Crossroads in the Combined-Modality Management of Gastroesophageal Junction Carcinomas

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ABSTRACT

An epidemiologic shift in esophageal and gastric carcinomas has occurred in recent years in the Western world. Adenocarcinoma of the distal esophagus and gastroesophageal junction (GEJ) is now the predominant esophageal carcinoma, and proximal gastric cancers now account for nearly half of gastric carcinomas. Tumors involving the GEJ appear to be a distinct clinical entity that presents a challenge to oncologists due to issues in staging and classification and uncertainties regarding optimal treatment approach. Beyond surgical resection as the primary treatment modality, the roles of neoadjuvant or adjuvant therapies in GEJ cancers are not clearly defined. This article reviews the major randomized trials of combined-modality treatment in populations with esophageal and gastric cancers that included patients with GEJ carcinomas and discusses how the findings relate to and inform the management of GEJ tumors. In general, preoperative or perioperative chemotherapy appears to improve survival, and the addition of neoadjuvant or adjuvant chemoradiotherapy increases locoregional control and appears to improve survival. Although GEJ tumors account for only 20% to 35% of cancers in the most relevant randomized trials, the available data suggest that trimodality therapy with chemotherapy, radiation, and surgery is a reasonable treatment approach for GEJ tumors. Further clinical trials are needed to define the optimal sequencing and combinations of surgery, radiotherapy, and chemotherapy. These trials should include appropriate definitions and stratification of GEJ tumors in order to facilitate translation of findings to treatment practice.

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Esophageal cancer is a relatively uncommon but deadly malignancy. In the United States, it has an annual incidence of more than 15,000 cases and is the 7th leading cause of cancer death in men. Worldwide, it ranks in the top 10 of the most common cancers, with more than 300,000 cases diagnosed each year.[1] More than 90% of diagnosed patients eventually die of their disease.[2]

Historically, squamous cell carcinoma has been the most common histology in esophageal cancer. The last 3 decades, however, have witnessed an epidemiologic shift in the histologic type and location of esophageal cancers. The incidence of adenocarcinoma of the esophagus has been rising at an alarming rate of approximately 5% to 10% per year since the mid 1970s, an increase that is more rapid than that of any other adult solid malignancy.[3] Previously representing fewer than 15% of all esophageal carcinomas, adenocarcinoma of the distal esophagus and gastroesophageal junction (GEJ) replaced squamous cell carcinoma as the predominant esophageal carcinoma in the United States and Western Europe in the 1990s and now accounts for more than half of all esophageal cancers.[4]

In parallel with the emergence of esophageal adenocarcinomas, there has been an epidemiologic shift in the types of gastric cancer, 90% of which are adenocarcinomas. Although gastric cancer incidence has been declining in the past century in the United States, it still remains the second leading cause of cancer-specific mortality worldwide.[5] There has been a recent five- to sixfold increase in the incidence of proximal gastric cancers in the United States,[6] and they now account for nearly half of all gastric cancers among men living in the United States.[4] Thus, the Western world is seeing a trend of proximal to more distal esophageal cancers and distal to more proximal gastric cancers that intersect in the area of the GEJ. Indeed, in synchrony with the epidemiologic shifts of esophageal and gastric carcinomas, the incidence of GEJ tumors has increased by fivefold over the past 20 years.[3]

GEJ carcinomas pose a challenge to oncologists for several reasons. They appear to represent a distinct clinical entity that is discrete from either esophageal or

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gastric cancers, yet GEJ tumors also share oncologic characteristics with both. Randomized trials to date, however, have not treated these tumors as a distinct disease entity, commonly grouping them together with esophageal or gastric cancers. This article provides an overview of the combined-modality treatment of GEJ carcinomas, focusing on the major randomized clinical trials involving locally advanced esophageal or gastric adenocarcinomas that provide information on GEJ carcinomas. Issues in classification and staging of disease are also discussed.

CONTROVERSIES IN STAGING AND CLASSIFICATION

Staging

Esophageal and gastric carcinomas are staged according to the American Joint Committee on Cancer (AJCC) guidelines[7] and International Union Against Cancer (UICC)[8] staging systems, both of which are TNM based. The TNM staging system for esophageal cancer was originally based on squamous cell carcinomas, but is also applied to adenocarcinomas. Although many clinicians and investigators consider GEJ adenocarcinomas to be a distinct clinical entity, the AJCC and UICC staging systems group them with esophageal or gastric carcinomas. According to the AJCC, "in clinical practice, tumors arising within the [esophagogastric] junction and gastric cardia that have minimal (2 cm or less) involvement of the esophagus are considered primary gastric cancers."[7] The UICC defines a junctional tumor as esophageal in origin if more than 50% of the tumor mass involves the esophagus and gastric in origin if more than 50% of the tumor involves the stomach.[8] In the literature, the staging systems for both esophagus and stomach are used for GEJ tumors, depending on the authors.

