Management of Gastroesophageal Tumors

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LEARNING OBJECTIVES

After completing this course, the reader will be able to:

1. Discuss the surgical management of carcinoma of the esophagogastric junction and discuss the role of neoadjuvant multimodal therapy in the treatment of these tumors.
2. Provide an overview of the classification of gastroesophageal tumors.
3. Describe the latest developments in the diagnosis and staging of gastroesophageal tumors as well as newer options for palliative therapy.

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ABSTRACT

The incidence of adenocarcinomas of the gastroesophageal junction has increased in recent years. These tumors possess distinct pathophysiologic characteristics. Although the consensus is that an R0 resection (complete microscopic and macroscopic resection) is the goal when operating for curative intent, much controversy remains regarding other aspects of patient management. There is lack of consensus regarding the type of surgery to perform, the role and extent of lymphadenectomy, and the role of neoadjuvant therapy. Utilizing an evidence-based approach, this review article provides an overview of the management of gastroesophageal junction carcinomas with particular emphasis on current areas of controversy.

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INTRODUCTION

Over the past quarter century, Western populations have seen a shift in both the location and lethality of gastric cancers. Although distal gastric cancers have become rare, the incidence of adenocarcinomas of the proximal stomach and distal esophagus has risen [1–3]. The behavior of these proximal tumors makes them a unique entity. The pliability of the gastric cardia, as well as the deep location of the gastroesophageal junction, often masks the vague symptoms caused by early-stage lesions. Furthermore, 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 [4]. Thus, these tumors often present at a relatively advanced stage [5]. Based on the 2005 American Cancer Society statistics, 14,520 new cases of esophageal cancer will be diagnosed, with an estimated 13,570 deaths per year (http://www.cancer.org). Carcinoma of the esophagus remains...
one of the most lethal malignancies, with reported 5-year survival rates ranging from 16% to 32% [6–12].

There is no controversy that an R0 resection (complete microscopic and macroscopic resection) is the goal when operating for curative intent [4]. However, controversy does exist in three aspects of patient management: the type of surgery to perform, the role and extent of lymphadenectomy, and the role of neoadjuvant therapy. This review article details the current methods of treatment for tumors of the esophagogastric junction, highlights areas of controversy, and reviews the data on the efficacy of different approaches.

**CLASSIFICATION**

There has been longstanding confusion in both the classification and treatment of carcinomas arising in the area of the gastroesophageal junction. Whereas thoracic surgeons treated all esophagogastric tumors as esophageal in origin, general/gastrointestinal (GI) surgeons approached them as gastric cancers. Furthermore, it seems that there was little attempt to differentiate tumors arising in the gastric cardia from esophageal tumors even though their origin and biologic behavior were different [13]. 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 [14].

Siewert et al. [14] developed the most widely adopted classification system for adenocarcinomas arising in the proximity of the esophagogastric junction. Gastroesophageal junction tumors are defined as being within 5 cm proximal and distal of the anatomic cardia. They are further differentiated into three distinct tumor entities: type I (adenocarcinoma of the distal esophagus arising from an area with specialized intestinal metaplasia of the esophagus and which may infiltrate the esophagogastric junction from above), type II (true carcinoma of the cardia arising from the cardiac epithelium or short segments with intestinal metaplasia at the esophagogastric junction, “junctional carcinoma”), and type III (subcardial gastric carcinoma that infiltrates the esophagogastric junction and distal esophagus from below) [14].

Type I tumors are a distinct entity that should be treated as a distal esophageal cancer. Most of these tumors arise from areas of intestinal metaplasia in Barrett’s epithelium as a consequence of chronic gastroesophageal reflux. Increased surveillance programs have led to the diagnosis of these tumors at an earlier stage, and they can occasionally be managed by limited surgical or endoscopic treatment [9]. In contrast, type III tumors represent proximal gastric cancer and should be approached in accordance with gastric cancer guidelines [9]. 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 [9]. 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 [9].

**METHODS FOR PREOPERATIVE STAGING**

Perhaps even more important than defining the subtype of gastroesophageal junction tumor is accurate pretreatment staging. Surgical resection offers the only chance for cure, and most patients undergoing R1 (residual microscopic disease) or R2 (residual macroscopic disease) resections could just as easily have been palliated with a combination of chemotherapy, radiation, and endoluminal stenting. Hence, determining both the extent of disease and local resectability is an essential step before commencing any type of therapy.

