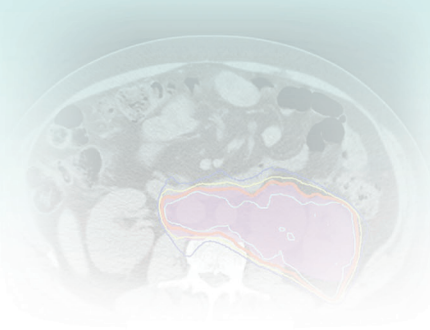
CHAPTER

45 Cancer of the Esophagus



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INCIDENCE

Esophageal cancer is the eighth-most common cancer worldwide and is endemic in Asia, South and East Africa, and Northern France. Esophageal cancer accounts for approximately 1% of cancers in the United States and is associated with an 85% mortality rate. In 2012, 17,460 (13,950 men and 3,510 women) in the United States were diagnosed with esophageal cancer, resulting in approximately 15,000 deaths (12,040 men and 3030 women).

BIOLOGIC CHARACTERISTICS

The predominant histologic types are squamous cell carcinoma and adenocarcinoma. Major prognostic factors are local tumor extent, presence of nodal involvement or distant metastases, and pathologic response to therapy. Approximately 15% to 30% of adenocarcinomas and 5% to 13% of squamous cell carcinomas overexpress Her-2/neu.

STAGING EVALUATION

Staging evaluates the extent of primary tumor, involvement of lymph nodes, and presence or absence of metastases. Staging evaluations should include a history and physical examination, blood count and chemistries, endoscopy with biopsy, 18-fluorodeoxyglucose positron emission tomography (FDG-PET) with computed tomography (CT) imaging and endoscopic ultrasound (EUS).

DEFINITIVE THERAPY

Surgical resection is the primary therapy for resectable esophageal cancer. Cure rates of 60% to 80% are achieved in the rare patient found to have disease confined to the esophagus without nodal involvement. Preoperative chemoradiation (for resectable squamous and adenocarcinomas of the esophagus) and perioperative chemotherapy (for distal and esophagogastric adenocarcinomas) significantly improve survival in patients with more advanced locoregional disease amenable to surgical resection. Concurrent chemoradiation therapy provides a significant improvement in overall survival and local control over radiation alone for both squamous and adenocarcinomas. There is no demonstrated benefit to escalation of radiation dose in this setting.

Postoperative chemoradiation has demonstrated a survival benefit for patients with stage IB-IV, M0 resected gastroesophageal junction and gastric adenocarcinomas who have not received preoperative therapy compared to surgery alone. Chemotherapy alone in the preoperative setting has demonstrated a small survival advantage over surgery alone.

PALLIATION

Patients with unresectable esophageal cancer causing obstruction or bleeding may obtain palliation with concurrent chemotherapy and radiation. In patients with poor performance status who cannot tolerate systemic therapy, external beam radiation or brachytherapy is a reasonable option for palliation of dysphagia. Esophageal stenting should also be considered. Radiotherapy is also used for palliation of symptomatic distant disease such as bone or brain metastases. Intraluminal brachytherapy with or without the addition of external beam irradiation is occasionally used for palliation.

INTRODUCTION

The diagnosis and management of esophageal cancer continues to evolve. Advances in the operative and postoperative management and rational applications of multimodality therapy have produced modest improvements in survival rates over the last 25 years.[1] In this chapter, we review biologic and epidemiologic factors associated with esophageal cancer. We also discuss review the rationale for and results of combined-modality approaches, as well as the use of palliative therapies. We conclude with a summary of current treatment recommendations and a discussion of several important clinical trials in progress.

ETIOLOGY AND EPIDEMIOLOGY

Esophageal cancer is the eighth-most common cancer worldwide[1] and is endemic in developing nations with wide variations in prevalence between low- and high-incidence regions (Asia, South and East Africa, and Northern France).[2] In 2012, 17,460 patients (13,950 men and 3510 women) in the United States were diagnosed with esophageal cancer, resulting in approximately 15,000 deaths (12,040 men and 3030 women).[3] The incidence of esophageal cancer continues to rise and has increased 5% over the last 2 years in contrast to 2010, when 16,640 Americans were diagnosed with esophageal cancer, and there has been a 14.6% increase in incidence over the previous 5 years.[4,5] Esophageal cancer represents only approximately 1% of new cancers in the United States, but approximately 85% of patients die of their disease without significant overall improvement over the last 25 years.[3-5] In 2008, esophageal cancer was the fifth leading cause of death in males age 40 to 79.[3]

Esophageal cancers are histologically classified as either adenocarcinoma or squamous cell carcinoma. Both squamous cell and adenocarcinomas are more common in males, however the incidence of squamous cell carcinoma is declining in North America and Western Europe as the incidence of adenocarcinoma of the distal esophagus and gastroesophageal junction is increasing, currently representing approximately 70% of all esophageal carcinomas in the United States.[6] Squamous cell carcinoma remains dominant in endemic regions and underdeveloped parts of the world.[6-8]

TABLE 45-1 Incidence of Adenocarcinoma of the Esophagus

Investigator	Years	Adenocarcinoma (%)
Smithers[14]	1936-1951	7.3
Hesketh/Conn. Register[12]	1983-1986	22.9
Birgisson[15]	1987-1994	73.5
Steyerberg[16]	1991-1999	52.0
Brown[6]	2000-2004	61.1*

*White males and females only.

