Navigating the GE Junction

New insights and best practices

GASTRIC/ GE JUNCTION CANCER

Resources & Tools for the Multidisciplinary Team

This article is part of ACCC's "Improving Quality Care in Gastric/GE Junction Cancer" education program. For this project, ACCC is pleased to partner with Debbie's Dream Foundation: Curing Stomach Cancer, a non-profit organization dedicated to raising awareness about stomach cancer; advancing funding for research; and providing education and support to patients, families, and caregivers. Financial support of this project is provided by Lilly Oncology. ACCC is solely responsible for content. Additional tools and resources are available online at www.accc-cancer.org/gastric.

BY ALEXANDRA HOWSON, MA, PHD

Fast Fact At the GEJ, the lower esophagus divides from the proximal stomach, and esophageal squamous epithelium changes into the columnar epithelium of the gastric cardia. The GEJ is the predominant site for adenocarcinomas of the upper GI tract.

Community cancer centers are seeing an increasing number of patients with gastroesophageal cancers, including tumors of the gastroesophageal junction (GEJ). GEJ tumors are rare but highly aggressive, with low overall survival rates.[1] GEJ tumors are characterized by two distinct histologic subtypes: squamous cell carcinoma and adenocarcinoma. The incidence of squamous cell esophageal carcinoma—associated with cancer of the distal stomach—is decreasing in Western Europe, Australia, and North America, whereas the incidence of adenocarcinoma—associated with cancers of the lower esophagus and gastric cardia—is rising rapidly.[2]

In the U.S., the incidence of adenocarcinoma is rising fastest among white men (4 to 10 percent annually since 1976),[3] and is especially prevalent in certain geographical areas, such as coastal South Carolina, Washington, D.C., and Baltimore, Md.[4] GEJ cancers comprise more than 90 percent of all esophageal adenocarcinomas.[5–8]

What Causes GEJ?

Esophageal adenocarcinomas, including those at the GEJ, can develop from multiple interactions between environmental and genetic factors (Table 1, page 56).[8] Chronic irritation from gastroesophageal reflux is considered the strongest individual risk factor for esophageal adenocarcinoma and Barrett's esophagus, a precursor to GEJ tumors.[2,8] Although reasons for rising reflux rates are unclear, increasing obesity, body mass index, and central and intra-abdominal adiposity (body fat) may play a role.[8] Exposure to *heliobacter pylori* infection increases the risk for gastric cancer; however, this bacterium is thought to protect against developing esophageal adenocarcinoma.[8]

Although early stage esophageal and GEJ cancers are generally asymptomatic, patients can experience dyspepsia (indigestion), or gastrointestinal bleeding if ulcerated lesions are present. However, most patients present at an advanced stage, commonly with dysphagia (difficulty swallowing), although odynophagia (painful swallowing), regurgitation, and weight loss can also occur.[1,9] Table 2, page 56, compares symptoms in gastric and GEJ cancer.

Community cancer centers are seeing an increasing number of patients with gastroesophageal cancers, including tumors of the gastroesophageal junction.

Classification & Staging

Until recently, GEJ tumors were treated as esophageal or gastric tumors. In the 1990s, GEJ tumors were classified into three anatomical types defined by proximity to the epicenter of the tumor (Table 3, page 57).[10] But the anatomical origins of GEJ adenocarcinomas are not always readily distinguishable between gastric cardia or lower esophageal adenocarcinomas.[11]

While GEJ tumors share some ontological characteristics with both esophageal and gastric cancers, insights into the epidemiology

Table 1. Epidemiology of Risk Factors for GEJ Tumors

Squamous Cell Carcinoma	Adenocarcinoma
Southeastern Africa, Iran, Asia	North America, Western Europe
Black ethnicity	White ethnicity
Smoking	Genetics
Alcohol	Obesity
Upper and middle esophagus	Lower esophagus
High-salt and processed-food diet	Esophageal inflammation
Low SES (socio-economic status), non-urban location	Male gender
Precursor pathological conditions (e.g., pernicious anemia, achlorhydria atrophic gastritis, gastric ulcers, adenomatous polyps)	Gastroesophageal reflux
Epstein-Barr virus	Barrett's esophagus
Gastric colonization with *H. pylori*	Chronic irritation

and biology of GEJ tumors have led to their reclassification as a heterogeneous clinical entity, with different outcomes based on primary tumor location, regional lymph node involvement, the presence of distant metastases, and histologic (tissue) grade.[1,5,12]