Preoperative endoscopy is usually the first test performed in diagnosing and staging the lesion. The findings on endoscopy are critical in determining the proximal extent of resection and ultimately dictate the appropriate operative approach. A standard evaluation also includes contrast enhanced abdominal and chest computed tomography (CT) scans to evaluate both the extent of local disease as well as to search for hepatic, pulmonary, nodal, and other metastases.

If no distant disease is identified, patients should then undergo endoscopic ultrasound (EUS). EUS is currently the most reliable method available for clinical staging of esophagaeal or esophagogastric carcinomas [15] that do not have distant disease on CT scan. The accuracy of EUS for T-staging ranges between 75% and 90% [16, 17]. Given that the stage of the tumor affects the extent of resection, EUS is an important adjunct to preoperative planning. In one recent review, EUS was superior to CT scan for staging of esophageal cancer [18]. CT, however, remains superior to EUS for detecting distant lymph node metastases such as at the celiac axis [19] or the supraclavicular region [20].

Finally, some have advocated the use of laparoscopy and laparoscopic ultrasonography to detect the presence of intra-abdominal metastases. In one recent series, laparoscopic ultrasound provided N- and M-staging that was superior to CT or EUS [21]. Adding these methods to conventional staging protocols avoids noncurative laparotomies in 11%–48% of patients with GI tumors [22]. This is
especially true for malignancies that can be palliated nonoperatively [21].

**Surgical Approach**

In patients with no evidence of distant metastases and who are fit for surgery, surgical resection is the mainstay of therapy for gastroesophageal junction tumors. A complete resection of the tumor and its entire lymphatic drainage offers the best hope for long-term survival [23].

Both tumor stage (particularly nodal involvement or N stage) and resection margins (R status) are significant prognostic factors [9, 12, 24]. R status has been the variable most consistently reported to be associated with prognosis and is also the variable most likely to be influenced by surgical technique [8, 24–26]. 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 [24].

Type I tumors are generally treated by total esophagectomy to obtain adequate proximal margins and remove all mediastinal lymph nodes. The management of type II and III tumors, however, remains controversial [8, 12, 24]. Numerous surgical approaches have been reported for type II tumors. These include abdominothoracic en bloc esophagectomy, subtotal esophagectomy with resection of the proximal stomach, total gastrectomy with transthiatal resection of the distal esophagus, and resection of the proximal stomach and distal esophagus with esophagogastrostomy [23].

Patient factors such as body habitus, prior surgery, and pulmonary function are important in selecting the appropriate surgical approach. Although each approach has its advantages and disadvantages, no option has demonstrated a clear survival benefit over the others provided that adequate margins are obtained and an adequate lymphadenectomy is performed. Bile reflux esophagitis can be a difficult problem to manage if reconstruction includes an intrathoracic esophagogastrectomy, but complex reconstructions with colon or jejunal interpositions carry an even higher morbidity rate. Therefore, many surgeons attempt to place the esophagogastic anastomosis in either the abdomen or neck and use the gastric remnant as the conduit of choice [9, 10, 14, 24, 27, 28].

To ensure clear margins, intraoperative frozen sections should be used liberally [9]. However, even frozen section can lead to false-negative results. In a recent study by Ito et al. [24], a recommendation was made to achieve a gross proximal resection margin length of at least 6 cm and a distal resection margin length of at least 4 cm, regardless of tumor location. However, the authors had two caveats: first, that the degree of mural extension by gastric cardia adenocarcinomas is strongly correlated with T stage, and second, that margin lengths reported in their study were measured on prefixed fresh specimens immediately after resection. Thus, intraoperative decisions should be made based on margin length requirements that may need to be significantly greater than those derived from postresection specimens. This is especially pertinent to T3 and T4 tumors [24].

**Lymphadenectomy**

More than two thirds of patients with esophageal and gastric cancers in Western populations will have lymph node metastases at the time of surgery [29]. As stated previously, nodal status is nearly as important as R status in determining prognosis and treatment for tumors of the gastroesophageal junction. Lymphadenectomy improves the accuracy of pathologic staging in both gastric and esophageal cancers and provides locoregional control [30–32]. The optimal extent of a lymphadenectomy and its impact on survival are extremely controversial. In a study by Karpeh et al. [33], patients with stage II and III gastric cancer who had fewer than 15 lymph nodes examined had significantly lower 5-year survival rates. This finding was confirmed in other studies [24, 34]. Thus, sampling of at least 15 lymph nodes and preferably 20–25 lymph nodes is necessary for accurate staging [35].