Data from the Surveillance Epidemiology and End Results (SEER) program of the National Cancer Institute demonstrated that the incidence of esophageal cancer in white males steadily increased by 45% in the United States between 1975 and 2004, with the incidence of adenocarcinoma increasing by 463%, and the incidence of squamous cell carcinoma declining by 50% during the same time period.[6] In contrast, the overall incidence of esophageal cancer has remained constant among white females, although there have been similar trends observed with a 335% increase in the incidence in adenocarcinomas and a 29% decline in the incidence of squamous cell carcinomas.[6,9] The incidence of squamous cell carcinoma has shown a significant decline in black males beginning in 1992,[10] but it remains the most common cell type among blacks in the United States,[11] despite the twofold to threefold increase in incidence of adenocarcinomas in black males and females. Interestingly, a review of the New England tumor registries[12] demonstrated that the incidence of adenocarcinoma has increased even when tumors located at the esophagogastric junction have been excluded, and data from the National Cancer Institute's SEER database (1973-2001) found no evidence of histologic reclassification of esophageal squamous cancers or anatomic reclassification of adenocarcinomas of the gastric cardia to explain this trend.[13] Table 45-1 reflects recent changes in the prevalence of adenocarcinoma of the esophagus over the span of several decades.

Racial disparities have been observed in the esophageal cancer population. Males who are black are more likely to present with advanced or metastatic disease, resulting in a survival rate that is 60% of that for males who are white.[3,4] In a multivariate regression analysis controlling for age, gender, marital status, tumor histologic type, and tumor location, black race was associated with worse survival rates. In this study analyzing SEER data, when the tumor status, surgical technique, and radiotherapeutic modality were added to the model, race was no longer significantly associated with survival rates.[11] Provocative data from Steyerberg[16] and others[17,18] also suggested that the underuse of potentially curative surgery may, in part, explain the poorer survival rates observed for patients who are black with locally advanced disease because a population-based analysis showed that once data had been corrected for treatment received, there was no difference in survival rates between patients regardless if they were white or black. It has been postulated that the increased incidence of disease and increased mortality rates observed in patients who are black are reflections of socioeconomic status and dietary risk factors but not ethnicity. Squamous cell carcinoma remains the most common histologic type among males who are black[11] and may be associated with worse outcomes, facts that could explain some of the observed racial disparities in survival rates.[12] In one population-based study there appeared to be a risk for developing esophageal cancer in patients who are black beyond what could be attributed to alcohol and tobacco use.[19] The reasons for the apparent racial difference in risk from the same level of alcohol and tobacco use could be associated, in part, with increased mutations in the *TP53* gene in esophageal cancers found in patients who are black, as reported by Baron et al.[20]

PREVENTION AND EARLY DETECTION

The use of tobacco is an established risk factor for squamous cell carcinoma of the esophagus and also for adenocarcinoma, but to a lesser extent[21]; smoking cessation reduces the risk of only squamous cell carcinoma, however.[22-24] In addition, patients with both squamous cell and adenocarcinomas of the esophagus are at increased risk of developing second primary cancers, including lung and head and neck malignancies, which are also correlated with tobacco use.[25,26] Alcohol consumption has been shown to be a risk factor for squamous cell carcinoma but not adenocarcinoma.[21,27] Other environmental factors associated with the development of squamous cell cancers include thermal injury and exposure to nitrates and potentially carcinogenic nitrosamines, asbestos fibers, or water contaminated with petroleum products.[28-30] In addition, the presence of human papillomaviruses (HPV-16 and HPV-18) may be risk factors for the development of cancers of the esophagus.[31]

Obesity and high body mass index (BMI) have been established as strong risk factors for development of esophageal adenocarcinoma but not squamous cell carcinomas.[27,32,33] Those individuals who are in the 75% highest BMI range have a 7.6-fold increased risk of developing adenocarcinoma of the esophagus compared to those with lower BMIs.[34,35] Obesity-related comorbid illnesses that contribute to the development of esophageal cancer include gastroesophageal reflux disease (GERD) and type 2 diabetes. One study demonstrated that the presence of type 2 diabetes was associated with an increased risk of developing esophageal, among other cancers, whereas treatment with metformin reduced the risk.[36] Diet affects both types of esophageal carcinomas, with increased intake of fruits and vegetables associated with a reduced incidence of cancer.[37] Lifestyle changes, including weight loss and exercise, postulated to reduce the risk of developing esophageal adenocarcinoma, are currently being investigated.

