the indication for different LRT differs based on location of tumour, size of tumour, stage of liver disease (Child/MELD status) and available expertise of centres, it would be very difficult to conduct a randomised controlled trial. Over all TACE is common LRT, but RFA scores over it marginally in terms of tumour necrosis [32, 33]. In various non-comparative studies using various forms of LRT (RFA, TACE, etc.), multi-therapies reported the highest overall 5-year survival rates [2]. However it should be noted that the studies were not compared with historical controls, and since they are non-comparative, some of the patients included were non-transplant candidates (selection bias).

8.9 Bridging Therapy in Indian Scenario (No Data Available)

The data on wait list mortality, average wait time and post-transplant outcomes in HCC from India are not available in literature. Wait times and dropout rates are expected to be variable in different states based on their organ donation rates and

differences in minimal listing criteria. Organ donation rates in India were 0.5 PMP in the year 2015 [34], abysmally low to justify DDLT for HCC's beyond standard criteria. Deceased donors in India are allocated based on in-house priority (donor hospital), waiting period or institutional rotation. Except for the fulminant liver failure cases, there are no guidelines available to prioritise HCC patients on the DDLT wait list. Role of bridging therapy in India would be very selective as majority of the patients would receive LDLT. [35] The criteria for transplantation are variable among different centres; some of the centres offer LT to HCC beyond UCSF criteria. [36] However majority of the DDLT programmes in India follow the UCSF criteria [37]. In view of the above, there is no specific trend for wait time statistics available for HCC patients. Hence it appears a reasonable strategy to subject all the wait-listed HCC patients to some form of bridge therapy while waiting for the organ. Another indication for bridge therapy would be recipients waiting for availability of suitable living donor especially if the projected wait is more than 3 months. This situation arises if the prospective donor has a fatty liver and needs time for weight loss and dietary modification to reverse it. The INASL (Indian National Association for Study of the Liver) task force [38] on HCC made following consensus guidelines based on the literature available: (1) T2 HCC patients awaiting DDLT should be offered bridging therapy, (2) patients beyond conventional criteria can be offered LDLT with guarded prognosis (anticipating 50% recurrence rates) and (3) patients beyond conventional criteria can be offered DDLT after downstaging (if LDLT is not an option) [38]. Although the INASL consensus statements were not based on the evidence available from Indian literature, it can still form a baseline for setting up our own protocols in future. Downstaging appears a reasonable approach to cull-out patients beyond UCSF having bad tumour biology in the LDLT setup. In summary, currently no recommendations can be made on bridge/downstaging therapy in HCC awaiting LT in India due to paucity of data. However it appears reasonable to follow the guidelines laid down by international societies till substantial data is available in future.

8.10 Guidelines from Asian Countries on Bridge/ Downstaging Therapy for HCC

1. The Korean Liver Cancer Study Group and National Cancer Centre (KLCSG-NCC) recommends bridging therapy whenever the wait times are unpredictable and considers downstaging therapy in appropriate situations [39].
2. The Taiwan Liver Cancer Association predominantly favours liver resection as the treatment of choice for HCC even if it meets Milan criteria. Salvage liver transplant is offered in the event of recurrence or liver failure. The Taiwanese group did not focus upon the role of bridging therapy or downstaging in their recent guidelines on management of HCC [40].
3. The Japanese Society of Hepatology (JSH) does not provide any recommendation on bridge therapy in wait-listed patients. JSH also adds that the current

evidence is insufficient to recommend downstaging for HCC beyond standard criteria. One of the reasons for this is that JSH recommends LT only in HCC within Milan with Child C (preferentially) status and age <65 years [41].
4. The recent Asia-Pacific Clinical Practice Guidelines (APASL) do not provide any recommendation on LRT either as a bridge or as a downstaging therapy [42].
5. The recent review on Chinese guidelines on management of HCC also does not provide any information on the use of LRT as a bridge/downstage therapy [43].

Most of the above countries have predominantly living donor programmes, and there is no consensus on minimum acceptable recurrence rates and survival rates for expansion of criteria for HCC to justify the principle of double equipoise. It would be very difficult to conduct randomised studies on bridge/downstaging therapy in the LDLT scenario. Justifying bridge/downstaging therapy in LDLT is a conundrum because at present we do not know when the good biology may turn into the bad one while waiting. The possibility of a tumour spreading while we're waiting for tumour biology to become apparent is a very real one.

8.11 Take-Home Messages

Based on the best available evidence and guidelines:

1. Patients within Milan criteria (T2 HCC) should be offered bridge therapy if the probability of waiting time is more than 6 months.
2. Patients beyond Milan criteria (but within UCSF) can be considered for downstaging within Milan criteria.
3. Current evidence does not prefer one LRT over other for bridging or downstaging. Decision should be based upon size of the tumour, location of tumour, status of liver disease, centre experience, etc.

Editorial Comments
Liver transplantation, as has been mentioned by the authors, is curative for liver cancer in patients with cirrhosis as it removes the cancer as well as the cirrhotic liver in which the tumour developed (as long as the patient meets the criteria for liver transplantation). Due to a shortage of donors, not all eligible patients can undergo liver transplantation. During the waiting period, the tumour can progress and render the patient unsuitable for transplantation. Bridging treatments have been introduced to slow down or reverse progression of the disease. This can avoid patients becoming unsuitable for transplantation. Dropout rates have been reported to be related to tumour size >3 cm and waiting time exceeding 3–6 months [44]. Other risk factors are multiple tumours, alphafoetoprotein levels >200 mg/mL and ineffective bridging therapy [10].

A number of studies have shown that bridging therapy can decrease the dropout rate [45–47]. One study showed complete response to bridging therapy (non-surgical) in nearly half the patients [45]. Locoregional bridging therapy has been variously reported to improve post-transplant survival. While Terzi et al. [48] showed better survival, another large study did not support this view [49]. If at all, the survival improves, it is limited to patients who have a complete pathological response following locoregional therapy [49, 50].

Various options are available for bridging therapy as the authors have enumerated. These can be surgical (resection) or non-surgical. There are multiple non-surgical options and include transarterial chemoembolisation (TACE), transarterial radioembolisation (TARE), radiofrequency ablation (RFA), percutaneous ethanol injection (PEI), microwave ablation (MWA), high-intensity focused ultrasound (HIFU), stereotactic body radiotherapy (SBRT) and sorafenib (as an adjunct to other modalities such as TACE). The pros and cons of these modalities are listed below.

Modality	Pros	Cons
Liver resection	Can be curative, transplantation can be done if tumour recurs	Most expensive, high complication rates, only compensated cirrhotics suitable
TACE	Most common bridging option, most effective non-surgical method, can treat multiple tumours, efficacy improves with super selective technique	Cannot be done in the presence of portal vein thrombosis, hepatic arteriovenous fistula and ascites
TARE	Efficacy as good as TACE if not better, can be done even when portal vein is thrombosed	Restricted availability, costly
RFA	Very effective for tumours ≤3 cm	Risk of bleeding, not suitable for tumours near the gall bladder, blood vessels, bile ducts
MWA	Similar efficacy as RFA if not better, can be done even near a blood vessel	Limited experience, cannot be done for lesions near the gall bladder and bile ducts
SBRT	Suitable for lesions near bile duct	Bowel perforation is a risk
HIFU	Suitable for patients with portal vein thrombosis	Cannot be done for lesions near bile duct
PEI	Suitable for small lesions, near the gall bladder	Not as effective as RFA
Sorafenib	Delays progression of disease (inhibits angiogenesis), better efficacy when used with TACE, TACE causes necrosis by embolising feeding vessel and sorafenib prevents angiogenesis	Limited studies and not used for bridging as sole agent, has been used with TACE

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Chapter 9
Adjuncts to Liver Resection

Ragini Kilambi and Senthil Kumar

9.1 Introduction

Liver resection is based on a sound understanding of segmental anatomy which essentially defines the relationship between elements of the vasculobiliary tree and its associated parenchyma, made largely of organized cords of hepatocytes. Carl Langenbuch is credited with performing the first elective liver resection in 1888. The initial approaches focussed on directly splitting the parenchyma by mechanical means (finger 'fracture' or 'Kelly-clysis') with bleeding controlled by sutures as it arose. Pringle, in 1908, reported temporary occlusion of vascular inflow at the porta as a means of reducing blood loss while transecting the liver.

During the early days of liver surgery, perioperative mortality from major liver resections, which was performed only in selected specialized centres, was in the range of 50%. In modern surgical practice, this has been dramatically reduced to less than 5%. Advances in anaesthesia, asepsis, transfusion medicine and perioperative intensive care have all had a vital contribution in making resection safe and more widely available. From the surgical point of view, three factors have changed both surgeon performance and patient outcomes: (1) better patient risk profiling leading to better patient selection and preoperative optimization; (2) refinement and standardization of the techniques of vascular control, haemostasis and transection; and (3) technological advances that have made a wide array of gadgets available that assist, directly or indirectly, a quick and safe resection.

For the purpose of this review, technical adjuncts are those that are either specialized modifications of standard surgical steps or conditions under which surgery is performed. Technological adjuncts cover those that use special gadgets or interventions that make liver surgery safe, quick or precise (Table 9.1). However, the combination of resection and ablative techniques, such as RFA, for bilobar lesions,

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Table 9.1 Adjuncts in liver resection

• *Technical adjuncts*
– Vascular control
Pringle
Outflow control
In situ perfusion
– Low central venous pressure (CVP)
– Associating liver partition and portal vein ligation for staged hepatectomy (ALPPS)
• *Technological adjuncts*
– Transection (energy sources)
Cavitron ultrasonic surgical aspirator (CUSA)
Waterjet
Harmonic scalpel
LigaSure
Radiofrequency ablation (RFA)
Microwave
Saline-linked radiofrequency sealing device (Aquamantys, TissueLink)
Staplers
Diathermy—monopolar/bipolar
– Haemostasis
Systemic
Topical
• *Miscellaneous*
Preoperative imaging
Preoperative optimization
Portal vein embolization (PVE)
Biliary drainage
Intraoperative techniques
Intraoperative ultrasound-directed surgery
Indocyanine green (ICG)-assisted liver surgery

although could be construed as adjuncts is beyond the remit of this review. Similarly, the advances in preoperative imaging and the various techniques of screening for bile leak at the end of the transection are not discussed.

9.2 Technical Adjuncts

9.2.1 Vascular Control

9.2.1.1 Vascular Inflow Occlusion

Mass clamping the portal triad at the hepatoduodenal ligament which shuts both the portal venous and hepatic arterial flow (vascular inflow occlusion) is a useful adjunct in liver resection. This was first described by Hogarth Pringle from Glasgow in

1908, who applied this, in the setting of liver trauma. The Pringle manoeuvre could be applied in a continuous or intermittent fashion and in both normal and cirrhotic livers. The technique involves encircling the hepatoduodenal ligament with a tape, the free ends of which pass through a piece of rubber tubing which gently tightens the loop snugly around the hepatic pedicle.

Although the maximum recorded ischaemic times for continuous and intermittent Pringle in noncirrhotic livers are 90 min and 348 min, respectively, a more conservative approach is used in actual practice [1, 2]. The maximum reported cumulative ischaemic time after intermittent Pringle in a cirrhotic liver is 204 min [3].

Intermittent Pringle, employed in consecutive cycles of occlusion and release, is the most widely used technique. The most common practice is to use intermittent clamping (ischaemia) for 15 min followed by a declamping (reperfusion) interval of 5 min. There is, however, a wide variation in the period of ischaemia (10–30 min) and the reperfusion (3–10 min) used in practice. Continuous Pringle may be used for up to 90 min in healthy livers (noncirrhotic, nonsteatotic, noninflammed, non-cholestatic) and up to 50 min in diseased livers (including cirrhotic) [4].

The consensus is that intermittent Pringle is better tolerated than continuous Pringle, especially in diseased livers. Ischaemic preconditioning (IPM), in which a short period of ischaemia (10 min) followed by reperfusion (10 min) is performed before an intended longer period of ischaemia (<75 min of continuous Pringle), protects the liver by attenuating the reperfusion injury [4, 5]. Cirrhotic livers and steatotic livers benefit more from IPM.

9.2.1.2 Total Vascular Exclusion (TVE)

Tumours involving the confluence of hepatic veins or the cava are not usually resectable by conventional techniques, as this requires a complete asanguinous field and often involves vascular reconstruction. TVE makes this feasible and involves a controlled occlusion of inflow as well as the outflow. The inflow occlusion is as for a standard Pringle. The outflow occlusion has two variants—(1) with caval occlusion which involves clamping the supra and infrahepatic cava and (2) without caval occlusion, which involves clamping the hepatic veins. Caval occlusion needs a veno-venous bypass to preserve haemodynamic stability. The portal flow is also diverted by a portosystemic venous bypass. The safe time up to which the liver tolerates ischaemia during TVE is about 60 min [4].

9.2.1.3 Total Vascular Exclusion + In Situ Cold Perfusion

The limitation of TVE alone is that hepatic warm ischaemia beyond 60 min exponentially increases the risks of post hepatectomy liver failure (PHLF) and influences mortality. The cytoprotective effects of core visceral hypothermia when

combined with TVE results in the extension of the safe time available by a few hours, as cold ischaemia is better tolerated than warm ischaemia. In situ cold perfusion is accomplished by cannulating the gastroduodenal artery for arterial perfusion and the portal vein for portal perfusion. There also needs to be a caval vent as an outlet to drain the effluent. Systemic and portal veno-venous bypass should be in place.

9.2.1.4 TVE + Ante Situm Resection

Ante situm resection is a technique which disconnects the outflow while retaining continuity of the inflow. After infrahepatic caval control, the suprahepatic cava is cut below a clamp, and this allows the liver to be delivered close to the wound. The inflow control, cold perfusion and veno-venous bypass are standard. The advantage of this technique is that it provides the much needed mobility and access to the liver while keeping the inflow structures in continuity. Elimination of the need to transect and later anastomose the inflow structures reduces morbidity.

9.2.1.5 Ex Vivo Resection

This is an extension of the above techniques and involves an explant of the liver with or without the cava. Cold perfusion with a preservation solution protects the liver when the resection is being carried out on the bench. The liver is later autotransplanted applying the transplant techniques. Morbidity and mortality of ex vivo resection are high, as often the remnant is small and involves vascular and biliary reconstruction. There should be a backup plan of salvage liver transplantation when contemplating ex vivo resection.

9.2.2 Low Central Venous Pressure (CVP)

Although the practice of maintaining a low CVP in liver surgery has not been directly linked to a reduced morbidity, it is known that perioperative blood transfusion is associated with adverse postoperative and oncological outcomes after liver resection [6]. Maintaining a low central venous pressure (CVP) of under 5 mmHg, during parenchymal transection, reduces blood loss and need for blood transfusion. This is often done by a combination of strategies by the anaesthetist, including fluid restriction, reverse Trendelenburg position, glyceryl trinitrate infusion and diuresis (mannitol/frusemide). Caval clamping and hepatic inflow occlusion are also surgical techniques that may occasionally be used to achieve a lower CVP. The ideal method to lower CVP and the ideal range of pressure has not been established.

9.2.3 *Associating Liver Partition and Portal vein ligation for Staged hepatectomy (ALPPS)*

The technique of associating liver partition and portal vein ligation for staged hepatectomy, known as the *ALPPS procedure*, is a short interval, two-staged liver resection which involves an open right portal vein ligation and in situ parenchymal transection in the right trisectionectomy plane in the first stage [7]. The second stage performed 1–2 weeks later involves a right trisectionectomy. Compared to PVE, ALPPS produces an accelerated hypertrophy of the future liver remnant (FLR) in a much shorter time span. The main downside of ALPPS is the high morbidity and mortality in most reported series. Salvage ALPPS may have a place in patients who do not show an adequate hypertrophy response to PVE. It is a relatively new technique whose place in the surgical armamentarium will be defined with accumulating global experience.

