Esophageal Cancer

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Introduction

Esophageal cancer is an ominous disease worldwide, with a 5-year survival ranging from 4 to 40%, depending on stage, and an 18% overall 5-year survival [1].

In recent years, a sixfold increase in incidence for adenocarcinoma in the United States and Canada from 1975 to 2000 has been documented, making it the most rapidly increasing cancer in North America [2].

Because early esophageal cancer (EC) is frequently asymptomatic, the majority (about 60%) of patients have advanced cancer when diagnosed, with dysphagia as the most common presenting symptom.

The most common histologic types of EC are squamous cell carcinoma (SCC) and esophageal adenocarcinoma (EAC), with the majority in the Western world being EAC. Less than 2% of all esophageal cancers are mesenchymal tumors (GIST, leiomyosarcoma) or small cell carcinoma. Lymphoma, neuroendocrine tumor, and melanoma can also develop in the esophagus, but with even lower incidence [3].

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Epidemiology

- EC is the eighth most common cancer worldwide and the sixth leading cause of cancer-related mortality [4].
- Its incidence varies greatly geographically. Squamous cell carcinoma (SCC) is the most prevalent histological type worldwide, particularly in countries of East Asia, Eastern Africa, and South America. In Western countries such as the United States, Canada, United Kingdom, Finland, France, and Australia, there is a predominance of esophageal adenocarcinoma (EAC).
- Asia represents 75% of the world's burden of EC, with an age-standardized rate for incidence (ASR-I) in Eastern Asia of 11/100000. China alone accounts for 50% of the world's EC incidence [1].
- The overall incidence for SCC increases with age, reaching a peak in the seventh decade. Major risk factors for SCC are alcohol consumption and tobacco use. Smoking, in combination with alcohol, has been proven to have a synergistic effect and increases the relative risk with an OR for combined alcohol and tobacco use of 3.28 (95% confidence interval (CI), $P = 0.05$) [5].
- Race and gender are also known risk factors. The relative risk in men who use both heavy tobacco and alcohol is 35.4 in white males and 149.2 in black males, compared to men of the same race and region who were non-smokers or drinkers [6]. The average male:female ratio for SCC is 2.5, and for EAC the ratio is 4.4 [1].
- From 1975 to 2004, the incidence of EAC among white American males increased by more than 460% and by 355% among white American females [7].
- Obesity and gastroesophageal reflux (GERD) have a distinct link to EAC. Therefore, adenocarcinoma of the esophagus occurs predominantly in the distal esophagus or gastroesophageal junction, compared to SCC which occurs mostly in the cervical, proximal, and mid thoracic esophagus. GERD is related to the development of Barrett's esophagus (BE) and the risk of developing EC is 50–100 times more likely in those with BE [8]. However, less than 5% of patients diagnosed with adenocarcinoma of the esophagus have a prior diagnosis of BE [9].

Diagnosis and Staging

Progressive dysphagia, initially to solids and later to soft and liquid diet, is usually the presenting symptom and is associated with general signs of malignancy such as weight loss and anemia. As dysphagia to solids is a relatively late symptom, EC is usually diagnosed in advanced stages. The incidence by stage defined as localized, regional, and distant disease in Eastern countries is 33%, 37.8%, and 17.3%, respectively, mostly for SCC [10]. In the Western population, particularly North America, localized disease accounts for 24%, 36% is regional and 40% presents with distant disease at the time of diagnosis with 67% of patients presenting with EAC [11, 12].

Diagnosis at the early stage is usually the result of a fortuitous incidental finding after an upper endoscopy for other symptoms.

Clinical staging is critical for deciding whether a patient is a candidate for endoscopic resection, upfront surgery, induction therapy, or palliation. The staging workup may include esophagogastroduodenoscopy (EGD) + biopsy, barium swallow, endoscopic ultrasound (EUS), CT, and FDG PET/CT. In upper and middle thoracic tumors, a bronchoscopy should be considered to rule out bronchial/tracheal involvement. Involvement of these structures would be a contraindication for radiation due to the high risk of post-radiation fistula and also precludes surgical therapy.

EGD and Barium Swallow

- Endoscopy allows for an anatomic evaluation of the tumor in relation to the hiatus and squamo-columnar junction, along with tumor length, degree of circumferential involvement, degree of obstruction, and presence of Barrett's esophagus.
- Endoscopy also allows for histological diagnosis by biopsy. Histopathologic cell type and grade markedly influence survival and guide management.
- Barium swallow has been used as the initial diagnostic test in the past but has largely been supplanted by endoscopy.

