s, visit our website www.ejaypee.com, for detailed information on gastroenterology books, visit our website www.ejaypee.com, for detailed information on gastroenterology books,

KB's Management of GASTROINTESTINAL CANCERS

Basics & Perspective



Kirti Bushan

Forewords
SH Advani
Nagraj G Huilgol

JAYPEE

Contents

SECTION 1: Cancers of Esophagus

1. Surgical Anatomy of Esophagus 3
2. Epidemiology of Esophageal Cancer 12
3. Etiology and Risk Factors of Esophageal Cancer 16
4. Pathology of Esophageal Cancers 26
5. Pathogenesis of Esophageal Cancers 31
6. Diagnosis of Esophageal Cancers 37
7. Tumor Node Metastasis (TNM) Staging and Stage Grouping of Esophageal Cancers 46
8. Management of Premalignant Lesions and Early Esophageal Cancers 51
9. Surgery in Esophageal Cancers: Principles, Extent of Resection, and Role of Lymphadenectomy 57
10. Minimal Invasive and Salvage Esophagectomy 72
11. Prevention and Management of Complications of Radical Esophagectomy 79
12. Neoadjuvant Chemotherapy and Surgery versus Surgery Alone in Resectable Esophageal Cancer 93
13. Neoadjuvant Chemoradiation Followed by Surgery in Esophageal Cancers 101
14. Neoadjuvant Chemoradiotherapy versus Neoadjuvant Chemotherapy Followed by Surgery in Esophageal Cancers 108
15. Role of Definitive Chemoradiation in Esophageal Cancers 112
16. National Comprehensive Cancer Network-based Treatment Guidelines for Esophageal Cancers 115

SECTION 2: Cancers of Stomach

17. Surgical Anatomy of Stomach 123
18. Epidemiology of Stomach Cancer 132
19. Etiology of Stomach Cancer 140
20. Pathology and Pathogenesis of Stomach Cancers 156
21. Diagnosis and Staging of Stomach Cancers 167
22. Role of Surgery in Gastric Cancer Management 176

23. Lymphadenectomy in Gastric Cancers: Current Status and Future Prospects....187
24. Role of Laparoscopic Surgery in Gastric Cancer....201
25. Multimodality Treatment of Gastric Cancers....209
26. Targeted Therapies in Gastric Cancer....215
27. National Comprehensive Cancer Network Guidelines for Cancer Stomach Management....223
28. Gastroesophageal Junction Cancers....228

SECTION 3: Cancers of Small Intestine

29. Surgical Anatomy of Small Bowel....249
30. Epidemiology, Etiology and Risk Factors of Small Intestine Cancers....254
31. Pathology and Pathogenesis of Small Bowel Cancer....259
32. Diagnosis and Staging of Small-bowel Cancer....264
33. Role of Surgery and Adjuvant Treatment in Small-bowel Cancer....268
34. Management of Neuroendocrine Neoplasm....273
35. Management of Gastrointestinal Stromal Tumors....285

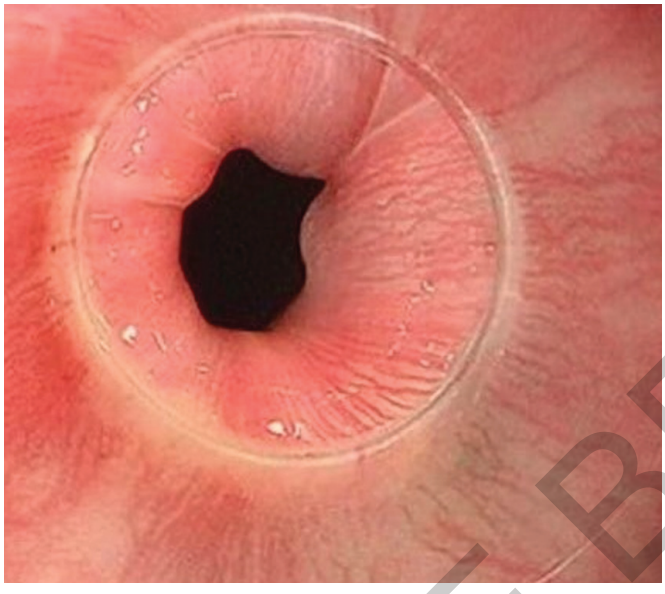
SECTION 4: Cancers of Colon, Rectum, and Anal Canal

36. Surgical Anatomy of Colon, Rectum, and Anal Canal....303
37. Epidemiology and Risk Factors of Colorectal Cancer....314
38. Molecular Biology: Genetic Events and Hereditary Syndromes Associated with Colorectal Cancers....326
39. Pathology and Pathogenesis of Colorectal Cancers....334
40. Diagnosis and Staging of Colorectal Cancers....343
41. Role of Surgery in Management of Colon Cancers....356
42. Adjuvant Treatment for Resectable Colon Cancer....382
43. Management of Stage IV (Metastatic) Colon Cancer....384
44. Role of Surgery in Rectal Cancers....389
45. Role of Radiotherapy and Chemotherapy in Rectal Cancers....404
46. Epidemiology and Risk Factors of Anal Cancers....410
47. Pathology, Pathogenesis, and Molecular Biology of Anal Canal Cancers....415
48. Diagnosis and Staging of Anal-canal Cancers....422
49. Management of Anal-canal Cancers....426

Index....*431*

CHAPTER

28 Gastroesophageal Junction Cancers



Gastroesophageal junction—a distinct pathophysiologic entity at crossroads of esophagus and stomach—cancers here pose a serious challenge because there is a lack of consensus regarding management.

INTRODUCTION

This chapter discusses gastroesophageal junctional anatomy, epidemiology, and etiology of cancers arising from gastroesophageal junction (GEJn). The classification of gastroesophageal cancers and what makes these cancers a distinct entity is also discussed. The management of these cancers has been thoroughly addressed.

GASTROESOPHAGEAL JUNCTION CANCER: RESULT OF EPIDEMIOLOGICAL SHIFT

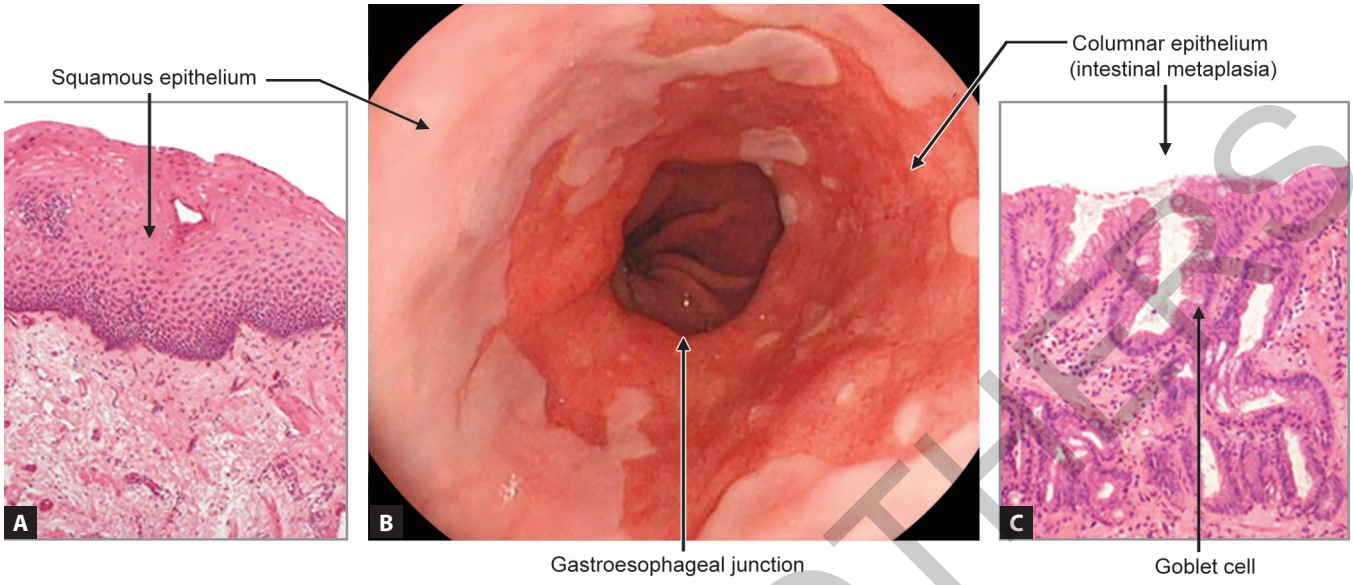
Over the past decades, there has been observed an epidemiological shift in the incidence and distribution of cancers within the esophagus and stomach away from distal gastric adenocarcinomas and proximal SCC esophagus toward the junction of esophagus and stomach (GEJn).[1,2] Taken together, this has led clinicians to increasingly label these tumors as adenocarcinoma of GEJn. More than 90% of GEJn tumors are adenocarcinomas. GEJn tumors seem to be a distinct pathophysiologic entity, separate from esophageal and gastric carcinomas yet with some oncologic features of each.[3]

GASTROESOPHAGEAL JUNCTION: DEFINITION

Where the esophagus ends and the stomach begins has been a bone of contention for decades between the histologist, physiologist, gastroenterologist, radiologist, and surgeon. It has been defined anatomically, physiologically, radiologically, endoscopically, and histologically. Several landmarks have been used to define the GEJn. A simple definition of GEJn is point where tubular esophagus meets gastric pouch. GEJn is the region between which the stratified squamous mucosa-lined esophagus ends, and the columnar mucosa-lined stomach begins [squamocolumnar junction (SCJ), or Z line endoscopically] **(Figs. 1 and 2)**. SCJ may mark the GEJn provided the patient does not have a distal esophagus replaced by columnar epithelium as seen with Barrett's esophagus (BE). As the SCJ shifts toward proximally when there is columnar metaplasia of the esophagus[4,5] or in rare cases, the SCJ shifts distally into the stomach,[6] it cannot be used as an anatomical landmark of the GEJn.

For many, the esophagogastric junction is a muscle and not a mucosal junction. The boundary of the esophagus is at the upper esophageal sphincter and lower esophageal sphincter (LES) at the oral and anal ends, respectively. The distal end of the LES is the esophagogastric junction.[7] The landmark externally is the collar of Helvetius (or loop of Willis) where the circular

JAYPEE BROTHERS



Figs. 1A to C: Endoscopic view of gastroesophageal junction.
Courtesy: Dr Kirti bushan.

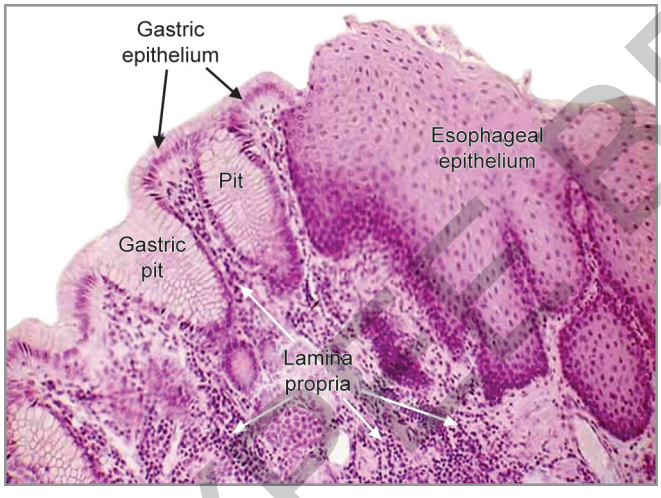


Fig. 2: Microscopic view of gastroesophageal junction.
Source: https://ar.inspiredpencil.com/pictures-2023/gastroesophageal-junction-histology-labeled

muscle fibers of esophagus join the oblique muscle fibers of stomach **(Fig. 3)**.