In 2002, de Manzoni et al. [8] found that stage pN2 and pN3 were grave prognostic indicators. In this study, multivariate analysis revealed that the pT category was less important than the N category; univariate analysis revealed that survival greater than 3 years was restricted to pN0 and pN1 subgroups, regardless of the pT status. The authors subsequently concluded that chances for cure are limited to pN0 and pN1 patients [8].

There are generally two types of lymphadenectomies performed for gastric cancers. A D1 dissection refers to the removal of the stomach and lesser and greater omentum with associated N1 lymph nodes (station 1–6 lymph nodes; Fig. 1) [36]. A D2 dissection involves a more extensive gastrectomy with removal of N2 lymph node (stations 7–15; Fig. 1) and typically includes a splenectomy and distal pancreatectomy [30]. A final category, the D3 dissection, would include nodes within the porta hepatis and periaortic regions.

Surgeons in the West tend to adopt a more minimalist approach to lymph node dissection, arguing that lymph node involvement signifies systemic disease, and thus, survival remains unchanged despite extensive dissection [4]. The reluctance to perform radical lymphadenectomy by Western centers is also due to the increased morbidity and mortality risk, particularly if a splenectomy or pancreatectomy is performed [37, 38].

In an attempt to resolve the discordant results between Japanese and Western literature, two large studies were conducted to examine the value of extended lymphadenec-
The British Medical Research Council conducted a multicenter, prospective, randomized, controlled trial comparing D1 and D2 resection in 400 patients undergoing potentially curative resection for gastric carcinoma [37]. They found no difference in 5-year survival rates (35% vs. 33%), but the D2 patients had higher postoperative morbidity (46% vs. 28%) and hospital mortality (13% vs. 6%) [37]. The Dutch Gastric Cancer Group conducted a similar large trial comparing D1 and D2 lymphadenectomies in 711 patients treated with curative intent [36]. To ensure surgical quality control, a Japanese surgeon trained the Dutch surgeons in surgical technique and also monitored the operative procedures. Again, there was no significant difference in overall survival (11-year follow-up, 30% vs. 35%), with higher morbidity (25% vs. 43%) and mortality (4% vs. 10%) in the D2 group of patients [36].

Other studies have resulted in conflicting findings. The Italian Gastric Cancer Study Group recently published an interim analysis of a prospective, randomized surgical trial comparing morbidity and mortality in 162 gastric cancer patients randomly assigned to receive either D1 or D2 lymph node dissections [39]. The D2 dissections in this study did not include resection of the spleen or pancreas. No significant difference was found in postoperative morbidity (10.5% vs. 16.3%) or mortality (1.3% vs. 0%) between the groups. This suggests that D2 gastrectomy with pancreas preservation is safe and acceptable in the West when performed in high-volume centers [39]. Although a more extensive lymphadenectomy has not been proven to confer a survival benefit, this study questions the assertion that a D2 dissection results in more complications than does a D1 resection.

Interestingly, more extensive resection of the spleen and pancreas may actually be unwarranted in many instances [29]. For lower esophageal adenocarcinomas, the most common sites of lymph node involvement include the right and left paracardiac lymph nodes and the left gastric lymph nodes (Fig. 1). The greater and lesser curvatures along with the celiac, common hepatic, and splenic artery/hilum lymph nodes are less commonly involved. Given that many trials have demonstrated that splenectomy is tightly associated with an increased risk of postoperative complications, evidence suggests that splenectomy be reserved for those patients with obvious lymph node metastases or infiltration of the splenic hilum [23].

In a recent trial by Yu et al. [40], patients with gastric adenocarcinoma were prospectively and randomly assigned to total gastrectomy with and without splenectomy. Total gastrectomy and splenectomy was associated with slightly higher morbidity and mortality rates, slightly greater incidence of lymph node metastases at the splenic hilum and splenic artery, and a marginally higher survival rate. In the end, however, there were no statistically significant differences among the two groups. The authors therefore concluded that prophylactic splenectomy was unnecessary for the removal of macroscopically negative lymph nodes near the spleen in this patient population [40].

