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# Advances and Controversies in the Management of Locally Advanced Gastro-esophageal Adenocarcinoma

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**Abstract**

Esophageal adenocarcinoma (EAD) has been recently described as 'the silent epidemic' because of its rapidly rising incidence. Two-thirds of patients with esophageal adenocarcinoma present with locally advanced disease. In spite of recent advances in cancer therapy, the treatment of locally advanced esophageal and gastroesophageal junction (GEJ) adenocarcinoma remains challenging. Current standard of care for fit patients with locally advanced esophageal adenocarcinoma is trimodality therapy with concurrent platinum-based chemotherapy and ionizing radiation followed by surgical resection. Numerous modifications of the surgical technique are being practiced, but in general Ivor Lewis esophagectomy with celiac and peri-esophageal lymph node dissection is considered standard of care. The depth of invasion (T stage), number of involved lymph nodes, pathologic complete response to preoperative therapy, number of resected lymph nodes at the time of surgery, and preoperative nutritional status are important prognostic factors. No postoperative therapy has been shown to improve outcomes in patients with residual disease at the time of surgery. A number of newer agents including EGFR tyrosine kinase inhibitors, monoclonal antibodies against EGFR, HER2 targeted therapy, immunotherapy, and anti-angiogenic agents are currently being evaluated to improve the outcomes of these patients. The optimum management of GEJ adenocarcinoma remains debated, however currently available evidence suggests that it should be treated as esophageal rather than gastric tumors except for type III tumors, which can be, treated as gastric carcinoma with perioperative chemotherapy.

**Keywords**

Locally advanced esophageal adenocarcinoma, Gastroesophageal junction adenocarcinoma, Trimodality therapy, Concurrent chemoradiation, Targeted therapy

## Introduction

The incidence of adenocarcinoma originating at the distal esophagus and gastroesophageal junction (GEJ) has increased dramatically in western countries mainly in the adult white male population. Esophageal cancer is now the eighth most common cancer worldwide with chronic gastroesophageal reflux disease (GERD) and a high body mass index (BMI) representing the two major risk factors [1,2]. Despite more aggressive surveillance identifying early adenocarcinoma within Barrett's esophagus changes, the vast majority of patients still present symptomatically with locally advanced disease. Five year survival rates for esophageal cancer have improved modestly over last 30 years, from 5% between 1975-1977 to 19% between 2001-2007 [2]. The optimum management of locally advanced esophageal adenocarcinoma is surrounded by many controversies which is further complicated by uncertainties regarding classification of GEJ adenocarcinoma.

The location of GEJ tumors has been a source of controversy in regard to their definition, staging, and management. The conventional Siewert's classification scheme places GEJ tumors into 3 types [3]. Type I is defined as a tumor of the distal esophagus (1-5 cm proximal to the cardia), which usually arises from intestinal metaplasia of the esophagus (Barrett's esophagus) and may infiltrate the GEJ from above. Type II is defined as a tumor of the cardia (1 cm proximal and 2 cm distal to the cardia), which arises from the cardiac epithelium or short-segment of intestinal metaplasia at the GEJ. Type III is defined as a subcardiac gastric carcinoma (2-5 cm distal to the cardia), which may infiltrate the GEJ and distal esophagus from below. In contrast, the 7$^{th}$ edition of the UICC TNM classification (2010) system has defined GEJ tumors as all tumors located 5 cm proximal and distal to the endoscopically defined cardia, which is determined as the proximal end of gastric folds [4]. There is uniform consensus that locally advanced type I and II adenocarcinomas are optimally treated with trimodality approach with concurrent chemoradiotherapy followed by surgery as they are esophageal tumors. Type III tumors have however been considered by some as gastric cancer and treated accordingly using perioperative chemotherapy approach tested in the MAGIC trial [5], while others utilize trimodality therapy for Type III tumors as well. From a surgical standpoint, surgery for type I and II tumors typically involves an esophagogastrectomy through combined abdominal and thoracic approaches. For type III tumors, total gastrectomy may be additionally necessary with Roux- en- Y esophagojejunostomy reconstruction.

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Here we will discuss advances and prevailing controversies in the staging, optimum use of multimodality therapy, and type of surgery in the management of locally advanced esophageal and GEJ adenocarcinoma.

## Defining Locally Advanced Esophageal and GEJ Adenocarcinoma in the 7th AJCC TNM Staging System

Staging of esophageal and GEJ cancer has been extensively changed and improved in the 7th edition of the American Joint Committee on Cancer (AJCC), Cancer Staging Manual [6]. Notable changes with respect to locally advanced disease include changes in the T4 and N classifications. T4 tumors are now appropriately divided into T4a and b, with T4a being resectable (invading pleura/diaphragm/pericardium) and T4b being unresectable (invading trachea/aorta). N status now reflects the number of lymph nodes involved rather than simply the presence or absence of lymph nodes involvement with N1, N2, and N3 designations equating to metastasis in 1-2, 3-6, ≥ 7 regional lymph nodes respectively. Pathologic Stages IIA to IIIC are considered 'locally advanced' [7]. In addition, the 7th TNM staging system recognizes the differences in biology of esophageal squamous and adenocarcinomas separating each into their own TNM staging system. These differences allow better survival stratification but complicate interpretation of trials that employed the old staging system.

## The Role of PET/CT and EUS in Esophageal Adenocarcinoma

Current standard clinical staging includes transesophageal ultrasound (EUS) and PET/CT scan. A recent systemic review concluded that PET CTs were recommended to improve the accuracy of M staging in patients who were potential candidates for curative therapy; however, no recommendation was made for or against the use of PET for the assessment of treatment response [8].