Gastroesophageal junction nowadays is identified endoscopically by landmarks like proximal end of gastric folds (PEGF) and the distal end of esophageal palisade vessels (DEPV)[8] **(Figs. 4A and B)**. At present, the mucosal esophagogastric junction (EGJn) can be defined endoscopically as the distal ends of esophageal longitudinal fine palisade vessels that meet the proximal ends of gastric longitudinal mucosal folds **(Figs. 5A and B)**.[9]

Another proposed anatomic landmark for the GEJn is the angle of His, which has been used for surgically resected or autopsy specimens. Although the angle of His can be surmised during endoscopy with retroflexed views, it can be difficult to determine its precise location if hiatal hernia is present.

EPIDEMIOLOGICAL TREND

At the turn of the 20th century, adenocarcinomas of the GEJn were uncommon, overshadowed by the far more common distal gastric and proximal squamous esophageal cancers. In the past 30 years this relationship has reversed. The incidences of proximal esophageal cancer and distal gastric cancers have declined significantly, whereas the incidences of distal esophageal and proximal gastric cancers are both on the rise.

The incidence of GEJn tumors has rapidly increased in West as reported by various population-based studies.[2,10,11] Worldwide, the increased incidence of GEJn lesion is homogeneous among Western countries such as USA, Canada, Sweden, UK, and most parts of Europe. The incidence of adenocarcinomas of GEJn, cardia, and esophagus has increased by 4–10% each year since 1976 in USA among men.[12-14] Similarly, in Canada an increase of incidence of distal esophageal and proximal gastric adenocarcinomas was recorded from 1964 to 2002.[15] In contrast, among Eastern Asian countries,

JAYPEE BROTHERS

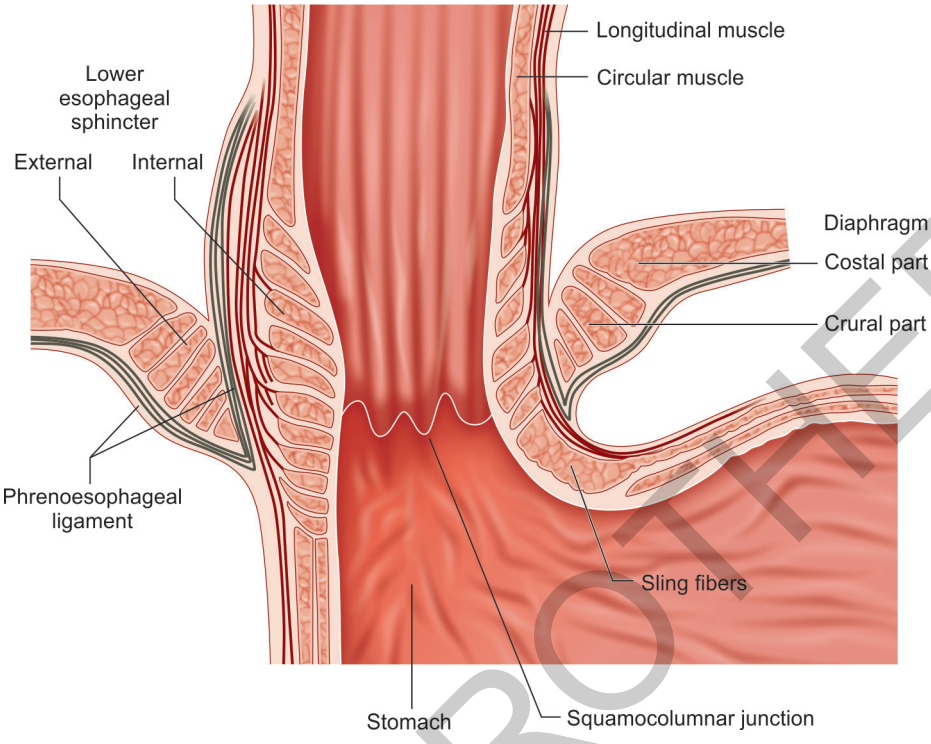
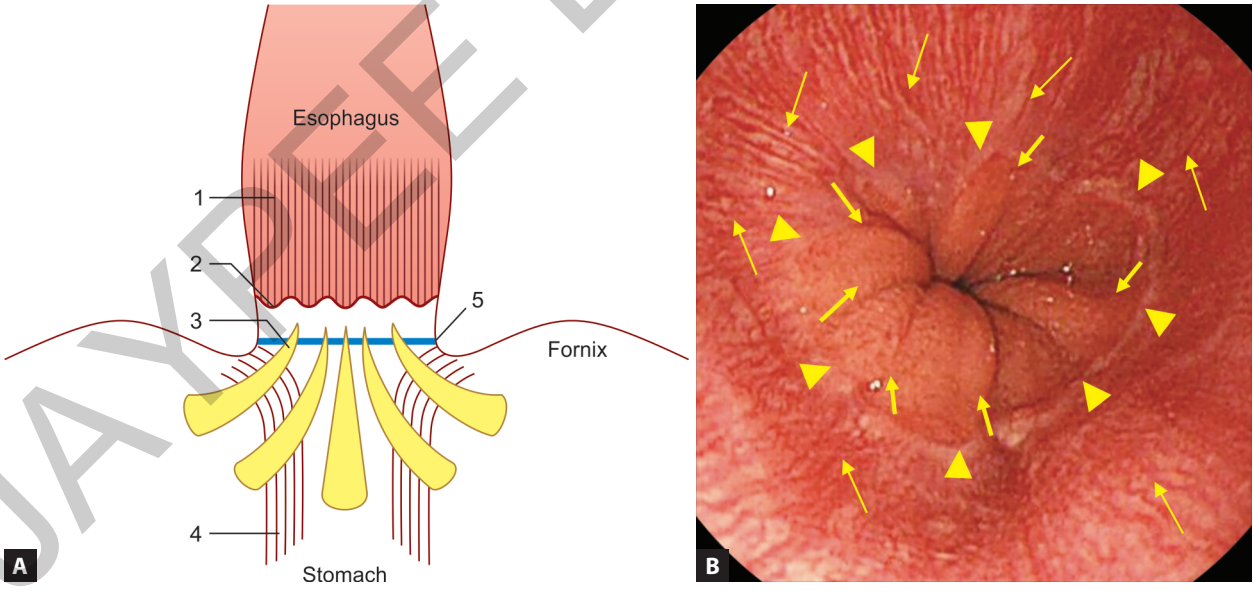
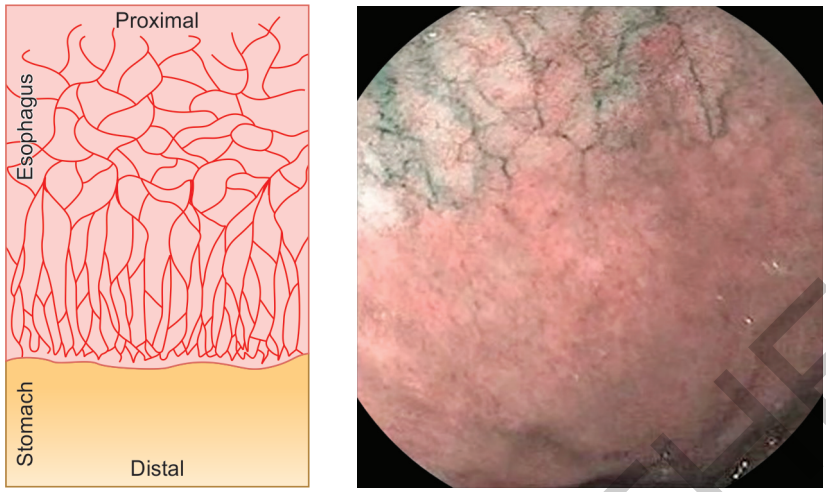


Fig. 3: Gastroesophageal junction.
Source: Mittal RK, Balaban DH. The esophagogastric junction. N Engl J Med. 1997;336(13):924-32.



Figs. 4A and B : Landmarks of gastroesophageal junction: (A) Schema of the landmarks used for gastroesophageal junction (GEJn). Endoscopic view of the GEJn (1) palisade vessels, (2) squamocolumnar junctional line (Z line), (3) proximal end of the gastric folds (PEGF), (4) gastric sling fibers; and (5) angle of His; (B) Distal end of Palisade vessels (DEPV - thin arrows), squamocolumnar junctional line (Z-line) (arrow heads) and the end of gastric folds (thick arrows) are shown.
Source: Sugano K, Spechler SJ, El-Omar EM, McColl KEL, Takubo K, Gotoda T, et al. Kyoto international consensus report on anatomy, pathophysiology and clinical significance of the gastro-oesophageal junction. Gut. 2022;71(8):1488-514.

JAYPEE BROTHERS



Figs. 5A and B: Distal end of palisade blood vessels.
Source: Kumagal Y et al Dis Esophagus 2012; The Practicing Endoscopist. What are the Palisade Veins?. The Practicing Endoscopist. Published Jan 26, 2024. https://thepracticingendoscopist.com/p/palisade-veins

the non-gastroesophageal lesions are predominant and squamous cell carcinomas are more frequent than adenocarcinomas.

Gastroesophageal junction adenocarcinomas can arise from precursor atrophic gastritis which is of intestinal or diffuse type similar to gastric non-cardia cancer (GNCC). It can also arise from gastroesophageal reflux disease (GERD) which is of intestinal subtype similar to esophageal adenocarcinomas (EAC).[16,17] These two distinct etiologies may be the explanation for the more gradual rise in the incidence of GEJn adenocarcinomas in Western countries. Predominant risk factors for GEJn tumors include: GERD, BE, and obesity, alcohol abuse, smoking, male sex, and Caucasian ethnicity.[18-21]

Gastroesophageal Reflux Disease

Gastroesophageal reflux disease in a dose-dependant manner contributes to etiology of GEJn and distal esophageal adenocarcinomas. In Western countries, GERD is a major health burden and reported prevalence is one in every three adults.[17,22] In Asian countries which seemed to be GERD-free zone, recent reports suggested its rapid surge in Asia with a reported prevalence of 15% for erosive esophagitis and of up to 20% for reflux symptoms. In a recent epidemiological study, the incidence of GERD was 22.2% in South India, 25% in Taiwan, 3.5% in South Korea, and 23.4% in in Japan.[23] However, the prevalence of BE and EAC remains low in this region.[24] The reasons for this trend are decreased *Helicobacter pylori* (*H. pylori*) infection rates and improved diagnostic ability of endoscopic methods for GERD compared with that in the past.[25]

Obesity

Obesity causes increased incidence of GERD and BE.[26] Obesity has become a social problem that cannot be ignored. Not only Western countries but Asian countries also have this problem. Westernization of diet and lifestyle, decreased physical activity combined with an increase in overeating might be possible reasons for this trend. As per recent epidemiological study, the percentage of obesity defined as body mass index of >25 kg/m^2 in men and women was 22.9% and 24.7% in Japan, 43.2% and 47.4% in India, 26.9% and 31.1% in China, and 35.6% and 29.8% in Korea, respectively.[27,28] The incidence of body mass index showed an increasing trend from 1995 to 2000, but since 2005 it has hardly changed. Thus, obesity is a serious problem worldwide, but it is less serious in Asia than in Western countries.