Endoscopic Ultrasonography (EUS)

- EUS is the most sensitive test for locoregional staging in EC. EUS can determine the depth of tumor invasion (cT), as well as confirm nodal involvement of suspicious paraesophageal or perigastric lymph nodes through fine-needle aspiration (cN). EUS is however a costly and operator-dependent procedure which may not be available in all centers.
- The greatest impact of EUS is defining those who will benefit from neoadjuvant chemoradiotherapy and surgery versus early-stage patients who may only require surgery. It cannot reliably differentiate between T1a and T1b, limiting its effectiveness in defining patients who may be candidates for endoscopic therapy.
- The accuracy of EUS for evaluating primary tumor and nodal status has been reported to be 85% and 75% respectively, while the sensitivity has been reported to be in the range of 85–95% for primary tumor evaluation and 70–80% for nodal evaluation [13].
- Obstructing lesions limit the passage of the EUS scope, precluding evaluation in patients with advanced disease. However, such patients generally have locally advanced disease (T3 or T4) and have a high probability of N+ disease. Therefore they will be candidates for combined modality therapy on this basis alone.

CT

- CT of the chest and abdomen is useful in initial staging for evaluating the primary tumor, regional nodes, and metastatic disease. Identification of distant

metastatic disease on CT obviates the need for PET-CT. CT is also useful to determine the location of the tumor as well as involvement of adjacent structures.
- CT angiogram may be useful to determine the patency and quality of the right gastroepiploic artery, especially in situations where the patient has evidence of atherosclerosis elsewhere.

FDG-PET/CT

- FDG-PET CT is useful to determine a) the baseline FDG uptake of the primary tumor prior to induction therapy, b) the presence of locoregional disease, c) the presence of distant metastatic disease, and d) response to therapy (post-treatment).
- SCC and EAC have differential uptake in FDG-PET. Most studies have found a high degree of FDG-avidity in SCC at the primary tumor site. The majority of false negatives appear to be in small-volume tumors [14]. In contrast, insufficient or absent FDG uptake by the primary tumor is more frequently encountered in EAC. However, this depends on tumor growth type, differentiation, and mucus content.
- Non-avid EAC tumors are often poorly differentiated, showing a diffuse, non-intestinal growth type and mucus-containing tumor type (signet ring variant) [15].
- FDG-PET is superior to contrast-enhanced CT for the detection of metastatic nodes [10]. The sensitivity, specificity, and accuracy of PET-CT is 52%, 94%, and 84%, respectively, compared to 15%, 97%, and 77%, respectively, for CT [16].
- PET has also been shown to have higher accuracy (82% vs 64%) and sensitivity (74% vs 47%) when compared to CT and EUS for the detection of distant metastatic disease [17].
- The degree of FDG-avidity may potentially be used to assess response to induction therapy [18].
- One limitation of FDG-PET is the difficulty of detecting nodes close to the primary tumor (3 cm or less). Intense FDG uptake by the primary tumor can often obscure the detection of nearby associated nodal metastasis, leading to false negatives.
- False positives can also be the result of inflammatory disease causing increased FDG uptake, such as sarcoidosis.

Staging, AJCC, Eighth Edition

For the purpose of staging, the esophagus is usually divided in three anatomic compartments: cervical, thoracic, and abdominal esophagus. The thoracic esophagus is also divided arbitrarily into equal thirds: upper, middle, and lower.

The cervical esophagus anatomically lies in the neck, bordered superiorly by the hypopharynx and inferiorly by the thoracic inlet at the level of the sternal notch. It extends from 15 to 20 cm measured from the incisors. Cancers located in the cervical esophagus are staged as upper thoracic esophageal cancers and not as head and neck cancers [19].

For staging purposes, the AJCC, Eighth Edition, includes gastroesophageal junction tumors which have an epicenter within 2 cm of the cardia (Siewert types I/II). Tumors with an epicenter more than 2 cm distal to the cardia are staged as gastric cancers (Tables 9.1, 9.2, 9.3, 9.4, 9.5, 9.6).