In addition to anatomy, the staging recommended by the 2010 American Joint Committee on Cancer (AJCC) is based on pathological data from three continents and 4,627 patients who underwent esophagectomy alone with no induction therapy.[13] This data-driven resource harmonizes clinical and pathologic staging for GEJ, and includes some important changes with implications for staging workup. Nodal staging is defined by the number of pathologically involved nodes rather than by location. For planning and prognosis purposes, all tumors arising at the GEJ, or adenocarcinomas arising in the proximal 5 cm of the stomach and crossing into the GEJ, are staged according to the TNM system for esophageal adenocarcinoma.[2,13]

In clinical trials, patients with both adenocarcinoma and squamous cell carcinoma have often been treated together, potentially obscuring differences in outcomes associated with histology-based treatment.[6] However, when compared stage-for-stage to patients with distal gastric cancers, patients with GEJ and cardia adeno-

Table 2. Symptoms in Gastric and GEJ Cancer

Gastric Cancer	GEJ Cancer
Weight loss	Dysphagia (progressing from solids to liquids)
Dysphagia	Weight loss
Dyspepsia	Hoarseness
Vomiting	Odynophagia
Anorexia	Anemia
Early satiety	Chest pain in the absence of myocardial infarction
Hematemesis	
Iron deficiency anemia	

Table 3. GEJ Cancer Siewart Classification
Type I: Esophageal
Distal esophageal adenocarcinomas with an epicenter 1-5 cm above the cardia: these tumors have similar epidemiological and histological characteristics to esophageal adenocarcinoma.
Type II: Cardia
Adenocarcinomas with the epicenter within 1 cm above and 2 cm below the cardia: complex etiology with epidemiological and histological characteristics sitting between Type I and II.
Type III: Subcardial
Noncardia gastric adenocarcinomas with an epicenter 2-5 cm below the cardia, with or without extension into the esophagus: may be similar to distal noncardia gastric cancers.

carcinomas carry a worse prognosis, with lower survival and higher rates of local and distal recurrences.[13] Notably, adenocarcinomas and squamous cell carcinomas at the GEJ are distinct entities that may benefit from different treatment approaches, and that respond differently to systemic chemotherapies and targeted agents.[5] Therefore, accurate tumor diagnosis and staging are key to effective management of GEJ cancer.

Precise local staging helps to determine the depth of tumor spread, eligibility for resection, and presence and extent of lymph node metastasis to determine the likelihood of regional control.[14] In addition to clinical examination; blood count; liver, pulmonary, and renal function tests; several complementary imaging modalities provide pathological and anatomic data to support tumor staging (see Table 4, page 58).

How is GEJ treated?

For esophageal cancer patients with localized disease, including GEJ tumors, surgery remains the gold standard for patients who are medically fit for resection (e.g., transhiatal and transthoracic esophagectomy).[8] Because locally advanced disease is associated with a high risk for recurrence, adjuvant therapy has emerged as a strategy that appears to improve survival for patients undergoing surgery; however, there is considerable debate over the advantages of dual modality therapy (chemotherapy plus surgery) over multimodality therapy (chemoradiation and surgery) for this patient population.[18]

Pre-operative Chemotherapy. Several clinical trials in the U.S. and in Europe have investigated pre-operative chemotherapy followed by surgery, with or without post-operative chemotherapy. For instance, the British MAGIC trial compared three cycles of epirubicin, cisplatin, and 5-FU followed by surgery and three cycles of post-operative chemotherapy in 503 patients with esophageal cancer, 26 percent of whom had GEJ cancer.[19] This clinical trial demonstrated improved five-year survival for the perioperative chemotherapy group compared with surgery alone (36 percent vs. 23 percent).