Figure 1. Gastric cancer lymph node stations. Lymph node stations surrounding the stomach: 1, right cardiac nodes; 2, left cardiac nodes; 3, nodes along the lesser curvature; 4, nodes along the greater curvature; 5, suprapyloric nodes; 6, infrapyloric nodes; 7, nodes along the left gastric artery; 8, nodes along the common hepatic artery; 9, nodes around the celiac axis; 10, nodes at the splenic hilus; 11, nodes along the splenic artery; 12, nodes in the hepatoduodenal ligament; 13, nodes at the posterior aspect of the pancreas head; 14, nodes at the root of the mesentery; 15, nodes in the mesocolon of the transverse colon; 16, paraaortic nodes.

Lerut et al. [4] found that esophagectomy with three-field lymph node dissection could be performed with low mortality and acceptable morbidity. There was a low incidence of locoregional lymph node recurrences with or without distant metastasis (15%), and the overall 5-year and disease-free survival after R_0_ resection was more than 41% [4]. In another 2004 study, a population-based analysis of the Finnish Cancer Registry looked at 402 patient records demonstrating type I and II adenocarcinoma of the esophagogastric junction [41]. Only 12.5% of all patients diagnosed with cancer survived more than 5 years. It was found that operative resection offered the best chance for cure. The 5- and 8-year survival rates in surgically treated patients were 29% and 26%, respectively. The 5-year survival rate in patients with two-field lymphadenectomy was significantly better than in those with a less extensive surgery (50% vs. 23.2%), and the 8-year survival rates were 43% and 21%, respectively [41]. It is important to note, however, that this study was a retrospective analysis of non-randomized data. Thus, the groups being studied may not be comparable.

For esophageal cancer, extended three-field lymphadenectomy is widely practiced in Japan [42]. In a large, multicenter study, it seemed that nearly one in three patients had unforeseen lymph node metastases in the cervical lymph nodes. Furthermore, there was an improved overall 5-year survival compared with two-field dissection. Such outcomes have been reproduced many times in the Japanese literature yet have not been as reliably reproduced in Western studies. This may be due to the fact that much of the Japanese data relates primarily to squamous cell carcinoma [43, 44], whereas adenocarcinoma of the esophagus is more prevalent in the West. The difference in results may also reflect a difference in surgical experience or technique in performing lymphadenectomy [29]. The lack of reproducible results, along with potential morbidity such as a 15%–70% risk of recurrent laryngeal nerve damage [4], has led to the general reluctance of Western surgeons to perform extended lymphadenectomy for gastroesophageal junction tumors.

There is currently not enough evidence to support performing extended lymphadenectomies in all patients with tumors at the gastroesophageal junction [30]. However, extended lymphadenectomy may improve the prognosis of a subgroup of patients with gastric or esophageal cancer who have a limited number of positive lymph nodes. In addition, despite the fact that D2 lymphadenectomy has not been shown to be superior, it does seem to have the advantage of more accurate pathologic staging. As a result, some major cancer centers still perform a D2 resection, as supported by the National Comprehensive Cancer Network treatment guidelines (http://www.nccn.org).

Given the controversy surrounding lymph node dissec-

**NEOADJUVANT THERAPY**

Since carcinomas of the gastroesophageal junction often present at an advanced stage, neoadjuvant therapy has many theoretical benefits. Neoadjuvant therapy may reduce the size of the tumor, thereby improving chances of an R_0_ resection; treat micrometastases; and allow accurate assessment of the completeness of pathologic response, all of which may influence decisions on postoperative treatment [53]. In addition, certain chemotherapeutic agents may have radiosensitizing properties [54], and the increased oxygenation of undisturbed tissue in the tumor bed also enhances the effects of preoperative radiation therapy [30]. 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.

Many phase II trials have investigated neoadjuvant combination therapy using a variety of regimens in patients with both resectable and nonresectable disease [55–58]. These trials generally show that neoadjuvant chemotherapy produces extended disease-free and overall survival compared with historical controls. Unfortunately, comparisons between different series is difficult because of nonstandardized selection criteria and small numbers of patients [59].

It has been found that neoadjuvant therapy with a cisplatin-based polychemotherapy regimen followed by surgical resection markedly improves survival [23]. Other active agents include fluorouracil, methotrexate, doxorubicin, epirubicin, and mitomycin. Combination therapy clearly leads to improved response rates relative to monotherapy. Some of the original neoadjuvant trials employed fluorouracil, doxorubicin, and mitomycin and fluorouracil, doxorubicin, and high-dose methotrexate (FAMTX) [60]. Other randomized control studies have confirmed that FAMTX should be the reference treatment [61].