The confusion in staging GEJ cancers becomes evident when comparing the TNM staging of esophageal and gastric carcinomas (Table 1). For example, since the esophagus is not covered by visceral peritoneum and does not have a serosa, a transmural tumor would be staged as T3 in the esophagus and only T2 in the gastric staging system. The most notable difference is in the N staging. Esophageal N staging is defined by the distance of metastatic lymph nodes (regional or not), whereas stomach N staging is related to the number of metastatic nodes, which has been demonstrated to have prognostic significance. The number of involved lymph nodes has also been reported to be of prognostic significance for adenocarcinoma of the esophagus and GEJ;[9] however, the TNM staging does not account for this.

Staging of tumors that have epicenters clearly located in the distal esophagus and subcardial region is typically straightforward, but staging of tumors that are located in the true junctional region is problematic. In particular, debate exists among clinicians regarding how to differentiate between gastric cardia carcinomas involving the GEJ from distal esophageal and GEJ tumors extending to distally involve the proximal stomach.

Classification

In an attempt to provide a uniform system for the definition and classification of GEJ tumors, Siewert and colleagues[10] proposed a classification system that divided adenocarcinomas arising within 5 cm proximal and distal to the anatomic cardia into 3 subtypes (Table 2). This system has been proposed as a useful tool for the selection of appropriate surgical approaches and extent of resection. Type I and II tumors typically arise in Barrett's epithelium in the esophagus as a result of chronic gastroesophageal reflux disease[11] and the clinical distinction between these two types is

Table 1. TNM staging for carcinomas of the esophagus and stomach

Stage	Esophagus	Stomach
T stage	T1: invades lamina propria or submucosa T2: invades muscularis propria* T3: invades adventitia* T4: invades adjacent structures	T1: invades lamina propria or submucosa T2: invades muscularis propria or subserosa* T3: invades serosa, no adjacent structures* T4: invades adjacent structures
N stage*	N1: regional nodes†	N1: 1–6 regional nodes N2: 7–15 regional nodes N3: >15 regional nodes

*Notable differences.
†Regional nodes in gastroesophageal junction tumors defined as lower esophageal (below the azygous vein), diaphragmatic, pericardial, left gastric, and celiac nodes.
From Greene et al.[7]

Table 2. Siewert classification for gastroesophageal junction carcinomas

Classification	Description
Type I	Adenocarcinoma of the **distal esophagus,** which usually arises from an area of Barrett's esophagus and which may infiltrate the GEJ from above. Located more than 1 to 5 cm proximal to GEJ.
Type II	True carcinoma of the **cardia** arising from the cardiac epithelium or an area of Barrett's esophagus at the GEJ. Also referred to as "junctional carcinoma." Located within 1 cm proximal and 2 cm distal to GEJ.
Type III	**Subcardial** gastric carcinoma that infiltrates the GEJ and distal esophagus from below. Located more than 2 to 5 cm distal to GEJ.

Abbreviation: GEJ = gastroesophageal junction.
From Siewert & Stein.[10]

often blurred. GEJ tumors as referred to in this article generally are defined as primarily involving the distal esophagus with extension into the GEJ (type I) or originating in the GEJ with limited infiltration of the distal esophagus and/or gastric cardia (type II). Type III tumors are essentially proximal gastric cancers and typically should be treated with gastric carcinoma approaches;[12] therefore, they are not included in the discussion of GEJ tumors in this article.

Although it has been proposed that type I tumors be treated as distal esophageal cancers, the optimal management of type II or true junctional tumors remains unclear. Some evidence suggests that true junctional carcinomas behave more like proximal gastric tumors than distal esophageal adenocarcinomas.[12] The true prognostic significance and validity of such a classification remain unclear.[9] Many authors have proposed a need for separate classification and staging systems for GEJ tumors that differ from those for both esophageal and gastric carcinomas. For clinical trials studying GEJ tumors, analysis of Siewert types I and II as one grouping is likely the most feasible and appropriate approach, given what we understand of the biology.