In spite of utilization of EUS and PET/CT, there remains a possibility of understaging some patients especially those with clinical T2N0 disease (stage IB if well or moderately differentiated, stage IIA if poorly differentiated). A retrospective study of 69 patients with T2N0 disease reported that half of the patients who proceeded directly to esophagectomy were understaged, and half of the patients who underwent neoadjuvant therapy were staged either the same or higher on the final pathologic staging [9]. Two other retrospective studies including one from our institution reported similar rates of understaging of cT2N0 disease with currently available staging techniques [10,11]. From these data, it is logical to offer neoadjuvant chemoradiotherapy to patients with cT2N0 disease with good performance status because of very high rate of clinical understaging. These data also confirm that EUS is best suited for staging T3 and T4 disease.

The role of EUS and PET/CT in the post-treatment setting remains undefined, especially in predicting complete pathologic response (pCR). Repeat endoscopy often identifies only fibrosis or ulceration; however, residual tumor is not infrequently located deep to the mucosa. Moreover, it is difficult to differentiate between chemoradiation treatment effect and residual tumor by EUS. Similarly PET scan lacks specificity as post-treatment inflammation is often FDG (18-fluorodeoxyglucose) avid, making it indistinguishable from residual tumor particularly early after treatment [12]. However, approximately 8-10% of the patients develop systemic metastases during chemoradiation therapy and post treatment PET/CT can be helpful in such patients to avoid a large and futile surgical procedure [13-15].

## The Role of Chemotherapy and Radiation Therapy

Early in the experience of surgical treatment for esophageal cancer it became quickly apparent that surgery alone unfortunately did not cure most patients. Five year survival rate with surgery alone for T2N0 esophageal adenocarcinoma ranges between 50-60%, and significantly declines to 15% or less in node positive disease. Addition of radiotherapy to surgery also did not lead to significant improvement in outcomes. Moreover, retrospective studies of the pattern of relapse after curative esophagectomy showed that distant relapse accounted for one third of the cases of treatment failure indicative of the need for systemic therapy in locally advanced disease in addition to locoregional therapy with surgery and radiation [16,17]. Several clinical trials have been conducted evaluating different combinations of these three modalities in various sequences in an attempt to improve overall outcomes (Table 1).

One of the earlier trials comparing preoperative chemotherapy with 5-fluorouracil (5-FU) and cisplatin followed by surgery versus surgery alone failed to show any survival benefit of neoadjuvant chemotherapy. In addition, there was no difference in the rate of locoregional or distant recurrence between the two treatment arms. However, this trial did show that preoperative chemotherapy was tolerable and did not increase surgical morbidity or mortality [18]. Further attempts at improving the outcomes led to addition of radiotherapy in the preoperative setting. This approach was associated with encouraging results in a small pilot study [19]. A subsequent randomized trial comparing neoadjuvant concurrent chemoradiation (5-FU + cisplatin + vinblastine + 45 Gy radiation) followed by surgery with surgery alone showed a trend towards improved 3-year overall survival (OS) with trimodality approach, but failed to reach statistical significance (30% vs 16%, p = 0.15), likely because the study was powered to detect only a large difference in median OS [20].

Two trials establishing the role of concurrent chemoradiotherapy in esophageal cancer include the RTOG 8501 and CROSS trial. RTOG 8501 was a randomized controlled trial comparing chemoradiotherapy using 4 courses of 5-FU 1000 mg/m$^2$ daily for 4 days plus cisplatin 75 mg/m$^2$ on first day plus 50 Gy radiation to radiation alone (64Gy) in patients with adenocarcinoma (16%) or squamous cell carcinoma (84%) of thoracic esophagus (SCC) [21]. Patients who received concurrent chemoradiotherapy had higher clinical or pCR rate, fewer local and systemic relapses, better median OS compared to those who received radiation alone (12.5 mo vs 8.9 mo), and improved 1- and 2-year survival rates of 50% and 38% respectively. However, the rate of Grade 3 or 4 toxicities was higher in the combined therapy group. The updated long-term follow up results showed that 5-year OS was 26% in combined therapy group compared to 0% in radiation alone group [22]. The CROSS trial randomly assigned 363 patients with potentially resectable esophageal or GEJ carcinoma to receive either neoadjuvant chemoradiotherapy using weekly paclitaxel 50 mg/m$^2$ plus carboplatin AUC 2 and radiotherapy (41.4 Gy) over 5 weeks followed by surgery or surgery alone. The rate of R0 resection (complete resection with negative margins) was significantly higher in patients who received neoadjuvant chemoradiation (92% vs 69%). Approximately 29% of the patients who received preoperative chemoradiotherapy achieved pCR. In addition, OS was significantly better with preoperative chemoradiotherapy which persisted with longer (median 84-month) follow-up (5-year OS 47% vs 33%). The preoperative chemoradiotherapy was well tolerated, with 7% grade 3 or worse hematologic toxicity and < 13% grade 3 or worse non-hematologic toxicity without any differences in postoperative morbidity or mortality between the two groups [23,24]. Notably, in contrast to prior studies, this study did include about 23% of the patients with GEJ adenocarcinoma and a larger number of esophageal adenocarcinoma (75%) compared to SCC (25%) which makes it relevant to the patients with GEJ carcinoma treated in the western world. One limitation of the CROSS trial is the fact that two-thirds of the patients on this trial had N1 disease based on the 6th TNM staging system defined as involvement of regional lymph nodes but the actual number of involved lymph nodes in patients on chemoradiation arm remains unclear. The median number of positive lymph nodes at the time of surgical resection was 0 (range 0-1) on chemoradiation arm and 2 (range 1-6) on surgery alone arm. It is unclear if patients with N3 disease (defined as ≥ 7 lymph nodes) should be treated using the same approach. Another smaller study conducted by Walsh et al. comparing concurrent chemoradiation (5-FU + cisplatin + 40 Gy radiation) followed by surgery with surgery alone showed similar