Multimodal Pre-operative Therapy. A landmark multicenter Phase III study found neoadjuvant chemoradiation superior to surgery alone.[20] Using endoscopic ultrasound and laparoscopic staging, the CROSS trial randomly assigned 364 patients with carcinoma of the esophagus (75 percent of whom had adenocarcinoma of the lower esophagus or GEJ) to surgery alone vs. pre-operative chemoradiotherapy (carboplatin and paclitaxel plus 41.4 Gy of external beam radiotherapy). Pathologic complete response occurred in 23 percent of the patients with adenocarcinoma who had chemoradiation and median five-year survival was also superior for this group vs. the surgery-alone arm (49 months vs. 24). Operative mortality was <4 percent in both groups.

> For esophageal cancer patients with localized disease, including GEJ tumors, surgery remains the gold standard for patients who are medically fit for resection.

Table 4. Recommended Imaging Modalities in Staging Workup[1,15]

Flexible endoscopy with biopsy is recommended to assess mucosal and submucosal penetration and confirm histologic classification. Endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD) can precisely define the presence or absence of submucosal invasion and guide therapy.[16]
Baseline CT scan of chest and abdomen to evaluate for local, nodal, intra-abdominal, and thoracic metastatic disease.
Fluoride-18 fluorodeoxyglucose (FDG) positron emission tomography (PET) imaging is a standard of care for node staging and detection of metastases to determine patient eligibility for surgical resection. Functional imaging may also identify early responders to chemotherapy.[17]
Endoscopic ultrasonography with fine needle aspirate of lymph nodes is an additional staging study to confirm nodal status, improve accuracy of clinical staging, and guide therapy in the absence of metastatic disease.[1]
Laparoscopy is considered optional in GEJ cancer patients with no evidence of M1 disease.
HER2 testing for all patients with metastatic GEJ cancer at the time of diagnosis.

Current Practice Recommendations. Although there has been conflicting evidence regarding the effects of perioperative chemotherapy on survival and other outcomes, a recent systematic review that evaluated data from 14 Phase III clinical trials comparing surgery alone to surgery and perioperative chemotherapy (alone or in combination with radiotherapy) found that treatment with perioperative chemoradiation in patients with GEJ adenocarcinomas was significantly associated with longer survival compared with surgery alone (HR 0.81, CI 0.73-0.89; p<0.0001).[21] For patients with localized node negative/node positive adenocarcinoma and no metastases (i.e., T1b, T2-T4a), National Comprehensive Cancer Network (NCCN) guidelines favor pre-operative chemoradiotherapy, and recommend many other treatment options combined with surgery, including definitive chemoradiation for patients who decline surgery or with T4b tumors, and pre-operative chemotherapy.[15]

Improving Treatment of GEJ

The following are key strategies for improving the care and treatment of patients with GEJ cancer.

Upfront multidisciplinary team planning and pre-treatment counseling is essential to optimize patient outcomes. Patients with GEJ tumors require clinical expertise from several disciplines, including:

- Surgical oncology
- Medical oncology
- Radiation oncology
- Gastroenterology
- Pathology
- Oncology nurses
- Dietitians
- Social workers
- Cancer program administrators and office managers
- Patient navigators
- Data managers.

This multidisciplinary team is essential in caring for patients with GEJ cancer throughout the clinical pathway. A primary contact (e.g., nurse specialist) can ensure continuity of care, help patients navigate interventions in a timely fashion, and coordinate pre- and post-operative nutritional and psychological support, post-operative follow-up, and, if necessary, specialized rehabilitation.

Prior to treatment, GEJ tumor histology and location must be staged via AJCC staging classifications.[11]

With GEJ cancer, only 11 to 21 percent of patients will present with potentially resectable disease and have the physiologic capacity to tolerate surgery.[11] To determine whether patients will be able to tolerate pre-operative chemoradiation, providers must assess their physiologic status.[18]

Treatment of GEJ cancer can negatively impact health-related quality of life (HRQoL) due to the development of dyspnea, fatigue, and eating restrictions. Providers should recognize that acute post-operative complications, comorbidities, and advanced tumor stage are predictors of risk for deterioration in HRQoL.[8]

Providers can improve outcomes in patients with GEJ cancer by modifying risk factors before surgery, optimizing nutritional status, and educating patients about what to expect.[9]