GERD predisposes to Barrett's esophagus and both are associated with an increased risk of adenocarcinoma of the esophagus, with severe long-standing disease.[22,38-41] The incidence of GERD appears to be increasing in the United States. Barrett's esophagus is known to be associated with GERD and is a precursor lesion for esophageal adenocarcinoma, although most Barrett's lesions do not proceed to carcinoma. The normal squamous mucosa is damaged by chronic GERD and is replaced by columnar metaplasia in Barrett's esophagus that predisposes to malignancy.[42] A 30% to 60% increased risk of development of esophageal adenocarcinoma has been demonstrated in patients with Barrett's esophagus.[40] Long-standing GERD, length of Barrett's esophagus, male gender, age, and hiatal hernia size are strongly associated with high-grade dysplasia[43-45] and are thought to be a predictor for development of adenocarcinoma in patients with Barrett's esophagus. The risk of development of esophageal malignancy increases from 4% in patients with Barrett's esophagus with low-grade dysplasia to 59% in patients with high-grade dysplasia.[46] Biomarkers such as aneuploidy and loss of heterozygosity of p53,[47-49] cyclin D1,[50] and P16[51] have been associated with increased risk of progression from high-grade dysplasia to adenocarcinoma, whereas p53 expression has been correlated with treatment response.[49]

Medical management of Barrett's esophagus is designed to control GERD symptoms using proton pump inhibitors (PPIs) and histamine receptor antagonists. Patients with Barrett's esophagus with high-grade dysplasia should undergo surgical

resection or alternative local strategies, such as endomucosal resection (EMR), cryoablation, radiofrequency ablation (RFA), or photodynamic therapy (PDT).[52] Some have postulated that the use of pharmaceutical agents for the treatment of GERD (i.e., antisecretory agents and therapies to relax the lower esophageal sphincter) have precluded necessary surveillance required for the detection and management of Barrett's esophagus and is therefore related to the recent increase in the incidence of Barrett's esophagus–associated adenocarcinomas.[53] Nonetheless, efforts continue to improve early detection of Barrett's esophagus. Endoscopy is performed on patients with severe symptomatic GERD, especially those with a family history of esophageal cancer or Barrett's esophagus, and can evaluate progression of metaplasia to dysplasia or carcinoma, but the rate of progression is fairly low.[54] Guidelines of the American College of Gastroenterology currently recommend surveillance every 3 years for patients without dysplasia until none is detected on two consecutive endoscopies, as confirmed by biopsy. If high-grade dysplasia is discovered, followup endoscopy should be performed at 3 months to rule out adenocarcinoma and repeated each 3 months thereafter.[55]

The use of chemopreventive agents are under investigation. Nguyen[56] reported the results of a retrospective observational study of 344 patients with Barrett's esophagus demonstrating that prescription use of PPIs is associated with a reduced risk of high-grade dysplasia or cancer with adjustment for gender, age, and the length of duration of Barrett's esophagus and the use of nonsteroidal antiinflammatory drugs (NSAIDs) or aspirin resulted in a nonsignificant trend toward a lower incidence of high-grade dysplasia and cancer.[56] A meta-analysis demonstrated that the use of NSAIDs decreases the risk of both squamous cell carcinoma and adenocarcinoma, with odds ratios of 0.58 and 0.67, respectively.[57] Similar results were reported in a prospective cohort study.[58] Currently, there is a large multicenter, randomized controlled clinical trial (AspECT) evaluating the long-term chemopreventive effect of esomeprazole with or without aspirin.[59]

Dysplastic lesions as well as carcinomas of the esophagus have been shown to overexpress the cyclooxygenase-2 (COX-2) enzyme.[60-62] COX-2 expression is correlated with the proliferative activity in dysplastic lesion and was found to be increased, in a stepwise fashion, with the transition from normal esophageal tissue to low-grade dysplasia to high-grade dysplasia, suggesting that COX-2 is involved in the early stages of carcinogenesis and that interruptions in the dysplasia-carcinoma sequence could be an important part of a chemoprevention strategy.[63] In a recent animal study, celecoxib was shown to significantly decrease the risk of Barrett's esophagus and prevent the development of esophageal adenocarcinoma in a rat surgical model with mixed reflux of acid and duodenal juice.[64] COX-2 may be an effective selective target of chemoprevention for adenocarcinoma of the esophagus in humans but requires further clinical evaluation.

The human epidermal growth factor receptor 2 (*HER-2*) gene or HER-2 protein expression has been associated with the development of esophagogastric and gastric adenocarcinomas.[65] The Her-2/neu oncogene is overexpressed or amplified in preneoplastic lesions and may indicate an increased risk of developing esophageal adenocarcinoma among patients with Barrett's esophagus.[66] Chemoprevention with targeted therapies, such as trastuzumab, are being investigated.[67]