More recently, it has been found that the cisplatin-based combination of epirubicin and cisplatin along with protracted venous infusion of fluorouracil (ECF) has improved response rates and 2-year survival rates compared with FAMTX [62]. Among combination chemotherapy regimens, best survival results are achieved with regimens containing fluorouracil, anthracyclines, and cisplatin. In this category, ECF is best tolerated [63]. ECF seems to be one of the most active treatments in advanced disease [59, 62] and resulted in a 2-year survival of 13.5% compared with 5.4% for FAMTX.

Kaklamanos et al. [64] performed a meta-analysis to determine the effect of neoadjuvant treatment on both long-term survival and treatment-related mortality in patients with resectable esophageal cancer [64]. Eleven randomized trials were reviewed. The authors found that preoperative chemotherapy improved 2-year survival compared with surgery alone. In fact, there was an absolute difference of 4.4% that increased to 6.3% when the four most recent studies were analyzed. However, treatment-related mortality did increase by 1.7% for patients with neoadjuvant chemotherapy and by 3.4% for patients with neoadjuvant chemoradiotherapy when compared with surgery alone [64].

In a recently published study by Cunningham et al. [65], patients with resectable adenocarcinoma of the stomach, esophagogastric junction, or lower esophagus were randomly assigned to either perioperative ECF (three preoperative cycles and three postoperative cycles) or surgery alone. Compared with the surgery group, the perioperative-chemotherapy group had a higher likelihood of overall survival and progression-free survival, with a 5-year survival rate of 36% versus 23% [65].

ECF results in high response rates, particularly in patients with locally advanced disease, and extends survival of patients going on to have complete surgical excision of residual disease. However, not all studies have confirmed significant differences in response and survival rates among three different regimens with and without cisplatin [66].

Many studies have examined multimodality neoadjuvant therapy that combines chemotherapy and radiation therapy. It has clearly been shown that treatment with radiation plus concurrent chemotherapy is superior to radiation alone [67, 68]. One proposed explanation of this benefit is the ability to enhance local control by taking advantage of the radiosensitizing effects of chemotherapy while treating occult systemic metastases [54, 69]. Many older retrospective studies compared patients who had neoadjuvant therapy with fluorouracil and radiation to control patients. These studies clearly demonstrated that esophageal adenocarcinoma responds to treatment based on fluorouracil-based chemotherapy in combination with radiotherapy [70–72].

A number of randomized controlled trials have also compared neoadjuvant treatment for resectable cancer of the esophagus and gastroesophageal junction versus surgery alone (Table 1). However, it is difficult to compare results from these trials to current practice. There is great variability in the types of treatment protocols used. In addition, many of these trials contain small numbers of patients, and there is a preponderance of patients with squamous cell carcinoma, whereas adenocarcinoma is the most common tumor type seen in Western countries during the past decade.

Perhaps the most compelling evidence in favor of neoadjuvant chemoradiation therapy comes from a more recent prospective randomized controlled trial. In this study of 113 patients with esophageal cancer (predominantly lower esophageal and cardia carcinomas), multimodality therapy was found to be superior to surgery alone for patients with resectable adenocarcinoma of the esophagus [53]. The median survival of patients assigned to multimodality therapy was 16 months compared with 11 months for those assigned to surgery alone. Follow-up continued for 1, 2, and 3 years wherein, respectively, 52%, 37%, and 32% of patients in the multimodality arm were alive. In contrast, only 44%, 26%, and 6% of patients assigned to surgery were alive at the respective time points. The survival advantage favoring multimodal therapy reached significance at 3 years [53].

Fiorica et al. [54] looked at six randomized controlled trials in a meta-analysis of preoperative chemoradiotherapy for resectable esophageal cancer. Chemoradiotherapy plus
surgery significantly reduced the 3-year mortality rate compared with surgery alone. In addition, preoperative chemoradiotherapy downstaged tumors as evidenced by pathologic analysis of resected specimens. Similar to Kaklamanos et al. [64], these authors found that the risk for postoperative mortality was higher in the group who had neoadjuvant chemoradiotherapy. It is important to note, however, that the number needed to treat to benefit from neoadjuvant therapy (n = 10) was much less than the number who would be harmed by it (n = 25) [54].