AJCC, Eighth Edition, staging system includes cTNM, yTNM for post-neoadjuvant treatment restaging, pTNM for pathologic staging after esophagectomy alone, and ypTNM for pathologic staging after esophagectomy with induction therapy, where histology and tumor location are included. SCC staging pTNM includes tumor location.

Table 9.1 Primary tumor (T): all carcinomas

T category	T criteria
TX	Tumor cannot be assessed
T0	No evidence of primary tumor
Tis	High-grade dysplasia, defined as malignant cells confined to the epithelium by the basement membrane
T1	Tumor invades the lamina propria, muscularis mucosae, or submucosa
T1a	Tumor invades lamina propria or muscularis mucosae
T1b	Tumor invades the submucosa
T2	Tumor invades the muscularis propria
T3	Tumor invades adventitia
T4	Tumor invades adjacent structures
T4a	Tumor invades the pleura, pericardium, azygos vein, diaphragm, or peritoneum
T4b	Tumor invades other adjacent structures, such as the aorta, vertebral body, or airway

Table 9.2 Regional lymph nodes (N): all carcinomas

N category	N criteria
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in 1–2 regional lymph nodes
N2	Metastasis in 3–6 regional lymph nodes
N3	Metastasis in ≥7 regional lymph nodes

Table 9.3 Distant metastasis (M): all carcinomas

M category	M criteria
M0	No distant metastasis
M1	Distant metastasis

Table 9.4 Histologic grade: all carcinomas

G	G definition
GX	Grade cannot be assessed
G1	Well differentiated
G2	Moderately differentiated
G3	Poorly differentiated

Table 9.5 Definition of location: squamous cell carcinoma

Location category	Location criteria
X	Unknown
Upper	Cervical esophagus to lower border of azygos vein
Middle	Lower border of azygos vein to lower border of pulmonary vein
Lower	Lower border of inferior pulmonary vein to stomach, including GE junction

Table 9.6 SCC and adenocarcinoma post-neoadjuvant treatment stages (ypTNM)

ypT	ypN	ypM	Stage
T0–2	N0	M0	I
T3	N0	M0	II
T0–2	N1	M0	IIIA
T3	N1	M0	IIIB
T0–3	N2	M0	IIIB
T4a	N0	M0	IIIB
T4a	N1–2	M0	IVA
T4a	NX	M0	IVA
T4b	N0–2	M0	IVA
Any T	N3	M0	IVA
Any T	AnyN	M1	IVB

Treatment

Treatment of EC is based on a multimodal approach that is determined by the histologic subtype, location, and clinical staging (cTNM). This approach may include upfront resection for early-stage disease (endoscopic or surgical), neoadjuvant therapy (chemoradiotherapy or chemotherapy) followed by surgery, definitive chemoradiotherapy, or palliative systemic treatment.

The treatment of thoracic esophageal cancer is generally determined by cTNM; however, many centers would alter the approach for locally advanced disease depending on SCC or EAC, in some cases with a preference toward definitive chemoradiotherapy for SCC and trimodality therapy for EAC.

Cervical Esophagus

- Pharyngo-laryngo-esophagectomy (PLE) was considered the gold standard of treatment for cervical SCC for many years. However, it is associated with a high incidence of postoperative morbidity and mortality. Anastomotic leakage and operative mortality are both described at ~9% [20]. It also causes a significantly compromised quality of life.
- Definitive chemoradiation (CRT) has evolved as a curative treatment modality for cervical esophageal SCC. Studies have shown similar overall survival with

definitive CRT compared to surgery, with a superior post-therapeutic quality of life compared to PLE, particularly because laryngectomy is avoided.
- Definitive CRT includes a three-dimensional conformal approach with a total radiation dose of 60–68 Gy. Cisplatin and 5-FU based chemotherapy is given concurrently for a total of four cycles [21].

High-volume institutions treating esophageal SCC have reported their results comparing PLE to definitive CRT in cervical esophageal cancer. Median overall survival for patients treated with PLE was 19.9 months vs 24.9 months among those treated with CRT. After stratifying for intent of resection (R-category) in the PLE patients and response to chemotherapy in the CRT, patients with curative PLE (R0) had a median survival of 22.4 months vs 28.6 months in CRT responders [21]. Therefore, definitive chemoradiation has emerged as the treatment of choice for patients with cervical SCC.