BIOLOGIC CHARACTERISTICS AND MOLECULAR BIOLOGY

The HER2/neu oncogene is overexpressed in esophageal cancers (15% to 30% of adenocarcinomas and 5% to 13% of squamous cell carcinomas)[68-70] and has been associated with tumor invasion, lymph node metastases, and poor prognosis.[66,68,71] Her-2/neu positivity is identified in 21% of gastroesophageal tumors compared to 33% of gastric tumors.[72] Typically both immunohistochemistry and fluorescence in situ hybridization (FISH, which expresses the ratio between the number of copies of the Her-2 gene and the number of chromosome 17 centromeres) are used to test to identify HER-2 overexpression. However gastric cancer cells demonstrate incomplete HER-2 membrane staining in a basolateral pattern and increased tumor heterogeneity compared to breast cancer cells, which may lead to underestimation of HER-2 overexpression using standard techniques.[73,74] Hence, Hoffman et al developed a modified HER-2 scoring system using 10% stained area cut-off for resected specimens, and no cut-off for biopsies to better identify patients with gastroesophageal and gastric cancers that would be candidates for anti-HER-2 therapy.[75] This method was validated and subsequently used in the Trastuzumab for Gastric Cancer Trial (ToGA) trial.[73,76] HER-2 testing with immunohistochemistry using the modified scoring system is currently recommended for all patients with metastatic esophagogastric or gastric adenocarcinomas at the time of diagnosis. FISH is reserved for confirmation of equivocal immunohistochemistry results (2+), although some institutions routinely perform both tests on all patients.

Overexpression of the epidermal growth factor receptor (EGFR) is found in both esophageal squamous cell carcinomas and esophageal adenocarcinomas, as well as their precursor lesions, such as squamous dysplasia and Barrett's esophagus.[77-79] Overexpression of EGFR on immunohistochemical testing occurs in approximately 80% of patients with esophageal adenocarcinoma and squamous cell carcinoma.[80] Additionally, amplification of the *EGFR* gene has been detected by FISH analysis in 8% to 30% of esophageal adenocarcinomas.[81,82] Clinical studies have shown that increased EGFR expression is associated with an overall decrease in survival rates in patients with esophageal cancer.[83] Ongoing trials continue to evaluate the efficacy of EGFR inhibitors, erlotinib[84-86] and cetuximab,[87-91] in addition to chemotherapy in patients with advanced disease.

Vascular endothelial growth factor (VEGF) expression levels and microvessel density are significantly higher in cancerous tissues compared with normal tissues and Barrett's dysplastic tissues.[92,93] VEGF expression has been correlated with tumor differentiation, depth of invasion, and lymph node metastases.[94,95] VEGF is overexpressed in 30% to 60% of esophageal cancers, and studies have demonstrated a correlation between high levels of VEGF expression, advanced stage, and poor overall survival rates.[96-102] A meta-analysis of 1,453 patients from 19 studies has correlated VEGF overexpression in Asian patients with esophageal carcinoma with poor prognosis, especially for those with squamous cell histology; however no correlation was observed for non-Asian patients.[103] Ongoing clinical trials are evaluating the potential benefit of the addition of VEGF inhibitors to chemotherapy for patients with advanced tumors.[104-106]

COX-2 is another molecular target that has significance in cancer development and progression, and inhibition of COX-2 activity results in enhanced radiosensitization of tumor tissue but not normal tissue.[107,108] Selective COX-2 inhibition has been shown to directly inhibit tumor neovascularization.[109] The combination of these effects suggests potential enhancement of selective tumor targeting by COX-2 inhibition.

Mutations in the p*53* gene are present in up to 80% of esophageal cancers. Interestingly, the mutations for squamous tumors, which are in A-T base pairs, are different from the mutations usually seen in adenocarcinomas.[110] Data from Montesano[110] indicate that the mutations common to

squamous tumors are correlated with smoking. Mutations in the *p53* gene are an early event in the carcinogenic process. There is no concordance between *p53* gene mutations and the accumulation of the p53 protein nor are *p53* gene mutations independently predictive of clinical outcome.[111] In vitro data showed that wild-type p53 protein levels increased after chemotherapy.[111,112] Despite this correlation, p53 is not currently used in clinical practice.

Additional molecular abnormalities include cyclin D1, a cell cycle-regulating protein involved in the G_1 phase to S phase transition. Overexpression of cyclin D1 has been observed in approximately 30% to 40% of esophageal adenocarcinomas and squamous cell carcinomas.[113] Inactivation of the *p16* gene, a tumor suppressor gene, occurs in a significant number of esophageal cancers,[51] and restoring p16 expression appears to inhibit the proliferation and tumorgenicity of esophageal cancers.[112] These represent but a few of the potential molecular targets for directing therapies in future clinical studies.

PATHOLOGIC FINDINGS AND PATHWAYS OF SPREAD

The predominant histologic types of esophageal cancer are squamous cell carcinomas and adenocarcinomas and should be established by biopsy for staging and treatment purposes. Approximately 20% of esophageal squamous tumors involve the upper "cervical" esophagus, although the majority is found in the middle esophagus, defined as the segment of esophagus from the aortic arch to the inferior pulmonary vein and usually representing the segment at 25 cm to 32 cm from the incisors. The remaining 30% of squamous tumors are found in the distal esophagus (at 33 cm to 42 cm from the incisors). In contrast, more than 90% of adenocarcinomas are found in the distal esophagus and gastroesophageal junction. Other malignant histologic types are unusual but include adenosquamous, mucoepidermoid, and adenoid cystic tumors and malignant tumors with endocrine differentiation (small cell cancers). Histologic review of esophagectomy specimens with early-stage disease revealed little difference between the rate of submucosal spread and the rate of lymph node metastasis for squamous cell carcinomas and adenocarcinomas.[114]