**Table 1:** Clinical Trials Evaluating Chemotherapy with or without radiotherapy in addition to surgery in Locally Advanced Esophageal and GEJ Cancer.

| Trial | Treatment Arms | Patients (N) | Histology | GEJ tumors (%) | pCR Rate | Rate of R0 resection | Survival | Loco-regional Failure | Comments |
|---|---|---|---|---|---|---|---|---|---|
| Kelsen et al. [18] | Preop Chemo (5-FU + Cis) → Surgery | 213 | Adeno 54%<br>Epidermoid Carcinoma 46% | Included,<br>Number not specified | Data not available | 62% | mOS: 14.9 mo<br>2-yr OS: 35% | 32% | Preoperative chemotherapy was tolerable. No increase in operative morbidity or mortality. |
| | Surgery | 227 | | | | 59% | mOS: 16.1 mo<br>2-yr OS: 37% | 31% | |
| RTOG 8501 [21,22] | CRT (5-FU + Cis + 50Gy radiation) | 100 | Adeno 16%<br>SCC 84% | Only patients with thoracic esophagus tumors included | NA | NA | mOS: 12.5 mo<br>5-yr OS: 26% | 39% | Severe and life threatening side effects in 44% and 20% of patients receiving CRT vs 25% and 3% in patients who underwent XRT alone. |
| | Radiation alone (64 Gy) | 100 | | | | | mOS: 8.9 mo<br>5-yr OS: 0% | 52% | |
| Urba et al. [20] | Preop CRT (5-FU + Cis + Vinblastine + 45Gy) → Surgery | 50 | Adeno 75%<br>SCC 25% | GEJ tumor patients included<br>Number not specified | Adeno: 24%<br>SCC: 38% | Gross total resection: 96% | mOS: 16.9 mo<br>3-yr OS: 30% | 19% | Grade 3/4 hematologic toxicity 78% in multimodality arm. |
| | Surgery | 50 | | | NA | Gross total resection: 90% | mOS: 17.6 mo<br>3-yr OS: 16% | 42% | |
| CROSS [23,24] | Preop CRT (Carbo + Paclitaxel +41.4 Gy) → Surgery | 178 | Adeno 75%<br>SCC 23%<br>Large-cell Undifferentiated Carcinoma 2% | 23% among the adenocarcinoma patients had GEJ tumor | 29% | 92% | mOS: 49.4 mo<br>5-yr OS: 47% | 22% | Grade 3 and 4 hematologic toxicity: 7% and 1% respectively in multimodality group. |
| | Surgery | 188 | | | NA | 69% | mOS: 24 mo<br>5-yr OS: 33% | 38% | |
| Walsh et al. [25] | Preop CRT (5-FU + Cis + 40Gy) → Surgery | 58 | Adeno 100% | 38% patients with tumors of the cardia | 25% | Data not available | mOS: 16 mo<br>3-yr OS: 32% | Data not available | - |
| | Surgery | 55 | | | NA | | mOS: 11 mo<br>3-yr OS: 6% | | |
| CALGB 9781 (Tepper et al.) [26] | Preop CRT (5-FU + Cis + 50.4 Gy) → Surgery | 30 | Adeno 75%<br>SCC 25% | Patients with GEJ tumor included, number not specified | 40% | Data not available | mOS: 4.48 yr<br>5-yr OS: 39% | Data not available | Trend towards improved OS in trimodality group. Trial closed early because of poor accrual. |
| | Surgery | 26 | | | NA | | mOS: 1.79yr<br>5-yr OS: 16% | | |
| Burmeister et al. [28] | Preop CRT (5-FU + Cis + 35 Gy) → Surgery | 128 | Adeno 62%<br>SCC 37%<br>Mixed 1% | Patients with tumors of the cardia with predominant esophageal involvement were allowed but the number not stated | SCC 27%<br>Adeno 9% | 80% | mOS: 22.2 mo | 15% | 16% patients developed Grade 3-4 esophagitis, other grade 3-4 toxicity <5% |
| | Surgery | 128 | | | NA | 59% | mOS: 19.3 mo | 19% | |
| FFCD 9901 [27] | Preop CRT (5-FU + Cis + 45 Gy) → Surgery | 98 | Only stage I and II disease included<br>Adeno30%<br>SCC 70% | Data not available | 33.3% | 93.8% | mOS: 31.8 mo<br>5-yr OS: 41.1% | 15.3% | No improvement in OS or R0 resection, likely because most of the patients had stage I or IIA disease. Closed early because of futility.<br>Higher perioperative morbidity and mortality in trimodality group. |
| | Surgery | 97 | | | NA | 92.1% | mOS: 41.2 mo<br>5-yr OS: 33.8% | 28.9% | |
| POET [40] | Induction chemo → Surgery | 59 | Adeno only | GEJ only | 2% | 69.5% | mOS: 21.1 mo<br>3-yr OS: 27.7% | Data not available | Study closed early because of poor accrual |
| | Chemotherapy → CRT → Surgery | 60 | | | 15.6% | 72% | mOS: 33.1 mo<br>3-yr OS: 47.4% | | |
| MAGIC [5] | Preop chemo (Epirubicin + Cis + 5-FU) → Surgery → Postop chemo (same regimen) | 250 | All adeno<br>75% Gastric<br>14% Esophageal<br>11% GEJ | 11% | Data not available | Data not available | 5-yr OS: 36% | Data not available | Improved OS and PFS with perioperative chemotherapy<br>Rate of post-op complications similar between the 2 groups |
| | Surgery | 253 | | | | | 5-yr OS: 23% | | |