PATTERNS OF DISEASE

Most GEJ carcinoma patients present with locally advanced disease confined to the chest, with circumferential transmural tumor infiltration and lymph node involvement occurring in greater than 50% of patients. Two reasons may account for the late disease presentation—anatomic location and potential lymphatic spread. The deep location of the GEJ and pliability of the proximal stomach (gastric cardia) commonly mask the vague symptoms of early-stage lesions until the development of locally advanced disease.

The rich vascular and lymphatic networks and lack of adventitia of the esophagus promote early systemic and nodal disease dissemination. In addition, since GEJ adenocarcinomas have a borderline anatomic location, they frequently involve portions of both the thoracic esophagus and gastric cardia. As a result, these tumors have the potential to spread bidirectionally through lymphatic channels. Both lymphoscintigraphic[13,14] and clinical studies[15,16] have demonstrated that the patterns of lymphatic spread of GEJ tumors vary depending on the anatomic location of the lesions. Lesions originating in the lower esophagus (Siewert type I) primarily spread proximally into both the mediastinal and abdominal (paracardiac, left gastric) nodes, whereas those in the gastric cardia (Siewert type II) and subcardia (Siewert type III) drain preferentially to the abdominal nodes (paracardiac, left gastric, lesser curvature).[14]

COMBINED-MODALITY TREATMENT

For patients who have locoregionally confined disease and are candidates for surgery, surgical resection with curative intent is the standard of care and offers the best chances for long-term survival in GEJ adenocarcinomas. However, 5-year survival rates in contemporary surgical series rarely exceed 25% with surgical resection alone for locally advanced esophageal or gastric carcinomas.[17–19] This dismal outcome has prompted the evaluation of adding neoadjuvant, adjuvant, or perioperative therapies in several phase III randomized controlled trials. Although there are no published randomized trials that included only GEJ adenocarcinomas, a few major trials that included adenocarcinomas also included patients with GEJ tumors. Findings of these studies are reviewed for relevance to management of GEJ tumors (Siewert types I and II).

Chemotherapy and Surgery

One of the most important prognostic factors in GEJ tumors is the R status (extent of residual disease) after surgery.[20,21] R0 (no residual microscopic disease) resection of these tumors, however, may be particularly challenging due to the tendency for intramural spread and adjacent organ infiltration. The addition of preoperative or perioperative chemotherapy has been proposed as a strategy to downsize tumors and improve the chances of an R0 resection while also treating potential micrometastases.

Although randomized trials in locally advanced esophageal cancer have not always shown a consistent advantage to chemotherapy alone prior to surgery, results from

Table 3. Phase III trials of chemotherapy and surgery for resectable esophageal and gastric carcinomas including gastroesophageal junction cancers

Trial	N	Site	Histology	GEJ	CT regimen	Curative resection		OS		
						S	CS	S	CS	Yrs
Intergroup 0113[22]	440	E	SCC 46% ADC 54%	NR	CF: preop × 3, postop × 2	59%	62%	26%	23%	3
MRC[23,24]	802	E	SCC 31% ADC 66%	10%*	CF: preop × 2	54%		17% 60%†	23%†	5
FFCD 9703[25]	224	E/G	ADC 100%	64%*	CF: preop x 2-3	NR	NR	24%	38%†	5
MAGIC[28]	503	G	ADC100%	12%	ECF: preop × 3, postop × 3	66%	69%	23%	36%†	5

*Designated as cardia in study.
† Statistically significant.
Abbreviations: NR = not reported; GEJ = gastroesophageal junction; CT = chemotherapy; OS = overall survival; S = surgery alone; CS = chemotherapy plus surgery; E = esophageal; G = gastric; SCC = squamous cell carcinoma; ADC = adenocarcinoma; preop = preoperative; postop = postoperative; CF = cisplatin + 5-FU; ECF = epirubicin + cisplatin + 5-FU; MRC = Medical Research Council; FFCD = Fédération Francophone de la Cancérologie Digestive; MAGIC = Medical Research Council Adjuvant Gastric Infusional Chemotherapy.