9.3 Technological Adjuncts

9.3.1 *Devices to Aid Transection*

Several techniques and instruments have been developed in the past few decades to aid liver transection in order to improve safety, reduce bleeding, save time and attain good bilio- and haemostasis. The basic principle on which most of these instruments work is by removing the liver parenchyma and leaving behind vessels and ducts intact to be ligated separately or using energy to seal all the structures completely. The former is the preferred mechanism as it allows selective ligation of vessels and ducts and reduces both bleeding and bile leaks. Also, as it is under vision, it prevents inadvertent injury to the adjacent intraparenchymal structures. Devices that seal directly (termed precoagulation) run the risk of bleeding or bile leak in the event of incomplete coagulation as also lateral thermal damage. Often, more than one energy source and technological adjuncts are used during transection. The list of the technological adjuncts used in hepatic resections is long and ever growing. This itself is a testimony to the fact that no single instrument has been able to fulfil all the requirements uniformly in all the situations. The commonly used technological adjuncts have been summarized in Table 9.1.

Finger Fracture Though strictly not a technological adjunct, we discuss the finger fracture technique here as it was amongst the first techniques proposed to improve the safety of hepatic resections by reducing blood loss and bile leaks [8]. Introduced by Lin in 1954, it consisted of crushing the liver parenchyma between the thumb and finger of the operator. This left behind vessels and bile ducts which could be safely ligated and divided. Though this was an improvement over the sharp transection, especially when combined with a Pringle manoeuvre, it was nevertheless still associated with significant blood loss from small vessels which avulsed in the

process and led to persistent bleeding. Also, this technique led to loss of parenchyma owing to the blunt and wide area of dissection. Hence, it did not gain widespread acceptance. Further, with advancements in instruments available for liver resection, this technique is rarely used today.

Kelly-Clysis Kelly-clysis or the clamp crush technique was also introduced by Lin in 1974 as an improvement over his previously proposed technique of finger fracture [9]. It has since then become a commonly practiced technique which does not require any expensive gadgets. It consists of using a Kelly or artery forceps to crush the parenchyma between the jaws of the instrument, which leaves the vessels and biliary radicles intact for ligation and division under vision, thereby reducing the blood loss and bile leak rates. Given the simplicity of the technique and the associated advantages of low cost, speed and safety, this technique has become the standard against which all other techniques are compared. The technique has stood the test of time, and none of the randomized trials or meta-analysis performed till date have been able to prove the superiority of other techniques or gadgets over this technique [10, 11].

CUSA (Cavitron Ultrasonic Surgical Aspirator) (Fig. 9.1) This uses ultrasonic energy to fragment the liver parenchyma, leaving behind vascular and biliary structures. The transducer oscillates at a frequency of 23 kHz. A hollow conical tip is attached to it which transmits this ultrasonic energy and fragments the parenchyma. The high water content of hepatocytes renders them susceptible to the ultrasonic energy, whereas the vessels and ducts are spared owing to the high content of connective tissue which is poor in water and rich in intracellular bonds. The continuous flow of water cools the tip, and the suction and aspiration technology removes the fragmented parenchyma from the field providing a clear vision. Further suction technology also helps in drawing the tissue towards the tip of the probe, providing a coupling effect. The suction pressure, irrigation speed and the amplitude can be changed to suit the requirements. The vascular and biliary ducts can then be ligated and divided separately. Unipolar or bipolar diathermy is often

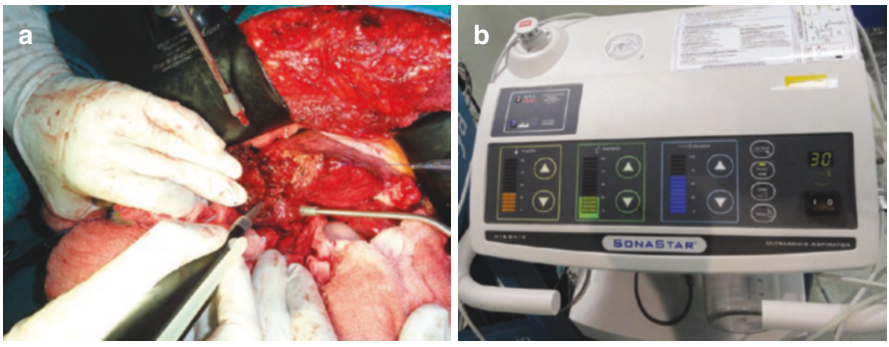

Fig. 9.1 (**a**) CUSA in liver resection. (**b**) CUSA machine

used for division of smaller structures, while the larger ones are either clipped or suture ligated before division. It fragments the parenchyma within a distance of 1–2 mm. CUSA machines with integrated electrocoagulation function are also available. CUSA probes that oscillate at different frequencies are available for application in various tissues. Further, CUSA can also be used without the need for vascular control. However, because of the need to separately ligate and divide even small structures, transection using CUSA becomes time consuming. Moreover, in cirrhotic livers, CUSA is not very useful as the fibrosis prevents easy parenchymal transection. Also CUSA has been reported to be associated with greater risks of venous air embolism, though there were no haemodynamic consequences [12]. Additionally, there is a learning curve associated with the device, which is rather cumbersome to use.

Fan et al. reported their experience with CUSA and compared it with their own historical controls and found a significantly lower rate of blood loss, transfusion requirement, complications and mortality [13]. However, these results have not been reproduced in randomized trials. Takayama et al. compared CUSA with the clamp crush technique in a randomized trial and failed to show any significant reduction in blood loss [14]. However, vascular occlusion was used in both arms which could have been responsible for reduction in blood loss in the clamp crush arm. Moreover, the standard transection technique of the group was clamp crush, which could have resulted in superior results in the clamp crush arm. Nevertheless, a UK national survey revealed that CUSA was used by over half the liver surgeons to aid transection [15]. It is one of the most popular techniques to help transection, possibly because of its ability to clearly see structures before division and avoidance of vascular occlusion.

Waterjet (Fig. 9.2) This works on a principle similar to CUSA, but instead of ultrasonic waves, it uses the kinetic energy of a pressurized jet of water to fragment the soft liver parenchyma. Rau et al. reported in their experimental studies that a pressure of 30–40 bar through a nozzle of 0.1 mm is adequate for fragmentation of normal parenchyma. They also found that cirrhotic livers required a pressure of 10 bars more than normal livers [16]. Similar to CUSA, the vascular and biliary structures need to be ligated separately. This too has an irrigation and suction technology

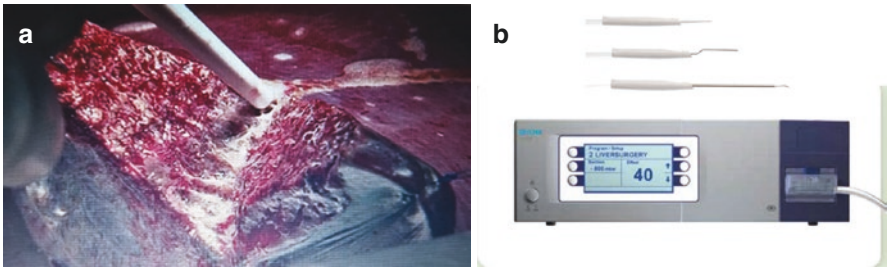

Fig. 9.2 (**a**) Waterjet in liver resection. (**b**) Waterjet dissection machine and applicators (Reproduced with permission from in.erbe-med.com)

integrated into the device to provide a clear field. The pressure of the water can be adjusted according to the nature of the liver. Cirrhotic livers are fibrotic and require a higher pressure for parenchymal disruption. However, this also places these livers at a higher risk of bleeding owing to disruption of small vessels. Newer models are also integrated with a diathermy machine, to provide the electrocoagulation function without needing to switch instruments. This saves time but both functions cannot be used simultaneously. A potential advantage of the waterjet system is the negligible necrosis that occurs at the margin. Further it allows dissection near the major hepatic veins and IVC also. One of the important drawbacks of the waterjet technique is splashes and spillage with potential for contamination. There may be a potential for spread of tumour cells as well exposure of the operator to the infective particles.

Rau et al. reported their experience with the use of waterjet in 350 patients and demonstrated reduced blood loss, lower transfusion requirements, faster resection and reduced need of Pringle manoeuvre [16]. However, most of the experience with waterjet has also come from this group alone.

Ultrasonic Scalpel (Harmonic®) (Fig. 9.3) This is an energy device that coagulates and cuts using ultrasonic energy. It is effective in sealing vessels 2–3 mm in diameter. The generator produces a frequency of 55.5 kHz at which the blades vibrate. The ultrasonic vibration of blades produces heat and denatures the proteins in the parenchyma forming a coagulum. Further saw-like motion of the blades then divides the tissue. Since very high temperatures are not attained, lateral thermal damage is limited. However, it is not capable of sealing large blood vessels, and hence this is not useful deep in the parenchyma where large vessels are likely to be encountered. Further, this may not be very effective at sealing bile ducts though the data regarding this is conflicting. Kim et al. reported high bile leak rates of up to 24% with the use of Harmonic shears [17]. However, Mbah et al. found it to be relatively safe in their study [18]. This device may be used alone only for resections of superficial lesions. They are usually combined with other instruments for other resections.

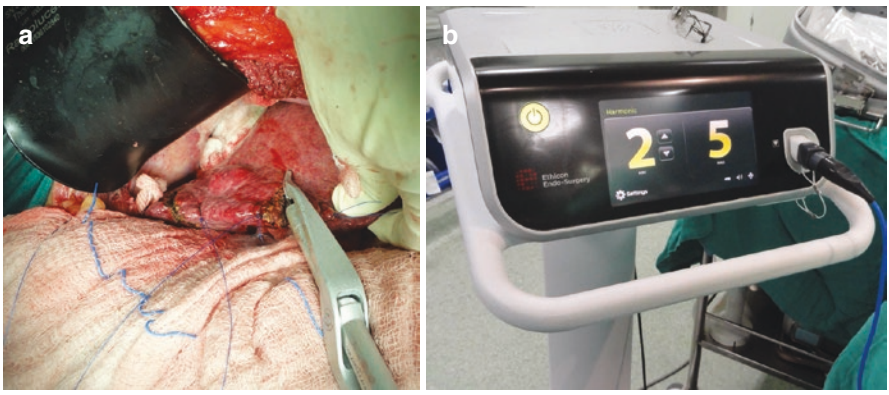

Fig. 9.3 (**a**) Ultrasonic scalpel in liver resection. (**b**) Ultrasonic dissection machine

They are useful in both laparoscopic and open settings. Primary advantages include ease of application, being smokeless, less lateral spread and lack of need for grounding.

Focus or Fusion Technology An advancement over the harmonic scalpel has been the development of Harmonic Focus. This has blades like the Kelly clamp, and the nonactivated instrument is used to crush the parenchyma. The residual vessels and ducts are then sealed using activated Focus depending on their size. This technique is proposed to increase speed, and reduce bleeding and postoperative biliary fistulae both [19].

Bipolar Vessel Sealing Device (LigaSure®) (Fig. 9.4) This device uses bipolar radiofrequency energy to achieve parenchymal transection and sealing of vessels and ducts. It is capable of sealing vessels up to 7 mm in diameter. It acts by denaturing the collagen and elastin fibres in the vessel walls and sealing the vessel. It has

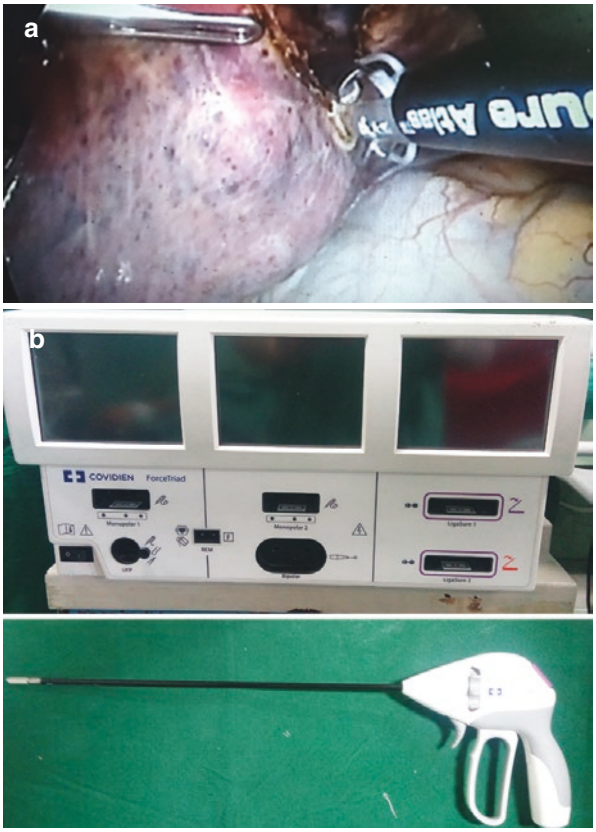

Fig. 9.4 (**a**) Bipolar vessel sealing device being used for laparoscopic liver resection. (**b**) Bipolar vessel sealing device and its laparoscopic probe

found its use primarily in laparoscopic liver resections, where peripheral liver lesions can be resected using LigaSure alone. LigaSure can be used directly for achieving coagulation of the parenchyma followed by transection or can be used in conjunction with the clamp crush technique. A clamp may be used to crush the parenchyma, and LigaSure is then used for sealing the vessels and transection. Similar to the Fusion Technology with Harmonic, LigaSure Precise is available with a clamp-like structure, which can be used to crush the tissue before sealing [20, 21]. LigaSure can also be used without vascular occlusion. The radius of coagulation is around 1 mm, hence reducing the tissue loss.

LigaSure has been found to increase the speed of transection, reduce blood loss and reduce complications [22]. Romano et al. reported a 17% rate of transfusions and complications with no bile leaks. Though some authors have reported it to be safe even in livers with cirrhosis, they found that its utility was reduced in patients with cirrhosis where it fails to achieve reliable sealing of vessels [23, 24]. They postulated that the fibrotic liver prevented adequate compression and also caused dispersal of the energy resulting in ineffective sealing of vessels and bleeding. Cost and availability are major factors affecting its routine usage. Also, a randomized trial failed to show any benefit of LigaSure over the clamp crush technique [25].

Radiofrequency-Assisted Transection (Fig. 9.5) This uses the same principle as in radiofrequency ablation of tumours, to ablate and divide the liver parenchyma along the desired plane of transection to achieve a rapid and bloodless resection. This was first described by Weber et al. in 2002 [26]. The technique involves marking the margins of the tumour on the surface of liver parenchyma using intraoperative ultrasound. After this, another line is marked on the liver capsule at a distance of 1 cm from the tumour. Early in their experience, the authors ensured a margin of 2 cm which was later reduced to 1 cm. The probe is positioned with the help of ultrasound.

The earliest probes used were monopolar probes which were the same as those designed for the purpose of tumour ablation. Currently multipronged bipolar probes are available which reduce the skin burns, lateral thermal damage and time [27]. However, the tissue necrosis in the remnant liver still remains significant. The primary disadvantage of this technique is that it ablates the entire parenchyma along with the vessels and ducts. Hence, inadvertent injuries to large ducts or vessels are possible. This is reflected in the results of a randomized trial which showed a higher incidence of postoperative complications in the radiofrequency arm (33%) compared to the clamp crush technique (none) [28]. Most surgeons also avoid its use near the hilum or hepatic veins where major structures are likely to be encountered. Also due to the significant tissue necrosis that it produces, there is loss of parenchyma, and this may be problematic in patients with cirrhosis and marginal volume. Further, large vessels may not be coagulated and sealed effectively leading to troublesome bleeding. The other issue is that it is time consuming. Further, its use near the hilum is discouraged owing to the risk of incomplete coagulation because of the heat sink effect.