pCR: Pathologic Complete Response; CRT: Chemoradiation; XRT: Radiotherapy; 5-FU: 5-fluorouracil; Cis: Cisplatin; OS: Overall Survival; SCC: Squamous Cell Carcinoma; Adeno: Adenocarcinoma; Carbo: Carboplatin; pCR: Pathologic Complete Response; GEJ: Gastroesophageal Junction.

results with improved median OS (16 vs 11 mo) and 3-year OS (32% vs 6%) with trimodality therapy compared to surgery alone [25]. Worth noting is the lower dose of radiation used in these trials which was justified by the plan for all patients to undergo surgical resection.

Another randomized phase III trial (CALGB 9781) was originally designed to randomize 475 patients with esophageal carcinoma to receive either preoperative chemoradiotherapy (cisplatin 100 mg/$m^2$ and fluorouracil 1,000 mg/$m^2$/d for 4 days on weeks 1 and 5 concurrent with 50.4 Gy radiation) followed by surgery or surgery alone. However, the trial was closed prematurely because of poor accrual. The pCR rate was 40% with preoperative chemoradiation, and 5-year OS was 39% in trimodality group compared to 16% in surgery group, which was not statistically significant most likely because of limited sample size; however, this was numerically impressive [26].

Contrary to above results, a phase III French FFCD 9901 trial comparing neoadjuvant chemoradiotherapy with 5-FU/cisplatin plus 45 Gy radiation followed by surgery to surgery alone in patients with stage I or II esophageal or GEJ cancer was closed early because of futility with no improvement in 3-year OS or rate of R0 resection, and higher perioperative morbidity and mortality in trimodality group. One plausible explanation for these results is that the patients with early stage esophageal cancer (T1N0) do not derive as much benefit from trimodality therapy compared to patients with high T stage tumor and/or positive lymph nodes. The trial included 19% of the patients with stage I disease and the actual sample size with stage II disease was small, and therefore the overall results did not show any statistically significant benefit [27]. In addition, the majority of the patients included in this study had SCC with high perioperative mortality after induction therapy likely attributed to comorbid pulmonary and hepatic conditions associated with risk factors such as smoking and alcohol consumption. Another trial by Burmeister et al. comparing neoadjuvant chemoradiation (5-FU + cisplatin + 35 Gy radiation) followed by surgery with surgery alone for resectable esophageal cancer, did not show any OS or progression free survival (PFS) benefit of trimodality approach, however, the rate of R0 resection was higher in trimodality group. A subgroup analysis showed that the patients with SCC had better PFS with chemoradiation, however the study was not powered to detect real magnitude of benefit in this subgroup [28].

In spite of the conflicting results from different trials, two meta-analyses by Sjoquist et al. and Gebski et al. have confirmed the survival benefit of neoadjuvant chemoradiation compared to surgery alone in locally advanced esophageal cancer, showing absolute 2 year survival benefit of 8.7% and 13% respectively [29,30]. Of note, the survival advantage of combined chemoradiotherapy has been demonstrated only with concurrent chemoradiotherapy approach rather than sequential approach [31-33]. The results of the trials addressing the role of adjuvant therapy have been conflicting, but in general, upfront surgery with adjuvant chemotherapy is not preferred. A randomized trial (JCOG9907) comparing neoadjuvant chemotherapy to adjuvant chemotherapy showed a significantly higher 5-year OS in the neoadjuvant therapy group [34]. In addition, the patients tolerate neoadjuvant therapy better than the adjuvant therapy as an Ivor Lewis esophagectomy is a major operation.

There has been no prospective trials comparing carboplatin/paclitaxel and 5-FU/cisplatin in the neoadjuvant setting, but a retrospective analysis of 165 patients showed that there was no difference in the pCR rate or 3-year OS between the two regimens. There were more Grade 3 or higher hematologic toxicity in 5-FU/cisplatin group (41% vs 25%), but nonhematologic toxicity were comparable [35]. In the absence of randomized controlled data, the choice of regimen should be guided by the side effect profile, patient preference, and institution experience. Traditionally the dose of radiation used in concurrent chemoradiation trials was 45-50Gy except for 41.4 Gy in CROSS trial. A randomized trial (INT0123) showed that increasing the radiation dose to 64.8Gy administered concurrently with 5-FU/cisplatin in neoadjuvant setting did not lead to improvement in pCR, loco-regional failure, or OS compared to standard 50.4 Gy dose [36]. Our institution policy continues to involve a total dose of 50.4Gy radiation considering the fact that a small number of patients might not undergo surgical resection following chemoradiation due to unanticipated events. We believe weekly carboplatin/paclitaxel or cisplatin/ 5-FU are both reasonable chemotherapy regimens.