Table 4. Phase III trials of neoadjuvant and adjuvant chemoradiotherapy plus surgery in resectable esophageal and gastric carcinomas including gastroesophageal junction cancers

								LRF		OS		
Trial	**N**	**Site**	**Histology**	**GEJ**	**CT**	**RT**	**pCR**	**S**	**CRS**	**S**	**CRS**	**Yrs**
Preoperative concurrent chemoradiotherapy												
Walsh[32]	113	E	ADC 100%	35%*	CF × 2	40 Gy 15 frx	25%	–	–	6%	32%† 85% pCR	3
Urba[33]	100	E	SCC 25% ADC 75%	NR	CVF × 2	45 Gy Hfrx	28%	42%	19%†	16%	30% 64% pCR	3
TROG[34]	256	E	SCC 37% ADC 62%	NR	CF × 1	35 Gy 15 frx	16%	40%	21%	MST 19mo	MST 22mo 49% pCR	3
CALGB 9781[35]	56	E	SCC 25% ADC 75%	NR	CF × 2	50.4 Gy 28 frx	40%	33%	44%§	16%	39%†	5
Postoperative concurrent chemoradiotherapy												
Intergroup 0116[52]	556	G	ADC 100%	20%	FL × 2‡	45 Gy 25 frx	40%	29%	19%†	41%	50%†	3

*Designated as cardia in study.
† Statistically significant.
‡ Induction chemotherapy followed by concurrent chemoradiotherapy and additional chemotherapy alone.
§ Sites of failure were reported for 12 and 9 patients in the surgery alone and trimodality groups, respectively.
Abbreviations: NR = not reported; GEJ = gastroesophageal junction; CT = chemotherapy; RT = radiotherapy; pCR = pathologic complete response; LRF = locoregional failure; OS = overall survival; S = surgery alone; CRS = chemoradiotherapy plus surgery; E = esophageal; G = gastric; SCC = squamous cell carcinoma; ADC = adenocarcinoma; CF = cisplatin + 5-FU; CVF = cisplatin + vinblastine + 5-FU; FL = 5-FU + leucovorin; frx = fractions; Hfrx = hyperfractionation; TROG = Trans-Tasman Radiation Oncology Group; CALGB = Cancer and Leukemia Group B; MST = median survival time; mo = months.

recent studies favor the use of a preoperative approach in this setting (Table 3).

The Gastrointestinal (GI) Intergroup Trial 0113 was a large, multicenter study performed in the United States that compared surgery with or without preoperative and postoperative (perioperative) chemotherapy with cisplatin and 5-fluorouracil (5-FU) in resectable esophageal squamous cell and adenocarcinomas.[22] Only those patients with response to chemotherapy and potentially curative surgery went on to receive an additional two cycles of postoperative chemotherapy with reduced doses of cisplatin. The majority of patients had adenocarcinomas (54%), but the published report did not specify the number of GEJ cases. Perioperative chemotherapy decreased the risk of microscopic resection margins from 8% to 4%. However, there was no suggestion of a disease-free or overall survival benefit or increased curative resection rates.

Contrasting results were obtained in a trial by the UK Medical Research Council (MRC) that included nearly twice as many patients as Intergroup 0113.[23] In the MRC OEO2 trial, patients with resectable esophageal cancer were randomized to two cycles of preoperative cisplatin and 5-FU or surgical resection alone. Patients with tumors involving the distal esophagus and gastric cardia/Siewert type II (10%) were included. The investigators did not specify how many of the distal esophageal tumors involved the GEJ, so it is not clear how many patients had Siewert type I tumors. Initial results showed that neoadjuvant chemotherapy modestly improved 2-year survival and curative resection rates by 9% and 6%, respectively. A recent update confirmed the survival benefit at 5 years, consisting of a 6% absolute benefit (7% for adenocarcinoma, 5% for squamous cell cancer).[24] Upon pathologic evaluation of the resected surgical specimens, tumors that were pretreated with chemotherapy were smaller and had less nodal involvement and soft tissue extension.

Similar survival benefits were reported in a recent European trial that was presented in abstract form. The FFCD 9703 trial compared preoperative cisplatin and 5-FU to surgery alone in 224 patients with adenocarcinoma of the stomach and lower esophagus.[25] The majority of patients had cancer of the cardia/Siewert type II (64%) and an additional 11% had distal esophageal tumors. Preoperative chemotherapy improved 5-year disease-free and overall survival by absolute values of 13% and 15%, respectively.