Helicobacter pylori

The persistence of *H. pylori* infection in gastric epithelium causes atrophic gastritis and decreased gastric acid secretion. However, *H. pylori* infection has a suppressive effect on GERD, BE, Barrett's esophageal adenocarcinoma, and GEJ adenocarcinoma. It has been

JAYPEE BROTHERS

reported that *H. pylori* infection in cardia cancers in Western countries is less compared to Asian countries where *H. pylori*-induced gastric cancer rates are high in both non-cardia and cardia cancers.[29] When compared with distal gastric adenocarcinomas, *H. pylori* infection rate in GEJ adenocarcinoma was significantly lower, and the degree of histological gastritis in the gastric body was also significantly lower.[30]

In Asian countries such as Japan there are two types of GEJ adenocarcinoma reported—one that is not associated with *H. pylori* infection as in Western countries and another that is associated with *H. pylori* infection. McColl described two types of pathogenesis of GEJn adenocarcinomas—one that is associated with atrophic gastritis and low-gastric acid secretion (similar to distal gastric cancers) and another type that is associated with excessive acid secretion with or without *H. pylori* infection (similar to esophageal adenocarcinomas).[31] A large number of patients with chronic gastritis have undergone *H. pylori* eradication therapy in Asian countries, including Japan. At present, it is reasonable to assume that the widespread use of *H. pylori* eradication therapy for chronic gastritis will not directly lead to an increase in the incidence of esophageal adenocarcinoma and GEJn adenocarcinoma, although further studies are needed to clarify this important issue.

To summarize, both gastric cardia and lower esophageal adenocarcinomas are distinct from non-cardia gastric cancers in terms of underlying risk factors. For distal esophageal AC, gastroesophageal reflux and subsequent Barrett's metaplasia are leading causes but same association could not be established for gastric cardia cancer. Gastric cancers are associated with *H. pylori* infection, chronic gastritis, and low-acid production, whereas GEJn tumors are associated with high acid production and are inversely associated with *H. pylori*. Alcohol intake and tobacco use are important risk factors for SC esophagus while as GERD and obesity are important risk factors in GEJn adenocarcinomas.[32]

CLASSIFICATION OF GASTROESOPHAGEAL JUNCTION TUMORS

Gastroesophageal junction cancers have been bone of contention between different treating faculties with thoracic surgeons treating them as esophageal cancers and gastrointestinal surgeons treating them as gastric cancers. This led to longstanding confusion and chaos in classification and treatment of GEJn tumors. With advancement and better understanding regarding origin and biological behavior of esophageal and gastric cancers, a consensus was reached that EGJn cancers are distinct category from the standpoint view of epidemiology, genetics, pattern of spread and prognosis.

Thus, in 1997, at the consensus conference of the International Gastric Cancer Association (IGCA) and the International Society for Diseases of the Esophagus (ISDE), it was agreed that a clear definition and classification of tumors arising near the esophagogastric junction was needed. The best and most commonly used classification is the Siewert and Stein classification.[33] This classification was approved at the Second International Gastric Cancer Congress, held in Munich, Germany, in April 1997, and has since been accepted worldwide.[33,34]

- The Siewert-Stein classification classes tumors of the GEJn according to the relationship between the epicenter of the tumor and the gastro-esophageal junction **(Fig. 6)**.
- Siewert type I cancers are located between 1 and 5 cm above the GEJ and are generally considered to arise against the background of BE in the lower esophagus.

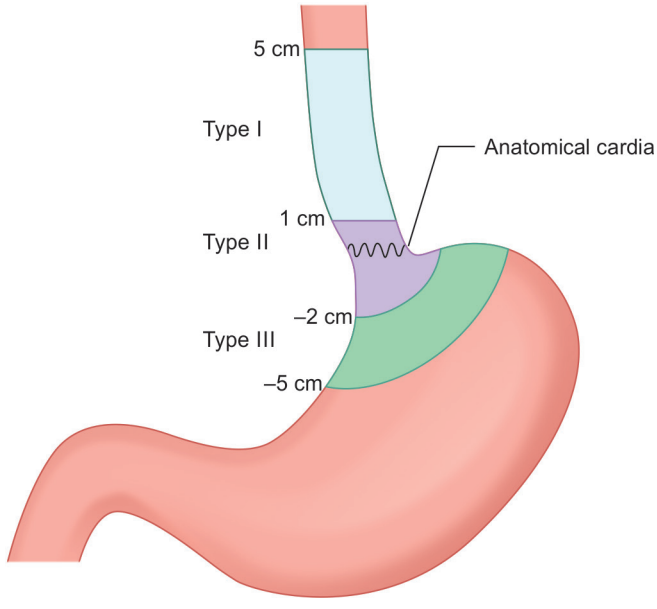


Fig. 6: The Siewert classification of gastroesophageal (GE) junction adenocarcinomas.
Source: Brown AM, Giugliano DN, Berger AC, Pucci MJ, Palazzo F. Surgical approaches to adenocarcinoma of the gastroesophageal junction: the Siewert II conundrum. Langenbecks Arch Surg. 2017;402(8):1153-8.

JAYPEE BROTHERS

- Siewert type II cancers are located between 1 cm above and 2 cm below the GEJ and are considered to be true gastric cardia tumors.
- Siewert type III cancers are located between 2 and 5 cm below the GEJ, with invasion of the esophagus, and are considered to be subcardial gastric cancers.
- In Japan, Nishi's classification system defines GEJ cancer as a tumor with an epicenter between 2 cm above and 2 cm below the GEJ, regardless of its histological subtype **(Figs. 7 and 8)**.[35-37]

GASTROESOPHAGEAL JUNCTION TUMORS: A DISTINCT PATHOPHYSIOLOGIC ENTITY

Gastroesophageal junction adenocarcinoma has a unique distinct pathophysiologic characteristics which make it a distinct entity when compared with esophageal or gastric cancers. The deep location of the GEJn, as well as the pliability of the gastric cardia, often masks the vague symptoms caused by early-stage lesions leading to delayed

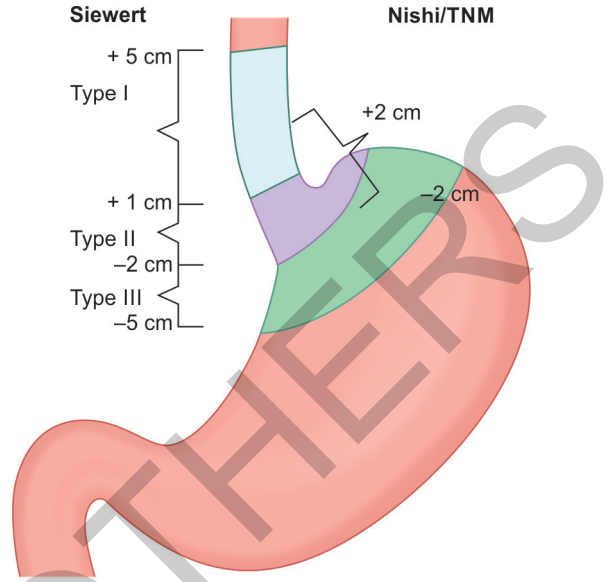
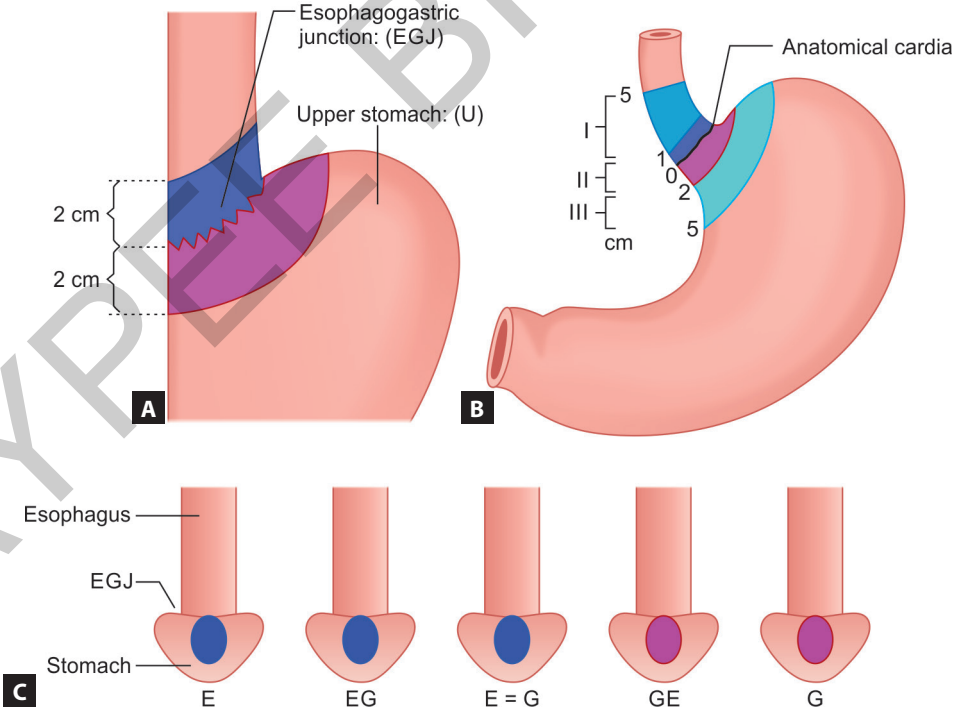


Fig. 7: Nishi's classification of gastroesophageal junction (GEJn) cancers.
Source: Mickael C, Minoa J, Nadja N, Stefan M. Recent management of esophago-gastric adenocarcinoma. Glob Surg. 2017;3(3).



Figs. 8A to C: Definition and description of esophagogastric junction (EGJn) cancer. Nishi's classification (A) adopted by the tumor, node, and metastasis (TNM) classification of malignant tumor 8th edition; the terms "E, EG, E=G, GE, and G" were used to describe the subtypes depending on the epicenter location at the oral "E" and anal "G" portions of the EGJn.
Source: Liang R, Bi X, Fan D, Du Q, Wang R, Zhao B. Mapping of lymph node dissection determined by the epicenter location and tumor extension for esophagogastric junction carcinoma. Front Oncol. 2022;12:913960.

JAYPEE BROTHERS

presentation. Due to the strategic location at the crossroads of two major body cavities, lymphatic spread occurs in two directions—proximally into the mediastinum and distally to the celiac lymph nodes (LNs). Thus, these tumors can spread easily and present in advanced stage.

Gastroesophageal junction cancer is a biologically aggressive disease with early LN involvement. For stage-for-stage, GEJn cancers have a much worse prognosis than more distal gastric cancers, with worse survival and higher rates of both local and distant recurrences. About two-third patients have positive LNs at the time of presentation. The 5-year survival rate (YSR) drops from 60–65% to 10–15% if there is LN involvement.[38] The poor prognostic factors include differentiation and grade of tumor, nodal involvement, extra capsular extent, lymphovascular invasion, perineural invasion, RO resection, and response to therapy.