Thoracic Esophagus

Clinical Stage 0-I

Endoscopic Resection

- Lesions that do not infiltrate beyond the mucosa or lamina propria (cT1a) are rarely accompanied by lymph-node metastasis (<5%) [22]. Endoscopic resection is therefore a potentially curative treatment for such lesions.
- Lesions that reach the muscularis mucosae or infiltrate the upper submucosa (up to 200 μm: SM1) are associated with a 10% rate of lymph-node metastasis. Endoscopic resection remains feasible for selected patients with no clinical or radiologic evidence of lymph-node metastasis. However, surgical resection is also an appropriate option for fit patients with T1b SM1, given the lymph node metastasis rate. The decision to proceed with endoscopic resection versus upfront surgery requires a careful discussion with the patient regarding benefits of either treatment.
- Lesions showing deep invasion of the submucosa (more than 200 μm; SM2, SM3) are associated with a 25–50% rate of lymph-node metastasis and therefore fit patients should be offered upfront surgical resection.
- Lesions requiring a circumferential mucosal resection exceeding two-thirds of the circumference of the esophagus are relative contraindication for endoscopic treatment, considering the high rate of postoperative stenosis [23]. These patients are considered for upfront surgery.

Definitive Chemoradiotherapy in SCC

- Can be an alternative for patients with mucosal cancers that are too wide to be resected endoscopically.
- A phase II study of definitive chemoradiotherapy for stage I SCC of the esophagus (JCOG 9708) demonstrated a complete response rate of 96% and a 2-year

survival rate of 93% [24]. These results, comparable to radical surgery in Japan, are currently being studied in a phase III study JCOG 0502.

Clinical Stage II-III (except cT4)

Neoadjuvant Chemoradiotherapy Followed by Radical Surgery

A number of different regimens for preoperative induction therapy with chemotherapy or chemoradiotherapy have been described (Table 9.7). Prior to 2015,

Table 9.7 Randomized clinical trials (RCT) comparing neoadjuvant chemoradiation treatment and surgery vs surgery alone in esophageal cancer

Study	Methods	Results
Urba et al. 2001 [25]	RCT, $N = 100$ Surgery alone vs chemoradiation followed by surgery. Chemoradiation: Cisplatin +5FU + vinblastine Radiation: 1.5 Gy twice/day × 21 days Surgery: Transhiatal esophagectomy, day 42	Median follow-up = 8.2 years Median OS = 17.6 months vs 16.9 months 3-year OS = 16% vs 30% [HR 0.73 (95% CI, 0.48–1.12) $p = 0.15$]
Medical Research Council Oesophageal Cancer Working Party 2002 [26]	RCT, $N = 802$ CS arm ($N = 400$): Cisplatin +5FU +/− radiation followed by surgery S arm ($N = 402$): Surgery alone Primary endpoint: Survival time by intention to treat	OS was better in the CS group (hazard ratio 0.79; 95% CI 0·67–0·93; $p = 0·004$). Median survival was 512 days (16·8 months) in the CS group vs 405 days (13·3 months) in the S group (difference 107 days; 95% CI 30–196). 2-year survival rates were 43% and 34% (difference 9%; 3–14).
RTOG trial 2007 [27]	RCT, $N = 443$ Preoperative chemotherapy followed by surgery vs surgery alone Pre-op chemo ($N = 216$): 3 cycles of cisplatin +5FU Radiation therapy not part of preoperative treatment plan Primary endpoint: Overall survival	No difference in overall survival for patients receiving perioperative chemotherapy compared with the surgery-only group
CROSS trial 2015 [28]	RCT, $N = 368$ Weekly neoadjuvant chemoradiotherapy (intravenous carboplatin and intravenous paclitaxel for 23 days) with concurrent radiotherapy followed by surgery, or surgery alone Primary endpoint was overall survival, analyzed by intention-to-treat	Median OS for chemoradiation plus surgery vs surgery alone SCC: 81.6 vs 21.1 months (HR 0·48 [95% CI 0·28–0·83]) EAC: 43.2 vs 27.1 months (HR 0·73 [95% CI 0·55–0·98]; log-rank $p = 0·038$).

most induction therapy was being performed with cisplatin/5FU followed by surgery for resectable clinical stage II-III esophageal cancer. However, the CROSS trial introduced a new regimen of neoadjuvant chemoradiation of intravenous carboplatin [AUC 2 mg/mL per min] and paclitaxel [50 mg/m2 of body-surface area for 23 days] with concurrent radiotherapy (41.4 Gy, given in 23 fractions of 1.8 Gy on 5 days per week). This regimen has shown the highest survival benefit for resectable stage II/III EC. The median overall survival for SCC was 81.6 vs. 21.1 months for trimodality therapy vs. surgery alone. For EAC, median overall survival was 43.2 vs. 27.1 months in the experimental arm vs. surgery alone [28].