Two meta-analyses of several randomized trials also suggested an absolute survival benefit of 4% to 7% with neoadjuvant chemotherapy in patients with resectable esophageal cancer.[26,27] In the recent Gebski et al meta-analysis, preoperative chemotherapy was beneficial only for adenocarcinomas.[27]

Additional insights are available from studies evaluating adjuvant chemotherapy in gastric cancer patients that also included patients with GEJ and distal esophageal cancers (Table 3). The MRC gastric cancer working party performed a randomized study, often referred to as the MAGIC trial, of perioperative chemotherapy in gastric carcinoma.[28] Although the majority of patients had gastric cancer, the results of this trial are relevant to GEJ tumors, since more than 20% of patients had either GEJ/Siewert type II (12%) or distal esophageal/Siewert type I (15%) cancers. The chemo-

therapy regimen consisted of three cycles of epirubicin, cisplatin, and 5-FU (ECF) given preoperatively and postoperatively. Of note, more extensive nodal dissections (D2 dissections) were the most common surgery performed. Approximately one third of the patients in the chemotherapy arm were considered inoperable and did not receive postoperative chemotherapy. Of the remaining eligible patients, 60% received all scheduled chemotherapy. Perioperative chemotherapy resulted in a 25% reduction in relative risk of death, which translated into an absolute 13% increase in 5-year overall survival rate. In addition to reducing the rate of distant metastases from 37% to 24%, chemotherapy decreased local failures from 21% to 14% compared to surgery alone. Curative resection rates, however, were not improved, and no pathologic complete responses were observed in the perioperative chemotherapy arm.

Neoadjuvant Chemoradiotherapy and Surgery

Although these trials collectively support a survival advantage with adjuvant chemotherapy, they showed consistently low rates of pathologic complete responses and marginal to no effects on curative resection rates.[22,23,28] In addition, local recurrences still appear to be a significant component of treatment failure after neoadjuvant chemotherapy, as demonstrated in the MAGIC trial.[28] To further improve these outcomes, other investigators have evaluated the role of adding local therapy in the form of radiotherapy to chemotherapy and surgery. The rationale for this approach is that improvement in control of locoregional and perhaps distant micrometastatic disease may improve survival outcomes.

Phase III randomized trials of neoadjuvant chemoradiotherapy have primarily involved patients with esophageal cancers (Table 4). Both sequential and concurrent chemoradiotherapy regimens have been used. Major randomized trials evaluating neoadjuvant chemotherapy followed by radiotherapy have consistently shown no survival advantage.[29–31] Since these trials included only squamous cell carcinomas, the results may not be applicable to GEJ adenocarcinomas. The majority of the concurrent chemoradiotherapy randomized trials, however, have included predominantly patients with adenocarcinomas. The most commonly used chemotherapy regimen in these trials was cisplatin plus 5-FU.

A relatively small randomized study from Ireland compared surgery alone to preoperative concurrent chemoradiotherapy with cisplatin and 5-FU in 113 patients with esophageal adenocarcinomas.[32] Thirty-five percent of patients had tumors involving the gastric cardia (Siewert type II). Type I tumors were also likely included, but the report did not specify the percentage of patients with distal esophageal lesions involving the GEJ. The experimental arm showed a large, significant improvement in overall survival at 3 years. In addition, regional nodal involvement at surgery was decreased from 82% to 42% with neoadjuvant chemoradiotherapy. Criticisms of the study, however, included a short median follow-up of only 10 months and a very poor overall survival rate (6%) in the surgery alone arm, which is inconsistent with those reported in modern surgical series (17%–39%).

In contrast, two other randomized studies did not reveal a significant survival advantage with preoperative chemoradiotherapy. Investigators at the University of Michigan randomized 100 patients with locoregional esophageal squamous cell cancer (n = 25) or adenocarcinoma (n = 75) to preoperative cisplatin, 5-FU, and vinblastine concurrently with twice daily radiation (hyperfractionated) or surgical resection alone.[33] The report did not specify the percentage of patients with GEJ tumors, but the population likely included patients with Siewert type I and II lesions. Although a statistically significant improvement in locoregional control was seen in the concurrent chemoradiotherapy group, only a trend in overall survival benefit was observed despite a near doubling of survival at 3-years (surgery 16%, chemoradiotherapy 30%). Patients who achieved a pathologic complete response, however, had a 3-year overall survival of 64%. A recent study from Australia showed no improvement in locoregional control or survival with concurrent radiotherapy cisplatin and 5-FU.[34] However, this trial used less intensive chemotherapy (only one cycle) and lower radiation doses than most other trials.