From the pathological point of view, there are two separate pathways carcinogenesis in esophagogastric junction—one is the "Barrett pathway" and the other one is "gastric pathway;" an additional pathway that is "independent junctional pathway" has been doubted to exist.[39] In addition, differences in biomarker and molecular tumor characteristics between gastric cardia cancer and esophageal adenocarcinoma seem to exist.[40]

PREOPERATIVE WORKUP

Accurate pretreatment staging is essential to determine both the extent of disease and local resectability. The first test to perform is endoscopy, which helps in diagnosis by doing biopsy and locating tumor properly while assessing surrounding areas. A standard evaluation also includes contrast-enhanced abdominal and chest computed tomography (CT) scans of chest and abdomen. If no distant disease is identified, patients can undergo endoscopic ultrasound (EUS) or PET scan or diagnostic laparoscopy. In general, initial staging of locoregional disease is usually best done with a combination of CT and EUS, while staging of possible distant metastatic disease is best assessed with fluorodeoxyglucose positron emission tomography/computed tomography (FDG-PET/CT).[41]

The findings on endoscopy are critical in determining the proximal extent of resection and ultimately dictate the appropriate operative approach **(Fig. 9)**. Endoscopic biopsy helps in diagnosis. It also helps in identifying epicenter of tumor. The biopsy tissue can be submitted for HER 2 receptor studies, MSI, PDL 1 and even NGS study.

Given that the stage of the tumor affects the extent of resection, endoscopic ultrasonography (EUS) is the most reliable adjunct to preoperative planning in GEJn cancers that do not have distant disease on CT scan. Endoscopy with ultrasound gives us very accurate T-staging, which is the depth of the penetration of the tumor to the esophageal and gastric wall. Endoscopic ultrasound is about 85–90% accurate for T-stage. It also gives us some idea about nodal staging with about 60–70% accuracy.[42] Increasingly, gastroenterologists are combining endoscopic ultrasound with a fine needle aspirate of the LNs to get pathologic confirmation of nodal status. With this combination, the accuracy of LN staging goes up to as high as 90%. EUS helps to identify high-risk T3 node-positive patients who would be appropriate candidates for neoadjuvant chemotherapy than surgery alone. The outcome with surgery at this stage is quite poor as up to 30–35% of tumors are inoperable if we go for upfront surgery, and long-term survival ranges from 20 to 25% with primary surgical management alone.[43]

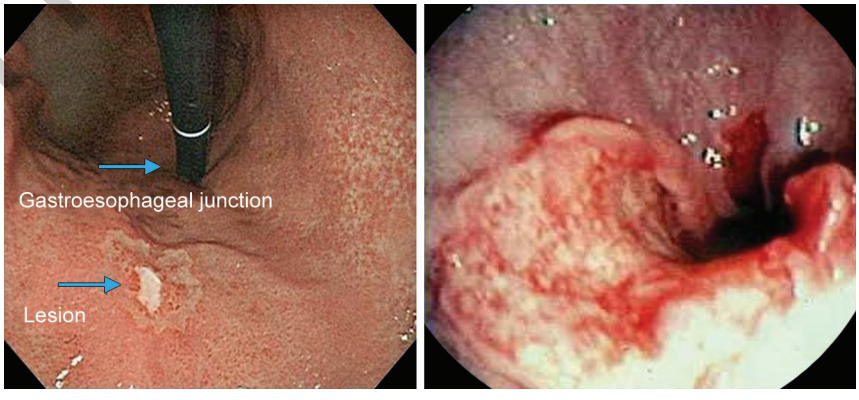


Fig. 9: Endoscopic view of early and advanced gastroesophageal junction (GEJn) cancer.
Source: Jihoon Kim et al. J Gastric Cancer. 2012;12(3):187-93.

JAYPEE BROTHERS

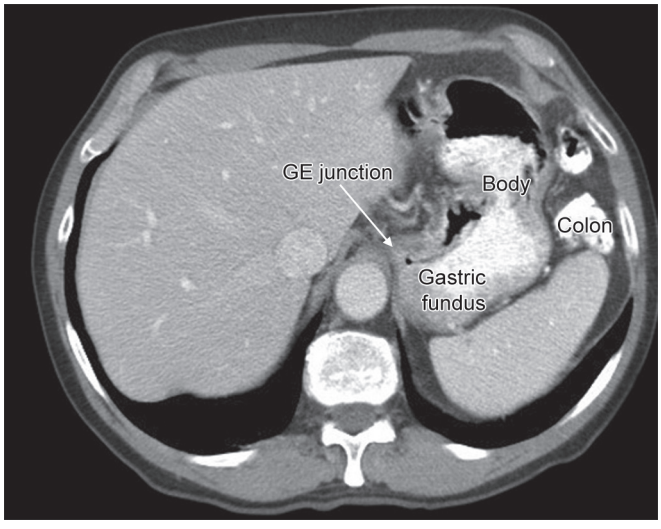


Fig. 10: Computed tomography (CT) scan showing gastroesophageal junction (GEJn) and stomach.
Source: https://animalia-life.club/qa/pictures/ge-junction

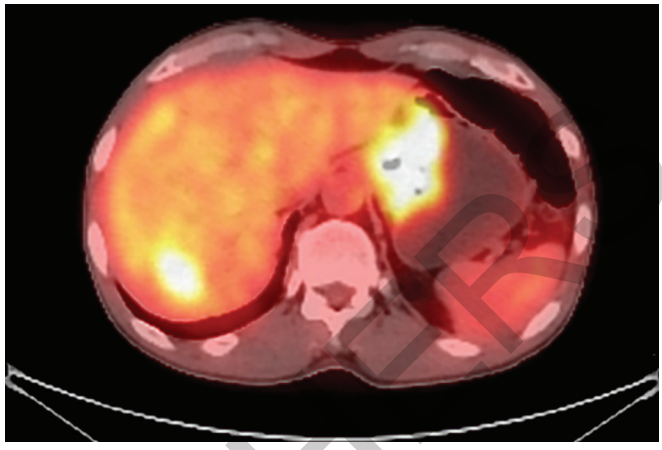


Fig. 11: Fluorodeoxyglucose positron emission tomography (FDG PET) scan showing gastroesophageal junction (GEJn) cancer with liver metastasis.
Source: Radiopaedia.org. (2021). Gastroesophageal junction cancer with liver metastasis (PET-CT). Case study. [online] Available from https://radiopaedia.org/cases/gastrooesophageal-junction-cancer-with-liver-metastasis-pet-ct [Last accessed March 2026].

Contrast-enhanced computed tomography (CECT) chest abdomen and pelvis remain the preferred staging method to evaluate tumor at primary level and also rule out regional and metastatic spread **(Fig. 10)**. CT scan is highly accurate in determining local and regional tumor extent and also hepatic and pulmonary metastases. But CT has lower sensitivity (30–60%) compared to EUS (85%) for detecting enlarged nodes >1 cm.[44]

Fluorodeoxyglucose positron emission tomography/computed tomography also has limited ability to differentiate between cT1, cT2, and cT3 tumors.[41,45] Whole body FDG PET scan is more helpful in determining metastatic disease and can upstage 15% patients who were deemed amenable to surgery with no metastasis **(Fig. 11)**.[46] Another important value of PET scan is to assess response to treatment (chemotherapy or radiation). So, all of the tests complement each other. So, generally patients who have a 65% or greater improvement in SUV tend to have a better pathologic response found at surgery and also better survival. So, PET scan has both prognostic and predictive value.

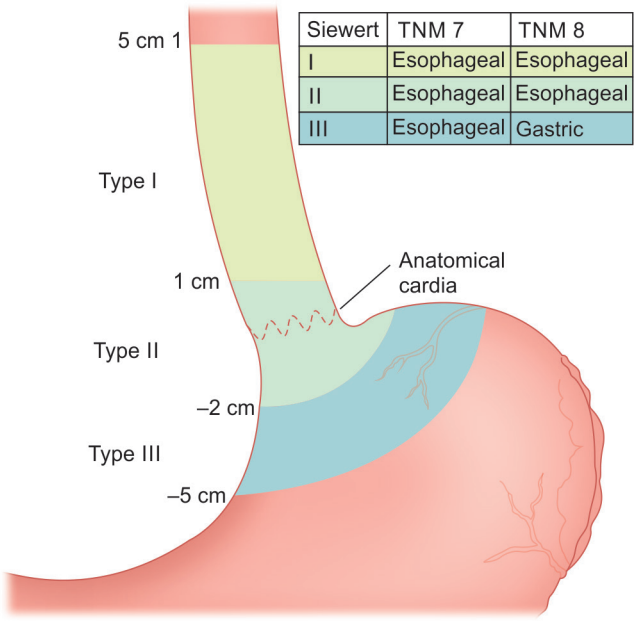
Diagnostic laparoscopy and laparoscopic ultrasonography have been advocated to detect occult metastasis not picked up by imaging. The results of various series studying diagnostic laparoscopy have been contrasting. Some series have reported laparoscopic ultrasound superiority over CT or EUS in N and M staging. If added to conventional staging protocols, diagnostic laparoscopy could avoid noncurative laparotomies in 11–48% of patients.[47] The other series have suggested that laparoscopy will identify occult peritoneal metastasis in only about 5% of patients with GEJn cancers.[48] In contrast, in patients with distal gastric cancers, laparoscopy will identify anywhere from 25 to 35% of metastatic disease in the abdomen that cannot be appreciated with other imaging studies. So, the role of laparoscopy for staging is less well defined in GEJn cancers.

STAGING

The International Union Against Cancer has adopted the term "GEJn tumors" into its 7th edition of the tumor, node, metastasis (TNM) classification in 2010.[49] In this edition, cancers with an epicenter in the lower thoracic esophagus, GEJn, or within the proximal 5 cm of the stomach that extend into the GEJ or esophagus (Siewert type III) were stage grouped, similar to EACs.[50] So, all GEJn cancers were classified as esophageal cancer and not gastric cancer. This triggered a controversy because it was based not based on molecular or therapeutic clinical data, which indicate that these tumors are a separate entity. Rather, it is based on data-driven anatomic cancer characteristics associated with survival and prognosis.

Subsequently, it was revised in the 8th edition, in 2017. As of the 8th edition of the AJCC Cancer Staging Manual,

JAYPEE BROTHERS



Siewert	TNM 7	TNM 8
I	Esophageal	Esophageal
II	Esophageal	Esophageal
III	Esophageal	Gastric

Fig. 12: Siewert tumor, node, metastasis (TNM) 7 and TNM 8 classification.
Source: Mazer LM, Poultsides GA. What Is the Best Operation for Proximal Gastric Cancer and Distal Esophageal Cancer? Surg Clin North Am. 2019;99(3):457-69.

tumors with an epicenter <2 cm into the gastric cardia and involving the GEJn (type I and type II) are staged as esophageal adenocarcinoma[51] **(Fig. 12)**. Conversely, tumors with an epicenter located >2 cm into the gastric cardia and involve the GEJn (type III) are staged as gastric adenocarcinoma. This is in contrast to the 7th edition in which GEJn tumors were all staged as esophageal tumors.[52]

GASTROESOPHAGEAL JUNCTION TUMORS: A THERAPEUTIC CHALLENGE

Gastroesophageal junction tumors pose a serious challenge because there is a lack of consensus regarding management of GEJn tumors. The areas of controversy include the type and extent of surgery to be performed, the role and extent of lymphadenectomy, and the role of multimodality treatment (adjuvant or neoadjuvant therapy).