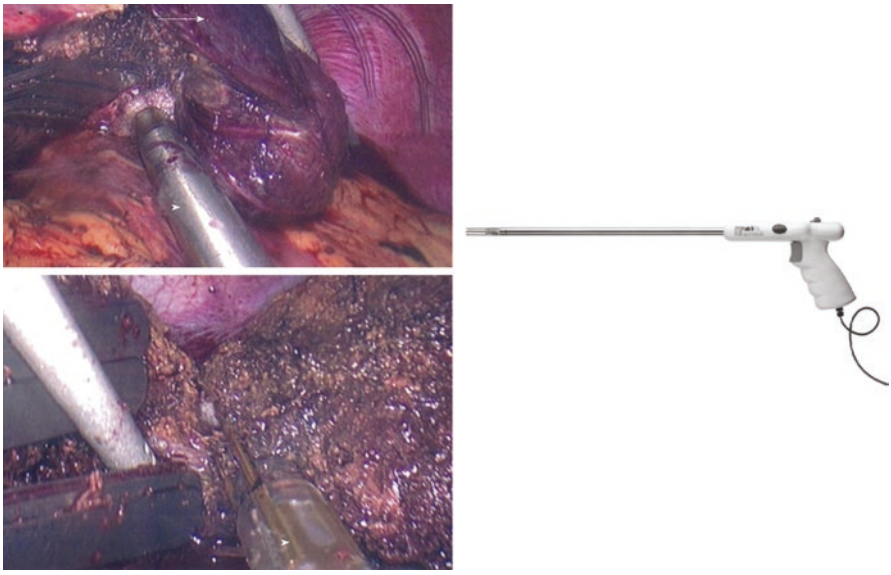

Fig. 9.5 Radiofrequency device (Habib 4×) being used for resection. (Reproduced with permission from Acharya M, Panagiotopoulos N, Bhaskaran P, Kyriakides C, Pai M, Habib N. Laparoscopic resection of a giant exophytic liver haemangioma with the laparoscopic Habib 4× radiofrequency device. World J Gastrointest Surg. 2012 Aug 27; 4(8): 199–202)

Most of the experience with this technique has come from a single group. Pai et al. reported on the experience with bipolar radiofrequency device (Habib 4X) in 604 liver resections (206 major and 398 minor). The median blood loss was only 155 mL, with a blood transfusion rate of 12.5%. The morbidity rate was 23.5%, and mortality rate was 1.8%, which is similar to that with other techniques [29]. However, as stated earlier, a randomized trial did not show any benefit but instead a higher rate of complications. Whether lack of adequate experience was responsible for inferior results is unclear.

Microwave The use of microwave energy in liver surgery was described first in 1981 [30]. Similar to the radiofrequency-assisted transection, this uses microwaves to achieve coagulative necrosis along the proposed line of transection. The needle probe is attached to the generator through a handpiece. The needle is inserted into the liver parenchyma, preferably under ultrasound guidance. The microwaves produce heat that causes denaturation of proteins and coagulative necrosis. Once the parenchyma changes colour to greyish white, the needle is removed and advanced. The radius of coagulation achieved is 5 mm.

Initial reports suggested that though it increased the speed of transection and reduced blood loss, it led to increased postoperative complications in the form of bile leak, collections and fever [31]. Part of it was related to inability of microwaves to seal the biliary channels effectively and partly to the necrotic surface of

the remnant liver. Further its use near the hilum remains controversial owing to the high risk of injury to major structures. However, a recent study reviewing 1118 liver resections did not bear this out [32]. The median intraoperative blood loss was 250 mL, and bile leak was noted in 3% and collections in 3.3%. They reported successful use of microwave tissue coagulator even near the hilum. Bile leak rates were comparable to other techniques. However, this could be due to the fact that majority of the resections carried out were minor and nonanatomical. One of the main advantages of this technique however is the fact that no inflow occlusion is required, making it attractive in cirrhotics. Further most patients in this study had diseased livers, thus demonstrating the efficacy of this technique even in cirrhosis. However, the main deterrent to its widespread application remains tissue loss of the remnant liver and the high incidence of bile leaks and collections apart from issues of availability.

Saline-Linked Radiofrequency Sealing Device (Aquamantys®, TissueLink®) This combines the principle of bipolar electrocoagulation with irrigation. The bipolar cautery coagulates the tissue but restricts the current flow to between the two prongs of forceps. This therefore prevents both skin burns and lateral damage. The continuous irrigation prevents the burnt tissue from sticking to the forceps and cools the area preventing eschar formation. Aquamantys is a commercially available disposable sealer that has a fixed flow of saline and fixed distance between the tips to ensure the same coagulant effect in each use. This is termed as the Transcollation technology that uses saline to improve the tissue sealing effect. Once adequate coagulation is achieved, the tissue can be divided using scissors or cautery. If a sharp tip is being used, it can be used to divide the tissue by gentle traction with the tip itself. The side of the tip is also useful for achieving cut surface coagulation and haemostasis. The device is capable of sealing vessels 3–6 mm in diameter. Larger vessels need to be clipped or ligated. This can be used either as the primary technique for parenchymal transection or in conjunction with other techniques. Curro et al. studied it in 12 cirrhotic patients and found it to be safe, feasible and associated with low blood loss and minimal tissue loss [33]. Kaibori et al. studied its use with CUSA and compared it with a standard bipolar cautery with CUSA and found it to be superior in terms of speed, blood loss and requirement of ties [34]. However, it is a relatively new technique, and safety issues are yet to be resolved completely. A study comparing irrigated bipolar sealer to monopolar cautery found a significantly higher rate of cut surface complications including abscess formation [35]. Though a few studies have shown that it reduces the bleeding and reperfusion injury, it is very time consuming. Xia et al. showed significantly less blood loss and reperfusion injury in cirrhotic livers while using TissueLink when compared to clamp crush technique [36].

Staplers (Fig. 9.6) Staplers may be used either for division of major vascular pedicles, liver parenchyma or both. The use of staplers for division of portal and hepatic veins was proposed over 20 years ago and has become standard during both open and laparoscopic procedures. Endovascular staplers are also being used for parenchymal

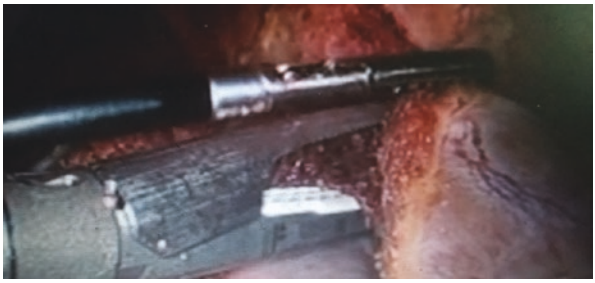

Fig. 9.6 Stapler being used for division of vascular pedicle in laparoscopic liver resection

transection in both major and minor resections. They are especially useful in left lateral sectionectomy or minor resections where the thickness of parenchyma to be transected is less. In major hepatectomies, the parenchyma is first crushed and fragmented with a clamp, to reduce the thickness and allow application of the stapling device. They can effectively seal both blood vessels and biliary radicles and allow for rapid and safe division of parenchyma. After completion of transection, the surface haemostasis is performed as usual using mono- or bipolar electrocautery and/or argon plasma beam coagulation.

In a retrospective review of 1174 patients undergoing parenchymal transection using a stapler device (77% major resections and 23% minor resections), the median operating time was 206 min, and blood loss was 300 mL. Only 11% required blood transfusions, and the overall morbidity and mortality were 14% and 3.2%. The safety profile is further validated by the median length of hospital stay of only 7 days. Rare instances (1.1%) of stapler misfire were noted which resulted in bleeding and mortality [37]. Further advantages include the lack of need for vascular control. This is especially useful in patients with liver disease or cirrhosis who tolerate vascular exclusion poorly [38]. Further, staplers are extremely useful in laparoscopic liver resections and have in fact increased in popularity with increasing utilization of minimally access approach for hepatectomy. They are easy to learn and add to the speed and safety. A large database study of 1499 laparoscopic liver resections compared the use of staplers (746 resections) for parenchymal transection with other methods (735 resections) and found significantly shorter operative times, less blood loss and reduced transfusion requirements. Though surgical margins were found to be less in this study in the stapler arm, there were no clinical implications as both groups had similar recurrence and overall and disease free survival rates [39]. Further battery-powered staplers such as *iDrive* are available today, which make the use of staplers in all locations, angles and tissue thickness ergonomically convenient, easy and safe.

One of the main drawbacks of using staplers is the high cost associated with these devices. However, some authors believe that the reduction in operating time, reduced transfusions and complications offset the direct costs [38]. Also, some authors have raised concerns of bile leak with staplers, but large studies have not uniformly demonstrated this risk [37, 40].

Electrocoagulation This includes the routinely used monopolar and bipolar diathermy. This is used in conjunction with other devices for dividing small vessels and ducts and fibrous tissue. In addition, these are also used for achieving surface haemostasis. They may also be used for obtaining biopsies from surface lesions or attaining haemostasis thereafter.

Choosing Between the Technologies

The plethora of gadgets to aid transection makes it difficult to choose one. Evidence to support any single device is sparse. The quality of trials available to test these ever increasing devices is poor, with a high risk of bias and significant heterogeneity in inclusion criteria. Further, continuous advancements, modifications and improvements in available devices make it difficult to draw conclusions from the trials.

In a landmark trial, Lesurtel et al. randomized 100 patients to one of the four techniques of clamp crush, CUSA, waterjet or dissecting sealer [41]. They found that the clamp crush technique was the best in terms of resection time, blood loss, transfusion requirement and cost. However, vascular occlusion was used only along with the clamp crush technique, which may bias the result in its favour. Arita et al. compared the clamp crush technique with the saline-linked radiofrequency coagulator and found similar results with no benefit for the sealing device [42]. A randomized trial however did find lower blood loss and faster transection when energy devices were used in liver resections compared to using silk ties. Here the transection in both groups was carried out by CUSA or clamp crush [43]. Rahbari et al. conducted a meta-analysis of seven randomized trials and found no benefit of any device over the clamp crush technique [11].

A recently published meta-analysis concluded that none of the special devices offers any benefit in terms of blood loss, transfusion requirement, morbidity or mortality [10]. What they did note was a higher incidence of adverse events with radiofrequency dissecting sealer, whose use should therefore be restricted to clinical trials.

The final choice of the device used to aid in transection depends on the personal choice of the surgeon, their experiences, knowledge of devices, location of the tumour, the proposed surgical procedure, availability of instruments, their potential complications and cost considerations. Currently, most surgeons use a combination of these devices in transection, to reduce blood loss and increase speed.

9.3.2 Haemostasis

Despite the plethora of gadgets and techniques available to aid the transection of liver parenchyma, bleeding from the cut surface still remains a major issue which ultimately determines the outcomes. Therefore, surgeons continue to rely on a mix of systemic and topical agents which can aid in the haemostasis and biliostasis.

9.3.2.1 Systemic

Several drugs have been tried systemically in an attempt to enhance and aid haemostasis after liver resections. These include tranexamic acid, aprotinin, antithrombin III, recombinant factor VIIa and desmopressin. The use of these agents in liver resections is an extrapolation of their utility in other surgical procedures such as orthopaedic or cardiovascular ones. Of these currently only tranexamic acid is routinely used. Others have been forgone due to either lack of efficacy, cost or side-effects [44–46]. It is postulated that liver resection creates a state of accelerated fibrinolysis or hyperfibrinolysis. In addition, a significant proportion of resections involve diseased livers which also add to this fibrinolytic state. Therefore, it was postulated that antifibrinolytic agents like aprotinin and tranexamic acid would reduce bleeding. The role of aprotinin has been studied in only 1 randomized trial in 1999 with 97 patients which showed that it reduces blood loss and transfusion requirements in liver resections [47]. However, no further trials have been conducted to test its utility and safety profile. Furthermore, a higher risk of renal failure, thromboembolic events and mortality was noted in patients undergoing cardiac surgery, which has discouraged its use. Additionally cost considerations have also impeded its use. Tranexamic acid has also been tested in only one randomized trial in 2006 and found to significantly reduce the blood loss and transfusion requirements and operating time [48]. However, tranexamic acid is believed to be associated with a risk of thromboembolic events. Its safety profile needs further elucidation in prospective trials.

Data regarding the utility of systemic agents in liver resections is sparse. Limited data is available in favour of tranexamic acid and aprotinin. However, good-quality trials are needed before their routine use can be recommended [49]. At present, selective use of these agents based on the thromboelastographic profile of the patient may be prudent.

9.3.2.2 Topical Haemostatic Agents

As the name states, these are applied topically to the cut surface of the liver to produce haemostasis. These include surface application of energy or pharmacological agents.

Energy Devices These include surface application of electrocautery or argon plasma coagulation. Electrocoagulation has previously been discussed.

Argon Plasma Coagulation (Fig. 9.7) Here, a beam of argon gas is directed from the tip of the probe to aid in the conduction of the radiofrequency energy to the tissue. The energy is delivered through ionized gas, and hence, the probe does not touch the tissue, preventing sticking of the tissue also. Further, the beam is ionized and autodirected towards the tissue with area of least resistance. As it dessicates and chars, the resistance rises, and the beam gets redirected to the raw uncoagulated area. It is faster than other coagulation systems and provides a more superficial and uniform coagulation, reducing deeper tissue damage. Further, it is smokeless and

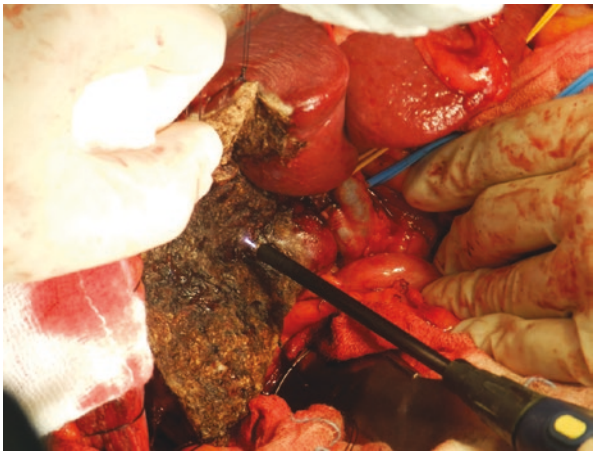

Fig. 9.7 Argon plasma coagulation of cut surface

produces less charring. However, its use should be avoided in laparoscopic resections as it increases the risk of gas embolism. Helium plasma coagulator has also been introduced with the same principle using helium gas.

Pharmacological Agents These consist of either directly acting agents which form the clot to achieve haemostasis or a matrix which stimulates endogenous clot production. The final step in the common pathway to clot formation is the formation of fibrin from fibrinogen by thrombin and polymerization of fibrin to form a stable clot. The directly acting agents generally contain fibrinogen and thrombin in separate vials which can be mixed and applied to the surface. These are also available bound to a matrix, resulting in a carrier-bound fibrin sealant. Several different formulations are available that differ in the percentages of these components and the presence of additional substances like antifibrinolytic agents, calcium, etc.

Some of the commonly used agents consist of:

1. Those that mimic endogenous coagulation:
   (a) Fibrin sealants: Tisseel®, Hemaseel®, Quixil®
   (b) Carrier-bound fibrin sealants
      - Collagen fleece coated with fibrinogen and thrombin: TachoSil®, TachoComb®
      - Gelatin and thrombin: FloSeal®
      - Collagen and thrombin: CoStasis®
2. Those that provide a matrix for endogenous coagulation:
   (a) Cellulose: Surgicel®, Nu-knit®
   (b) Gelatin: Gelfoam®, Spongostan®
   (c) Collagen: Tissuefleece®, Duracol®

Studies on the efficacy of topical haemostatic agents have shown a statistically significant reduction in the time to haemostasis. The clinical relevance of this finding remains unclear. Since the transfusion requirement is primarily determined by the loss occurring during transection rather than from the cut surface, the clinical relevance with regard to haemostatic potential remains unclear. The other function for which these agents are used is biliostasis. The effect of bile on these agents has been the subject of a few experimental studies. Bile salts have anticoagulant effects and have been shown to prevent the conversion of fibrinogen to fibrin [50]. This could potentially interfere with the biliostatic effect of these agents. However, Fonouni et al. conducted an animal experiment on a porcine model comparing the biliostatic potential of two commercially available sealants with control when applied to the cut surface. They found that the sealant group showed a significant reduction in the incidence of bile leakage [51]. Regardless, most other in vitro experimental studies have failed to reproduce these results. Further, other in vivo studies have also not shown a consistent benefit as far as biliostasis is concerned. Though a small study by Noun et al. showed a significant reduction in the drain output and drain fluid bilirubin, a well powered randomized trial failed to show any difference in bile leak rates [52, 53].

Recent meta-analysis has concluded that though the topical haemostatic agents reduced time to haemostasis, they did not reduce transfusion requirements, collections or bile leak rates [54, 55]. Hence, there seems to be inadequate evidence to support the routine use of topical haemostatic agents. However, surveys amongst liver surgeons reveal that they are popular and used by majority of surgeons with an intent to reduce bleeding, bile leak and collections [56, 57].