A growing body of evidence suggests that the two major histologic subtypes of esophageal carcinoma differ in disease biology and response to treatment. A population based cohort study evaluated 287 patients with esophageal cancer who were not a candidate for esophagectomy. One hundred and ten patients received definitive chemoradiotherapy (dCRT) and 177 patients received definitive radiation (dRT). Disease free survival (DFS) at 2- and 5- years was 24 and 9% for SCC versus 10 and 2% for adenocarcinoma patients (P = 0.006). OS after 2 and 5 years was 29 and 14% for SCC patients versus 17 and 3% for adenocarcinoma patients (P = 0.044). DFS was higher in the dCRT group compared with dRT patients (P = 0.016). The locoregional failure rate was lower in the dCRT group and in SCC patients [37]. In addition, the OS of patients with SCC was somewhat better than the patients with adenocarcinoma treated with multimodality therapy in both the CROSS and RTOG 8501 trials further confirming the difference in the disease biology and response to therapy between the two histologic subtypes.

It has been consistently shown that the patients who achieve pCR meaning pathologic absence of residual disease in the surgical specimen after neoadjuvant chemoradiotherapy have better DFS and OS [38,39]. Hence, it is logical to think that intensification of preoperative therapy would lead to improved outcomes. While no randomized trials have compared the approach of sequential induction chemotherapy followed by chemoradiotherapy with standard chemoradiotherapy, only one published trial, the German POET trial, has compared this approach with induction chemotherapy alone followed by surgery in patients with GEJ adenocarcinoma. The pCR rate was significantly higher after induction chemotherapy followed by chemoradiotherapy, and there was a non-significant trend towards better median and three-year survival (47 versus 28%, p = 0.07) in this group. In spite of this numerically better survival, induction chemotherapy approach is not used since this was a small study and it is uncertain whether these results can be extrapolated to SCC and adenocarcinoma of the thoracic esophagus [40].

Another approach to deliver chemotherapy in conjunction with surgery is perioperative chemotherapy which was evaluated in MAGIC trial [5]. In this trial, 503 patients were randomized to receive either perioperative chemotherapy consisting of epirubicin, cisplatin, and fluorouracil with 3 preoperative and 3 postoperative cycles or surgery alone. Patients who received perioperative chemotherapy had significantly smaller tumor size at the time of surgery, and improved OS as well as PFS compared to surgery alone while the rates of postoperative complications and mortality were comparable. Notably, the majority of patients in this trial received all 3 cycles of preoperative chemotherapy, but only one postoperative cycle most likely because of morbidity associated with major surgery. Majority of the patients in this trial had gastric carcinoma. Only 14% had lower esophageal adenocarcinoma and 11% had GEJ tumors and therefore this approach has not been widely utilized for the treatment of esophageal cancer, but continues to be an option for Type III GEJ tumors.

There is a dearth of high quality randomized trials specifically for patients with GEJ adenocarcinoma and therefore optimum management is not well established. POET trial which included only GEJ adenocarcinoma patients, closed early because of poor accrual. Other trials, such as CROSS, MAGIC, and INT-0116 did include patients with GEJ adenocarcinoma (11%, 11.2%, and 20% respectively); however, none of these trials were specifically powered to determine benefit of tested therapeutic intervention in this subgroup. With the availability of genomic sequencing, it is becoming more apparent that GEJ tumors are biologically more similar to esophageal cancer than gastric cancer [41,42]. Recent data also showed that 49%

of the mutated genes in GEJ tumors were unique to these tumors as compared to gastric cancers providing further justification to design trials that are unique to GEJ tumors [43].

For highly obstructive tumors, nutritional support during chemoradiation is important. Studies have shown increased surgical morbidity and mortality in patients with hypoalbuminemia as a marker of malnutrition [44]. In our experience, approximately one third of patients require nutritional support during chemoradiation. Some surgeons have favored laparoscopic Jejunostomy tube placement to avoid inadvertent damage to gastroepiploic vessels, which are the sole blood supply to the gastric conduit used for reconstruction. In our experience, PEG tube placement has been safe and more expeditious. Another strategy has been esophageal stent placement prior to chemoradiation, which allows normal eating. Some of the drawbacks of stent placement include pain, stent migration, and in our experience, surrounding mediastinal tissue fibrosis making subsequent esophagectomy more challenging.

## Role of Surgery, Timing, and Patient Selection

As repeat clinical staging to determine a pCR after chemoradiation remains an imperfect science and only a distinct minority of patients achieves pCR after current chemoradiation regimens, most institutions have subscribed to a strategy for resection after chemoradiation for locally advanced adenocarcinomas. In addition, about 39% of the patients treated with chemoradiation in RTOG 8501 trial had loco-regional disease recurrence. There are no large randomized trials comparing chemoradiation with or without surgery in esophageal adenocarcinoma, however, two meta-analyses showed improved OS and decreased loco-regional recurrence rate with addition of surgery to chemoradiation [45,46]. Therefore surgical resection remains the standard of care after chemoradiation in the treatment of locally advanced esophageal cancer. There are no randomized controlled data in GEJ adenocarcinoma showing that addition of surgery to chemoradiation improves survival.

The optimal timing of surgery remains unknown. Radiation-induced tumor necrosis may increase over time and studies of neoadjuvant radiotherapy for rectal cancer suggest that a longer interval between radiation and surgery may actually result in improved pCR and decreased postoperative morbidity [47,48]. On the other hand, there are theoretical concerns that waiting longer could make the dissection more difficult due to increased radiation induced fibrosis of surrounding normal tissues as well as a possibility of allowing for tumor regrowth, increasing the risk of recurrence. Most institutions, perhaps somewhat arbitrarily, allow 5 to 8 weeks after the completion of chemoradiation for bone marrow and functional status recovery prior to planned surgery [49].