The esophagus is a hollow tube approximately 25 cm in length that extends from the pharynx to the stomach and consists of three parts: the cervical, thoracic, and distal esophagus. The cervical esophagus lies just left of the midline behind the larynx and trachea. The upper portion of the thoracic esophagus passes behind the tracheal bifurcation and left main stem bronchus, and the lower thoracic esophagus runs behind the left atrium. The distal esophagus is an area approximately 6 to 8 cm in length merging into the gastroesophageal junction. Adenocarcinomas of the esophagogastric junction are classified into three types based anatomic location and the epicenter of the tumor.[115] The current classification system identifies tumors 1 cm to 5 cm above the esophagogastric junction as distal esophageal tumors (Siewert Type 1), those tumors with the epicenter or mass located within 1 cm proximal and 2 cm distal to the esophagogastric junction are classified as true carcinomas of the cardia (Siewert Type 2), and subcardial tumors with epicenter located 2 cm to 5 cm distal to the esophagogastric junction (but may be infiltrating the esophagogastric junction) are classified as Siewert Type 3.[115] In addition to the Siewert classification, the revised American Joint Committee on Cancer (AJCC) staging system specifies that tumors that meet the criteria for Siewert Types 1 and 2 are classified as adenocarcinomas of the esophagus for the purposes of staging.[116] Those meeting criteria for Siewert Type 3 are classified as gastric cancers.[116]

In the esophagus, mucosal lymphatics merge with a submucosal plexus, which then merges with lymphatic channels in the muscularis. These channels communicate with an extensive network of cooperating lymphatics that extend longitudinally throughout the esophagus and eventually drain into nodal groups as cephalad as the internal jugular lymph nodes and as caudal as the celiac lymph nodes. The nodal groups at risk for involvement in cancers of the cervical esophagus include the supraclavicular and upper paratracheal nodes. The nodes at risk for gastroesophageal tumors include the pulmonary ligament, paracardial, left gastric, common hepatic, splenic, and celiac nodes. The esophagus lacks a serosal surface and is only separated from adjacent structures by a loose connective tissue, the adventitia. The adventitia provides little barrier to local spread, and as a consequence, tracheoesophageal and esophagobronchial fistulas develop in 5% to 10% of patients with cancer of the esophagus.

CLINICAL MANIFESTATIONS, PATIENT EVALUATION, AND STAGING

More than 90% of patients present with progressive and worsening dysphagia often resulting in significant weight loss. Other findings include odynophagia, chest pain, cough, and fever associated with possible respiratory fistulas, hoarseness associated with tumor involvement of the recurrent laryngeal nerve, and melena resulting from intraluminal bleeding.

Patients with newly diagnosed esophageal cancer should undergo a complete history and physical, physical examination, upper endoscopy with biopsy, complete blood count, serum chemistries, coagulation studies, and a contrasted CT scan of the chest and abdomen. An endoscopic ultrasound (EUS) with or without fine-needle aspiration (FNA) and 18-FDG–positron emission tomography (PET; FDG–PET) or PET/CT are also recommended. Her-2/neu testing is also recommended. The initial workup identifies patients with locoregional cancer and those with metastatic (M1) disease. In patients with locoregional disease who are deemed fit for surgery, cardiac and pulmonary function as well as nutritional status should be evaluated. Jejunostomy or nasogastric feeding tubes may be considered for those patients in need of nutritional support. A gastric feeding tube is not recommended. Laparoscopic staging of the peritoneum with washing can be considered for adenocarcinomas, if there is no other evidence of distant metastases.

The TNM staging system for esophageal cancer according to the AJCC is based on the pathologic review of pathologic specimens of patient undergoing primary surgical treatment for esophageal cancer without adjuvant therapy.[116] The AJCC staging manual, seventh edition, is shown in Box 45-1. This staging system incorporates a risk-adjusted analysis of the data generated by the Worldwide Esophageal Cancer Collaboration (WECC) for more than 4,500 patients, which correlates decreased survival with squamous histology, increasing depth of invasion, involvement of regional nodes, and presence of distant metastases.[117] Esophageal cancers are staged according to the histologic subtype, depth of invasion, presence of regional lymph nodes or distant metastatic disease, and grade and location of tumor. Some difficulties have arisen because this is a surgical staging system and many patients are now treated initially without resection, making accurate pathologic staging impossible. Patient outcomes are correlated with surgical pathologic stage and do not take into account the impact of adjuvant therapy. Other limitations of this staging system include inclusion of the proximal 5 cm of the stomach,

BOX 45-1 TNM Staging of Esophageal Cancer[15]

Histologic Grade

G1	Well differentiated
G2	Moderately differentiated
G3	Poorly differentiated
G4	Undifferentiated