Chemical Cauterization Chemical cauterization of the cut surface has been studied in rat models using ferric sulphate and ferric chloride. This has been found to be useful in achieving haemostasis in a significantly shorter time [58, 59]. However, the efficacy in vivo and adverse effect profile needs to be studied before this can be brought into routine practice.

9.4 Miscellaneous

9.4.1 Portal Vein Embolization

The limits of resection are dictated by the probability of leaving behind a safe volume of functional liver, which has an adequate vascular inflow, venous outflow and biliary drainage. Preoperative portal vein embolization (PVE) is the elective obliteration of portal blood flow to a selected portion of the liver, a few weeks prior to intended major liver resection, with the intention of eliciting a hypertrophic response in the non-embolized portion. Haemodynamic and humoral factors are involved in the hypertrophic response. The purpose is to augment the volume and potentially the function of the future liver remnant (FLR) beyond a safe threshold, so that the

risk of post hepatectomy liver failure and its attendant complications including sepsis, multi-organ failure and mortality are avoided or minimized. This usually takes the form of a right portal vein embolization, performed in preparation of a planned future major right-sided resection such as an extended right hepatectomy (in a normal liver) or a right hepatectomy (in a cirrhotic liver). Very rarely, a left portal vein embolization may be indicated before a left-sided resection. The percutaneous PVE can be performed by a transhepatic or transjugular route. The direct transhepatic puncture of the portal vein under image guidance is the classical and most commonly performed technique. There are two minor but important variations, the ipsilateral (same side as the tumour/intended resection) and the contralateral approach, depending on which portal vein is punctured. Embolization of the portal vein branches to segment IV increases the volume of hypertrophy in the remnant in a planned right trisectionectomy.

The percentage increase of standardized FLR (i.e. FLR/estimated total liver volume) that could be expected after PVE at 4–6 weeks ranges from 8 to 13%, although some studies have reported higher rates [60–64]. When expressed as a percentage augmentation from the baseline FLR, this would be a 40–62% increase [64].

PVE is indicated when the FLR is deemed inadequate or unsafe, *and* there is a reasonable prospect of an increase in the volume of FLR to an extent that would shift the FLR to a zone that would permit safe resection. Though there is no universal consensus on what would be an ideal minimum FLR, most experts would agree on the following broad practical guidelines for considering PVE [65–67]:

1. In an otherwise normal liver (unusual in clinical practice):
   (a) A standardized FLR of <20%
   (b) FLR to body weight ratio of <0.5% [Truant criterion] [68]
2. In the presence of significant steatosis/cholestasis/chemotherapy-associated steatohepatitis/chronic hepatitis (most patients would fall in this category):
   (a) A standardized FLR of <30%
   (b) FLR to body weight ratio of <0.8%
3. In the presence of cirrhosis (Child A):
   (a) A standardized FLR of <40%
   (b) FLR to body weight ratio < 1.4%
   (c) FLR of <250 mL/m^2 [Shirabe criterion] [69]

The volume increase may further be augmented by addition of TACE beforehand, concomitant segmental arterial occlusion, hepatic venous occlusion, stem cell transplantation and branched-chain amino acid supplementation. PVE is well tolerated with a mortality risk of 0.1% and major morbidity risk of 2–3%. The dropout rate of patients who have PVE but do not proceed to resection is up to 25% [70].

9.4.2 Biliary Drainage

Jaundice from biliary obstruction has a wide range of adverse effects which may impact postoperative outcomes. There is experimental evidence for increased bacterial translocation, endotoxemia, reduced Kupffer cell function, increased pro-inflammatory cytokines (TNFα/IL-6) and suppressed cell-mediated immunity [71]. Clinically, liver resection is associated with higher morbidity in jaundiced patients [72]. Poorer oncological outcomes have been recorded in distal obstructions needing a pancreaticoduodenectomy, when the serum bilirubin levels are >18 mg/dL, although there is no conclusive evidence along those lines in liver resections [73]. Biliary drainage, on the other hand, reduces pro-inflammatory cytokines [74] and causes hypertrophy of the liver remnant, when it is drained. The downside of drainage is procedure-related cholangitis, re-intervention rates, prolonged hospital stay, cost, delays in time to surgery and an increase in the risk of tumour seeding.

The volume and functional quality of FLR and the presence of cholangitis are two of the key determinants of PHLF [75]. Although absolute bilirubin level alone has not been shown to be an independent predictor of PHLF, most surgeons would prefer to have the bilirubin less than 5 mg/dL (or 3 mg/dL) before embarking on a major hepatectomy. However, there are centres which have reported safe upfront major liver resections in cohorts of patients with a median bilirubin in the range of 18 mg/dL [76]. If reduction in bilirubin is the goal, then drainage of as little as 30% of the liver would suffice. Major liver resection without drainage has been associated with increased perioperative infective complications and bile leak [72]. The mortality also increases if the FLR is <50% and the obstructed biliary system is undrained [72, 76].

In summary, preoperative biliary drainage when used selectively could be a useful adjunct to liver resection. The indications are summarized in Table 9.2.

9.4.3 Ultrasound-Directed Parenchymal Sparing Resection (Torzilli Technique)

Torzilli has pioneered an intraoperative ultrasound-guided, parenchymal sparing technique which is especially useful in multiple bilobar metastases as seen in colorectal cancer [77]. Two-staged resections which are the standard for bilobar metastasis have a dropout rate of up to 40% which can be avoided by this parenchymal sparing technique [78]. The key principles which set this technique apart from

Table 9.2 Indication for biliary drainage

1. Cholangitis
2. FLR borderline: 30–50%—drain FLR
2. FLR < 30%—drain bilaterally and add PVE
3. Need for PVE
4. Need for hepatopancreaticoduodenectomy

the standard resections are an adequate exposure and mobilization of the liver (with a thoracoabdominal approach, if necessary); a detailed mapping of the lesions under contrast-enhanced ultrasound; accepting minimal (even zero mm) margins; shaving lesions off veins; and resection and reconstruction of hepatic veins, if necessary. Perioperative outcomes (blood loss; general and liver specific morbidity) are better, and oncological outcomes have been shown to be at least on par with conventional two-staged resections [78].

9.4.4 Real-Time Functional FLR Assessment and Fluorescence-Guided Navigation Surgery

The kinetics of indocyanine green (ICG), a fluorescent dye, which is taken up by the liver and excreted in the bile with no enterohepatic circulation, has some unique properties which make it a clinically useful measure of liver function. The ICG plasma disappearance rate (ICG PDR) and retention at 15 min (ICG-R15) are the two commonly used parameters. The normal PDR is >18%/min and the normal ICG-R15 is <10% (or up to 14%). These may be calculated by measurement of the concentration of the dye on serial blood samples or non-invasively by finger spectrophotometry using appropriately calibrated machines. Although ICG has been in clinical use for many years now, for the preoperative stratification of liver function, and this has been incorporated into patient selection algorithms, the intraoperative real-time functional assessment of the liver remnant using ICG is a relatively new concept. ICG PDR after trial clamping of the inflow to the liver being resected has been shown to correlate well with the post resection ICG PDR as well as the incidence of PHLF and hospital stay [79, 80]. Lau et al. have coined the acronym ALIIVE for this technique, which stands for assessment of liver remnant using ICG clearance intraoperatively during vascular exclusion [80]. This technique simulates a post resection-state liver function, at a final intraoperative checkpoint, just before vascular ligation, which would be the point of no return. This increases the margin of safety and makes it possible to make critical decisions even at an advanced stage of the operation. For example if in a planned right trisectionectomy, the intraoperative ICG estimation points to an inadequate functional FLR, then one may resort to an ALPPS procedure; or on the other hand, in a planned ALPPS procedure, if the ICG predicts an adequate functional remnant, then a one-stage resection could be done. Currently, the clinical experience is limited, and more data is needed to draw safe and consistent cut-offs for intraoperative ICG kinetics that could be used reliably in decision-making.

As an extension, the optical properties of ICG-laden tissues have been used to develop systems, which have a number of practical applications in liver resection. Fluorescence imaging using ICG has been in clinical use in other branches of medicine since the 1970s, but its application in liver surgery is a relatively recent development. ICG emits fluorescence when excited by near infra-red light. This needs a specialized imaging system such as the *photodynamic eye* (PDE; Hamamatsu Photonics; Japan).

Applications in liver surgery include liver mapping for segmental resections, tumour visualization and intraoperative cholangiography. For mapping of liver segments, a 5 mg dose of ICG is injected in the portal vein branch of interest and imaged with a PDE-type system. Repeat injection with or without arterial clamping or even a Pringle manoeuvre may be required to prevent washout and cross-contamination from systemic circulation, if prolonged imaging is required.

Well-differentiated HCC has impaired biliary excretion and hence retains ICG. Poorly differentiated HCCs and metastasis do not take up ICG but compress surrounding normal parenchyma resulting in a rim-type fluorescence. Sensitivity is best for tumours within 5 mm of the surface. The interval between ICG injection and imaging should ideally be at least 2 days, and a single dose of 0.5 mg/kg administered within 14 days of surgery is sufficient to visualize tumours [81]**.**

ICG fluorescence cholangiography offers a road map of the biliary tree while avoiding irradiation and the need for a C-arm. It is also useful in identifying cut surface bile leaks that may be missed by other techniques [82]. For cholangiography the recommended dose is 2.5 mg ICG about half an hour before induction or 10 mg, 24 h before surgery [81].

9.5 Summary

Liver resections are complex surgical procedures, fraught with issues of bleeding, bile leaks, prolonged surgery, inadequate liver remnant and postoperative liver failure. Advances made in the surgical and anaesthetic techniques and technology are increasingly allowing rapid and safe resection with minimal bleeding and few postoperative complications. Further these may help in achieving resection of tumours in central locations or overcoming the issue of insufficient volume. The first step to achieving better outcomes has been an improvement in our understanding of the anatomy of the liver and its vasculobiliary tree. Surgical and anaesthetic techniques that have been developed to reduce bleeding include modifying the vascular inflow and/or outflow and lowering the central venous pressure. Though these are not required for every resection, an understanding of these measures and their effects is paramount for the liver surgeon to safely complete resection in difficult situations.

The other potential target for improving outcomes is the technique of parenchymal transection itself and treatment of the cut surface. Though several devices have been developed to reduce blood loss during transection and decrease postoperative complications, no single technique has shown uniformly consistent results. The age-old technique of clamp crush appears to be best in terms of blood loss, speed, safety and complications. The cut surface can be managed with electrocoagulation or argon plasma coagulation beam or through the use of topical haemostatic agents. Again, no single technique has emerged as superior to the others. In general, surgeons use a mix of all available techniques in different permutations and combinations to achieve a safe resection and good outcome.

Other adjuncts help in improving the quantity and quality of the future liver remnant to reduce chances of postoperative liver failure. A preoperative portal vein embolization can be used to increase future liver remnant volumes. An upcoming alternative is ALPPS which can be used either directly or after a failed PVE. Preoperative biliary drainage is advocated in jaundiced patients to improve the quality of the remnant liver and render resections safer.

To conclude technical and technological advances have made liver resection safe and feasible in most patients. A proper surgical planning utilizing the available options judiciously in the preoperative and intraoperative period is essential for achieving the best results.

Editorial Comments

Liver surgery has become safer than in the past due to a better understanding of the surgical anatomy and a number of technological advances. The improved resectability of liver tumours (both primary and secondary) has led to improved survival. Apart from technical innovations, advances have taken place in technology facilitating safe liver surgery. The authors have adequately dealt with both these aspects in their review. I would like to add the following:

1. *Hemihepatic or sequential vascular occlusion* selectively blocks the inflow to the tumour-bearing liver or its segment. It thus preserves blood supply to the remaining liver. Moreover, it prevents splanchnic congestion. Haemodynamic instability too is minimized or avoided with this technique. Sometimes, when the tumour infiltrates the hepatic vein or inferior vena cava, there can be substantial backflow, and total vascular occlusion may be required. An alternative to total vascular occlusion is extra-parenchymal control of the hepatic vein and/or the suprahepatic vena cava [83].
2. *Acute normovolemic haemodilution.* Major bleeding can be a problem during hepatectomy requiring multiple blood transfusions. This is undesirable because it hampers postoperative recovery and affects the oncological outcome. The haemodilution technique has been shown in a randomized study by Maithel and Jarnagin [84] to not increase the requirement for blood transfusion and being as effective as standard management.
3. *VIO soft coagulation system.* This is a new coagulation device used in hepatic resection. All standard electrosurgical systems produce sparks and cause carbonization and adherence of the electrodes to the liver tissue. As a result haemostasis is not complete causing persistent bleeding. The VIO soft coagulation system avoids these because only joule heat is generated with a voltage limit of 200 v. As a result the coagulation with this device is superior to standard coagulation devices [85].
4. *Cryoablation* [86]. As with radiofrequency ablation, cryoablation expands the boundaries of liver resection. It is especially useful in metastatic bilobar disease due to colorectal malignancies. For cryoablation of liver tumours,

vacuum-insulated coaxial probes are placed during resection under ultrasound guidance. Initially a spinal needle is placed under intraoperative ultrasound guidance, and then probe(s) are placed in the tract thus created. The lesion is then ablated, and it is monitored by the appearance of an iceball (cryoablated tissue) which is hyperechoic with posterior acoustic shadowing. Apart from the tumour, 1 cm circumferential margin of normal tissue surrounding the tumour is also ablated. Once the tissue is frozen, the probes are rewarmed and quickly removed. The needle tract is plugged with a haemostatic agent. Though rare, cryoshock may occur. It is attributed to release of cytokines from tumours which may cause organ failure and disseminated intravascular coagulation. Raised transaminases and a low platelet count are harbingers of this. However, it occurs only when a large amount of tissue is cryoablated. Other cryo-related complications are liver abscess, bile leak, bleeding and pleural effusion. These problems are commonly seen during simultaneous colorectal resection including cryoablation of liver secondaries along with colorectal resection.

5. *3D visualization during laparoscopic liver resection*. This improves depth perception and helps identify intraparenchymal blood vessels and bile ducts. 3D technology also helps surgeons to complete a hepatectomy faster [87].
6. *Augmented reality guidance system*. Preoperative CT is routinely used for staging and surgical planning for liver cancers. However, identifying important structures within the liver parenchyma can still be a challenge. The augmenting reality guidance system has been developed to provide real-time intraoperative fluoroscopic 'C'-arm cone beam CT images. The images projected on a screen can help surgeons navigate easily during surgery and identify vital structures [88].
7. *Laparoscopic liver surgery with robotic instruments*. Laparoscopic liver resection has been in practice for some years now. One of the problems is the limited movement of the rigid instruments. This compromises the surgeon's movements and often leads to musculoskeletal pain. To avoid these and improve laparoscopic liver resection, robotic instruments are being developed which will improve ergonomics and surgical skill [89].
8. *Robotic liver surgery*. Liver resection by robotic surgery is in the evolving phase. There are a number of benefits. It avoids the limitations of laparoscopic liver resection mentioned above. This in turn improves tissue handling and suturing. In robotic surgery the surgeon sits at a console unlike in laparoscopic surgery where the surgeon is struggling with the instruments. The camera and the retractors are controlled by the surgeon, while in laparoscopy it is in the hands of the assistants. A distinct advantage is a short learning curve. The results of robotic liver surgery are similar to laparoscopic liver surgery in terms of operating time, blood loss, bile leak, morbidity and hospital stay. The cost of the robotic procedure is high, and this is hampering its wider use [90].

Conflict of Interest Statement The authors declare no conflicts of interest. The list of commercially available devices and products is by no means complete, and several other products may be available in each category which are beyond the scope of this review.

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Chapter 10
Advances in Gastrointestinal Surgery

T. K. Chattopadhyay

10.1 Oesophagus

10.1.1 Advances in the Diagnosis and Management of Achalasia Cardia

Achalasia is a motility disorder of the oesophagus. The exact pathophysiological mechanism of this disease remains elusive. The most accepted hypothesis is the destruction of ganglion cells of the myenteric plexus containing both excitatory and inhibitory nerve fibres resulting in an imbalance between the two [1, 2]. The absence of peristalsis in the oesophageal body and failure of relaxation of the lower oesophageal sphincter (LES) manifest clinically as dysphagia, regurgitation and pain in the chest.