Surgery

McKeown vs Akiyama: For SCC of the thoracic esophagus, a two- vs. three-field lymph-node dissection has long been a matter of discussion between the East (Japan) and the West.

The McKeown esophagogastrectomy may be used for SCC or EAC. It includes 1) an initial thoracic approach with esophageal dissection and radical lymphadenectomy, including nodes over the level of the azygous vein and recurrent laryngeal nerve, 2) a subsequent abdominal approach for construction of the gastric conduit and abdominal lymph node dissection, and 3) a third cervical approach to complete the cervical esophagogastric anastomosis in the neck. The Akiyama operation follows the same steps as the McKeown, though it includes a radical cervical lymph node dissection at the time of the cervical anastomosis.

In Japan, the radical cervical lymph node dissection improved outcomes slightly in patients with SCC of the thoracic esophagus, though the 5-year survival rate did not reach 70% [22]. Patients included in the CROSS trial had a two-field lymph-node dissection with a similar 5-year overall survival close to 70%. Overall, morbidity described for the Akiyama approach is 58%, with pulmonary complications occurring in 32.8%, cardiac dysrhythmias in 10.9%, and persistent recurrent laryngeal nerve problems in 2.6% [29].

Ivor Lewis: This two-field operation is primarily used for EAC located below the level of the carina. An abdominal approach is used to fashion the gastric conduit and to perform a radical lymph node dissection of the left gastric, common hepatic, and splenic arteries. Many surgical groups include a pyloroplasty as a standard to prevent delayed gastric emptying of the conduit, although this is decreasing in frequency. The second step in the operation is the thoracic approach for the thoracic esophageal dissection and radical lymph node dissection including inferior mediastinal nodes as well as the infracarinal lymph nodes. The anastomosis is completed above the azygous vein, with mechanical surgical staples or hand-sewn.

A Chinese trial published in 2015 compared Ivor Lewis esophagectomy (midline abdominal dissection followed by right thoracic dissection and anastomosis in the chest) with Sweet esophagectomy (left thoracoabdominal incision) for esophageal SCC [30]. It showed less morbidity, shorter hospital stay, fewer reoperations, greater lymph node yield, and a trend toward lower in-hospital mortality for the Ivor Lewis group.

Resection margins and en-bloc lymph node dissection: Many studies have compared transhiatal esophagectomy (THE) with the transthoracic esophagectomy (TTE), either McKeown or Ivor Lewis approach.

Both TTE and THE for thoracic esophageal cancer consider an abdominal and mediastinal lymph node dissection. The abdominal lymphadenectomy includes perigastric stations 1, 2, and 3 dissected en bloc with the specimen, left gastric nodes (station 7), celiac trunk, and common hepatic and splenic artery nodes (stations 8, 9, and 11).

TTE approach, however, enables an en-bloc dissection of the mediastinal nodes and a better control of the circumferential radial margin (CRM) compared to THE [31, 32].

Locoregional recurrences are predominant failure patterns in CRM-positive patients. In the first study of CRM involvement by Sagar et al., significantly more patients with a positive CRM (55%) developed a local recurrence as compared to those without involvement of the CRM (13%) [33]. Chao et al. found a significant influence of an involved CRM not only on locoregional but also on distant recurrences, while an involvement of the CRM of less than 1 mm was associated with early locoregional recurrences [34].

Longitudinal resection margin for thoracic esophageal cancer has not been as clearly defined as it has for distal/GEJ tumors. However, >3 cm proximal margin for SCC would render less than a 5% risk of margin involvement. For EAC, 7–10 cm proximal and 5 cm distal margins would be considered adequate.

TTE enables a better lymph node dissection compared to THE [32]. The optimum number of lymph nodes dissected will be dependent on T and N(+) stage. In pN + M0 cancers and 1 to 6 nodes positive, optimum lymphadenectomy is 10 for pT1, 15 for pT2, and 29 to 50 for pT3/T4 [35].