The last decade has witnessed a trend toward consolidating

Table 5. ICD Code Changes Related to Treatment of GEJ Cancer

ICD-9 150 Malignant Neoplasm of Esophagus	ICD-10 C15 Malignant Neoplasm of Esophagus
• 150.0 malignant neoplasm of cervical esophagus	• C15.0 cervical part of esophagus
• 150.1 malignant neoplasm of thoracic esophagus	• C15.1 thoracic part of esophagus
• 150.2 malignant neoplasm of abdominal esophagus	• C15.2 abdominal part of esophagus
• 150.3 malignant neoplasm of upper third of esophagus	• C15.3 upper third of esophagus
• 150.4 malignant neoplasm of middle third of esophagus	• C15.4 middle third of esophagus
• 150.5 malignant neoplasm of lower third of esophagus	• C15.5 lower third of esophagus
• 150.8 malignant neoplasm of other specified part of esophagus	• C15.8 overlapping lesion of esophagus
• 150.9 malignant neoplasm of esophagus, unspecified	• C15.9 esophagus, unspecified
151.0 malignant neoplasm of cardia	C16.0 malignant neoplasm of cardia
230.1 carcinoma *in situ* of esophagus	D00.1 carcinoma *in situ* of esophagus
235.5 neoplasm of uncertain behavior of other and unspecified digestive organs	D37.7 neoplasm of uncertain or unknown behavior of other digestive organs (including esophagus)

high-risk cancer resections at high-volume hospitals, which can achieve perioperative mortality of ≤5 percent.[6] Fewer complications occur in high-volume settings and, if they do occur, are likely to be handled more effectively.[8,22] Community providers can partner with providers at these high-volume hospitals to ensure continuity of care as GEJ cancer patients transition between care settings.

> To determine whether patients will be able to tolerate pre-operative chemoradiation, providers must assess their physiologic status.

Accurate documentation of procedures in the patient's medical record is important for effective reporting and timely reimbursement. As International Classification of Diseases (ICD) codes migrate from ICD-9 to a more specific ICD-10, healthcare providers need to document the correct treatment and sequencing codes across the patient trajectory (see Table 5, above).[23]

The Future of GEJ Treatment

Even with perioperative chemotherapy or pre-operative chemoradiation, outcomes for patients with GEJ cancer remain poor. But there is hope on the horizon. Multiple molecular pathways involved in the pathobiology of GEJ cancer may serve as the basis for novel therapeutic agents. For instance, human epidermal growth factor receptor-2 (HER2)-positive tumors are overexpressed in esophageal and GEJ tumors. As a result of the Trastuzumab for Gastric Cancer (ToGA) trial,[24] in which 20 percent of enrolled patients had GEJ adenocarcinoma, trastuzumab presents an option in combination with chemotherapy as a first-line treatment for HER2-neu positive patients with inoperable GEJ cancer.[15] Several Phase III studies are ongoing that signal potential refinements in standards of care for patients with GEJ, as well as research to identify predictive and prognostic biomarkers. OI

Alexandra Howson, MA, PhD, Snoqualmie, Wash., is a trained qualitative researcher and medical sociologist with experience with several funded research projects on public health initiatives.

References

1. Varghese TK, Jr., Hofstetter WL, Rizk NP, et al. The society of thoracic surgeons guidelines on the diagnosis and staging of patients with esophageal cancer. *Ann Thorac Surg*. 2013;96(1):346-356.

2. Wheeler JB, Reed CE. Epidemiology of esophageal cancer. *Surg Clinics N America*. 2012;92(5):1077-1087.

3. Cellini F, Morganti AG, Di Matteoa FM, et al. Clinical management of gastroesophageal junction tumors: past and recent evidences for the role of radiotherapy in the multidisciplinary approach. *Rad Oncol*. 2014;9:45.

4. Kallman JB, Arsalla A, Park V, et al. Screening for hepatitis B, C and non-alcoholic fatty liver disease: a survey of community-based physicians. *Alimentary Pharmaco Therapeutics*. 2009;29(9):1019-1024.

5. Strong VE, D'Amico TA, Kleinberg L, Ajani J. Impact of the 7th Edition AJCC staging classification on the NCCN clinical practice guidelines in oncology for gastric and esophageal cancers. *JNCCN*. 2013;11(1):60-66.