The disease is diagnosed with the help of a barium swallow showing a typical 'bird's beak' appearance and is treated with a cardiomyotomy. However, a number of patients did not benefit from a cardiomyotomy possibly because they had oesophageal dysmotility disorders that could be diagnosed only with oesophageal manometry. This necessitated the adoption of oesophageal manometry to select the right patients for this operation. Conventional manometry (CM) identifies an aperistaltic oesophagus with the inability of the LES to relax adequately. High-resolution manometry (HRM) that was developed subsequently provides more information, had a better sensitivity and was easier to do than conventional manometry [3–6]. HRM has since been adopted in the Chicago classification of oesophageal motility disorders. Based on the findings of HRM, achalasia can be divided into four types:

Type I: No evidence of oesophageal pressurization
Type II: Presence of oesophageal compression

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Type III: Associated with more than one spastic contraction
Type IV: Oesophagogastric junction outflow obstruction (OGJOO)

These four types are characterized by the pattern of contractility of the distal oesophagus, varying from an absence of contractility to a normal pattern.

In CM an eight-channel water-perfused manometry catheter that has a sensor at the tip is used. The catheter is passed into the oesophagus through the nose and the manometer placed in the distal oesophagus keeping the distal pressure lumen 3 cm above the LES. Patients are allowed ten consecutive swallows of 5 ml water every 20 s. During the procedure, basal and residual LES pressures and contraction amplitude of the oesophageal body and its duration are obtained. The distal oesophageal amplitude (DEA) is measured 3 cm and 8 cm above the LES. The average of the two is taken as a measure of DEA. The LES pressure is determined by a pull-through technique of the manometry catheter. CM criteria for classification of achalasia are:

Type I: Eight of ten swallows elicit contraction of <30 mmHg
Type II: Two or more contractions >30 mmHg
Type III: At least two spastic waves (>70 mmHg for 6 s)

In HRM, 32 solid-state sensors placed 1 cm apart are used [7]. The manometry assembly is passed through the nose and placed from the hypopharynx to the stomach. First, the basal sphincter pressure is assessed over 5 min. The patients are then allowed ten 5 ml swallows. Manometric data are collected and using suitable software pressure readings are converted to topographic plots so as to obtain a continuous picture of pressure of the entire segment of the oesophagus. For the diagnosis of achalasia, intergraded relaxation pressure (IRP), pan-oesophageal pressurization, absent normal oesophageal peristalsis, preserved fragments of distal peristalsis or premature contractions are ascertained. Based on the manometric data, achalasia is classified as type I with mean IRP ≥15 mmHg and absent (100%) peristalsis; type II with mean IRP ≥15 mmHg, no normal peristalsis and pan-oesophageal pressurization with ≥20% of swallows; and type III with IRP ≥15 mmHg, no normal peristalsis, preserved fragments of distal peristalsis or premature contractions with ≥20% of swallows. Parameters of HRM used in the Chicago classification are IRP, distal contractile integral (DCI) and distal latency (DL) [4, 8, 9].

Deglutitive relaxation of LES is measured by IRP which when ≥15 mmHg suggests failure of relaxation and is diagnostic of achalasia. Deglutitive contraction of the distal oesophagus is evaluated by DCI and DL. DCI reflects contraction of the distal segment of the oesophagus, its length and amplitude. DCI above 8000 mmHg.cm indicates hypercontractility (weak swallow), and DCI below 100 mmHg is suggestive of aperistalsis. DL is a measure of premature contractions (representing inhibitory neuronal dysfunction) and is characteristic of distal oesophageal spasm and type III achalasia. DL of <4.5 s is suggestive of premature contractions.

Achalasia is diagnosed with inadequate LES relaxation and absent peristalsis (not necessarily absent pressurization or contractility). Based on these, three different types of oesophageal contractility have been observed [10, 11]:

Type 1: Minimal oesophageal pressurization
Type 2: Pan-oesophageal pressurization from UES to LES
Type 3: Premature (spastic) contraction

HRM has improved our understanding of oesophageal motility disorders, but several limitations still exist. First, many patients with achalasia have IRP <15 mmHg, and some have intact peristalsis on HRM. This is possibly due to the time required for achalasia to progress from when these parameters are maintained to when these are absent. This probably is the natural history of the disease [12]. Second, some patients may have low LES pressure, especially in type I achalasia. With functioning luminal imaging probe (FLIP), IRP <3 and <5 mmHg have been reported [13]. FLIP can also demonstrate the distensibility index on high-resolution impedance manometry. A value of 2.8 mm^2/mmHg has been shown to be diagnostic of achalasia [14]. Timed barium swallow can show oesophageal pressurization in these patients [15]. Third, fragments of peristalsis can be detected following myotomy. This is possibly because weak peristalsis is not detected on HRM preoperatively. As a result when the outflow obstruction has been addressed by myotomy, the same peristaltic pattern can be seen (unmasking effect rather than truly recovered peristalsis) [16]. Fourth, ganglion cell destruction is more severe in type I than in type II achalasia suggesting the latter represents an earlier stage of the disease as has been shown by Sodikoff et al. [17]. Thus, the absence of recovery of peristalsis after myotomy is indicative of progression of disease with aganglionosis, and its reverse indicates intact ganglion cells with an intact myenteric plexus. OGJOO is another spectrum of achalasia. In this condition the IRP is >15 mmHg but with intact peristalsis. Its diagnosis is ascertained with endoscopic ultrasound (EUS), FLIP and CT scan [18]. A number of conditions other than oesophageal motility disorders can be responsible for the 'dysphagia' such as infiltrative disease, eosinophilic oesophagitis, vascular pathology, sliding hernia, obesity and even malignancy. In addition, manometric parameters similar to OGJOO have been observed after antireflux or bariatric procedures [19]. A point to note is that most patients with abnormal manometry have minimal symptoms (if at all symptomatic). Even in the latter, up to half the patients recover spontaneously [20].

10.1.1.1 Treatment

There is no curative treatment for achalasia. All the treatment options currently available aim to relieve the functional obstruction. With this, the progression of oesophageal dilatation is halted. However, oesophageal motor activity (contractility) varies from patient to patient. While there is lack of contraction in some, the

oesophagus is spastic in others. The results of treatment vary with the type of disease (type I, II or III) [11]. Type II (by far the commonest type) responds better than the others. Nearly 90–100% success has been reported with myotomy or pneumatic dilatation for type II [21–23].

Apart from the three types of achalasia, Chicago classification v.3.0 also identifies other conditions mimicking achalasia, the so-called achalasia syndrome. These include [24]:

- OGJOO: IRP >15 mmHg and persistent peristalsis (of type I–III achalasia). Some of these can be early stage of achalasia, while others can resolve spontaneously.
- Absent contractility: IRP ≤15 mmHg, absent peristalsis.
- Distal oesophageal spasm (DES): IRP normal or increased and >20% premature contractions with DL <4.5 s. This too may represent evolving achalasia.
- Jackhammer oesophagus: IRP normal or increased and >20% swallow with DCI >8000 mmHg. 5 cm.
- Opioid use: IRP >15 mmHg, peristalsis normal, hypercontractile or premature.
- Distal obstruction due to any cause: IRP normal or increased, peristalsis decreased or normal, may need further investigation to exclude an obstructive pathology including a stricture or tumour by EUS, CT or MRI.

Each of these is managed differently. For treatment the site and extent of obstruction, proximal dilatation of the oesophagus and mechanical obstruction as in some patients with the achalasia syndrome will need to be taken into account. One should also consider the presence or absence of a concomitant epiphrenic diverticulum and hiatus hernia.

The various treatment options available are:

Drug Therapy Drugs that can reduce LES pressure are calcium channel blockers, nitrates, botulinum toxin and phosphodiesterase inhibitors. These drugs can decrease LES pressure but their effect does not last long. The drugs have side effects, and more importantly these do not prevent progression of achalasia including oesophageal dilatation. Relief from dysphagia can be obtained but the effect is short lasting and the relapse rate high. These are thus reserved for patients who are not fit to undergo more effective therapy for any reason [24].

Pneumatic Dilatation It is done using a cylindrical balloon placed across the LES under fluoroscopy. The balloon is inflated using a handheld monometer. Recently, a hydraulic dilator has been introduced and can be used along with FLIP. It does not require fluoroscopy [25].

Heller's Myotomy It is the traditional method of treatment and has been in use long before balloon dilatation was available. It has stood the test of time. It used to be done by the open approach but is now being done by the laparoscopic approach. Laparoscopic Heller's myotomy is now the standard surgical therapy for achalasia cardia. A 5–7-cm-long longitudinal incision is made in the anterior wall of the distal oesophagus (5 cm on the oesophagus extending for 2 cm in the cardia).

The procedure may be completed with fundoplication to avoid gastro-oesophageal reflux. However, I do a short segment myotomy, do not advocate a 2-cm-long gastric incision to avoid reflux and hence do not do a fundoplication. The results of pneumatic dilatation and myotomy have been studied extensively. Most studies suggest that both procedures are equally effective (90%) [26–28]. The risk of perforation (1%) in both procedures is also similar. Pneumatic dilatation is less invasive and less expensive than laparoscopic myotomy [29]. In view of this, pneumatic dilatation is currently the treatment of choice for type II achalasia.

Per-Oral Endoscopic Myotomy (POEM) Using an endoscope, an incision is made in the mucosa in the mid-part of the oesophagus to create a submucosal tunnel extending up to the gastric cardia. A myotomy of the circular muscle is then done from inside the tunnel starting at the bottom (cardia) progressing proximally across the LES. POEM has the advantage that the incision on the circular muscle can be extended if required as in the management of type III achalasia. It has been reported to have a 92% response rate [30].

To summarize, in achalasia the LES fails to relax, and there can be additional lack of peristalsis with premature contraction with pan-oesophageal pressurization. All these can be evaluated by HRM and FLIP. A number of conditions apart from these are now described under the common term ‘achalasia syndrome’ and are classified as type I–IV varieties. Pneumatic dilatation has emerged as the treatment of choice for type II achalasia. Laparoscopic Heller’s myotomy is equally effective, but the 7-cm-long incision (2 cm on the cardia) causes a high incidence of reflux, thus requiring some form of fundoplication. Drug therapy is not recommended as it is less effective, is short lasting and has side effects. POEM may have a role in some forms of the ‘achalasia syndrome’. Hence, based on the findings of the HRM, pneumatic dilatation is recommended for LES abnormality as in type II achalasia, surgical myotomy for more advanced LES abnormality with oesophageal dilatation, sigmoid mega oesophagus and epiphrenic diverticulum. POEM can be used to treat especially type III achalasia.

10.2 Stomach

10.2.1 Prevention of Metachronous Gastric Cancer with Helicobacter pylori Treatment

Early gastric cancer limited to the mucosa or submucosa is being treated with endoscopic resection with a high cure rate. However, these patients often have glandular atrophy which has the potential to develop into a fresh focus of cancer. Choi and colleagues from Korea reported their experience of *H. pylori* treatment following endoscopic resection for early gastric cancer [31]. They studied 470 patients of

early gastric cancer or high-grade adenoma who had undergone endoscopic resection. These patients were randomized to receive either anti-*H. pylori* treatment or placebo and were followed up for at least 1 year. They assessed the incidence of metachronous gastric cancer as well as any improvement in the grade of atrophy (compared to the pretreatment characteristics). They included 396 patients in the intention to treat analysis, 194 in the treatment group and 202 in the placebo group. Over a median follow-up of nearly 6 years, metachronous gastric cancer was detected in 7.2% of patients in the treatment group versus 13.4% in the placebo group ($p = 0.03$). Improvement in the grade of atrophy was seen in 48.4% of patients in the treatment group versus only 15% in the placebo group ($p < 0.001$). What is surprising is that *H. pylori* treatment failed to lower the incidence of adenoma. Even more significant was that patients in the treated group survived longer than those in the placebo group. The reduction of metachronous gastric cancer noted in this study has been reported by others too [32–34].

10.3 Colon

10.3.1 Colonic Ischaemia

Ischaemic conditions due to variety of causes affect the colon more often than other parts of the gastrointestinal tract. This is related to the vascular supply of the colon and changes in mesenteric blood flow.

It presents in various forms from gangrene, peritonitis and shock to transient attacks of ischaemia with minimal symptoms. While gangrene and peritonitis have a high mortality, the transient episodes of ischaemia are usually self-limiting. In some patients the disease becomes chronic resulting in strictures following repeated episodes of ischaemia. It occurs more frequently in the elderly who have a history of atherosclerosis. The condition should be suspected on the basis of the clinical presentation and can be confirmed by colonoscopy or imaging.

10.3.1.1 Magnitude of the Problem

Colonic ischaemia, based on hospital data, is reported to occur in 7.2–16.3 cases per 100,000 person-years [35]. These patients are likely to be those with disease serious enough to require hospitalization. However, most patients with colonic ischaemia have non-specific and minimal symptoms and do not seek medical advice. Hence, such patients may be misdiagnosed as irritable bowel syndrome, infective colitis or inflammatory bowel disease. Consequently, the true incidence is likely to be higher. Colonic ischaemia, in one study, has been shown to be the third leading cause of lower gastrointestinal tract bleeding [36]. The disease is reported to be common in women [37].

10.3.1.2 Pathophysiology

From the pathophysiological point of view, colonic ischaemia develops due to reduced blood supply to a level below which it fails to maintain the demand for functional (metabolic) and structural integrity of the bowel. Ischaemia can be either occlusive or non-occlusive. The former usually occurs due to thrombosis or embolism and the latter due to low flow states as in hypotension resulting in decreased colonic perfusion [38]. In colonic ischaemia, major vascular occlusion is usually not seen. Mostly, ischaemia is non-occlusive and affects the microcirculation [39]. Following such injury, haemorrhage and oedema can occur in the submucosal layer. The overlying mucosa may slough off forming an ulcer mimicking acute colitis. This is reversible ischaemia. In the irreversible form of ischaemia, the gut loses its viability and becomes gangrenous. In the chronic form of the disease, the damaged segment undergoes fibrosis due to which a stricture is formed.

Simultaneously, continuing hypoperfusion causes the release of pro-inflammatory cytokines which along with endotoxin (the colon has this in abundance) increases mucosal permeability resulting in ulceration. Due to loss of the epithelial barrier, translocation of bacteria occurs both in the portal and systemic circulation. In most cases the episodes are transient and circulation is restored quickly. The resultant reperfusion injury activates the complement systems and produces free radicals both of which cause apoptosis of the colonocytes [40].

10.3.1.3 Vascularity of the Colon

The colon has three sources of blood supply—the superior mesenteric artery (supplying the right colon up to one-third of the right side of the transverse colon), the inferior mesenteric artery (supplying two-thirds of the transverse colon, descending colon and rectosigmoid area) and the superior haemorrhoidal artery providing the rectum an additional supply. These arteries form arcades along the mesenteric border of the entire colon. These arcades can be incomplete in the region of the splenic flexure and the rectosigmoid junction, resulting in suboptimal collateral flow in these areas and making these areas vulnerable to ischaemia (critical point). This traditional concept has been questioned in recent studies because ischaemia in these regions was not seen frequently [41, 42]. In fact, involvement of the hepatic and splenic flexure has been reported in 1.2% and 4.8% of instances, while the sigmoid colon was involved in 20.8%. In contrast, the non-critical areas involved more frequently are the following: the left colon in 32.6%, distal colon in 24.6%, right colon in 25.2% and entire colon in 7.3% [42]. It has also been observed that right colonic ischaemia has a worse prognosis (higher requirement of surgical intervention and a higher mortality) [42, 43].

Though rare, ischaemia can also occur following occlusion of colonic veins due to phlebosclerosis. This is more common in Asians with the right colon being involved by phlebosclerosis [44].

10.3.1.4 Clinical Features

Patients with colonic ischaemia usually present with sudden-onset, mild to moderate lower abdominal pain. They usually have a strong desire to defecate but pass only some blood. These symptoms are, by no means, specific for the disease and can occur with other conditions including inflammatory bowel disease or severe infective colitis especially due to *Escherichia coli*, *Cytomegalovirus* and viral hepatitis [39, 45–47].

Longstreth and Yao reported that 87% of patients present with mild pain, 84% with haematochezia, 56% with diarrhoea and 30% with nausea [48]. Though pain is more severe in right-sided colonic disease, rectal bleeding is rare. Even when bleeding occurs, it is never profuse or voluminous enough to warrant blood transfusion [38].