Cancer Location

Upper thoracic	20 cm-25 cm from incisors
Middle thoracic	>25 cm to 30 cm from incisors
Lower thoracic	>30 cm to 40 cm from incisors
Esophagogastric junction	Includes cancers whose epicenter is in the distal thoracic esophagus, esophagogastric junction, or within the proximal 5 cm of the stomach (cardia) that extends into the esophagogastric junction or distal thoracic esophagus (Siewert III). These stomach cancers are stage grouped similarly to adenocarcinoma of the esophagus

Primary Tumor

TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	High-grade dysplasia
T1	Tumor invades lamina propria, muscularis mucosae, or submucosa
T1a	Tumor invades lamina propria or muscularis mucosae
T1b	Tumor invades submucosa
T2	Tumor invades muscularis propria
T3	Tumor invades adventitia
T4	Tumor invades adjacent structures
T4a	Resectable tumor invading pleura, pericardium, or diaphragm
T4b	Unresectable tumor invading other adjacent structures, such as aorta, vertebral body, trachea

Regional Lymph Nodes

Nx	Regional nodes not assessed
N0	No regional lymph node metastasis
N1	Metastasis in one to two regional lymphnodes*
N2	Metastasis in three to six regional lymphnodes*
N3	Metastasis in seven or more regional lymph nodes*

Distant Metastasis

MX	Distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis

STAGE AND PROGNOSTIC GROUPINGS FOR ESOPHAGEAL CANCER

Adenocarcinoma

Stage 0	Tis, N0, M0, grade 1 or X
Stage I A	T1, N0, M0, grades 1-2 or X
Stage I B	T1, N0, M0, grade 3
	T2, N0, M0, grades 1-2 or X
Stage IIA	T2, N0, M0, grade 3
Stage IIB	T3, N0, M0, any grade
	T1-2, N1, M0, any grade
Stage IIIA	T1-2, N2, M0, any grade
	T3, N1, M0, any grade
	T4a, N0, M0, any grade
Stage IIIB	T3, N2, M0, any grade
Stage IIIC	T4a, N1-2, M0, any grade
	T4b, any N, M0, any grade
	Any T, N3, M0, any grade
Stage IV	Any T, any N, M1, any grade

Squamous Cell Carcinoma

Stage 0	Tis, N0, M0, grade 1 or X, any location
Stage I A	T1, N0, M0, grade 1 or X, any location
Stage I B	T1, N0, M0, grades 2 or 3, any location
	T2-3, N0, M0, grade 1 or X, lower esophagus or X
Stage IIA	T2-3, N0, M0, grade 1 or X, upper and middle esophagus
	T2-3, N0, M0, grade 2 or 3, lower esophagus or X
Stage IIB	T2-3, N0, M0, grade 2 or 3, upper and middle esophagus
	T1-2, N1, M0, any grade, any location
Stage IIIA	T1-2, N2, M0, any grade, any location
	T3, N1, M0, any grade, any location
	T4a, N0, M0, any grade, any location
Stage IIIB	T3, N2, M0, any grade, any location
Stage IIIC	T4a, N1-2, M0, any grade, any location
	T4b, any N, M0, any grade, any location
	Any T, N3, M0, any grade, any location
Stage IV	Any T, any N, M1, any grade, any location

**Regional lymph nodes include any paraesophageal node extending from cervical nodes to celiac nodes.*

emphasis on number of involved nodes, rather than size or location relative to the primary tumor, and failure to discern between resectable and unresectable disease.[116] Diagnostic tools are used to evaluate local extent of primary tumor (EUS, endoscopy), identify and quantify lymph node involvement (EUS), and identify metastatic disease (FDG-PET).

EUS performed before therapy evaluates the depth of tumor invasion (T) and presence of enlarged or abnormal regional (mediastinal and perigastric) lymph nodes (N).[118,119] Preoperative EUS results in accurate T stage in 59% of patients and 82% accuracy in patients with transmural tumor extension.[120] EUS has been reported to be 87% accurate for detecting mediastinal nodal disease,[121] which is improved when confirmed by EUS-guided FNA[122-125]; however EUS is inadequate for objective pathologic response evaluation after neoadjuvant chemoradiation.[126,127] Combining diagnostic studies improves staging accuracy. One study compared CT, EUS, and EUS-FNA for preoperative lymph node staging and found EUS-FNA to be more sensitive than CT (83% versus 29%) and more accurate than both CT and EUS (87% versus 51% and 74%, respectively).[125] Review of CT or PET-CT imaging before EUS staging is recommended to identify obstructing tumors that may increase the risk of perforation and identify areas concerning for nodal involvement before the procedure. In addition thoracoscopic staging can be used to further increase the accuracy of tumor penetration and lymph node staging to 88%, as demonstrated in a cooperative group trial of patients undergoing subsequent surgery.[128]

The importance of staging for the selection of surgical candidates cannot be overstated. Cancers confined to the epithelium and muscularis mucosa and without nodal involvement are defined as stages I and II. In a clinicopathologic review of

165 patients with esophageal cancer treated with resection only, Holscher et al[129] observed 0% lymph node metastases in patients with disease confined to the mucosa compared with 18% for tumors with submucosal spread. The 5-year overall survival rate reported for patients with node-negative disease was 63%. Lymph node involvement was shown to be a strong independent predictor of poor survival following surgery alone. Tumors invading the adventitia or surrounding structures have a worse outcome, and there is almost always associated nodal involvement.