The goal of defining the optimal treatment for GEJn tumors has been elusive for a number of reasons. Mostly GEJn cancers have been included in trials designed primarily for either esophageal or gastric cancers. The number of GEJn patients is very less in trials studying esophageal or gastric cancer, in the range of approximately 20%.[53,54]

Since these tumors are at crossroads prompting Siewert and Stein to classify GEJn tumors in three categories. In fact, the Siewert classification has significant surgical implications, given the differing pattern of nodal spread between type I and type III tumors, in particular.[33] Even using this classification system, however, it is often quite difficult to distinguish between tumor types such as a Siewert type II tumor from a type I or type III tumor, as many of these tumors are large and cross type boundaries.

Type I tumors are a distinct entity that should be treated as a distal esophageal cancer. In contrast, type III tumors represent proximal gastric cancer and should be approached in accordance with gastric cancer guidelines. The characterization of type II tumors, however, remains controversial. Most evidence suggests that these tumors behave more like proximal gastric tumors than distal esophageal adenocarcinomas. For example, in contrast to patients with type I tumors, only 10% of these patients have intestinal metaplasia in the distal esophagus. Furthermore, the lymphatic drainage pathways are such that type I tumors tend to drain more toward the mediastinal nodes, as well as to the celiac axis, whereas type II and type III tumors preferentially spread to the celiac axis nodes.[55]

Gastroesophageal junction tumors have an extensively rich lymphatic network and thus patients can have high risk of LN metastasis at the time of diagnosis. The lymphatic drainage occurs into both mediastinal and abdominal fields. A multicenter retrospective study conducted in Japan[56] reported that when GEJn adenocarcinoma invasion into lower esophagus was >2 cm, the lower mediastinal nodes were involved but if invasion is >3 cm metastasis in upper or middle mediastinal nodes was significantly higher. On the basis of these results, GEJ adenocarcinoma with a length of esophageal invasion of >3 cm has been suggested to be resected together with the upper and middle mediastinal LNs. However, no prospective studies have examined the incidence of mediastinal LN metastasis. More randomized controlled trials are warranted to evaluate the efficacy of mediastinal LN dissection.

ROLE OF SURGERY

In the multimodality era, surgery plays a pivoted role in treatment of GEJn cancers. In recent years, proper staging and patient selection combined with curative surgery and good postsurgical care have led to a marked reduction in surgical morbidity and mortality. After proper staging,

JAYPEE BROTHERS

patients can be divided into two broad categories—those with resectable disease versus those with unresectable disease. Among the former group, the mainstay of treatment is surgical resection. The aim of surgery is curative (R0) resection of primary tumor with negative margins and thorough lymphadenectomy. Achieving an R0 resection can be challenging due to the propensity of these tumors for intramural spread as well as their proximity to adjacent organs that cannot always be resected en bloc.

The optimal surgical approach and goal of curative (R0) surgery is determined by both patient and tumor related factors. The optimal surgical approach is determined by various patient factors such as body habitus, prior surgery, and pulmonary function. Primary bulky tumors with increased tendency of LN metastasis are subjected to neoadjuvant therapy. This helps to downstage tumor and facilitates R0 resection. Postoperative multimodal adjuvant therapy is beneficial in patients who are at high risk of local failure or of developing systemic disease. Randomized trials have shown that preoperative chemoradiation and perioperative chemotherapy have significantly improved survival in patients with resectable, locoregionally advanced esophageal and EGJn cancers.[57-59]

The various surgical options include—total radical esophagectomy, distal esophagectomy with proximal or subtotal or total gastrectomy **(Fig. 13)**. Three principal approaches are used to manage these cancers: the right transthoracic (RT) approach with right thoracotomy and laparotomy; the left thoracoabdominal approach and the transhiatal (TH) approach without thoracotomy. The approach is selected depending upon the Siewert tumor type and extent of lymphadenectomy depending upon pattern of LN metastasis **(Figs. 14A and B)**. Though each approach has its advantages and disadvantages, no option has demonstrated a clear survival benefit. A curative surgery with adequate margins and thorough lymphadenectomy helps improve survival rather than surgical approach.

Diagnostic laparoscopy may be useful in select patients for the detection of radiographically occult metastatic disease, especially in patients with Siewert type II and III tumors.[60] Positive peritoneal cytology in the absence of visible peritoneal metastases is associated with poor prognosis in patients with EGJn adenocarcinoma.[61] Patients with advanced tumors or node-positive tumors should be considered for laparoscopic staging with peritoneal washings.

The Siewert tumor type should be assessed in all patients with adenocarcinomas involving the EGJn. The surgical approaches for Siewert type I is radical esophagectomy with mediastinal lymphadenectomy. Siewert type III tumors are considered gastric cancers and the surgical approach is similar as for gastric cancers. There is a lot of controversy regarding management of type II GEJn cancers. The various surgical approaches recommended are abdominothoracic en bloc esophagogastrectomy, subtotal esophagectomy with resection of the proximal stomach, total gastrectomy with transhiatal resection of the distal esophagus, and resection of the proximal stomach and distal esophagus with esophagogastrostomy to ensure clear margins. To assess proximal margins, intraoperative frozen section should be liberally used.

Transthoracic *en bloc* esophagectomy appears to be the procedure of first choice for all patients who are likely to benefit from the complete nodal clearance (upper and lower mediastinal). For early distal esophageal adenocarcinoma where there is low probability of nodal involvement or for patients with associated comorbidity who may benefit from avoiding the thoracotomy, transhiatal esophagectomy is an ideal option.[62,63] With transhiatal esophagectomy upper mediastinal nodal

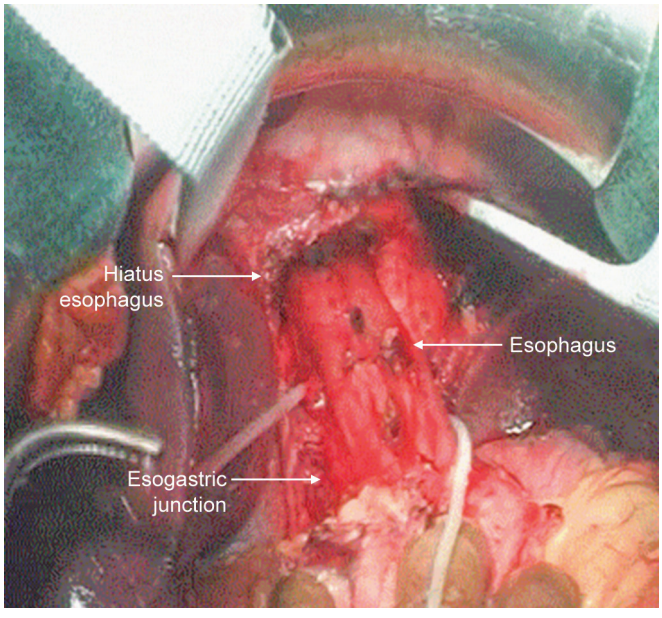
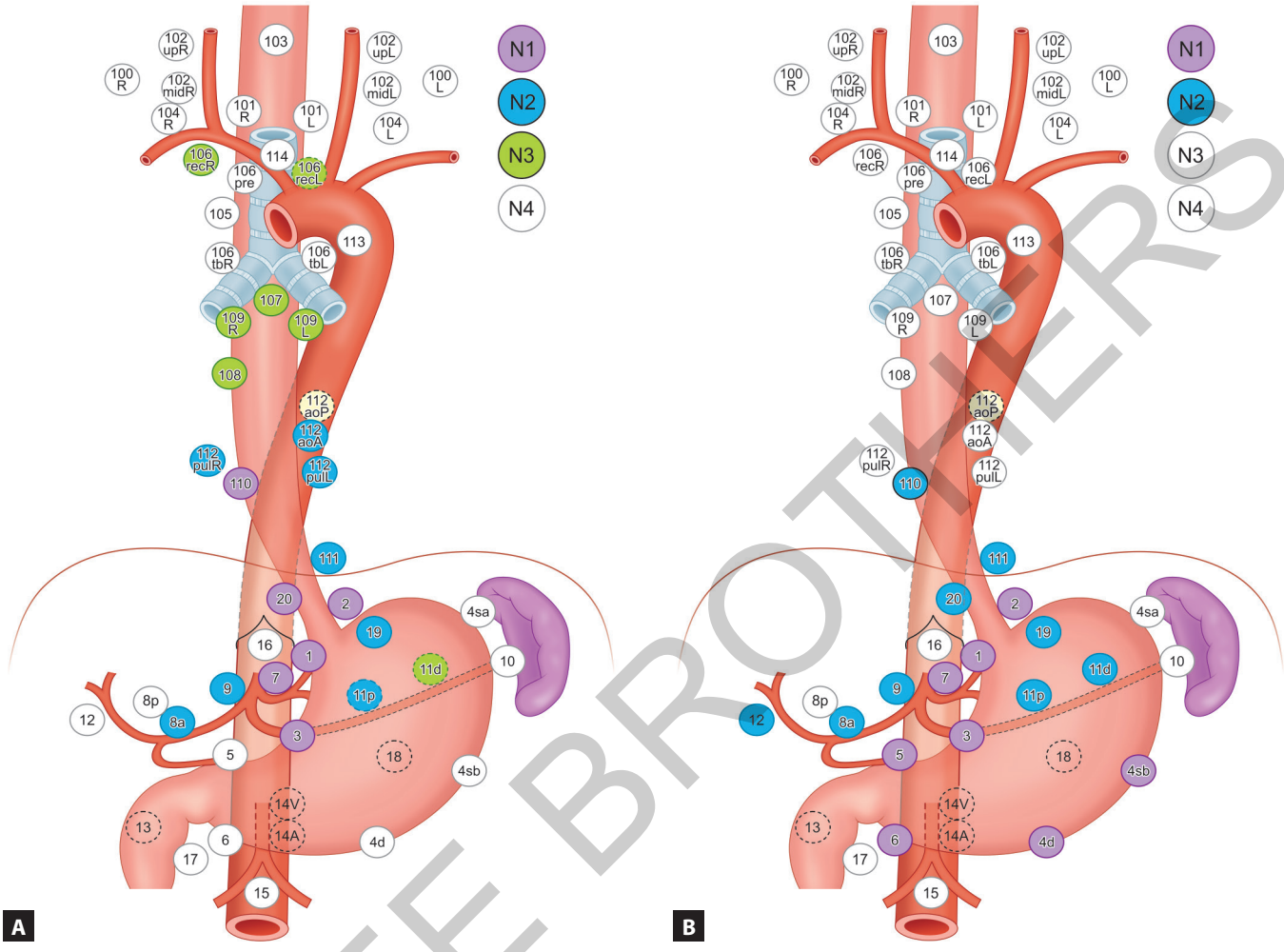


Fig. 13: Total gastrectomy with distal esophagectomy for Siewert III tumor.
Source: Mickael C, Minoa J, Nadja N, Philippe M, Stefan M. Recent management of esophago-gastric adenocarcinoma. Glob Surg. 2017;3(3).