6. Merkow RP, Bilimoria KY, McCarter MD, et al. Effect of histologic subtype on treatment and outcomes for esophageal cancer in the United States. *Cancer*. 2012;118(13):3268-3276.

7. Botterweck AAM, Schouten LJ, Volovics A, et al. Trends in incidence of adenocarcinoma of the oesophagus and gastric cardia in ten European countries. *Int J Epidemiol*. 2000;29:645-654.

8. Lagergren J, Lagergren P. Recent developments in esophageal adenocarcinoma. *CA: Cancer Journal Clin*. 2013; Apr 12.

9. Nieman DR, Peters JH. Treatment strategies for esophageal cancer. *Gastroenterol Clin North Am*. 2013;42(1):187-197.

10. Siewert JR, Richards FM, Werner M, Stein HJ. Adenocarcinoma of the esophagogastric junction: results of surgical therapy based on anatomical/topographic classification in 1,002 consecutive patients. *Ann Surg*. 2000;232:353-361.

11. Fox MP, van Berkel V. Management of gastroesophageal junction tumors. *Surg Clin North Am*. 2012;92(5):1199-1212.

12. McColl KE, Going JJ. Aetiology and classification of adenocarcinoma of the gastro-oesophageal junction/cardia. *Gut*. 2010;59(3):282-284.

13. Rice TW, Blackstone EH, Rusch VW. 7th edition of the AJCC Cancer Staging Manual: esophagus and esophagogastric junction. *Ann Surg Oncol*. 2010;17(7):1721-1724.

14. Allum WH, Blazeby JM, Griffin SM, et al. Guidelines for the management of oesophageal and gastric cancer. *Gut*. 2011;60(11):1449-1472.

15. National Comprehensive Cancer Network. *NCCN Guidelines: Esophageal and Esophagogastric Junction Cancers*; 2013. Available online at: www.nccn.org/professionals/physician_gls/f_guidelines.asp. Last accessed June 12, 2014.

16. Chennat J KV, Ross AS, et al. Complete Barrett's eradication endoscopic mucosal resection: an effective treatment modality for high-grade dysplasia and intramucosal carcinoma—an American single-center experience. *Am J Gastroenterol*. 2009;104(11):2684-2692.

17. Lordick F OK, Krause BJ, et al. PET to assess early metabolic response and to guide treatment of adenocarcinoma of the oesophagogastric junction: the MUNICON phase II trial. *Lancet Oncol*. 2007;8(9):797-805.

18. Shah MA. Unanswered questions in the management of gastroesophageal junction adenocarcinoma: an overview from the medical oncologist's perspective. American Society Clinical Oncology Education Book. ASCO; 2013.

19. Cunningham D, Allum WH, Stenning SP, et al. Perioperative Chemotherapy versus Surgery Alone for Resectable Gastroesophageal Cancer. *NEJM*. 2006;355:11-20.

20. van Hagen P, Hulshof MC, van Lanschot JJ, et al. Preoperative chemoradiotherapy for esophageal or junctional cancer. *NEJM*. 2012;366(22):2074-2084.

21. Ronellenfitsch U, Schwarzbach M, Hofheinz R, et al. Peroperative chem(radio)therapy versus primary surgery for resectable adenocarcinoma of the stomach, gastroesophageal junciton, and lower esophagus. *Cochrane Databse Syst Rev*. 2013;5.

22. Finks JF, Osborne NH, Birkmeyer JD. Trends in hospital volume and operative mortality for high-risk surgery. *NEJM*. 2011;364(22):2128-2137.

23. O'Malley KJ, Cook KF, Price MD, et al. Measuring Diagnosis: ICD Code Accuracy. Health services research. 2005;40(5):1620-1639.

24. Bang YJ, Van Cutsem E, Feyereislova A, et al. Trastuzumab in combination with chemotherapy versus chemotherapy alone for treatment of HER2-neu-positive advanced gastric or gastro-oesophageal junction cancer (ToGA): a phase 3, open-label, randomised controlled trial. *Lancet*. 2010;376:687-697.