Although much controversy still exists, these studies suggest that multimodality neoadjuvant therapy should be considered in patients with large tumors confined to the esophagus and draining lymph nodes (i.e., clinical or EUS T stage ≥2 or N stage >0) if the patient is a candidate for surgical resection [53]. However, although the evidence is promising, it is important to note that one of the reasons neoadjuvant therapy may increase survival is that it compensates for inadequate surgical resections. It is imperative that surgeons strive to attain an R0 resection with at least a

![Table 1. Randomized controlled trials of neoadjuvant treatment for resectable cancer of the esophagus and gastroesophageal junction versus surgery alone](http://theoncologist.alphamedpress.org/)

<table>
<thead>
<tr>
<th>Study</th>
<th>CA type</th>
<th>Accrual Period</th>
<th>Treatment</th>
<th>Control</th>
<th>Chemotherapy</th>
<th>XRT (total dose/number of cycles)</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nygaard [73]</td>
<td>SCC</td>
<td>1983–1988</td>
<td>50</td>
<td>41</td>
<td>Cisplatin, bleomycin</td>
<td></td>
<td>Survival higher in groups receiving preoperative XRT</td>
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<td>[group 2]</td>
<td></td>
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<tr>
<td>Nygaard [73]</td>
<td>SCC</td>
<td>1983–1988</td>
<td>47</td>
<td>41</td>
<td>Cisplatin, bleomycin</td>
<td>35 Gy/20</td>
<td>At 3y, survival advantage for multimodal neoadjuvant therapy</td>
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<td>[group 4]</td>
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<td>Urba [74]</td>
<td>Both</td>
<td>1989–1994</td>
<td>50</td>
<td>50</td>
<td>Cisplatin, 5-FU, vinblastine</td>
<td>45 Gy</td>
<td>No survival advantage</td>
</tr>
<tr>
<td>Apinop [75]</td>
<td>SCC</td>
<td>1986–1992</td>
<td>35</td>
<td>34</td>
<td>Cisplatin, 5-FU</td>
<td>Unspecified</td>
<td>No survival advantage</td>
</tr>
<tr>
<td>Bosset [76]</td>
<td>SCC</td>
<td>1989–1995</td>
<td>143</td>
<td>139</td>
<td>Cisplatin</td>
<td>37 Gy/10</td>
<td>No survival advantage but prolonged disease-free survival</td>
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<tr>
<td>Le Prise [77]</td>
<td>SCC</td>
<td>1988–1991</td>
<td>41</td>
<td>45</td>
<td>Cisplatin, 5-FU</td>
<td>20 Gy/10</td>
<td>No survival advantage</td>
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<tr>
<td>Roth [78]</td>
<td>Epidermoid</td>
<td>1982–1986</td>
<td>17</td>
<td>19</td>
<td>Cisplatin, bleomycin, vindesine</td>
<td></td>
<td>Survival advantage with preoperative chemotherapy</td>
</tr>
<tr>
<td>Law [80]</td>
<td>SCC</td>
<td>1989–1995</td>
<td>74</td>
<td>73</td>
<td>Cisplatin, 5-FU</td>
<td></td>
<td>No survival advantage</td>
</tr>
<tr>
<td>Ancona [82]</td>
<td>Epidermoid</td>
<td>1992–1997</td>
<td>47</td>
<td>47</td>
<td>Cisplatin, 5-FU</td>
<td></td>
<td>If complete pathologic response, improved survival</td>
</tr>
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Abbreviations: 5-FU, 5-fluorouracil; AC, adenocarcinoma; CA, carcinoma; SCC, squamous cell carcinoma; XRT, radiotherapy.
D1 lymphadenectomy in patients with resectable disease regardless of whether they had preoperative chemoradiotherapy. Clearly, more research is needed before there is a definitive stance on the use of neoadjuvant therapy for resectable tumors of the gastroesophageal junction. Recent interest in targeted therapies such as epidermal growth factor receptor (EGFR) inhibitors, antiangiogenic agents, and various cell-cycle inhibitors may also help expand the list of possible therapeutic alternatives [83, 84]. Ongoing phase II trials are currently evaluating such agents as gefitinib, an EGFR blocker, and oxaliplatin, a chemotherapeutic agent that has been effective in colorectal cancer (http://www.cancer.gov/clinicaltrials). The results of these clinical trials and other studies will hopefully offer improved options in the management of gastroesophageal cancer.