However, it is still unclear whether the more extensive removal of regional (metastatic or not) nodes contributes to the cure of patients with esophageal cancer.

Definitive Chemoradiotherapy and SCC

Chemoradiotherapy is a good definitive alternative for patients; however, neoadjuvant chemotherapy plus radical surgery has demonstrated the best long-term survival.

- In Japan, a phase II study was conducted to assess the effectiveness of definitive chemoradiotherapy in patients with stage II or III esophageal SCC (JCOG 9906). This study demonstrated a CR rate of 62% and a median survival time of 29 months, with 3- and 5-year survival rates of 44.7% and 36.8%, respectively [36].
- In a French trial comparing definitive chemoradiotherapy to neoadjuvant chemoradiotherapy followed by radical surgery, 259 patients with operable T3N0-1 M0 thoracic esophageal cancer, who had received two cycles of fluorouracil (5-FU) and cisplatin (days 1 to 5 and 22 to 26) and either conventional (46 Gy in 4.5 weeks) or split-course (15 Gy, days 1 to 5 and 22 to 26) concomitant radiotherapy, were randomized to surgery (arm A) or continuation of chemoradiation

(arm B; three cycles of FU/cisplatin and either conventional [20 Gy] or split-course [15 Gy] radiotherapy). Two-year survival rate was 34% in arm A versus 40% in arm B (hazard ratio for arm B vs. arm A = 0.90; adjusted $P = 0.44$). Median survival time was 17.7 months in arm A compared with 19.3 months in arm B. Two-year local control rate was 66.4% in arm A compared with 57.0% in arm B, and stents were required less often in the surgery arm (5% in arm A vs. 32% in arm B; $P < 0.001$). The 3-month mortality rate was 9.3% in arm A compared with 0.8% in arm B ($P = 0.002$) [37]. Neoadjuvant chemoradiation followed by radical surgery demonstrated a better local disease control; however, a higher perioperative mortality and similar overall survival were shown compared to definitive chemoradiation for SCC.

Clinical Stage III-IVa

Patients who fall in this clinical stage include those with cT4a, cN3, and cM0. They are usually treated with definitive chemoradiotherapy because survival outcomes after surgical treatment are generally poor. Phase II studies with cisplatin, 5-FU, and 60 Gy of radiotherapy in advanced thoracic esophageal cancer demonstrated a CR rate of 15–33% with a median survival time of 9–10 months [38, 39]. The addition of taxanes such as docetaxel to cisplatin plus 5-FU with concurrent radiotherapy (DCF-R) demonstrated a median progression-free survival of 11.1 months, and a median survival of 29.0 months with a survival rate of 43.9% at 3 years [40].

However, surgery may be still offered to patients with cT4aN1–2, given a more durable palliation with similar OS compared to definitive chemoradiation [41].

Clinical Stage IVb or Recurrent Disease

Palliation Chemotherapy in the setting of metastatic or recurrent disease is designed to improve survival and quality of life. Cisplatin plus 5-FU are the most commonly used regimens for combination palliative chemotherapy. Paclitaxel has demonstrated good results with acceptable toxicity as second-line treatment after platinum-based chemotherapy [42].

Palliation of symptoms such as dysphagia, pain, and bleeding can be treated with expandable endoscopic stents or radiotherapy including brachytherapy.

- When compared head-to-head, a 2004 randomized trial of brachytherapy versus self-expanding metal stents showed that long-term dysphagia relief was better with brachytherapy, with fewer complications and better quality of life scores [43].
- A 2005 study similarly showed more durable results with brachytherapy, although it is recognized that stents offer more immediate relief [44].

Abdominal Esophagus and Gastroesophageal Junction Adenocarcinoma (EAC)

Neoadjuvant and Adjuvant Therapies

- Induction therapy for EAC of the gastroesophageal junction (GEJ) remains controversial. This is because these tumors are often grouped together with proximal gastric cancers for the purposes of trial inclusion. This has led to a broad heterogeneity in practice. The main protocols that have been established are known as the MAGIC, POET, CROSS, and FLOT trials (Table 9.8).
- The MAGIC and CROSS regimens were considered to be standard of care until the presentation of FLOT. Longer-term follow-up and survival data with FLOT are highly anticipated and pending, but many centers adopted FLOT as standard of care when the results were presented, even prior to publication.