What is the outcome of these patients? Reports are conflicting on this. While some have reported adverse outcomes in 22% of patients (reaching up to 48% in right colonic ischaemia) [49], others have reported a favourable course, claiming that the surgical resection rate is only 8% with a mortality of 4% [48]. Nagata et al. [50] reported a particularly benign course in these patients and managed them on an outpatient basis. Only 5% of their patients had rebleed and 2% of these patients died at a follow-up of 2 years. Factors responsible for bad outcome include male gender, the presence of peritonitis, shock, hypotension, tachycardia and the absence of rectal bleed [49].

10.3.1.5 Factor Associated with Colonic Ischaemia

These vary—elderly patients with atherosclerotic vascular disease and end-stage renal disease are particularly prone to colonic ischaemia. Brandt et al. [38] reported that 90% of ischaemic colitis occurs in patients >60 years of age. Most patients develop colonic ischaemia due to hypovolaemia and hypotension; the resultant hypoperfusion is the key determinant of colonic ischaemia [51].

In younger patients, the risk factors for colonic ischaemia include smoking, the presence of hypercoagulable state, chronic constipation, abdominal fat deposition and connective tissue disease. Surgery on the aorta or mesenteric vasculature can also lead to colonic ischaemia. Even overdistention of the colon with increased intraluminal pressure during colonoscopy has been reported to be a risk factor for colonic ischaemia [52].

Various drugs have been shown to be associated with colonic ischaemia. These include antihypertensives, antipsychotics, antidiarrhoeals, immunosuppressives, oral contraceptives and vasoconstrictors [52]. Patients who abuse drugs also have a risk of colonic ischaemia as it has been reported with the use of cocaine, amphetamine, pseudoephedrine, etc. These agents essentially cause vasoconstriction resulting in reduced blood flow which in turn makes the blood hypercoagulable and prone to the formation of thrombi [52]. In addition, these also cause endothelial damage which hastens formation of thrombi. 5-Hydroxytryptamine, a drug used in the management of irritable bowel syndrome, has also been shown to be associated with colonic ischaemia, though the mechanism is not clearly understood [53].

Lastly, chronic obstructive airway disease has also a role to play in the development of colonic ischaemia with a 2.4-fold increased risk. The suggested mechanism is a systemic inflammatory response [49].

10.3.1.6 Investigations

The diagnosis is made on the basis of strong clinical suspicion which includes nature of symptoms and associated risk factors. All patients suspected to have colonic ischaemia then undergo cross-sectional imaging. They may also require endoscopy and biopsy. Blood tests, though not sensitive for the diagnosis of colonic ischaemia, can be done to assess severity of the disease.

Plain Abdominal X-Ray It is not useful for the diagnosis of ischaemia. However, it can help rule out colonic perforation by showing gas under the diaphragm. In the chronic variety of the disease, it can detect intestinal obstruction caused by stricture. An important finding on plain X-ray that can help make the diagnosis of colonic ischaemia is the thumb printing sign. This is due to mucosal oedema, a common finding in colonic ischaemia [45].

Barium enema can be done. However, it is not used as better imaging methods such as CT, US and MRI are available. Moreover, a barium study can aggravate ischaemia and increase the risk of colonic perforation. At present, it may be used in the evaluation of intestinal obstruction due to a stricture caused by ischaemia [54].

CT scan is currently the investigation of choice in the diagnosis of colonic ischaemia. It can detect other conditions of the colon mimicking colonic ischaemia such as colonic diverticulitis. It can correctly define the exact location of the ischaemic segment, its extent both longitudinal and transverse (transmural extension); the latter has a risk of perforation [45]. It can also detect pericolic fluid and a poorly demarcated segment suggesting acute ischaemia. In chronic ischaemia, on the other hand, fluid is absent around the involved segment with thickening of the bowel wall. In addition, the bowel is papery thin. Once the bowel gets reperfused, the bowel wall appears thick due to the presence of bowel wall oedema and haemorrhage compromising the calibre of the lumen [55]. CT can also detect colonic pneumatosis and non-enhancement of the affected segment suggesting gangrene and necrosis [45]. CT angiography can demonstrate vascular obstruction. However, it is not done because colonic ischaemia most often is a result of non-occlusive ischaemia related to a low flow state. It is reserved for patients with isolated right colon involvement due to obstruction of the superior mesenteric artery when a routine CT scan does not clinch the issue [56].

Colonoscopy and Biopsy As mentioned earlier, a definitive diagnosis of colonic ischaemia rests on the colonoscopic findings and biopsy, especially when imaging evidence of colonic ischaemia is not conclusive. At colonoscopy, one can see mucosal findings such as oedema and ulceration and also take a biopsy from an involved area. Colonoscopy should be done early in the course of the disease. It should not be done when features of peritonitis are present [38].

Blood Tests Various blood tests can be done. None of these are of diagnostic value because of their poor sensitivity and specificity. However, these can help assess disease severity. These include blood urea, creatinine, white cell count, lactate dehydrogenase, bicarbonate, haemoglobin and albumin. Stool test is usually done to detect ova, parasite and cyst. *Clostridium difficile* toxin and *E. coli* should also be tested in stool samples.

10.3.1.7 Treatment

It is based on the patient's clinical status, including haemodynamic stability and degree of ischaemia.

If patients are haemodynamically stable and there is no guarding or rebound tenderness (suggesting peritonitis), medical management is warranted. It includes restoration of blood volume, withholding oral feeds, antibiotics and correcting or removing the causative factor, if identified. These patients should be monitored carefully. Most patients with mild to moderate disease respond to these measures.

Patients who do not improve with the above or those who have features of gangrene with peritoneal signs should have a laparotomy and resection of the involved segment. Patients who require surgery have a high mortality and morbidity. The risk factors for unfavourable outcomes are ischaemia developing almost immediately after cardiac or aortic surgery, undue delay between time at presentation and surgery, patients with leucocytosis, lactic acidosis, etc. Right colon involvement has a poorer outcome [55, 57, 58]. Patients who recover from the acute episode but have a chronic course may develop a stricture presenting with obstruction. These patients can be managed with either endoscopic dilatation or surgical resection of the strictured segment.

10.3.2 Morphological Progression in Colonic Carcinogenesis and Its Utility in Clinical Practice

Colonic carcinogenesis encompasses the following sequential molecular events:

1. Apoptosis [59], inhibition allows mutation of colonocytes resulting in neoplasia.
2. Truncation of the APC tumour suppressor genes leads to loss of various genes through chromosomal instability [60, 61].
3. Loss of DNA mismatch repair genes due to either germline mutations in Lynch syndrome or epigenetic silencing (hypermethylation of hMLH1) results in diffuse genomic instability enhanced by environmental factors such as smoking, microbiota, etc. [61–63].
4. Hypermethylation of CPG (5′-C-phosphate-G-3′) tumour suppressor genes leads to transcriptional silencing as in serrated polyps.

Most tumours have multiple mutations [64]. Notwithstanding multiple genetic/epigenetic events, there appears to be a common signalling sequence. Colorectal cancers are biologically heterogeneous [65]. Heterogeneity is related to consensus molecular subtypes (CMS) which include:

(a) CMS 1 (microsatellite instability immune) seen in 14% of patients. They are hypermutated and microsatellite unstable with strong immune activation.
(b) CMS 2 (seen in 37% of patients) epithelial origin marked wingless-related integration site and v.myc avian myelocytomatosis viral oncogene homolog signalling activation [59].
(c) CMS 3 (metabolic, 13%), epithelial origin and evident metabolic dysregulation [59].
(d) CMS 4 (mesenchymal seen in 23%) has prominent transforming growth factor beta activation, stromal invasion and angiogenesis [66].

10.3.2.1 Inherited Colorectal Cancer

This can have either high or low penetrance. Of these, low penetrance accounts for the majority of patients.

High-Penetrance Lesions: Lynch syndrome is in this category. The syndrome is autosomal dominant and occurs due to genetic mutation. The genetic make-up in this condition can be ascertained by immunohistochemistry or microsatellite instability analysis of the tumour. However, its detection is problematic because of phenotype heterogeneity: for both colorectal (CRC) and extracolonic cancers. For detection of CRC, annual colonoscopy starting at 25 years of age has been suggested. However, as only up to 50% of patients who develop CRC are detected in this manner, its utility is being questioned particularly in view of the discomfort, cost and complications of a colonoscopy. Coupled with these concerns, one has to consider the low rate of detection of polyps in this group resulting in frequent negative colonoscopies. Hence, patients are often reluctant to have a surveillance colonoscopy.

Low-Penetrance Lesion: Familial CRC falls in this category. Since these are either low penetrance or polygenic, it is difficult to identify a particular family member who is likely to get the disease. Ideally, all members of the family need to be screened. Recent guidelines from the National Comprehensive Cancer Network (NCCN) recommend screening all first-degree relatives of patients detected to have CRC before 60 years of age. Colonoscopy should start at the age of 40 years and should be repeated every 5 years. For those whose first-degree relatives get CRC after 60 years, the screening should start at 50 years and be repeated every 5–10 years. Even for advanced adenomas in patients, the first-degree relative should have colonoscopy at the same age as of the index patient. Alternatively, colonoscopy can be done at 50 years of age with a repeat colonoscopy every 5–10 years [67].

10.3.2.2 Genetic Basis of Risk in Colorectal Cancer

Familial adenomatous polyposis (FAP), a high-penetrance disease, is associated with modifier loci in genes such as Min-1. Similarly, hereditary non-polyposis cancer is reported to have a polymorphic modifier gene such as cyclin D-1. CRC in this setting is reported to occur at an early age [68, 69]. Cancer-associated genes such as p53 and telomerase have also been reported [70, 71] in this form of familial disease. Other genes reported to have such associations are cytochrome p450 family [59], epoxide hydrolase 1, various glutathione transferase genes (mu1, pi1, theta1) and the haemachromatosis gene, HFE [72, 73]. However, it is not clear as to how these can be used to assess the risk in a given patient.

Low-penetrance disease, too, has been shown to have a genome-wide association with loci which predispose to the risk of CRC [74, 75]. It appears that epigenetic silencing may influence the above as seen by the loss of imprinting in insulin-like growth factor 2 (ILGF-2) gene [76]. This is important, because this gene can be detected in normal colonic mucosa in patients with CRC as well as in circulating lymphocytes. Loss of imprinting ILGF-2 in lymphocytes is 20 times more common in patients with CRC than in normal people. This highlights the correlation between the loss of imprinting of ILGF-2 and a high risk of CRC. However, its utility in CRC risk analysis is yet to be ascertained. In view of this, the present strategies do not help establish the correct relationship of the various genetic and epigenetic events with the development of CRC. What is needed is to establish the molecular characteristics of inherited CRCs and their phenotype. Since only 20–30% of first-degree relatives of patients with familial CRC develop the disease, this is required to avoid unnecessary colonoscopies [77].

10.3.2.3 Genetic Basis of Racial Differences

Both the incidence and mortality of CRC are higher in non-Hispanic blacks than their white counterparts [78, 79]. This difference continues even today, even though the incidence of CRC in general has decreased in the past two decades. One possible explanation for this may be related to the relative poor access to healthcare that blacks have. However, at the same time, they (blacks) do have biological differences. Notable among these are increased k-ras mutation, p53 transcriptosome, p27, Muc-1 and mRNA expression [80–82]. In addition, differences have been noted in transforming growth factor-β and mannose-binding lectin [83, 84]. CRC in blacks has more microsatellite instability [85]. Recently two genes, ephrin type A receptor 6 and folliculin have been shown to be mutated in African Americans [86]. CRC occurs earlier in this population, necessitating screening colonoscopy 5 years earlier when compared to the white population [87].

10.3.2.4 Interplay of Genetic and Environmental Factors

Genetic abnormality alone cannot explain the high risk of CRC, e.g. p53 gene has been shown to be related in only one-third of patients [88]. Along with this, the observation that 70% of CRC are related to lifestyle (environmental) factors tempts

implicating the two together. Factors in relation to lifestyle that increase the risk of CRC include diabetes, obesity, smoking, alcohol, etc. Obesity and diabetes (both more common in blacks than in whites) have been shown to have a 72-fold higher risk of CRC [89].

The interplay between genetic and environment factors is initiated on the colonic mucosa in a susceptible individual. This creates a local milieu conducive for genomic and metabolic alteration which promotes the required mutation for carcinogenesis. Nonetheless, the key factor here is anti-apoptosis [90]. As a result, colonocytes with a life span of 3–7 days are allowed to accumulate molecular factors necessary for tumorigenesis. Hence, adenomas are formed which can be either synchronous or metachronous, necessitating colonoscopic removal. Biologically, cellular, proteomic, epigenetic and ultrastructural abnormalities have been documented. Cellular abnormalities detected are reduced apoptosis and increased cell proliferation [91, 92]. Proteomic abnormalities include altered gene expression [93]. Epigenetic alterations include methylation and micro-RNA [94, 95]. Ultrastructural abnormalities include altered chromatin network [96]. Racial differences can possibly be explained by documented methylation of the gene and mRNA expression [97, 98].

10.3.2.5 Therapeutic Potential of Biological and Genetic Markers

Gene regulation is related to integrity of the chromatin structure. Dysregulation is the key to carcinogenesis. Unfortunately, structural and physical aspects (often referred to as the nano-environment) are, presently, neglected. Various workers have now suggested that increased heterogeneity of this environment can be used to good effect [99–102]. Physical variation in chromatin network can be targeted by modulating the chromatin nano-environment, the so-called chromatin protection therapy [83]. With the use of this technology, chromatin can be targeted resulting in decrease in genomic information available to the colonocytes. This will limit tumour formation and/or limit chemoresistance. As a result of this approach (chromatin-protected therapy), restoration of the normal chromatin nano-environment is likely to be achieved which will prevent the cancer cell from becoming chemoresistant.

10.4 Liver

10.4.1 Improving the Donor Pool and Reducing Demand for Liver Transplantation

It is quite frustrating for liver transplant programs to have an inadequate supply of donor livers. While the indications for liver transplantation have increased, the supply of donors has remained stagnant. How should we deal with this mismatch? One simple way is to adopt a strategy that can reduce the demand, and the other option is to take steps to increase the supply.

Once the demand is reduced, the available supply can be better utilized. For this to be successful, we should concentrate on conditions which are both preventable and treatable. The best example of this is hepatitis C virus (HCV)-related liver disease, one of the commonest indications of liver transplantation. The available evidence suggests that treatment with direct-acting antiviral (DAA) drugs can reduce HCV-related disease and its progression causing widespread damage to the liver. Thus, the requirement of liver transplantation will reduce and so will the waitlist mortality in these patients. Cholankeril et al. [103] compared the waitlist outcome of patients with HCV listed for liver transplantation before and after DAA drugs became available and showed that the addition to the waitlist decreased from 34% to 22%. Even the 90-day waitlist mortality was decreased by 16% following the use of DAA drugs. Almost similar results have been reported by Young et al. [104]

What emerges from these studies is that DAA drugs improve the outcome of treatment of HCV without increasing the load to the already overburdened liver transplantation program. Further, the risk of hepatocellular carcinoma (HCC) is also decreased with DAA therapy and hence the need for liver transplantation [105]. The other benefit of DAA drugs is reduction of graft failure due to recurrence of HCV. This previously affected a number of patients with HCV undergoing liver transplantation. Moreover better short-term survival has been reported in patients with HCV receiving DAA drugs [106]. The inferences from these studies can be summarized as:

1. DAA drugs can effectively treat HCV.
2. Hence, the incidence of HCC has come down.
3. Since a large number of patients with HCV are cured, the need for liver transplantation is reduced, thereby reducing the waitlist. As a result, patients who do not have HCV and are on the waitlist can be offered a donor organ, reducing their waiting period.

10.4.1.1 How Can the Donor Pool be Increased?

First, organs usually considered unacceptable can be made suitable for use. In this category are potential donors with HCV infection. Such donors have a high risk of transmitting HCV, and hence such organs are used only for patients with active HCV infection who are waiting for liver transplantation.