Unfortunately, some patients who complete neoadjuvant chemoradiation experience a significant decline in performance status mainly due to toxicity, and occasionally take many weeks to recover. Performing a major surgical procedure on a compromised patient can significantly increase the risk of morbidity or death. Kim and associates from MD Anderson retrospectively analyzed 266 patients who underwent post induction resection dividing them into patients who underwent resection less than 8 weeks following completion of chemoradiation (n = 150) and who underwent resection greater than 8 weeks (n = 116). The delayed group had higher toxicity and comorbid risk factors and therefore surgery was essentially performed as a 'salvage' procedure. In this study, a longer interval between neoadjuvant chemoradiation and surgery was not associated with a difference in postoperative morbidity, pathologic response, or OS [49]. A recent retrospective study of 848 patients compared the group of patients who underwent salvage esophagectomy after definitive chemoradiotherapy (n = 308) with the group that underwent neoadjuvant chemoradiotherapy followed by planned esophagectomy (n = 540). This study also showed no difference in 3-year OS, DFS, and in-hospital mortality between the 2 groups; however, the patients with salvage surgery had higher rate of anastomotic leak and surgical site infection [50]. While this approach would seem to make great sense, these studies are hampered by retrospective nature and the unknown true 'patient number dominator'.

Several studies have focused on analyzing the predisposing risk factors for morbidity and mortality after esophagectomy. Among these, the largest study analyzed 2315 esophagectomies performed from 2002 to 2007 in 73 participating centers in the Society of Thoracic Surgeons General Thoracic Database. Advanced age (> 75), FEV1 < 60%, insulin dependent diabetes, congestive heart failure, coronary artery disease, peripheral vascular disease, hypertension, higher American Society of Anesthesiology rating, smoking status, and steroid use were identified as predictors of adverse outcome [51]. Elderly patients above the age of 70 are at increased risk of pulmonary and cardiac complications, perioperative mortality following esophagectomy, and have reduced cancer-related 5-year survival compared with younger patients. These patients represent a high-risk cohort, who requires thorough assessment of medical comorbidity, targeted counseling, and optimized treatment pathways [52].

In high surgical risk patients who appear to have had a complete clinical response defined as both post-chemoradiation endoscopic biopsy showing no cancer and no pathologic uptake by PET, a careful observational approach may be reasonable. This notion is supported by two randomized clinical trials in squamous cell esophageal cancer [53,54]. Although careful observation appears to be justified in select patients who achieve a clinical response, in the absence of a validated prediction model, surgery as a planned approach must be encouraged for all patients with esophageal adenocarcinoma with good performance status following recovery from chemoradiation. Finally, the considerable short and long-term morbidity of the esophagectomy needs to be kept in mind. In patients who do not undergo planned esophagectomy, our practice is to perform periodic EUS and biopsies to detect early local recurrence which can be treated with salvage esophagectomy in patients with reasonable surgical risk. The subset of patients who are at very high or prohibitive operative risk with locally advanced adenocarcinoma who achieve good palliation after chemoradiation should receive best supportive care and surveillance only.

## Surgical Approach

The challenges of removing an organ traversing three anatomic zones in the body (neck, chest, and abdomen) and reconstitution of the gastrointestinal tract has led to considerable variation in the technique. Since initial description of esophageal resection with stomach reconstruction based on the right gastroepiploic vascular arcade was described by Sweet in 1945 [55], surgeons have developed several approaches for esophagectomy. Currently, the Society of Thoracic Surgery General Thoracic Surgery Database lists 14 different methods of performing esophagectomy highlighting the variability that exists today and underscores the challenges of quantifying and comparing outcomes between techniques [56]. Currently available surgical approaches can be broadly categorized into a) Open (Ivor Lewis "right thoracotomy/ laparotomy", McKeown "three port: right thoracotomy/laparotomy/neck", or left thoracoabdominal), b) Transhiatal (laparotomy/neck), c) Minimally invasive (thoracoscopic/ laparoscopic, occasionally robotic) or d) "hybrid" combining either thoracoscopic or laparoscopic with an open approach. The optimal approach remains debated to date.

There have been a few studies comparing one technique to another. Hulscher et al. reported a study of 220 patients with type I or II GEJ tumors randomly assigned to either transhiatal esophagectomy (THE) or transthoracic esophagectomy (TTE) with an extended mediastinal lymphadenectomy via right thoracotomy [57]. The rate of R0 resection was comparable between TTE and THE groups; however, the mean number of lymph nodes harvested was significantly lower in patients who underwent THE (31 vs 16). TTE group had higher postoperative morbidity including pulmonary complications and chylothorax, as well as longer duration of mechanical ventilation and the length of ICU and hospital stay; however, postoperative

mortality, cardiac complications, fistula formation, vocal cord paralysis, and wound infection were comparable between the groups. At 5-year follow-up, there was a trend toward a survival advantage in the TTE group; however, 5-year OS and DFS were not statistically significant. Subgroup analysis demonstrated that there was a significant survival benefit of 14% observed in patients with type I GEJ tumors who underwent TTE compared with THE patients. A meta-analysis involving 7,527 patients from 50 studies demonstrated no significant difference in morbidity, mortality or long-term survival among patients undergoing THE versus TTE (3). In this analysis, TTE had a higher risk for pulmonary complications, chylous leaks, and wound infection, while THE was associated with an increased incidence of anastomotic leaks and recurrent laryngeal nerve injury. While esophagectomies with chest incisions appear to have increased pulmonary morbidity, the strong trend toward inferior survival in the randomized study in the THE arm and the poor ability to dissect mid to upper peri-esophageal lymph nodes, there has been a shift away from THE in the surgical treatment of locally advanced adenocarcinoma.