A recent report from the GI Intergroup Cancer and Leukemia Group B (CALGB) 9781 trial supports the benefits of neoadjuvant chemoradiotherapy. This trial was initially designed to randomize 475 patients with resectable stage I to III esophageal squamous cell cancer and adenocarcinomas to esophagectomy with node dissection alone or preoperative cisplatin/5-FU delivered concurrently with radiation to doses that would be considered standard at many institutions (50.4 Gy).[35] Eligible patients included those with tumors of the thoracic esophagus below 20 cm and GEJ with less than 2 cm distal spread into the gastric cardia (Siewert types I and II). Although only 56 patients were accrued to the study (30 in the trimodality arm and 26 in the surgery alone arm), a statistically significant overall survival benefit was seen at 5 years (39% vs. 16%) in favor of those receiving trimodality therapy, and trimodality therapy was not associated with any increases in toxicity.

In addition, several meta-analyses of randomized trials of trimodality therapy vs. surgery generally have shown a benefit to trimodality therapy.[27,36–38] The most recent meta-analysis suggested that preoperative chemoradiotherapy reduces overall mortality by approximately 20%.[27]

A number of groups have assessed even more aggressive neoadjuvant approaches by adding an induction chemotherapy phase prior to neoadjuvant chemoradiotherapy and surgery. Although no randomized trials of this approach have been published, M. D. Anderson Cancer Center (MDACC) and Memorial Sloan-Kettering Cancer Center (MSKCC) have published their institutional experiences.[39–42]

Ajani and colleagues at MDACC reported a phase II trial of 38 patients with resectable esophageal cancer (82% distal esophageal or GEJ tumors) treated with induction cisplatin, paclitaxel, and 5-FU followed by concurrent radiation and 5-FU prior to surgical resection.[39] Potentially curative resections and pathologic complete responses were achieved in 92% and 23%, respectively, and an encouraging 5-year survival rate of 39% was observed.

Investigators at MSKCC evaluated the use of induction cisplatin and paclitaxel followed by preoperative chemoradiotherapy and found acceptable toxicity

levels and high overall response rates, including pathologic complete response in 26% of patients.[40] A phase I trial in 19 patients with locally advanced esophageal carcinoma at MSKCC showed relatively minimal toxicity and pathologic complete response in 27% of patients with induction weekly cisplatin and irinotecan followed by radiotherapy concurrently with cisplatin and irinotecan.[41]

Some authors have questioned the necessity for surgical resection after chemoradiotherapy in potentially resectable esophageal cancers, since radiation with concurrent chemotherapy alone results in survival similar to surgery for squamous cell carcinomas of the esophagus. Two relatively large randomized European trials have directly addressed this issue by comparing concurrent chemoradiotherapy alone to chemoradiotherapy followed by surgery.[43,44] Both trials showed significantly improved locoregional control and similar quality of life but no significant improvement in overall survival when surgery was included in treatment. It is important to note that the populations in these trials were restricted to, or predominantly consisted of, patients with squamous cell carcinoma of the esophagus.

There is a paucity of randomized data on the nonsurgical management of adenocarcinomas. The Radiation Therapy Oncology Group (RTOG) 8501 trial compared 64 Gy radiation therapy alone vs. 50 Gy concurrent with cisplatin/5-FU in patients with esophageal squamous cell and adenocarcinomas, and found only 13% survival at 5 years in patients with adenocarcinoma.[45] The phase III RTOG 0436 trial will be further evaluating nonsurgical management of esophageal cancers. Patients will be randomized to receive definitive concurrent cisplatin/ paclitaxel and radiation with or without the epidermal growth factor receptor inhibitor cetuximab.[46] This study will include squamous cell and adenocarcinomas of the esophagus or GEJ (Siewert types I and II) and will stratify patients according to histology.

In summary, the addition of preoperative chemoradiotherapy to surgery improves curative resection rates, increases pathologic complete response rates, and reduces locoregional recurrences in locally advanced esophageal carcinoma. However, data are inconclusive with regard to benefit in terms of overall survival. Neoadjuvant chemoradiotherapy is a reasonable standard of care for high-risk patients. For many physicians, trimodality therapy is preferred for patients who are medically operable with resectable locally advanced esophageal carcinomas as a strategy to maximize local control. This approach has been most commonly adopted by US physicians, whereas preoperative chemotherapy alone is favored for esophageal cancer in the UK and other parts of Europe. No randomized trials have directly compared these two approaches. What is clear, however, is that patients who achieve a pathologic complete response upon surgical resection (16%–28%) have improved long-term survival (49%–85% at 3 years).[32–34] Ongoing research is aimed at further increasing pathologic complete response rates with intensified systemic agents and at developing novel approaches to identifying the subgroup of patients who are likely to achieve such response.[47]