With the availability of DAA drugs, organs from HCV RNA-negative donors can be used in HCV-negative recipients [107]. Bari et al. [108] have suggested that these donors have a low risk of transmission and hence can be used in HCV-negative recipient when a HCV-positive recipient is not available. With informed consent, they transplanted HCV-positive organs in 25 HCV-negative recipients. HCV transmission was ascertained by HCV RNA testing 3 months after transplant and found to have occurred in 16%. The benefits of this approach have also been reported by Chhatwal et al. [109]. HCV-negative patients on the transplant waitlist were offered HCV-positive donors, and all such recipients were treated with DAA therapy for 3 months. They showed a longer survival in these patients. This benefit was particularly high in regions with a high prevalence of HCV-positive donors.

The other strategy to increase the donor pool is to do split liver transplants. This is particularly useful for children waiting for liver transplantation. This is important because children have a poor survival while waiting for a liver transplant. In fact, nearly half the children on the waitlist die in the absence of a donor [110]. The UK experience has shown that the poor outcome can be altered by split liver transplants. Moreover, splitting of the donor liver can benefit at least two recipients. As per data from 2011 to 2014, nearly one in five liver transplants in children in the UK was done using the split liver technique, and in the process, the waitlist mortality was eliminated [111]. This strategy can be adopted elsewhere too. It needs the desire to do it because 7% of available donor livers can be split. Perito et al. [112] using the UNOS database of 2010–2014 reported that there were enough liver donors available for split and could be used in children. In fact they emphasized that more livers suitable to be split were available than the number of children dying on the waitlist. The criteria for a liver to be split are donor age of 18–40 years, BMI <30 kg/m^2, minimal use of vasopressors, serum sodium value <160 mEq/l, bilirubin <3 mg/dl, steatosis ≤10%, no more than 7 days of hospital stay and absence of blood-borne infection. The technique of split liver transplant is demanding, expensive and needs skill. However, these factors must be overcome through appropriate processes because it can save the life of a patient. The main concern of a doctor!

The other strategy is to decrease the waitlist through supportive measures (e.g. bioartificial liver support) in patients with acute liver failure, allowing complete recovery of the native liver and eventual survival. Spheroid reservoir bioartificial liver (SRBAL) is one such device. It is composed of porcine hepatocyte spheroids. In an experimental animal study, this device has been used for the treatment of post-hepatectomy liver failure and has been shown to improve survival. It has also been shown to decrease serum ammonia levels and intracranial pressure [113]. The efficacy of SRBAL has also been reported by Li et al. [114]. The authors of this report have shown prolonged survival following post-hepatectomy liver failure in monkeys. They demonstrated lower bilirubin and ammonia levels and increased albumin levels in blood. Regeneration of the liver was also accelerated in the treated group. Various pro-inflammatory cytokines (IL-6, IL-12, IL-1B, IL-8, IL-2 and interferon gamma) are reduced, and cytokines responsible for liver regeneration were increased with SRBAL therapy. Thus SRBAL has the potential to accelerate liver regeneration with concomitant increased survival through a reduced hepatotoxic effect and inhibition of pro-inflammatory cytokines inducing a milieu conducive for liver regeneration. SRBAL needs to be now tested for its clinical efficacy.

10.4.2 Enhanced One-Stage Hepatectomy (EOSH) for Bilobar Hepatic Metastases from CRC

Hepatic resection is the treatment of choice for liver metastases from CRC. However, when metastases involve both lobes of the liver, surgical resection can be challenging because of the risk of postoperative liver failure due to loss of liver volume.

To tackle this, two-stage hepatectomy (TSH) was introduced [115] and is being used. Unfortunately, not all patients undergo the second stage because of progression of the disease in the waiting period [116]. Hence, if single-stage hepatectomy which removes all the lesions (superficial and deep) can be done, it may prevent the high dropout rate (25–30%) of TSH.

Torzilli et al. have been credited with enhanced one-stage hepatectomy (EOSH) [117, 118]. They published their experience with EOSH and compared the results with those of two-stage hepatectomy (TSH) [119].

10.4.2.1 Essential Steps of EOSH

A thoracoabdominal incision facilitates control of backflow bleeding and helps hepatic resection. An intraoperative ultrasound is used to identify proximity of the tumour(s) to the hepatic vein(s) and also to identify communicating channels between the hepatic veins. These communicating veins are preserved so that even if the hepatic vein needs division, it does not compromise venous drainage. This step helps preserve hepatic parenchyma. Following ultrasound evaluation of the venous anatomy, the liver is mobilized completely for vascular control and to define the plane of transection. This is followed by the removal of all metastatic nodules, separating them from the intrahepatic vascular structures. When the tumour infiltrates the hepatic vein, it is tangentially resected and reconstructed. Finally, an ultrasound is repeated to confirm adequate flow through communicating veins of the hepatic veins [115, 117].

10.4.2.2 Selection of Patients and Results

Patients with ≥6 bilobar colorectal liver metastases and ≥1 P zone lesions (in the vicinity of the portal vein) or H zone lesions (in the vicinity of the hepatic vein) were selected for EOSH. In the series by Torzilli et al. [119], all patients had P/H zone tumours, with 44% of patients having such tumours bilaterally. Preoperative staging was done with thoracoabdominal CT imaging, CEA level, hepatic MRI and a PET scan. Patients who were amenable for complete resection were selected.

Preoperative chemotherapy was given to almost all patients. Chemotherapy included 5FU, oxaliplatin and irinotecan. After 4–6 cycles of chemotherapy, restaging was done. Patients who responded were selected for EOSH; further chemotherapy was given to others until disease stabilization. Nearly 70% of patients had synchronous colorectal and liver resection. The remaining had liver resection first followed by colorectal resection. All patients underwent minor resections involving all lesions in both lobes. R0 resection was done in 17%. Though there was no operative mortality, acute liver failure and colorectal anastomotic leak developed in four and one patients, respectively. EOSH has been shown to have shorter operating time, less blood loss and shorter hospital stay [119].

Over a median follow-up of 33.7 months, the 5-year survival rate was 38.2% with 37.1% morbidity. Liver-specific morbidity was 22%, and recurrence rate was 86% for which re-resection was done in nearly 50% of patients [119].

To conclude, EOSH appears to be a safe and an effective alternative to TSH, and though it has a high R1 resection rate, overall long-term results in patients with a heavy burden of metastatic liver disease with a 5-year survival of 38% favour this approach. Its main advantage is that it is a 'parenchyma-preserving' approach which avoids the high dropout rate of TSH.

10.5 Biliary Tract

10.5.1 Percutaneous Cholecystostomy for Patients with Acute Cholecystitis

Acute cholecystitis is a complication commonly associated with gallstone disease in nearly 20% of patients [120]. When diagnosed early, they are best treated by cholecystectomy (usually laparoscopically) as it is safe, with a low morbidity and mortality [121, 122]. Unfortunately, nearly a quarter of patients with acute cholecystitis require conversion to open cholecystectomy mainly due to delayed presentation. Conversion cholecystectomy increases both morbidity and mortality [123–125].

An alternative strategy to treat patients who present late is percutaneous cholecystostomy (PC) without the need for general anaesthesia. It can be offered to patients who are not fit due to various reasons such as very old age, ischaemic heart disease, chronic kidney disease, uncontrolled diabetes and chronic airway disease particularly in elderly patients. Patients with acalculous acute cholecystitis too can be given this option because they are sicker and an operation under general anaesthesia is extremely hazardous. PC in such a situation is beneficial as it can effectively control severe inflammation, thereby resulting in decreased morbidity and mortality in high-risk patients. In selected cases this can even make sick patients suitable for a safer elective cholecystectomy (bridging therapy) [126–130].

PC, introduced by Radder in 1980 [131], has been established to be reliable and effective in the management of acute cholecystitis with a reported mortality of <3%. The procedure is cost-effective as well [132, 133].

The rationale for cholecystostomy is that it effectively decompresses an acutely inflamed gall bladder grossly distended with infected bile. With cholecystostomy most patients improve—90% get relief from symptoms within 72 h [134–136].

The indication for cholecystostomy is failure of medical treatment (antibiotic, analgesic and intravenous fluids) in patients presenting >72 h after the onset of acute cholecystitis, elderly patients with multiple co-morbid conditions including those with a high perioperative risk. It is also indicated in patients with suspected necrosis, perforation and impending rupture of a massively distended gall bladder which may cause deterioration of the patient with severe co-morbid conditions in

whom emergency cholecystectomy is not an option. The above features of high risk are ascertained on ultrasound and CT scan. These features are distension of gall bladder, thickening of its wall, presence of subserosal oedema, pericholecystic fluid collection, presence of gas in the gall bladder, abscess formation, bile duct dilatation, transient focal enhancement of the hepatic parenchyma or frank necrosis and perforation of the gall bladder. Pericholecystic infiltration too is an ominous finding [137].

While choosing the right treatment, one should assess the severity of acute cholecystitis as outlined in the Tokyo guidelines:

Grade I Mild acute cholecystitis: in a patient of acute cholecystitis with no organ dysfunction and limited gall bladder disease in which cholecystectomy is a low risk operation

Grade II Moderately severe acute cholecystitis with no organ dysfunction but gall bladder disease is too extensive and in which cholecystectomy is hazardous

Grade III Severe acute cholecystitis with organ dysfunction

For both Grades II and III, urgent or early gall bladder drainage is advised. Once patients improve, elective cholecystectomy is recommended. However, certain patients with severe co-morbid conditions are unfit for surgery. What is the best strategy in them is not clear in literature because even if cholecystostomy improves their condition, the outcome after removal of the cholecystostomy catheter is not known. The management begins with establishing an accurate diagnosis of acute cholecystitis based on clinical and imaging characteristics as mentioned earlier. Patients presenting within 72 h should undergo emergency cholecystectomy. Patients with gangrenous cholecystitis with or without peritoneal perforation should undergo open cholecystectomy. For the remaining group, PC is advocated as in high-risk patients with severe co-morbid conditions, severe cholecystitis not responding to conservative measures and suspected empyema and patients who refuse cholecystectomy.

The decision to do PC is taken after assessment of the risk-benefit ratio—a decision to be taken by a senior experienced surgeon [138]. Cholecystostomy, either transhepatic or transperitoneal, is based on the personal preference of the interventional radiologist. The procedure is done under ultrasound guidance, using aseptic technique and local anaesthesia using the Seldinger method in the transhepatic and a one-step method in the transperitoneal approach [120]. Following puncture of the gall bladder, a pigtail catheter is placed, and the contents sampled for bacteriological culture and sensitivity. Once the gall bladder is emptied of bile or pus, a contrast study is done under fluoroscopy to ascertain the position of the catheter and flow of contrast in the biliary system. The catheter is then fixed to the skin and is flushed three times a day. A tubogram is done towards the end of the first postoperative week. If the dye enters the duodenum with no holdup, then the catheter can be removed. If stones are detected in the CBD, an ERCP and stone clearance are done before the catheter is removed, usually 2 weeks after transhepatic and 3 weeks after transperitoneal approach. The complications of cholecystostomy include bile leak, bleeding and peritonitis but occur rarely. Catheter displacement may occur

frequently, but catheter replacement is not done routinely because patients even with a displaced catheter improve remarkably well. Those who do not may require replacement of the catheter. The complication rates following transhepatic or transperitoneal routes are similar [120].

Thus, PC is effective in the management of acute cholecystitis. After recovery from acute cholecystitis, all young patients should undergo laparoscopic cholecystectomy. For elderly patients, especially those with various co-morbid conditions, it is not clear if cholecystectomy should be done. One study showed recurrence of cholecystitis in 4.1% with 1-year survival of 82.2%. The authors of this study stressed that PC can be considered a definitive procedure in high-risk elderly patients [139]. Riall et al., on the other hand, recommended cholecystectomy during the index admission so as to prevent recurrent cholecystitis and readmission to hospital and to reduce costs [140].

10.5.2 Primary Sclerosing Cholangitis (PSC)

PSC is a disease of unknown aetiology. The presentation is quite variable. While some patients remain asymptomatic, others present with disease stable for a long time or present with chronic liver disease and associated cholangiocarcinoma. The disease can present as liver failure too. The disease has a strong association with ulcerative colitis and Crohn's disease. While some decades ago the disease invariably had a fatal outcome with patients dying of liver failure, more recently mortality most often is due to an associated cholangiocarcinoma. This paradigm shift has been brought about by liver transplantation.

10.5.2.1 Epidemiology

PSC is a rare disease, essentially occurring in western countries. The disease is rare in eastern countries and has not been reported in Alaskan natives [141–143]. Its prevalence and incidence is variable among various western nations ranging from 8.5 to 16.2 per 100,000 persons and 0.9–1.3 per person-years in North America and Europe [144]. These figures have come from centres specializing in managing patients with PSC. Reports of population-based studies from the Netherlands, California in the USA and the UK have shown far lower rates of both prevalence and incidence. The prevalence rates in these studies were 6, 4.3 and 3.85 per 100,000 population, respectively, and the corresponding incidence rates were 0.5, 0.41 and 0.41 per 100,000 person-years [145–147].

However, over a period, there seems to be an increase in incidence. This increase can also be due to more frequent diagnosis due to increased awareness and increased availability of MRCP as a tool for biliary tract imaging [145, 148]. The disease seems to be more severe in African Americans who are younger than their white counterparts [149].

10.5.2.2 Diagnosis

PSC is diagnosed on the basis of conjugated hyperbilirubinaemia, multifocal bile duct strictures and segmental dilatation on biliary imaging (MRCP/ERC) [150]. Before the diagnosis, one must rule out secondary causes of strictures due to trauma, ischaemia, infection and tumour. MRCP is preferred over ERCP because it is non-invasive and avoids procedure-related complications of ERCP. However, ERCP has the advantage of being able to dilate the stricture and collect bile sample for cytology to ascertain if a cholangiocarcinoma is present. Liver biopsy is not required for diagnosis [151]. The so-called characteristic onion skin appearance (suggesting periductal fibrosis) is seen in no more than 14% of cases [152], mostly with small duct disease which may not be detected on imaging.

10.5.2.3 Spectrum of the Disease

PSC can present in various forms. In the classic form, the disease is detected with segmental biliary stricture (intra- or extrahepatic or both)—the so-called large-duct PSC. Small-duct PSC, however, cannot be detected on imaging. The diagnosis rests on liver biopsy which shows characteristic periductal fibrosis [150]. Small-duct disease is less frequent than the classic large-duct disease. Small-duct disease has similar frequency in males and females and does not progress to malignancy [153], and hence these patients have a better prognosis [145].

Some patients with PSC have features of autoimmune hepatitis (PSC-AIH overlap). Any of the two can manifest earlier than the other. It is important to ascertain the presence of AIH in PSC because such patients (PSC-AIH) may respond to immunosuppression [154]. Some patients may have raised IgG4; this poses a diagnostic challenge because IgG4 cholangiopathy can also be associated with strictures as seen in PSC. The latter group of patients respond to steroid therapy. Nearly 10% of patients with PSC have elevated IgG4. It is not clear whether this latter form of disease has any impact on the course of PSC [155].

The association of PSC with inflammatory bowel disease is yet another form of the disease. This association is seen in over two-thirds of patients. Men are more commonly affected [156]. When this association is seen, IBD is diagnosed several years before PSC in nearly 70% of patients. Both IBD and PSC can present synchronously in 10% of patients. With increasing frequency of diagnosis of PSC, the incidence of IBD seems to be decreasing [149]. Mostly ulcerative colitis is the dominant IBD in PSC (70–80%). Crohn's disease or indeterminate colitis is relatively uncommon [156].

Crohn's disease when associated with PSC usually presents with colitis rather than strictures. In PSC associated with IBD, the disease tends to be pancolitis or right-sided colitis. The rectum is usually spared and usually there is no backwash ileitis. Also, IBD in PSC is less common in women, but when it

occurs, Crohn's disease is more common in women than in men [157]. By and large the risk factors of PSC in IBD are male gender, non-smoker, pancolitis and history of appendectomy [157]. Overall, the incidence of PSC is 8% in patients with IBD [158]. A Swiss study, on the other hand, has shown a prevalence of 2% while evaluating patients of IBD and screening for PSC over a long follow-up of 20 years [157].

The development of colorectal cancer (CRC) in PSC associated with IBD is another issue. Even without PSC, the risk of CRC is high in IBD. In association with PSC, this risk is higher. Men at a young age are more commonly affected in comparison to patients of IBD without PSC [145, 159]. This increased risk of CRC has not been seen in patients with Crohn's disease associated with PSC. PSC with Crohn's appears to be a milder disease with better survival [156].