ADJUVANT THERAPY

A successful surgical resection does not always indicate complete cure. In a review of 50,169 patients in the U.S. who underwent gastrectomy between 1985 and 1996 [85], patients with stage IA disease (tumor confined to the gastric mucosa) had a 65% 10-year survival rate. However, patients with more advanced disease had a considerably lower 10-year survival rate, ranging from 3% to 42% [85]. These rates highlight the importance of considering adjuvant treatment in patients with advanced stages of gastroesophageal cancer.

Much evidence now supports the use of chemotherapy to improve outcome in patients found to have advanced disease at the time of surgery. Even after gastric resection with curative intent, there remains a 40%–65% chance of local or regional recurrence in the gastric remnant or tumor bed, anastomosis, or regional lymph nodes [86–89]. Therefore, locally directed adjuvant therapy plays an important role in patients with tumors of the esophagogastric junction [85]. Older studies did not show a survival benefit when comparing adjuvant chemotherapy with surgery alone [90, 91]. In contrast, a survival benefit was demonstrated when adjuvant therapy consisted of postoperative radiation with or without concomitant fluorouracil [92].

The U.S. Intergroup 0116 study was started in 1991 to examine the possible benefit of postoperative adjuvant multimodality treatment using radiotherapy and leucovorin-modulated fluorouracil [47]. After potentially curative resection of gastric cancer, 556 patients were randomly assigned to observation or adjuvant chemoradiotherapy. Approximately 20% of these patients had lesions present in the gastroesophageal junction. Three-year overall and disease-free survival were significantly better for patients in the latter group (52% vs. 41%, respectively, and 49% vs. 32%, respectively) showed that the degree of survival benefit for patients with adjuvant therapy was identical for both gastric and gastroesophageal junction carcinomas [47].

As with rectal and pancreatic cancers, postoperative multimodal therapy consisting of regional radiation plus systemic chemotherapy seems to reduce relapse risk and prolong survival in patients with tumors of the stomach or esophagogastric junction and should thus be considered in high-risk patients [30]. Given the results of the Intergroup 0116 study, postoperative chemoradiotherapy is slowly emerging as the standard of care in treating gastric cancer. Future areas of research need to evaluate new chemotherapeutic agents and improved modalities of radiation delivery and identify molecular markers that may indicate patients who are more likely to benefit from adjuvant therapy [30].

PALLIATIVE SURGERY

To palliate dysphagia, prevent aspiration, and improve quality of life, various endoscopic treatment modalities have been used. These include stents or laser therapy for those patients who present at an advanced stage, have poor general physical health, or both, and who cannot withstand
a palliative operation [41]. Mean survival after these approaches has been around 140 days [93]. Unfortunately, these modalities are occasionally ineffective. In such cases, consideration should be given to feeding tube placement or, in rare instances, palliative surgical resection in patients who are otherwise fit.

CONCLUSION

Tumors of the esophagogastric junction seem to be a distinct pathophysiologic entity, separate from esophageal and gastric carcinomas yet with some oncologic features of each. Accurate preoperative staging is crucial in the management of these tumors. A proposed diagnostic algorithm is shown in Figure 2.

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 goal is an R0 resection with associated adequate lymphadenectomy. Patient and tumor characteristics help determine the optimal surgical approach for achieving R0 status. At least 25 lymph nodes should be removed to adequately stage the tumor. Multimodal neoadjuvant therapy should be used liberally in patients with bulky tumors in an attempt to help the surgeon and the patient achieve an R0 resection. Postoperative multimodal adjuvant therapy is beneficial in patients who are at high risk of local failure or of developing systemic disease. In general, patients who may benefit from either neoadjuvant or adjuvant therapy should be encouraged to enroll in ongoing trials.

For patients whose disease cannot be completely resected, alternative measures exist for palliation of symptoms and control of local disease. Radiation therapy should be a mainstay for patients who have locally advanced disease with no evidence of distant metastases. Endoluminal stents and feeding tubes can be important tools for palliation of dysphagia. If there is no hope of cure, one must carefully consider the risks and morbidity of aggressive intervention versus the nonsurgical alternatives to palliate symptoms and provide the best quality of life for the patient.

DISCLOSURE OF POTENTIAL CONFLICTS OF INTEREST

The authors indicate no potential conflicts of interest.

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Management of Gastroesophageal Tumors