Table 9.8 Randomized clinical trials (RCT) comparing neoadjuvant or perioperative treatment in GEJ and gastric adenocarcinoma

Study	Methods	Results
MAGIC trial (2006) [45]	503 patients with gastric and GEJ cancer patients 25% of the population consisted of lower esophagus and GEJ tumors Compared 3 preoperative and 3 postoperative cycles of epirubicin, cisplatin, and fluorouracil (ECF) chemotherapy to surgery alone	5-year OS benefit with perioperative chemotherapy compared to surgery alone (36% vs 23%)
CROSS trial (2015) [28]	368 patients with esophageal and GEJ tumors (24%) Compared preoperative chemoradiotherapy (carboplatin, paclitaxel, and concurrent radiotherapy) to surgery alone	5-year OS of 47% in the chemoradiotherapy group, compared to 34% with surgery alone
FLOT trial (2019) [46]	716 patients with locally advanced, resectable gastric or GEJ adenocarcinoma Compared perioperative chemotherapy using fluorouracil, leucovorin, oxaliplatin, and docetaxel to the MAGIC regimen	Significant improvement in median overall survival of 50 months with FLOT compared to 35 months with ECF/ECX, giving a hazard ratio of 0.77 (95% CI 0.63–0.94)
POET trial (2009) [47]	119 patients with locally advanced AC of the lower esophagus or gastric cardia Randomized to 15 weeks of chemotherapy ($n = 59$) or 12 weeks of chemotherapy followed by 3 weeks of chemoradiotherapy ($n = 60$), followed by surgery	The study was closed early because of poor accrual, but showed a non-significant trend toward higher rates of complete response, lower recurrence, and improved survival with chemoradiotherapy

Based on the above data, patients with GEJ tumors should be offered preoperative chemoradiotherapy, with preoperative chemotherapy as an alternative. Ongoing trials will help define the optimal perioperative treatment of these cancers.

- Genomic characterization is identifying new options for biologic and targeted therapies to improve response rates and survival for gastroesophageal cancers.
- For patients with unresectable disease, the ToGa trial established a role for trastuzumab in the treatment of advanced HER2-positive GEJ AC (18% of study population) [48].
- Ramucirumab was also shown to increase overall survival for patients with advanced, pre-treated GEJ adenocarcinoma in the RAINBOW and REGARD trials [49, 50].
- Immune checkpoint inhibitors are actively being investigated for targeted therapy. Programmed death-ligand 1 (PD-L1) upregulation is seen in approximately 40% of gastroesophageal cancers, and PD-L1 inhibitors are showing encouraging results in select patients [51].
- It is likely that future neoadjuvant and adjuvant therapies will be guided by specific somatic genomic alternations and gene expression [52].

Surgical Therapy

The surgical approach has varied for GEJ tumors as well, and part of that variability comes from overlap in treatment by thoracic surgeons and upper GI surgeons.

- Resection is a mainstay in the treatment of GEJ cancer for fit patients who do not have disease involving distant sites or extra regional (para-aortic or mesenteric) lymph nodes. It is usually performed 4–6 weeks following preoperative therapy as part of the treatment plan.
- The surgical approach for Siewert 1 and 2 would be an Ivor Lewis esophagogastrectomy. However, the treatment for Siewert 2 EAC is a matter of debate since many upper GI surgeons would also treat with a D2 total gastrectomy and partial esophagectomy with a high intra-mediastinal esophago-jejunal anastomosis [53].
- The goals of surgery include complete (R0) resection of the primary tumor, with approximately a 7–10 cm proximal margin considering longitudinal intramural lymphatic progression. The optimum lymphadenectomy defined by pTNM is 10 to 12 nodes for pT1, 15 to 22 for pT2, and 31 to 42 for pT3/T4, depending on histopathologic cell type. In pN + M0 cancers with 1 to 6 nodes positive, optimum lymphadenectomy is 10 for pT1, 15 for pT2, and 29 to 50 for pT3/T4, but this remains debated in the literature [35].

Transthoracic Versus Transhiatal Esophagectomy

There is still controversy and limited evidence about the optimal surgical approach to tumors of the esophagogastric junction.

- A Dutch randomized trial in 2002 compared transhiatal esophagectomy to transthoracic McKeown esophagectomy for Siewert types 1 and 2 tumors. All patients

received partial gastrectomy and extended en-bloc lymphadenectomy. Less morbidity was observed with the transhiatal approach, but no difference in postoperative mortality [54]. However, there was a non-significant trend toward improved 5-year survival for Siewert type 1 tumors treated with the transthoracic approach [55].