JAYPEE BROTHERS



Figs. 14A and B: Lymph node dissection for esophagogastric junction (EGJn) cancer determined by the surgical approach. Two-field D3 dissection via transthoracic esophagectomy was adopted by the Japanese Classification of Esophageal Cancer (11th edition) (A), and D2 dissection via transhiatal extended gastrectomy was employed by the Japanese Gastric Cancer Treatment Guidelines (5th edition) (B).

clearance is not possible. With thoracoabdominal approach, lower mediastinal and abdominal clearance of D2 gastric nodes can be done.

The LN involvement has prognostic value especially the number of LNs removed which serve as an independent predictor of survival after esophagectomy. The SEER database of 4,882 patients who had ≥12 LNs examined had reduced mortality compared with those who had 0 to 11 LNs examined; patients who had ≥30 LNs examined had the lowest mortality of any group.[64] The Worldwide Esophageal Cancer Collaboration (WECC) database of 4,627 patients suggested thorough lymphadenectomy to be associated with increased survival.[65] Based on this study, optimum lymphadenectomy in node-positive cancers was 10 nodes for pT1, 15 nodes for pT2, and 29–50 nodes for pT3/T4. The National Comprehensive Cancer Network (NCCN) Guidelines recommend at least 15 nodes to be harvested for categorizing it as adequate pathologic nodal staging in patients undergoing esophagectomy without preoperative chemoradiation. According to Japanese data, at least 25 nodes need to be dissected for adequate staging.

The data is limited with no enough evidence to suggest and support extended lymphadenectomy in patients with GEJn tumors. Many studies have shown benefit of extended lymphadenectomy in subgroup of patients who have limited number of positive nodes. In addition, some major cancer centers still perform a D2 resection, as supported by the NCCN treatment guidelines.

JAYPEE BROTHERS

MULTIMODALITY TREATMENT OF GASTROESOPHAGEAL JUNCTION CANCERS

In the era of multimodality treatment, surgery alone is not sufficient and cannot be labeled as the only standard of care for management of GEJn cancers. GEJn cancers with locally advanced nature (T2,3 tumors with regional LN metastasis) have poor survival rates if treated with surgery alone.[66] In Western countries, 5-year survival rates are 50% and 25% in T2 and T3 tumors respectively, independent of the nodal status.[38] This has prompted many investigators across the globe to investigate multidisciplinary strategies such as chemotherapy or chemoradiation for patients with resectable GEJn cancers in an attempt to improve survival. The multidisciplinary therapeutic approaches include perioperative chemotherapy or postoperative chemotherapy or chemoradiation therapy either preoperatively or as an adjuvant therapy. However, the best therapeutic strategy for adenocarcinoma of the GEJ still remains a controversial issue.

The present state of knowledge leaves some patients with localized GEJn cancers treated with surgery alone, some with chemotherapy pre- and postoperatively, and some with trimodality therapy either preoperatively or postoperatively, depending mostly on the biases of the treating team of physicians. In the United States, because thoracic surgeons usually operate on GEJn tumors, most centers advocate the use of chemoradiation followed by surgery. Some centers do administer chemotherapy alone as a preoperative treatment. In Great Britain, they tend to use perioperative chemotherapy, with chemoradiation more often reserved for squamous cell cancers or for patients who are inoperable. In Europe, practices may differ even within the same country. In different areas in Germany, the use of perioperative chemotherapy predominates, whereas in other centers in Germany, chemoradiation followed by surgery is used. The French recently published a study of perioperative chemotherapy alone that showed a benefit, and increasingly in France, they are using chemotherapy alone and reserving chemoradiation for squamous cell cancers.

Neoadjuvant Therapy

The two approaches that are now used for GEJn cancers are both preoperative strategies. One is preoperative chemotherapy followed by surgery and then often followed by postoperative chemotherapy (perioperative chemotherapy). The second strategy is combining chemotherapy and radiotherapy (neoadjuvant chemoradiation) as a preoperative approach.

There are many benefits of neoadjuvant therapy. It helps clear micrometastasis, downstages primary tumor by reducing tumor volume thereby improving chances of an R0 resection; and allows accurate assessment of the completeness of pathologic complete response (pCR), all of which may influence decisions on postoperative treatment. In addition, certain chemotherapeutic agents may have radiosensitizing properties as oxygenation of tissue in the tumor bed enhances the effects of preoperative radiation therapy.[67] However, there is substantial morbidity associated with these regimens. Thus, the ISDE/IGCA consensus conference recommended that neoadjuvant therapy be restricted to patients with locally advanced tumors of the esophagogastric junction where an R0 resection is questionable.

Perioperative Chemotherapy

The landmark phase III MAGIC trial has demonstrated survival benefit of perioperative chemotherapy in gastroesophageal cancers.[54] Patients taking ECF (with epirubicin, cisplatin, and fluorouracil) regimen showed progression-free survival (PFS) and OS in patients with nonmetastatic stage II and higher gastric or EGJn adenocarcinoma when compared with surgery group alone. Al-Batran et al. in randomized controlled phase II/III FLOT4 trial, compared perioperative chemotherapy with fluorouracil, leucovorin, oxaliplatin, and docetaxel (FLOT) to the standard ECF regimen in patients with resectable nonmetastatic gastric or EGJn adenocarcinoma.[59]

In the phase II part of the study, out of 265 patients, 137 patients were randomized to ECF regimen (three cycles preoperatively and three cycles postoperatively) and 128 were randomized to FLOT regimen (four cycles preoperative and four cycles postoperatively). Results showed that FLOT was associated with significantly higher proportions of patients attained pCR with FLOT (16%) than was ECF (6%). Additionally, grade 3–4 adverse event, including neutropenia, leucopenia, nausea, infection, fatigue, and vomiting were less in FLOT group (25%) than ECF group (40%).

In the phase III part of the trial, out of 716 patients, 356 patients were randomized to FLOT regimen and 360 patients to ECF regimen.[68] The FLOT group showed median OS better in FLOT group (50 months as compared

JAYPEE BROTHERS

to ECF group (35 months). The adverse event percentage was the same in the two groups (27% in the ECF group vs. 27% in the FLOT group). Therefore, ECF should no longer be recommended in this setting. However, because of considerable toxicity associated with the FLOT regimen, the panel recommends its use in select patients with good performance status. The preferred perioperative regimen for most patients who have good to moderate performance status is FOLFOX.

Ychou et al. in the FNCLCC ACCORD 07 trial enrolled 224 patients of lower esophagus or EGJn with predominant histology being adenocarcinoma (75%). The study reported that perioperative chemotherapy with fluorouracil and cisplatin significantly increased the curative resection rate, DFS, and OS in patients with resectable cancer.[69] At a median follow-up of 5.7 years, the 5-year OS rate was 38% for patients in the perioperative chemotherapy group and 24% for patients in the surgery alone group. The corresponding 5-year DFS rates were 34% in perioperative chemotherapy group and 19%, in surgery alone group. Although this trial was prematurely terminated due to low accrual, the NCCN panel believes that perioperative fluorouracil and cisplatin is a viable treatment option for patients with locally advanced resectable esophageal or EGJn cancers.

Preoperative Chemoradiation Therapy

Many trials and studies have reported that preoperative chemoradiation is associated with improved overall survival (OS), disease-free survival (DFS), and pCR compared with preoperative chemotherapy or surgery alone in patients with locoregional esophageal cancer[70-72] The largest multicenter phase III CROSS trial, showed that preoperative chemoradiation with paclitaxel and carboplatin significantly improved OS and DFS compared with surgery alone in patients with resectable esophageal or EGJn cancers.[57] Out of 366 patients, 178 patients were randomized to chemoradiation arm (CRT) and 188 patients to surgery alone arm. Median OS was 49 months in CRT arm and 24 months in surgery alone arm. The R0 resection rate was also higher in the preoperative chemoradiation arm compared with the surgery alone arm. After a minimum follow-up of 24 months, the overall rate of recurrence was 35% in the preoperative CRT arm compared with 58% in the surgery alone arm.[73] Additionally, preoperative CRT significantly reduced locoregional recurrence from 34 to 14% and peritoneal carcinomatosis from 14 to 4%. Importantly, preoperative chemoradiation did not negatively impact postoperative health-related quality of life compared with surgery alone in patients participating in the CROSS trial.[74]

In a study which verified long-term results of the CROSS trial verified that after a median follow-up of 84.1 months, median OS was significantly improved in the preoperative chemoradiation group (48.6 months) than in surgery alone group (24 months).[75] Median OS for patients with adenocarcinoma was 43.2 months (CRT) and 27.1 months in surgery only group. These results confirmed the survival benefit for preoperative chemoradiation therapy with paclitaxel and carboplatin in patients with resectable esophageal or EGJn cancers. Therefore, the NCCN panel recommends combined paclitaxel and carboplatin as a category 1 preferred regimen for preoperative chemoradiation.

Fluorouracil/leucovorin calcium/oxaliplatin (FOLFOX)-based preoperative chemoradiation has also been recommended as a category 1 preferred option by the NCCN panel. Single arm phase II SWOG trial evaluated the efficacy and safety of preoperative FOLFOX combined with radiation therapy (RT).[76] Out of 93 patients with clinically staged II or III esophageal adenocarcinoma, 26 patients (28%) had confirmed pCR (95%) and 19.4% of patients experienced grade 4 treatment-related toxicities. At a median follow-up of 39.2 months, estimates of median and 3-year OS were 28.3 months and 45.1%, respectively. A small trial of 38 patients with stage II–IV esophageal adenocarcinoma also showed that FOLFOX combined with RT is safe and effective in the preoperative setting, with 38% of patients attaining pCR.[77]

Other recommended regimens for preoperative chemoradiation include 5 FU and cisplatin (category 1), irinotecan and cisplatin (category 2B), and paclitaxel and a fluoropyrimidine (fluorouracil or capecitabine [category 2B]).

In a prospective phase III CALGB 9781 trial which enrolled 56 patients with stage I–III EC, 30 patients were randomized to receive preoperative chemoradiation with fluorouracil and cisplatin followed by surgery and 26 patients to surgery alone.[78] At a median follow-up of 6 years, the median OS was 4.5 years in the preoperative CRT group versus 1.8 years in the surgery alone group. An improved 5-year OS rate of 39% was seen with CRT group as compared to surgery alone group (16%). The trial showed better long-term survival advantage with the use

JAYPEE BROTHERS

of preoperative chemoradiotherapy with fluorouracil and cisplatin in the treatment of esophageal cancer. In a single institutional retrospective trial that involved 44 patients, irinotecan and cisplatin showed modest activity with locally advanced esophageal carcinoma.[79] All patients underwent R0 resection, and the pCR rate was 25%. The median DFS and OS were 24 months and 34 months, respectively, and the 3-year OS rate was 46%.

If we look at all the data, we do see survival improvements for perioperative chemotherapy and preoperative chemoradiation. Still, there is a lot of debate as to which option is better as preference varies from institution to institution.