With the advances in minimally invasive surgical technique and instrumentation, minimally invasive esophagectomy (MIE) including purely minimally invasive and hybrid procedures have gained lot of interest. This approach theoretically avoids the morbidity associated with thoracotomy; however unlike THE, permits a complete mediastinal dissection. MIE has been compared with open esophagectomy in multiple series. Nagpal and colleagues performed a meta-analysis of 12 studies with a total of 672 patients who underwent open esophagectomy, hybrid MIE, or MIE [58]. The investigators concluded that MIE was associated with better operative and postoperative outcomes with significantly lower incidence of respiratory complications in comparison with the open esophagectomy group. There was no significant difference in anastomotic leak rate, anastomotic stricture rate, gastric conduit ischemia, chyle leak, vocal cord palsy, or 30-day mortality. The lymph node retrieval was comparable in all 3 groups. Another meta-analysis published by Danto et al. included 1586 patients from 17 case-controlled studies comparing open esophagectomy and MIE [59]. The lymph node yield was significantly higher in the MIE group and 5-year survival rates were similar in both the groups. The investigators concluded that MIE provides oncologic outcomes equivalent to those of open esophagectomy. Recently, a randomized controlled trial comparing open esophagectomy and MIE showed that MIE group had lower rate of pulmonary complications, shorter hospital stays, and better short-term quality of life. Overall mortality was similar between the groups [60]. While the results of these studies are encouraging, an analysis from the hospital episode statistics data by Mamidanna et al. showed that MIE was comparable to open esophagectomy in terms of 30-day morbidity and in hospital mortality; however, was associated with a higher re-intervention rate which in turn was associated with higher risk of morbidity, especially pulmonary and renal complications [61]. While results of MIE appear promising, a wide variability in MIE surgical techniques, a lack of standardized definitions of postoperative complications, and the retrospective nature of the vast majority of reports, make comparisons of MIE and open esophagectomy difficult at best.

In the absence of level 1 evidence, the choice of the type of surgery is dependent on a combination of location/extent of the disease and surgeon preference. In general, the technique that leads to minimum morbidity and compromise of the quality of life, while allowing adequate surgical margins (usually 4-6 cm distal and 6-8 cm proximal tumor free margins with frozen section control) and lymph node dissection should be preferred. The standard surgical approach utilized at our institute after neoadjuvant chemoradiotherapy for esophageal cancer is Ivor-Lewis esophagectomy (or Transthoracic Esophagectomy). In our experience, morbidity including respiratory complications is minimal with perioperative use of epidural catheters.

## Lymph Node Resection

Lymph node metastasis in esophageal cancer shows significant variability. In general, 50-60% of the patients with surgically resectable esophageal cancer have lymph node involvement at the time of presentation. The submucosal layer of the esophageal wall harbors extensive lymphatic channels which allow malignant cells to travel significant distances along the longitudinal esophageal axis before draining into regional mediastinal lymph nodes. Skip metastases to nodal stations distant from the primary tumor have been reported in up to 34% of patients when assessed using routine hematoxylin and eosin staining, and up to 70% when assessed using immunohistochemistry [7]. The lymphatic drainage of the distal esophagus is in continuity with the lymphatics of the proximal stomach accounting for involvement of both lower mediastinal and abdominal lymph nodes in 77% of the patients with locally advanced lower esophageal cancers [62].

Not only has the number of lymph nodes containing metastatic disease but the total number of lymph nodes removed during esophagectomy has been identified as prognostic. Rizk et al. analyzed a total of 4627 patients who underwent esophagectomy alone for esophageal cancer as part of the Worldwide Esophageal Cancer Collaboration. Greater extent of lymphadenectomy was associated with increased survival for all patients with esophageal cancer except at the extremes (TisN0M0 and ≥ 7 regional lymph nodes positive for cancer) and well-differentiated pN0M0 cancers [63]. Based on these data, the authors recommended resecting 10 nodes for pT1, 20 for pT2, and ≥ 30 for pT3/T4 to achieve maximum 5-year survival. In another study, Groth et al. analyzed 4882 patients who underwent esophagectomy in the SEER database. After adjusting for other factors, a significant difference was identified between the number of lymph node removed with regards to all-cause and cancer-specific mortality. Compared with patients who had no lymph node evaluation, only patients who had more than 12 lymph nodes examined had a significant improvement in mortality; while patients who had 30 or more lymph nodes examined had significantly lower mortality rates than the other groups [64]. It is still unclear as to what number of lymph nodes is considered optimum, whether 12 or 30. Several other studies have also shown that the number of lymph nodes removed is an independent predictor of survival after esophagectomy for cancer [65,66]. Speculation on why higher number of lymph nodes removed is associated with better survival include better clearing of microscopic disease as well as a surrogate for better surgery or better pathologic staging at high volume centers.

## Morbidity, Mortality, Quality of Life

Regardless of the specific approach, esophagectomy for locally advanced esophageal/GEJ tumors is one of the most invasive procedures in the gastrointestinal tract with traditionally high mortality and morbidity. However, in recent years there has been a significant decline in mortality from esophagectomy largely attributed to improvement in surgical techniques, perioperative care, and patient selection. A mortality of as low as 2.7% in 2315 esophagectomies has been reported at experienced centers in the STS General Thoracic Surgery database [67]. Surgery performed at a high-volume center and better preoperative nutritional and functional status have been shown to be associated with lower surgical mortality [56,68]. Major morbidities following esophagectomy include but are not limited to pulmonary complications such has pneumonia and prolonged mechanical ventilation, atrial dysrhythmias, anastomotic leak, conduit ischemia, recurrent laryngeal nerve injury, chylothorax, and wound infection [44,56,69,70].