10.5.2.4 Course of Disease

As mentioned in the beginning, the natural course of the disease is extremely variable. As many as 50% of patients are asymptomatic and diagnosed during the course of routine evaluation by liver function tests when an abnormality such as raised alkaline phosphatase, transaminases or gamma glutamyl transferase is detected. The bilirubin level can fluctuate, and the abnormal liver function test can spontaneously normalize due to yet unexplained reasons. In one study, 40% of such patients were shown to have normal alkaline phosphatase level (the commonest serum abnormality in PSC) in 1 year [160]. Incidentally, such patients have a high transplant-free survival [160].

Symptomatic patients commonly present with abdominal pain, pruritus, diarrhoea, jaundice and fever. If patients present after the development of cirrhosis, then ascites may be present, and there may be evidence or history of encephalopathy. The liver is enlarged in 43.6% and the spleen in 29.3% of patients [161]. Cholangiocarcinoma develops before cirrhosis with an incidence of 0.5–1% per year. Overall, the cumulative risk is 20% after 30 years. Hence, surveillance is important [155]. de Valle et al. reported that the median time from diagnosis of PSC to development of cholangiocarcinoma is 6 years. Others have reported that a substantial number of patients are diagnosed within 1 year of diagnosis of PSC [161]. Boonstra et al. reported that 80% of patients who develop cholangiocarcinoma die within 1 year [145]. Colorectal cancer (CRC) is another problem in PSC with an annual incidence of 0.5% with a cumulative risk of 13% in 30 years. With biannual colonoscopy, such patients can be treated successfully, with 16% of such patients dying from CRC as against 50% among those who do not undergo surveillance [145].

The mortality rates of PSC are best discussed in two time periods: before and after liver transplant. Takakura et al. [144] listed the causes of death in PSC in four time periods: before 1989, 1990–1999, 2000–2009 and after 2010 (Table 10.1).

Table 10.1 Cause of death from primary sclerosing cholangitis (PSC) over different time periods

Cause of death	Before 1989	1990–1999	2000–2009	After 2010
PSC related	66	40	21	18
Liver transplant related	13	42	53	49
Cholangiocarcinoma related	12	15	16	15
Other causes	8	2	8	13
Colorectal cancer related	1	1	2	5

All figures are percentages

10.5.2.5 Other Complications

In addition to the above, the other problems associated with PSC are stricture, cholangitis and osteodystrophy.

Dominant strictures by definition are ≤1.5 mm stricture of the common bile duct and/or ≤ 1 mm stricture within 2 cm of the bifurcation of two hepatic ducts [162]. It occurs in nearly half the patients with PSC during their lifetime, commonly presenting with jaundice, pruritus and cholangitis. Candida infection, when it occurs, in a dominant stricture should always raise the suspicion of cholangiocarcinoma. Survival in patients with a dominant stricture is 13.7 years as against 23 years without it [163].

Cholangitis occurs in over 5% of patients of PSC at the first presentation. It should be suspected when patients develop fever, abdominal pain and jaundice. The incidence of cholangitis in patients undergoing liver transplantation is 38% in one series [164].

Osteodystrophy or bone loss occurs commonly in patients with cholestatic liver disease such as PSC. It usually occurs in young males and bone loss occurs at the rate of 1% each year. It is refractory to treatment with calcium, vitamin D, hormones or steroids. When assessed by dual-energy X-ray absorptiometry, the risk of bone loss can be as much as 24 times in PSC. The risk factors for this are age above 54 years, BMI <21 kg/m^2 and long duration of IBD (>19 years) [165].

10.6 Pancreas

10.6.1 Nutritional Management of Acute Pancreatitis

Acute pancreatitis is a common intra-abdominal inflammatory condition of varied aetiology. The disease is mild in the vast majority of patients and has a favourable outcome. The acute severe form of the disease on the other hand is a lethal form with a high mortality and morbidity. A number of strategies have provided clinical benefit in severe acute pancreatitis (SAP). Of these, nutritional management is by far the most effective. SAP is associated with persistent end-organ failure, commonly respiratory, circulatory and renal. Treatment is targeted to support these

organs. As of now there is no definitive therapy for acute pancreatitis. Patients are managed with fluids, analgesics, antibiotics and nutritional supplements besides adequately treating local complications such as pseudocyst and walled-off pancreatic necrosis by suitable interventional methods, be it endoscopic or percutaneous. The focus here is nutritional support in the management of SAP.

10.6.1.1 Which Form of Nutrition: Parenteral or Enteral?

This depends largely on the functional integrity of the stomach and small intestine. Patients of SAP often have poor gastric emptying and paralytic ileus, which is made worse with the use of narcotics. Moreover, local complications of pancreatitis (peripancreatic fluid collections) can have a pressure effect on the stomach and/or duodenum. As a result oral feeds may not be possible in these patients. Patients on ventilator support also cannot be given oral feeds. Enteral feeding through the nasogastric or nasojejunal tubes is often not tolerated by patients because of discomfort. In addition, these tubes often get displaced or withdrawn. Reinsertion of the tubes, under endoscopic or radiological guidance, is cumbersome in such patients. All these factors favour parenteral feeding. The distinct advantage of enteral nutrition is that it prevents mucosal atrophy and transmigration of bacteria (an important cause of sepsis in SAP). Also, enteral feeding augments intestinal motility and is cheaper than parenteral preparations. Enteral nutrition improves motility in patients with paralytic ileus [166].

The relative merits of these forms of nutritional therapy have been evaluated in a systematic review [167]. Eight published randomized trials including a total of 348 patients were included. Enteral feeding was given through a nasojejunal tube and parenteral nutrition through a catheter placed in a central vein. Enteral nutrition was shown to reduce mortality, multi-organ failure, systemic infection and surgical intervention in comparison with parenteral nutrition. The length of hospital stay too was shown to be reduced. In view of these, enteral nutrition appears to be a better option while managing patients of SAP and has been recommended by the American College of Gastroenterology, American Gastroenterological Association and International Association of Pancreatology [168].

When should enteral feeding be started? Patients with mild acute pancreatitis can usually be started on oral feeds in 2–3 days. Those with moderately severe acute pancreatitis can be started on oral feeding only after a variable period and hence should receive enteral nutritional support [169]. Early enteral feeding has been shown to avoid end-organ failure in a large series of patients (1200). Enteral feeding started within 48 h of onset of illness was associated with organ failure in 21% of patients as opposed to 81% when enteral feeding was started after 48 h. This benefit of early enteral feeding has also been shown in a recent meta-analysis [170]. However, there was no benefit in mortality with early enteral feeding. In yet another randomized controlled trial [171], early enteral feeding (within 24 h) was compared with on-demand enteral feeding after 72 h. The primary endpoint of this study was major infection or death. The study did not detect any significant difference in the

primary endpoint in either group (early or on-demand feeding). However, it did show that patients receiving on-demand nutrition tolerated oral feeds without using a tube.

Should the feed be administered in the stomach through a nasogastric (NG) tube or in the jejunum through a nasojejunal (NJ) tube? Gastric feeding is thought to increase pain and aggravate pancreatitis due to food-induced pancreatic stimulation [168]. In view of this, NJ feeding is practised. However, placement of a NJ tube is cumbersome and needs a skilled endoscopist or radiologist. It causes more inconvenience to patients [172–175]. A nasogastric (NG) tube is thus an alternative. A number of studies have been published comparing NG and NJ feeding. The results of these studies can be summarized as follows: There was no difference in mortality. Feeds were equally tolerated in the two groups and NG feeding is simple. NG feed was not shown to increase pain and is thus as good as NJ feeding. A meta-analysis subsequently published showed no difference in mortality, hospital stay and infection rate between the two groups. Both forms of feeding were equally well tolerated. NJ feeding thus is not advised in the management of most patients with SAP. However, it still has a place when the patient has a high risk of aspiration. Also, patients on a ventilator and those not tolerating NG feed should be fed through NJ tube.

The other issue concerning enteral feeding in SAP is the composition of the feed. Various commercially available formulations include (1) polymeric formulations comprising complex lipids, carbohydrates and proteins and (2) elemental formulations comprising simple amino acids, carbohydrates and free fatty acids. Other formulations used are glutamine-rich feeds and feeds with probiotics, fibres, etc. [168].

Immuno-nutrition using arginine, glutamine and polyunsaturated fatty acids has been evaluated in multiple studies and compared with standard feeding. A meta-analysis [176] showed some benefit in mortality but not for prevention of infection, end-organ failure or inflammatory response. This benefit was not seen with the use of probiotics or fibre-based feeds. A systematic review did not show any benefit of immuno-nutrition or probiotics [177]. It also showed that polymeric formulations are as well tolerated as oligomeric ones (elemental).

10.6.2 Disconnected Pancreatic Duct Syndrome

This condition is defined as disruption of the main pancreatic duct resulting in discontinuity of the duct with the gastrointestinal tract. The term disconnected pancreatic duct syndrome or DPDS was coined by Kozarek et al. in 1991 [178]. It occurs in patients with SAP due to necrosis of the main pancreatic duct. The viable pancreatic remnant continues to secrete pancreatic juice which then collects inside (intra- or extrapancreatic) or drains outside (external pancreatic fistula, commonly through drains placed following percutaneous or surgical drainage).

DPDS can also occur in chronic pancreatitis, in pancreatic trauma or after pancreatic surgery. The incidence of the condition is, however, not known. About 10–30% of patients with SAP are reported to develop DPDS [179]. Lawrence et al. [180] reported an increasing incidence of the condition.

10.6.2.1 Pathogenesis

In SAP, it is not only the pancreatic parenchyma, which undergoes necrosis, but even the main pancreatic duct gets necrosed. It usually occurs in the central part of the duct. As a result, the distal remnant remains disconnected from the main duct due to which the exocrine secretion from the distal portion cannot enter the gastrointestinal tract and remains collected in the abdominal cavity (intra-/extrapancreatic) or drains outside in the form of an external pancreatic fistula following percutaneous or surgical drainage. Howard et al. reported that majority of patients with DPDS develop an external pancreatic fistula (70%) and a smaller number develop an intra-abdominal collection [181]. The commonest location of ductal disruption is the region of the neck and body of the pancreas because it is supplied only by the dorsal pancreatic artery unlike the rest of pancreas which has more than one source of blood supply [182].

10.6.2.2 Clinical Features

Patients with SAP who have undergone either surgical necrosectomy or percutaneous drainage of infected pancreatic necrosis and develop persistent external pancreatic fistula despite waiting for considerable time are suspected to have DPDS. The volume of fluid drained reflects the amount of viable exocrine pancreatic mass [183].

Most patients have pain, weight loss, malabsorption and nausea. Diabetes developing after DPDS is common. Due to loss of pancreatic enzymes, protein and electrolyte abnormalities occur. Patients may also develop nutritional deficiency. Complications of DPDS such as portal hypertension, pseudoaneurysm and pancreatic ascites can also occur. DPDS is more frequent in biliary pancreatitis than other causes such as due to alcohol intake. It has also been reported that 50% of patients with walled-off pancreatic necrosis who undergo percutaneous drainage develop DPDS [179].

10.6.2.3 Diagnosis

It is important to correctly diagnose DPDS because its treatment is quite different from other causes of post-pancreatitis fluid collections (e.g. pseudocyst). Post-necrosectomy fluid collections may also occur due to proximal duct obstruction. In the former, a cysto-gastrostomy/jejunostomy and in the latter

transpapillary drainage with stent placement can suffice. Partial disruptions leading to a fluid collection or external fistula too need to be differentiated as these are not true DPDS.

A number of imaging tools are available and include ultrasound, computerized tomography (CT), magnetic resonance cholangiopancreatography (MRCP), endoscopic retrograde cholangiopancreatography (ERCP) and fistulography and endoscopic or intraoperative ultrasound. Transabdominal US is not useful because it does not establish pancreatic ductal disruption and at best can demonstrate a peripancreatic fluid collection. MRCP is a non-invasive technique and is hence preferred over ERCP. However, ERCP can be therapeutic too. Fistulography can differentiate lateral (non-DPDS) or end fistula (true DPDS) [184]. The diagnostic imaging features of DPDS include: [179]

1. Disrupted pancreatic duct with viable pancreatic parenchyma distally and the presence of fluid collection on CT or MRI
2. Disconnected pancreatic duct on ERCP with inability to cannulate the distal duct
3. CT evidence of necrosis of pancreas of ~2 cm length at the region of the head and body, enhancing distal pancreas and pancreatic duct entering the collection at a right angle

10.6.2.4 Treatment

In the past surgery used to be the mainstay of treatment of DPDS. However, we now have a number of methods of treatment available. The treatment strategy largely depends on whether DPDS is associated with a collection or external fistula.

Treatment for Collection If the collection is asymptomatic and stable, one should pursue an expectant course. On the other hand, a symptomatic collection with pain, fever, etc. should have internal drainage (endoscopic) with or without passing a stent in the distal duct (if feasible). One must not drain such a collection percutaneously as an external pancreatic fistula will result.

Management of External Pancreatic Fistula First, one should establish DPDS. Next, the patient should be given a trial of somatostatin therapy. The fluid and electrolyte abnormalities should be corrected, and skin excoriation and infection should be prevented. Nutrition should be maintained. One should try endoscopic treatment as mentioned earlier. When all attempts fail to control the fistula, one should consider surgical treatment. Even when surgery has been decided, one should not hurry. Enough time should be allowed for all inflammation to subside and the fistula to stabilize. A fistula which drains >100 ml/day for more than 3 months needs surgical correction [183].

The surgical alternatives available are distal pancreatectomy with or without splenectomy, fistulo-jejunostomy using a Roux-en-Y loop, pancreatogastrostomy or pancreatojejunostomy. Cholecystectomy should be added to these (if not already done) in all patients.

Non-resectional methods are simple, quick, have less blood loss and are associated with fewer complications, shorter hospital stay and low endocrine and exocrine functional abnormalities [179, 183, 184]. Overall, the complications reported in these series is 6%. The incidence of intra-abdominal abscess associated with these techniques has been reported to be higher than resectional procedures [179]. The success rate of non-resectional procedures is as high as 80% [179]. There was no difference in terms of outcome of the three non-resectional methods mentioned above [179]. Resection of the pancreas along with the disconnected duct is a difficult procedure due to prior pancreatitis. The complications usually seen are bleeding, prolonged operation, and abnormalities of exocrine and endocrine pancreatic functions. However, resection is recommended for patients of DPDS with left-sided portal hypertension [179, 184]. When the remnant pancreas is less than 6 cm, then too a distal pancreatic resection is preferred [179]. The success rate of resectional surgery has been reported to be 75% [179]. However, pancreatic fistula rate is reported to be higher [184].

Non-surgical methods of treatment of DPDS include endoscopic treatment. It is successful in 61–75% of patients [185]. Though the results are inferior to those of surgical treatment, these are less invasive and with little mortality and morbidity. These can be repeated when necessary. However, recurrence occurs in half the patients. More importantly, endoscopic treatment improves both the local and general condition of the patient making them more suitable for surgical treatment when that is necessary.

Endoscopic treatment consists of an ERCP and stent placement along with drainage of the distal segment of pancreas. While drainage of the distal pancreatic remnant is difficult, unless it is achieved, transpapillary drainage may not be successful [179]. Various authors have reported successful cannulation of the distal duct with modern endoscopic techniques. Transpapillary drainage, however, effectively drains partial (lateral) disruption of the pancreatic duct [186].

When cannulation of the distal, disconnected duct fails endoscopically, one can attempt it using endoscopic ultrasound (EUS). EUS can locate the collection and the disconnected duct, and then a stent can be placed in the distal segment to drain it into either the stomach or the duodenum [187, 188]. These techniques are done under radiographic control (pancreaticography). Whether the prosthesis so used should be permanent or temporary is a matter of continuing debate. For adequate drainage, permanent stents are better but have the disadvantage of migration and infection [189]. Temporary stents, on the other hand, get blocked frequently, resulting in failure of closure of the fistula [190]. Cyanoacrylate glue has also been used to close the fistula in DPDS. The glue has been used both in the distal pancreatic duct and in the fistulous tract [191, 192].

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