PERIOPERATIVE CHEMOTHERAPY VERSUS PREOPERATIVE CHEMORADIOTHERAPY

Two multimodal approaches—preoperative chemoradiotherapy plus surgery and perioperative chemotherapy plus surgery—have been shown to improve survival outcomes in patients with resectable esophageal adenocarcinoma. The CROSS trial established preoperative chemoradiation as standard of care.[72] The perioperative chemotherapy was established as standard by results from MAGIC trial and a French trial by the Fédération Nationale des Centres de Lutte Contre le Cancer and Fédération Francophone de Cancérologie Digestive.[54,69]

On the basis of findings from the German FLOT4-AIO trial, which enrolled a mixed cohort of patients with esophageal, esophagogastric junction, and gastric adenocarcinoma, the use of FLOT has been widely established as the preferred perioperative chemotherapy regimen for gastroesophageal adenocarcinoma.[59]

In the multinational Trial of Preoperative Therapy for Gastric and Esophagogastric Junction Adenocarcinoma (TOPGEAR), the use of preoperative chemoradiotherapy at a radiotherapy dose of 45 Gy concurrent with fluorouracil chemotherapy did not lead to improved survival as compared with FLOT or a modified version of the regimen used in the MAGIC trial in patients with gastric or esophagogastric junction adenocarcinoma.[80] Similarly, the Neo-AEGIS trial, which compared the preoperative-chemoradiotherapy regimen used in CROSS (hereafter referred to as preoperative chemoradiotherapy) with FLOT or a modified version of the regimen used in the MAGIC trial, showed clinical equipoise regarding survival among patients with esophageal or esophagogastric junction adenocarcinoma.[81] Preoperative chemoradiotherapy and FLOT were, therefore, recommended as standards of care for the treatment of nonmetastatic resectable esophageal and esophagogastric junction adenocarcinoma.[82] Concerns remained about the preoperative-chemoradiotherapy regimen, particularly regarding inadequate control of systemic disease, and the FLOT regimen, owing to toxic effects of treatment and a somewhat low percentage of patients with R0 resection which was only 84% in the intention-to-treat analysis in the FLOT4-AIO trial.

In the ESOPEC trial, it was assessed whether FLOT was superior to preoperative chemoradiotherapy regarding overall survival among patients with resectable esophageal adenocarcinoma.[83] The ESOPEC trial was a phase 3, investigator-initiated, multicenter, unblinded, randomized, controlled trial conducted at 25 centers in Germany. A total of 438 patients were enrolled from February 2016 through April 2020. Of these, 221 were randomly assigned to the FLOT group and 217 to the preoperative-chemoradiotherapy group. Baseline demographic and clinical characteristics were generally balanced between the trial groups. Patients were followed until November 30, 2023, with a median follow-up of 55 months overall, 55 months in the FLOT group, and 54 months in the preoperative-chemoradiotherapy group. Eligibility criteria included a primary tumor with a clinical stage of cT1 cN+, cT2–4a cN+, or cT2–4a cN0 disease, in which T indicates the size and extent of the tumor (higher numbers indicate a more advanced tumor), and N indicates the presence (N+) or absence (N0) of cancer spread to the LNs, without evidence of metastatic spread. The primary endpoint was overall survival.

With a median follow-up of 55 months, overall survival at 3 years was 57.4% in the FLOT group and 50.7% in the preoperative-chemoradiotherapy group. Progression-free survival at 3 years was 51.6% in the FLOT group and 35.0% in the preoperative-chemoradiotherapy group. Among the patients who started the assigned treatment, grade 3 or higher adverse events were observed in 120 of 207 patients (58.0%) in the FLOT group and in 98 of 196 patients (50.0%) in the preoperative-chemoradiotherapy group. Serious adverse events were observed in 98 of 207 patients (47.3%) in the FLOT group and in 82 of 196 patients (41.8%) in the preoperative-chemoradiotherapy group. Mortality at 90 days after surgery was 3.1% in the FLOT group and 5.6% in the preoperative-chemoradiotherapy group.

JAYPEE BROTHERS

The trial results concluded that perioperative chemotherapy with FLOT led to improved survival among patients with resectable esophageal adenocarcinoma as compared with preoperative chemoradiotherapy.

POSTOPERATIVE CHEMORADIATION THERAPY

The effectiveness of postoperative chemoradiation on the survival of patients with resectable adenocarcinoma (stage IB to IV, M0; node positive 85%) of stomach or EGJn was studied by the landmark Intergroup-0116 (INT-0116).[53,84] Out of 556 patients, 281 patients were randomized to receive surgery followed by postoperative chemotherapy plus chemoradiation (bolus fluorouracil plus leucovorin before and after concurrent chemoradiation) and 275 patients were randomized to surgery alone. At a median follow-up of 5 years, median OS with postoperative chemotherapy plus chemoradiation was 36 months compared with surgery alone (27 months). The 3-year OS was 50% in chemoradiation arm versus 41% in surgery alone arm. The local recurrence rate was 19% in chemoradiation arm which was less than surgery alone (29%). After a median follow-up of >10 years, survival remained improved in patients treated with postoperative chemoradiation. Additionally, data from a retrospective analysis showed that postoperative chemoradiation resulted in improved 3-year DFS rates in node positive patients (37% vs. 24% after surgery alone).[85]

On the basis of the results of the INT-0116 trial, postoperative chemoradiation in patients with resected gastric or EGJn adenocarcinoma who have not received preoperative therapy was considered a standard option. The negative side of this trial was high-grade hematological and gastrointestinal toxicity (54% and 33%, respectively). Therefore, the doses and schedule of chemotherapy agents used in the INT-0116 trial are no longer recommended due to concerns regarding toxicity. The NCCN guidelines have recommended modifications to this regimen.

NOVEL TARGETED THERAPIES

The rationale for newer targeted therapies is that at present still survival rates are still poor with perioperative chemotherapy or preoperative chemoradiation. It seems unlike to make significant further progress with the use of conventional cytotoxic chemotherapy alone. So, targeted agents or molecularly targeted drugs, which more specifically attack growth promotion pathways in cancers, need to be investigated. The hope is that incorporation of these more specific targeted therapies will improve responses and also potentially suppress or delay the development of recurrent metastatic disease.

At present, three targeted therapeutic agents, trastuzumab, ramucirumab, and pembrolizumab, have been approved by the FDA for use in esophageal and EGJn cancers. Treatment with trastuzumab is based on testing for HER2 status.[86] Treatment with pembrolizumab is based on testing for microsatellite instability and/or PD-L1 expression.[87-89] As per NCCN guidelines, trastuzumab plus chemotherapy is recommended as first-line therapy for patients with HER2-positive metastatic adenocarcinoma. Ramucirumab, as a single agent or in combination with paclitaxel, and pembrolizumab (for MSI-H/dMMR tumors) are included as options for second-line or subsequent therapy for patients with metastatic disease. Pembrolizumab has also been included as a second-line therapy option for esophageal cancers with PD-L1 expression levels by CPS of ≥10 and as a third-line or subsequent therapy option for esophageal and EGJn adenocarcinoma with PD-L1 expression levels by CPS of ≥1.[90]

FUTURE PERSPECTIVES

Today multimodality treatment is key for managing GEJn cancers. Patients who are responders to the neoadjuvant therapy on response evaluation by imaging are subjected to definitive therapy. But still, there are subsets of patients who are non-responders. At present there is no test available to identify these subsets. Moreover, these patients suffer the side effects of chemotherapy. Maybe in future, we develop certain molecular characterization and on the basis of genetic profile we might be able to distinguish non-responders from responders. The molecular characterization by genomic profiling perhaps can predict LN status and survival, as in gastric cancer and Barrett's cancer and other entities.

The technical developments and renovations in the field of nuclear medicine can change the whole course of management of gastric cancers. New tracers and more sensitive detection systems may be helpful in pretreatment staging. In the near future, maybe new technical devices such as a new FDG-PET hand device, help to identify metastatic LN intraoperatively. The emphasis is on tumor biology so that numerous prognostic and predictive biomarkers can be identified in esophageal and GEJn cancer. At present none exists but who knows in near future

JAYPEE BROTHERS

biological prognostic markers will be a reality. For patients who achieve a pCR with chemoradiation, will there be a way that we can identify without surgery which patients are complete responders and thus do not require surgery? That is an open question, I think, and a major issue in trial development. We have come so far yet we are so far.

REFERENCES

1. Simard EP, Ward EM, Siegel R, Jemal A. Cancers with increasing incidence trends in the United States: 1999 through 2008. CA Cancer J Clin. 2012;62(2):118-28.
2. Pohl H, Welch HG. The role of overdiagnosis and reclassification in the marked increase of esophageal adenocarcinoma incidence. J Natl Cancer Inst. 2005;97:142-6.
3. Rusch VW. Are cancers of the esophagus, gastroesophageal junction, and cardia one disease, two, or several? Semin Oncol. 2004;31:444-9.
4. McClave SA, Boyce HW, Gottfried MR Early diagnosis of columnar-lined esophagus: a new endoscopic diagnostic criterion. Gastrointest Endosc. 1987;33:413-6.
5. Csendes A, Maluenda F, Braghetto I, Csendes P, Henriquez A, Quesada MS. Location of the lower oesophageal sphincter and the squamous columnar mucosal junction in 109 healthy controls and 778 patients with different degrees of endoscopic oesophagitis. Gut. 1993;34:21-7.
6. Derakhshan MH, Crumley A, Forshaw M, Mitchell DR, Going JJ. An unexpected mucosal metaplasia at the gastric cardia in longstanding pernicious anemia. Am J Gastroenterol. 2015;110:1505-6.
7. Makuuchi H. [What is the esophagogastric junction?]. Nihon Geka Gakkai Zasshi. 2015;116(1):24-8.
8. Boyce HW. Endoscopic definitions of esophagogastric junction regional anatomy. Gastrointest Endosc. 2000;51:586-92.
9. Huang Q. Definition of the esophagogastric junction: a critical mini review. Arch Pathol Lab Med. 2011;135(3):384-9.
10. Walther C, Zilling T, Perfekt R, Möller T. Increasing prevalence of adenocarcinoma of the oesophagus and gastro-oesophageal junction: a study of the Swedish population between 1970 and 1997. Eur J Surg. 2001;167:748-57.
11. Chow WH, Finkle WD, McLaughlin JK, Frankl H, Ziel HK, Fraumeni JF. Jr. The relation of gastroesophageal reflux disease and its treatment to adenocarcinomas of the esophagus and gastric cardia. JAMA. 1995;274:474-7.
12. Powell J, McConkey CC, Gillison EW. Spychal RT: Continuing rising trend in oesophageal adenocarcinoma. Int J Cancer. 2002;102:422-7.
13. Buas MF, Vaughan TL. Epidemiology and risk factors for gastroesophageal junction tumors: understanding the rising incidence of this disease. Semin Radiat Oncol 2013;23:3-9.
14. Devesa SS, Fraumeni JF Jr: The rising incidence of gastric cardia cancer. J Natl Cancer Inst. 1999;91:747-9.
15. Parfitt JR, Miladinovic Z, Driman DK. Increasing incidence of adenocarcinoma of the gastroesophageal junction and distal stomach in Canada—an epidemiological study from 1964-2002. Can J Gastroenterol. 2006;20:271-6.
16. Derakhshan MH, Malekzadeh R, Watabe H, Yazdanbod A, Fyfe V, Kazemi A, et al. Combination of gastric atrophy, reflux symptoms and histological subtype indicates two distinct aetiologies of gastric cardia cancer. Gut. 2008;57:298-305.
17. Nilsson M, Johnsen R, Ye W, Hveem K, Lagergren J. Prevalence of gastro-oesophageal reflux symptoms and the influence of age and sex. Scand J Gastroenterol. 2004;39:1040-5.
18. Marsman WA, Tytgat GN, ten Kate FJ, van Lanschot JJ. Differences and similarities of adenocarcinomas of the esophagus and esophagogastric junction. J Surg Oncol. 2005;92:160-8.
19. Lagergren J, Bergström R, Lindgren A, Nyrén O. Symptomatic gastroesophageal reflux as a risk factor for esophageal adenocarcinoma. N Engl J Med. 1999;340:825-31.
20. Lubin JH, Cook MB, Pandeya N, Vaughan TL, Abnet CC, Giffen C, et al. The importance of exposure rate on odds ratios by cigarette smoking and alcohol consumption for esophageal adenocarcinoma and squamous cell carcinoma in the Barrett's Esophagus and Esophageal Adenocarcinoma Consortium. Cancer Epidemiol. 2012;36:306-16.
21. Hoyo C, Cook MB, Kamangar F, Freedman ND, Whiteman DC, Bernstein L, et al. Body mass index in relation to oesophageal and oesophagogastric junction adenocarcinomas: a pooled analysis from the International BEACON Consortium. Int J Epidemiol. 2012;41:1706-18.
22. Bollschweiler E, Knoppe K, Wolfgarten E, Hölscher AH. Prevalence of reflux symptoms in the general population of Cologne. Z Gastroenterol. 2007;45:177-81.
23. Murao T, Sakurai K, Mihara S, Marubayashi T, Murakami Y, Sasaki Y. Lifestyle change influences on GERD in Japan: a study of participants in a health examination program. Dig Dis Sci. 2011;56(10):2857-64.
24. Goh KL. Emerging gastrointestinal and liver diseases in Asia Pacific: Implications to health care in the region (World Gastroenterology Organization: Asian Pacific Association of Gastroenterology Distinguished Global Lecture 2015) J Clin Gastroenterol. 2017;51:479-85.
25. Fujiwara Y. Recent epidemiology of GERD in the Japanese population. Nihon Shokakibyo Gakkai Zasshi. 2017;114(10):1781-9.
26. Chen Q, Zhuang H, Liu Y. The association between obesity factor and esophageal caner. J Gastrointest Oncol. 2012;3(3):226-31.
27. Sasazuki S, Inoue M, Tsuji I, Sugawara Y, Tamakoshi A, Matsuo K. Body mass index and mortality from all causes and major causes in Japanese: results of a pooled analysis of 7 large-scale cohort studies. J Epidemiol. 2011;21(6):417-30.