With the decline in postoperative mortality and overall improved outcomes of patients with locally advanced esophageal cancer, quality of life (QOL) following trimodality therapy has become an important consideration over the past decade. More than half of the patients suffer from one or more therapy related long term complications including neuropathy, dumping syndrome, delayed gastric emptying, reflux, and dysphagia significantly compromising the QOL. However, the QOL usually returns to baseline at 9 months postoperatively and more slowly after chemoradiation [71,72].

## Future Direction

A number of studies are underway to evaluate the role of newer therapies including targeted agents and immunotherapy in the treatment of locally advanced esophageal cancer. Epidermal growth factor receptor (EGFR) amplification and overexpression have been well described in esophageal carcinoma, especially in SCC, while EGFR mutation is a rare occurrence [73-76]. EGFR TKI erlotinib and monoclonal antibodies against EGFR such as panitumumab are currently being evaluated in combination with neoadjuvant chemoradiation in locally advanced esophageal cancer (NCT00686114, NCT01307956). Over recent years, immunotherapy has brought a paradigm shift in cancer therapeutics, especially in the treatment of heavily mutated cancers. Esophageal cancer is among the top five cancers with most number of somatic mutations indicative of the possibility of overexpression of neoantigens on the tumor making them more susceptible to immune recognition and subsequent destruction [77]. Upregulation of immune checkpoint pathways including Programmed Cell Death-1 (PD-1) pathway is one of the major mechanisms involved in tumor induced evasion of the host immune system including esophageal cancer. Immune checkpoint blockade is therefore a promising approach for cancer treatment. Pembrolizumab, a PD-1 inhibitor, has been shown to be safe and to have promising antitumor activity in advanced esophageal carcinoma [78]. Radiation has been shown to upregulate the PD-1 pathway making the tumor less susceptible to destruction by host immune system thereby increasing the chances of relapse. This provides rationale for inclusion of immune checkpoint inhibitor in the treatment of locally advanced esophageal cancer. One such clinical trial is currently under development at our center where the patients with locally advanced esophageal cancer who continue to have residual tumor in the surgical specimen after neoadjuvant chemoradiation and surgical resection, will receive PD-L1 inhibitor for 1 year. The primary endpoint of the study is 1-year RFS. The angiogenesis inhibitor bevacizumab is also being evaluated in combination with neoadjuvant chemotherapy in locally advanced esophageal and gastric cancer (NCT01212822). Finally, a phase III trial RTOG 1010 is evaluating the role of HER-2 directed therapy by comparing neoadjuvant chemoradiation with or without trastuzumab in patients with HER-2 overexpressing esophageal adenocarcinoma (NCT01196390). Currently ongoing clinical trials in locally advanced esophageal and GEJ adenocarcinoma are summarized in table 2.

## Conclusion

The treatment of locally advanced adenocarcinoma of the esophagus and GEJ remains a challenge. As with any complex disease, optimal outcomes require an experienced multidisciplinary team using an individualized approach. Current standard of care is trimodality therapy with neoadjuvant chemoradiation followed by surgical resection, including in patients with GEJ adenocarcinoma. Both carboplatin plus paclitaxel and 5-FU plus cisplatin are reasonable chemotherapy options. The achievement of pCR after neoadjuvant chemoradiotherapy is predictive of better DFS and OS. Patients with residual tumor at the time of surgery have poor prognosis and adjuvant chemotherapy has not been proven to improve survival in such patients. Newer therapeutic approaches including immunotherapy and targeted therapies are currently under investigation. In patients who are at high risk of postoperative complications and who have achieved clinical complete response after chemoradiation can be carefully observed reserving esophagectomy as a "salvage" procedure at the time of local recurrence. The optimum choice of surgical procedure remains unknown and largely depends on the location and extent of the tumor as well as surgeon preference. Despite the spectacular progress in the field of oncology over past decade, the prognosis of locally advanced esophageal and GEJ cancer remains poor necessitating exploration of newer therapies.

**Table 2**: Ongoing clinical trials in Locally Advanced Esophageal Adenocarcinoma.

| Agent(s) | Trial Design | Phase | ClinicalTrials.gov Identifier |
|---|---|---|---|
| Erlotinib | Concurrent chemoradiotherapy with Cis + Paclitaxel +/- Erlotinib in patients with locally advanced esophageal carcinoma | III | NCT00686114 |
| Panitumumab | Concurrent chemoradiotherapy with FOLFOX + XRT + Panitumumab in patients with locally advanced adenocarcinoma of esophagus or GEJ followed by surgery | II | NCT01307956 |
| Bevacizumab | Neoadjuvant and adjuvant FOLFOX with or without bevacizumab in treatment of locally advanced esophageal or GEJ tumors | II | NCT01212822 |
| Trastuzumab | Concurrent chemoradiotherapy with carboplatin + paclitaxel + XRT with or without trastuzumab in patients with locally advanced esophageal or GEJ adenocarcinoma with HER2 overexpression | III | NCT01196390 (RTOG 1010) |

(Cis: Cisplatin; XRT: Radiotherapy; GEJ: Gastroesophageal Junction)

## Disclosure Statement

The authors have no existing or potential financial conflicts of interest to disclose.

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