Adjuvant Chemoradiotherapy and Surgery

Postoperative chemoradiotherapy has been evaluated primarily in the setting of gastric carcinomas. There are few data supporting its value for esophageal tumors. Subtotal or total gastrectomy along with varying extent nodal dissection is the cornerstone of primary treatment for potentially curable gastric carcinomas. Surgical resection alone yields excellent survival rates for early gastric cancers, but survival is markedly lower for more advanced disease (10-year survival 3%–42%),[48] which is what is generally diagnosed in the United States and Europe. The risk of local or regional recurrence in the tumor bed, anastomosis, or regional nodes after surgical resection with curative intent remains high at 40% to 65% in most series.[49–51]

A recent analysis from MSKCC of recurrence patterns in 1,172 gastric cancer patients with R0 resections (D2 dissections in most patients) reported that locoregional failures occurred in more than half of patients with recurrence.[49] The poor outcomes and high risk of locoregional failure with surgical resection alone for locally advanced gastric cancer highlight the potential role of adjuvant locoregional therapy as well as adjuvant systemic therapy in GEJ tumors.

A landmark trial by the US GI Intergroup (INT 0116) provides the most convincing data so far in support of adjuvant chemoradiotherapy in potentially resectable, locally advanced gastric adenocarcinomas (Table 4).[52] Patients with tumors of the GEJ that extended at least 2 cm into the stomach and those with proximal gastric cancers accounted for 20% of the study population; according to the Siewert classification, these tumors were likely type II and III GEJ tumors. Compared to patients in the MAGIC trial and other series of surgery alone, patients in this trial generally had more advanced T3 and node-positive tumors. Patients were randomized after complete surgical resection to observation or "sandwich" adjuvant chemoradiotherapy in which induction 5-FU/leucovorin (LV) was followed by radiotherapy concurrently with 5-FU/LV and additional cycles of chemotherapy.

Postoperative chemoradiotherapy resulted in a statistically significant improvement in disease-free and overall survival. At 3 years, overall survival was increased by an absolute 9%. Kaplan-Meier estimates indicate that the survival advantage continues to increase over 5 to 7 years, reaching approximately 20%. This is an enormous benefit, considering the smaller improvements usually seen with adjuvant therapy in other adult solid tumors, particularly with use of single-agent chemotherapy. This survival benefit is consistent with recently published data from the Japan Clinical Oncology Group 9206 trial demonstrating a significant survival benefit (absolute 10% improvement at 3 years) with the addition of adjuvant S-1, an oral fluoropyrimidine, to surgery in gastric cancer patients who underwent D2 dissections.[53] Furthermore, the significant reduction in local failures in the chemoradiotherapy group (19% vs. 29% with surgery alone) in the INT 0116 trial suggests that improvement in local control was a major contributing factor to the survival benefit.

This study has been criticized for inadequate staging and surgery, particularly regarding the extent of lymphadenectomy. Only 10% of patients received the recommended D2 dissection and more than half the patients received less than a formal D1 dissection. This suboptimal surgery may

have contributed to inferior results in the surgery alone arm, raising the question whether chemoradiotherapy was compensating for substandard surgery, thereby resulting in an overestimation of the survival benefit. However, a recent retrospective analysis from Korea suggests that postoperative chemoradiotherapy may indeed be of benefit after D2 dissection,[54] and the previously mentioned study on patterns of failure from MSKCC show that local-regional failure is still a major problem after D2 dissection.[49] This issue can ultimately be resolved only through further randomized trials.

Little consensus exists regarding the optimal treatment approach for locally advanced gastric carcinoma. In the United States, many physicians have adopted the INT 0116 regimen of postoperative chemoradiotherapy as the standard of care. In other regions of the world, and to an increasing extent in the United States, postoperative or perioperative chemotherapy is preferred. The positive results with perioperative chemotherapy alone in the MAGIC trial[28] are compelling and raise the question of whether radiotherapy is needed in addition to chemotherapy in gastric cancer. As reported by the MAGIC trial investigators, local recurrences (14%) were still a major component of treatment failures in patients treated with ECF chemotherapy. Therefore, there is a strong rationale for using the combination of radiotherapy and ECF (or similar chemotherapy) to maximize local and distant control.