- A Japanese trial in 2006 compared left thoracoabdominal to transhiatal partial esophagectomy with total gastrectomy and D2 lymphadenectomy in both groups, for Siewert types 2 and 3 tumors [56]. The left thoracoabdominal group had a thorough mediastinal lymph node dissection below the left inferior pulmonary vein. The trial closed early after a planned interim analysis because it seemed unlikely that the thoracoabdominal approach would yield improved survival compared to the transhiatal approach and had greater morbidity and mortality.

Patients with Siewert types 1 and 2 tumors are thus preferentially treated with transthoracic esophagectomy and partial gastrectomy with D2 lymphadenectomy (Ivor Lewis) to ensure an adequate 7–10 cm proximal esophageal and 5 cm distal gastric margin. Siewert types 2 and 3 tumors can be treated with total gastrectomy, transhiatal partial esophagectomy, and D2 lymphadenectomy. If there is concern about achieving an adequate proximal margin, the transthoracic approach should be used.

Extent of Lymphadenectomy

For tumors at the GEJ, an adequate regional lymph node dissection involves periesophageal nodes and a D2 lymphadenectomy, which entails removing perigastric nodes and those along the hepatic, left gastric, celiac, and splenic arteries.

- Mediastinal lymph node dissection appears to be more important for type 1 tumors, where up to 85% of lymph node metastases occur in the mediastinum, compared to 30% for type 2 and 10% for type 3 tumors [57, 58].
- Types 2 and 3 tumors do not appear to benefit from mediastinal lymph node dissection as those with positive nodes in the mediastinum already have significant abdominal lymphadenopathy [57, 59]. This may be the rationale to avoid the transthoracic approach for type 3 tumors.
- The rate of cervical lymph node metastases for adenocarcinoma of the GEJ has not been well studied and the role of cervical lymphadenectomy remains to be elucidated. However, similar to the above scenario, patients with cervical lymphadenopathy generally already have mediastinal lymphadenopathy and further dissection may not impact outcome.

Optimum lymphadenectomy for esophageal cancer continues to be debated, but it is clear that lymphadenectomy is associated with better staging and improved survival. A 2010 study of over 4600 patients from the Worldwide Esophageal Cancer Collaboration published by Rizk and colleagues looked at the optimum lymphadenectomy to maximize survival by stage and suggested resecting 10 nodes for pT1, 20 for pT2, and > 30 for pT3/4 [35].

However, in the developing era of multimodal neoadjuvant treatment for locoregional control and tumor downstaging, recent studies have questioned the survival benefit of extended lymphadenectomy for esophageal cancer. Lagergren et al., in a Swedish cohort of 606 patients with esophageal cancer (83% EAC), were unable to prove a significant difference in 5-year all-cause or disease-specific survival comparing extended lymphadenectomy (21–52 nodes) to limited lymph node dissection (0–10 nodes) (HR, 0.98; 95% CI, 0.57–1.66) [60].

Minimally Invasive Approach

Esophagectomy, gastrectomy, and lymphadenectomy can be performed with an open or minimally-invasive approach (thoracoscopic and laparoscopic). The advantages of minimally invasive approach can include smaller incisions, less pain, fewer complications, and shorter admissions, while achieving equivalent lymphadenectomy and resection margins [61–63]. Experience is being gained with robotic esophagectomy at specialized centers. Early reports show its safety and feasibility, but definitive evidence regarding its utility over laparoscopic and thoracoscopic esophagectomy is currently unavailable [64].

Summary

Classification of tumors at the GEJ continues to evolve and remains somewhat controversial. Future genomic alteration analyses will likely impact classification of these tumors as esophageal or gastric. Multiple modalities are now available to clinically stage patients and those with locally advanced tumors should be considered for neoadjuvant and adjuvant therapies to improve survival. Surgical resection is a mainstay in curative-intent treatment and should involve an adequate lymphadenectomy for accurate staging. Postoperative outcomes are improving with advances in minimally invasive techniques, enhanced recovery programs, and centralization of esophageal surgery to high-volume centers. Survival for resectable disease continues to improve with multimodality treatment, and future targeted, biological, and immuno-therapies may improve prognosis for esophageal cancer.

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