The addition of FDG-PET to standard staging techniques has improved the detection of occult metastatic disease[130-134] and can result in up to 15% upstaging from M0 to M1 compared with CT and EUS.[131] In a meta-analysis reported by van Westreenen, FDG-PET showed limited sensitivity (0.51) and reasonable specificity (0.81) for the detection of locoregional metastases.[135] This study also demonstrated detection of distant lymphatic and hematogenous metastasis with a sensitivity and specificity of 0.67 and 0.97, respectively.[135] Taken in total, these data are compelling and have resulted in an increasing use of FDG-PET for the routine staging of patients with esophageal cancer.

Investigation of gene profiling[136] and biomarkers[137] to improve patient selection for surgical therapy is currently being investigated and may improve prognostic stratification in the future.

PRIMARY THERAPY

The management of patients with esophageal and esophagogastric junction cancers requires the expertise of several disciplines and support infrastructure. Treatment decisions should be made in an environment that fosters a multidisciplinary collaboration.

Single-Modality Therapy

Surgery

In 1913, Dr. Franz Torek[138] used a transpleural approach to perform the first successful resection of an esophageal carcinoma reconstructed with an external rubber esophagus. With improvements in anesthesia, subsequent surgeons used mainly a transthoracic approach with primary esophagogastric anastomosis, and in 1933, Ohsawa[139] reported extended survival rates in 8 of 20 patients who had a resection. In 1938, Adams and Phernister[140] were the first Western surgeons to successfully adopt the Japanese transthoracic technique. The results of these studies, however, revealed a discouraging 5-year survival rate of 5% to 10%.

Esophagectomy should be performed in high-volume centers by experienced surgeons for best results.[141] One standard option includes a transthoracic resection, or Ivor-Lewis procedure,[142] which allows better access to lesions in the upper two thirds of the esophagus and complete visualization of the esophagus. For distal tumors, this approach allows for resecting a substantial proximal margin and placing the anastomosis high in the chest (above the azygos vein), a technique that is thought to result in fewer anastomotic leaks and less postoperative reflux. The initial laparotomy is for exploring the abdomen for distant disease and mobilization of the stomach. The second incision is a thoracotomy incision for exposure and dissection of the esophagus. After tumor resection, the stomach is pulled through the hiatus for an intrathoracic anastomosis. An alternative transthoracic approach is the McKeown esophagogastrectomy (right thoracotomy followed by laparotomy and cervical anastomosis).[143]

The transhiatal procedure is an alternative to the transthoracic approach that uses abdominal and left cervical incisions, where the procedure is performed through the abdominal incision and the gastric conduit is drawn through the posterior mediastinum and the esophagogastric anastomosis is exteriorized in the cervical incision.[144] The esophagus is removed via blunt dissection and continuity is reestablished with a cervical esophagogastric anastomosis, which eliminates an anastomosis in the chest and the risk of a leak producing mediastinitis. The advantages for this technique include eliminating the morbidity associated with a thoracotomy.

Another acceptable approach is the left transthoracic or thoracoabdominal esophagastrectomy, which is a technique sometimes used for distal esophageal cancers that uses a contiguous left thoracic and abdominal incision through the eighth intercostal space.[145] The esophagogastric anastomosis is performed in the left chest superior to the pulmonary vein.

At present, there are no definitive data to suggest that one technique is superior to the others and long-term survival is not different between the two approaches.[146] In one review of 210 patients treated with either a transthoracic resection (n = 172) versus a transhiatal resection (n = 38), an increased incidence of tumor perforation (18%) and injuries to the recurrent laryngeal nerve (13%) following the transhiatal approach was observed.[147] Another retrospective study of 238 patients observed increased rates of wound infections, pneumothorax, and hospital mortality for patients treated with transthoracic resection.[148] In contrast, Stark et al[149] observed increased rates of respiratory complications and hospital mortality following transhiatal resection. Others have identified little or no difference in overall complication rates or operative mortality rates between the two surgical approaches.[150,151] These findings are consistent with a meta-analysis reported by Hulscher et al[152] who observed that the 5-year survival rate with surgery alone was approximately 20% after both transthoracic and transhiatal resections.

Surgery remains a major component of treatment for resectable disease and is usually performed with curative intent following adequate staging and pretreatment nutritional support. There has been a marked reduction in surgical morbidity and mortality with improvements in staging techniques, patient selection,[153] perioperative care and surgical experience, but improvements in cancer control have been modest. Moertel[154] reviewed 18 older surgical series involving 4109 patients treated with resection and found a 5-year overall survival rate of 9.6% (range, 3% to 20%).