An ongoing US Intergroup trial (CALGB 80101) is comparing postoperative ECF vs. postoperative 5-FU/LV (INT 0116 trial) chemotherapy. Both cohorts receive concurrent chemoradiotherapy with 5-FU. Another ongoing randomized trial from the Dutch Colorectal Cancer Group (CRITICS study) may assist in determining the need for postoperative radiation in gastric carcinoma by investigating whether chemoradiotherapy with cisplatin and capecitabine after preoperative ECC (epirubicin/cisplatin/capecitabine) and adequate (D1+) surgery leads to improved survival in comparison with postoperative ECC chemotherapy.

DISCUSSION

For resectable locally advanced GEJ tumors, the mainstay of primary therapy is surgical resection with an attempted R0 resection and adequate lymphadenectomy. As with esophageal and gastric carcinomas, multiple modalities are needed to optimize treatment outcomes.

Since there are no randomized trials exclusively in patients with GEJ tumors, the optimal management of GEJ carcinomas must be inferred from esophageal and gastric carcinoma trials that included adenocarcinomas of the GEJ (Tables 3 and 4). However, among the studies that included GEJ tumors in patient eligibility criteria, most did not provide clear definitions for such tumors, and most did not report the percentage of patients with GEJ tumors or the clinical outcomes in this subgroup of patients; applicability of the results of these trials to the combined-modality management of locally advanced GEJ carcinomas is, therefore, less than straightforward. The trials providing data most relevant to GEJ tumors are probably the MAGIC trial assessing perioperative chemotherapy in gastric adenocarcinoma;[28] the Irish trial evaluating neoadjuvant concurrent chemoradiotherapy in esophageal cancer;[32] and the INT 0116 trial[52] assessing postoperative chemoradiotherapy in gastric cancer, each of which included only patients with adenocarcinomas.

In the MAGIC trial, 26% of patients had either distal esophageal Siewert type I or GEJ type II tumors. In the Irish trial, 35% of patients had esophageal cancers involving the proximal stomach. In the INT 0116 trial,[52] 20% of patients had gastric cancers with involvement of the GEJ. Although these percentages are relatively small, the consistent overall locoregional control and survival benefits observed in these trials, as well as benefits shown in other esophageal cancer data,[35] suggest that it is reasonable to expect similar benefits in patients with GEJ tumors. In addition, since a local control advantage has been demonstrated for both gastric and esophageal cancers with the use of radiotherapy, it is likely that at least a local control benefit, and probably a survival benefit, would result from similar treatment of GEJ tumors.

The available data do not provide guidance on which multimodality approach might be best for GEJ carcinomas. A number of approaches involving different combinations of chemotherapy, radiotherapy, and surgery are reasonable (Table 5). The question remains whether GEJ tumors should be treated like esophageal adenocarcinomas—eg, with neoadjuvant chemoradiotherapy or chemotherapy followed by surgery—or more like gastric cancers—eg, with surgery followed by adjuvant chemoradiotherapy or with perioperative chemotherapy alone. It is likely that trimodality therapy will be the standard for the treatment of this disease; since radiotherapy improves local control for both esophageal and gastric cancers and chemotherapy has a survival benefit in both tumors, the combination is likely to be optimal.

Table 5. Combined-modality treatment approaches in locally advanced gastro-esophageal junction cancers

Treatment approach	Supportive data
C + S	MRC,[23,24] FFCD 9703[25]
C + S + C	MAGIC[28]
CR + S	Walsh,[32] CALGB 9781[35]
S + C + CR + C	Intergroup 0116[52]
*C + S + CR	
*C + CR + S	

*Under investigation.
Abbreviations: C = chemotherapy; S = surgery; CR = chemoradiotherapy.

From a practical point of view, the specifics of local therapy may depend heavily on the location and extent of disease. From a radiation oncologist perspective, a preoperative approach with chemoradiotherapy may be preferable for most GEJ tumors (Siewert types I and II) due to technical considerations. This approach may decrease the risk of treatment-related morbidity by allowing the delivery of safer radiation treatment fields and avoiding irradiation of a significant portion of the mediastinum and lungs when a patient undergoes cervical esophagogastrostomy and the anastomotic site and remaining stomach are to be included the radiation fields. In addition, preoperative radiotherapy with concurrent chemotherapy has been shown to be superior to postoperative therapy in a number of sites in the GI tract (eg, in rectal cancer), so it is not unreasonable to consider that the same might be true in GEJ tumors. Additional studies evaluating preoperative chemotherapy and

chemoradiotherapy are needed to define the proper sequencing and combinations of the three therapeutic modalities.

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Disclosures of Potential Conflicts of Interest

The authors indicated no conflicts of interest.