JAYPEE BROTHERS

28. Kim JJ. Epidemiology of gastroesophageal junction adenocarcinoma in Korea. J Gastric Cancer. 2018;18(4):328-38.
29. Kato M, Asaka M, Shimizu Y, Nobuta A, Takeda H, Sugiyama T. Relationship between *Helicobacter pylori* infection and the prevalence, site and histological type of gastric cancer. Aliment Pharmacol Ther. 2004;20(Suppl 1):85–9.
30. Kamada T, Kurose H, Yamanaka Y, Manabe N, Kusunoki H, Shiotani A. Relationship between gastroesophageal junction adenocarcinoma and *Helicobacter pylori* infection in Japan. Digestion. 2012;85(4):256-60.
31. McColl KE. Cancer of the gastric cardia. Best Pract Res Clin Gastroenterol. 2006;20(4):687-96.
32. Engel LS, Chow WH, Vaughan TL, Gammon MD, Risch HA, Stanford JL, et al. Population attributable risks of esophageal and gastric cancers. J Natl Cancer Inst. 2003;95:1404-13.
33. Siewert JR, Stein HJ. Classification of adenocarcinoma of the oesophagogastric junction. Br J Surg. 1998;85:1457-9.
34. Hasegawa S, Yoshikawa T, Cho H, Tsuburaya A, Kobayashi O. Is adenocarcinoma of the esophagogastric junction different between Japan and western countries? The incidence and clinicopathological features at a Japanese high-volume cancer center. World J Surg. 2009;33:95–103.
35. Misumi A, Murakami A, Harada K, Baba K, Akagi M. Definition of carcinoma of the gastric cardia. Langenbecks Arch Chir. 1989;374:221-6.
36. Japanese Gastric Cancer Association. Japanese classification of gastric carcinoma: 3rd English edition. Gastric Cancer. 2011;14:101-12.
37. Japan Esophageal Society. Japanese Classification of Esophageal Cancer. 2nd edition. Tokyo: Japan Esophageal Society; 2008.
38. Pedrazzani C, de Manzoni G, Marrelli D, Giacopuzzi S, Corso G, Minicozzi AM, et al. Lymph node involvement in advanced gastroesophageal junction adenocarcinoma. J Thorac Cardiovasc Surg. 2007;134(2):378-85.
39. Carneiro F, Chaves P. Pathologic risk factors of adenocarcinoma of the gastric cardia and gastroesophageal junction. Surg Oncol Clin N Am. 2006;15:697-714.
40. Lin J, Beerm DG. Molecular biology of upper gastrointestinal malignancies. Semin Oncol. 2004;31:476-486.
41. Tirumani H, Rosenthal MH, Tirumani SH, Shinagare AB, Krajewski KM, Ramaiya NH. Esophageal Carcinoma: Current Concepts in the Role of Imaging in Staging and Management. Can Assoc Radiol J. 2015;66(2):130-9.
42. Puli SR, Reddy JB, Bechtold ML, Antillon D, Ibdah JA, Antillon MR. Staging accuracy of esophageal cancer by endoscopic ultrasound: a meta-analysis and systematic review. World J Gastroenterol. 2008;14:1479-90.
43. Barbour AP, Rizk NP, Gerdes H, Bains MS, Rusch VW, Brennan MF, et al. Endoscopic ultrasound predicts outcomes for patients with adenocarcinoma of the gastroesophageal junction. J Am Coll Surg. 2007;205:593-601.
44. Kim TJ, Kim HY, Lee KW, Kim MS. Multimodality assessment of esophageal cancer: preoperative staging and monitoring of response to therapy. Radiographics. 2009;29:403–421.
45. Amin MB, Edge SB, Greene FL, Byrd DR, Brookland RK, Washington MK, et al. (Eds). AJCC Cancer Staging Manual. 8th edition. Springer; 2017.
46. Chatterton BE, Ho Shon I, Baldey A, Lenzo N, Patrikeos A, Kelley B, et al. Positron emission tomography changes management and prognostic stratification in patients with oesophageal cancer: results of a multicentre prospective study. Eur J Nucl Med Mol Imaging. 2009;36:354-61.
47. Florea, I.B., Hong, Y.K. Time to Discard the Staging Laparoscopy? Elucidating the Role for Routine Diagnostic Laparoscopy in Patients with Gastroesophageal Junction Malignancy. Ann Surg Oncol. 2025;32:27-9.
48. Alcasid NJ, Fink D, Banks KC, Susai CJ, Barnes K, Wile R, et al. The Impact of Diagnostic Laparoscopy on Upstaging Patients with Siewert II and III Gastroesophageal Junction (GEJ) Cancer. Ann Surg Oncol. 2025;32(1):258-64.
49. Rice TW, Rusch VW, Ishwaran H, Blackstone EH; Worldwide Esophageal Cancer Collaboration. Cancer of the esophagus and esophagogastric junction: data-driven staging for the seventh edition of the American Joint Committee on Cancer/International Union Against Cancer Staging Manuals. Cancer. 2010;116:3763-73.
50. Edge SB, Byrd DR, Compton CC, Fritz AG, Greene FL, Trotti A, (Eds). AJCC Cancer Staging Manual. 7th edition. New York: Springer; 2010.
51. Daiko H, Kato K. Updates in the 8th Edition of the TNM Staging System for Esophagus and Esophagogastric Junction Cancer. Jpn J Clin Oncol. 2020;50(8):847-51.
52. Sobin L, Gospodarowicz M, Wittekind C: TNM classification of malignant tumors. 7th edition. Oxford: Wiley-Blackwell; 2009.
53. Macdonald JS, Smalley SR, Benedetti J, Hundahl SA, Estes NC, Stemmermann GN, et al. Chemoradiotherapy after surgery compared with surgery alone for adenocarcinoma of the stomach or gastroesophageal junction. N Engl J Med. 2001;345:725-30.
54. Cunningham D, Allum WH, Stenning SP, Thompson JN, Van de Velde CJ, Nicolson M, et al. Perioperative chemotherapy versus surgery alone for resectable gastroesophageal cancer. N Engl J Med. 2006;355:11-20.
55. Kakeji Y, Yamamoto M, Ito S, Sugiyama M, Egashira A, Saeki H, et al. Lymph node metastasis from cancer of the esophagogastric junction, and determination of the appropriate nodal dissection. Surg Today. 2012;42:351-8.
56. Kurokawa Y, Hiki N, Yoshikawa T, Kishi K, Ito Y, Ohi M, et al. Mediastinal lymph node metastasis and recurrence in adenocarcinoma of the esophagogastric junction. Surgery. 2015;157:551-5.
57. van Hagen P, Hulshof MC, van Lanschot JJ, Steyerberg EW, van Berge Henegouwen MI, et al. Preoperative

JAYPEE BROTHERS

for detailed information on gastroenterology books, visit our website **www.ejaypee.com**, for detailed information on gastroenterology books, visit our website **www.ejaypee.com**, fo

KB's Management of GASTROINTESTINAL CANCERS

Basics & Perspective

The book comprehensively covers the management of cancers of esophagus, stomach, small bowel, colon, rectum, and anal canal. This book includes 49 chapters divided into four sections. For better understanding and conceptualization, all aspects in managing these cancers have been addressed in a systematic way. These include surgical anatomy, epidemiology and etiology, molecular biology, pathology and pathogenesis, diagnosis and staging, surgery, chemotherapy, radiation therapy, and recent guidelines. All major trials, recent advances, and current controversies are addressed.



Kirti Bushan MBBS MS DNB is a Senior Consultant Surgical Oncologist attached to reputed hospitals in Mumbai, Maharashtra, India. He is a versatile cancer surgeon with over 17 years of experience in the field of surgical oncology with around 10,000 major and supramajor surgeries to his credit.

He has done his preliminary education MBBS from Rajendra Medical College and Hospital (RMCH), Ranchi, Jharkhand. He did his Mastery of Surgery (MS) from Government Medical College, Jammu, Jammu and Kashmir. He completed his 3-year course of DNB superspecialization training in Surgical Oncology from the Rajiv Gandhi Cancer Institute and Research Centre (RGCI and RC), New Delhi. He has done Fellowship in Gastrointestinal Cancers Management from Medical College of Wisconsin (MCW), USA. He has done training in minimal access robotic surgery from University of Strasbourg, France.

He is the recipient of the Best Young Outstanding Oncosurgeon Award from the former President His Excellency Dr APJ Abdul Kalam. He has published a book on breast cancer sponsored by Breast Cancer Foundation of India (BCFI). He has also authored various publications in national and international journals of repute.

Shelving Recommendation
GASTROENTEROLOGY

ISBN 978-93-7202-010-6

Buy from ejaypee

JAYPEE BROTHERS