Regional lymph node involvement results in a worse outcome following esophagectomy.[155,156] One study demonstrated a 31% overall survival rate for all patients undergoing resection; only 13% of patients with nodal disease were alive at 5 years versus 44% for patients who were node-negative.[157] Another study demonstrated similar results with 5-year survival rates after surgery alone at 57% for patients who were node negative and 15% for node-positive disease.[158] Other investigators found that no patient with more than 30% regional nodal tumor involvement was alive at 5 years, whereas 45% of patients with less than 30% nodal disease were alive at 5 years.[129] These data indicate that in the limited cohort of patients who present without regional nodal involvement, many will do well with surgery alone, but patients found to have nodal disease are rarely treated successfully with surgery alone.

The optimum number of lymph nodes to be removed and examined at the time of resection is unclear. One retrospective analysis demonstrated that the number of lymph nodes removed at the time of surgery was an independent predictor of survival time and that the optimal threshold for this survival benefit was removal of 23 nodes.[159] Another study suggested at least 18 lymph nodes should be removed.[160] The largest retrospective analysis analyzed the SEER database for

29,656 patients with esophageal cancer and found that patients with more than 12 lymph nodes examined had a significant reduction in mortality compared to those without examination of lymph nodes. Those with 30 or more lymph nodes examined demonstrated the lowest mortality.[161] A report from the WECC database evaluating 4627 patients undergoing esophagectomy alone demonstrated increased survival with greater extent of lymphadenectomy in patients with pathologic pN0M0 staging.[156] However, extent of lymphadenectomy may only be prognostic because one study demonstrated that extent of lymphadenectomy did not predict survival in patients undergoing surgery alone for esophageal cancer.[162]

Esophagectomy remains the standard of care for high-grade dysplasia and superficial cancers; however, surgical morbidity and mortality may be substantial for patients who are medically unfit. More recently, minimally invasive esophagectomy (MIE) and endoscopic treatments have become treatment options for selected patients with early-stage localized esophageal cancer. MIE strategies include laparoscopic-assisted, thoracoscopic, or limited thoracotomy Ivor-Lewis or McKeown esophagectomies. A recent meta-analysis using data from 10 studies to evaluate the effects of MIE versus open esophagectomy on outcome demonstrated trends in favor of MIE, with reductions in morbidity, pulmonary complications, anastomotic leakage, mortality, length of hospital stay, operating time, and blood loss compared to open esophagectomies.[78,163-166] MIE is useful in older patients who are at increased risk for operative morbidity.[167] However, not all patients are candidates for minimally invasive procedures, especially those who have undergone prior abdominal surgery or who have bulky tumors or lymph nodes difficult to resect. No randomized trials have assessed whether MIE improves outcome compared with open esophagectomy. However, in the absence of prospective trials with adequate followup MIE remains investigational.[168,169]

The goal of EMR and ablative therapies is eradication of Barrett's esophagus and removal of the associated dysplasia (Tis) or early malignancy (well to moderately differentiated T1a tumors without evidence of lymphovascular invasion). EMR of Barrett's esophagus and high-grade dysplasia occasionally results in a diagnosis of esophageal cancer. Although EMR of visible lesions can be effective, there is a high rate of recurrence. EUS staging before EMR is recommended in the setting of high-grade dysplasia or early carcinoma.[170] All focal nodules should be resected rather than ablated and Tis and high grade dysplasia should be fully characterized for presence of nodularity, lateral spread, and multifocal disease. Patients with Tis or selected T1a tumors are candidates for curative therapy with EMR. EMR is considered therapeutic for completely excised moderately differentiated tumors <2 cm in diameter without evidence of invasion beyond the muscularis mucosa or lymphovascular spread. For patients with tumors in the submucosa or deeper, or evidence of lymph node involvement, esophagectomy remains the standard surgical treatment.

Data regarding the role of surgery in patients treated with definitive concurrent radiation and chemotherapy is presented in the section regarding combined modality therapy.

Ablative Therapies

Endoscopic ablative procedures (cryoablation, RFA, and PDT) are mainly used for Barrett's esophagus or dysplasia. Balloon-based RFA results in complete remissions in the majority of patients with Barrett's esophagus or high-grade dysplasia.[171] Endoscopic cryoablation is also an effective therapy in this setting.[172] PDT has been reported to provide local control in early esophageal cancers arising from Barrett's esophagus, ranging from 17% to 100%, and high-grade dysplasia, ranging from 75% to 100%.[173-175] There are no randomized studies that compare ablative therapies to EMR. Recurrence rates using ablative treatments are higher than with esophagectomy and require close endoscopic surveillance and retreatment in some patients. Ablative therapies may also be useful in achieving long-tem palliation of dysphagia, anorexia, or malnutrition.[176,177]

Chemotherapy

Esophageal cancer has a distant failure rate of more than 70%. A large number of chemotherapy agents have been evaluated for response (Table 45-2), but the response rates remain low, with only about 20% of patients having an objective response to a variety of single agents. Combination chemotherapeutic regimens have shown a higher response rate, the best responses being seen in patients receiving multiagent chemotherapy regimens (Table 45-3). Despite increased response rates, the duration of response is typically short and comparable to that seen with single-agent chemotherapy. New agents including targeted therapies remain under investigation.

Targeted Biologic Therapies

HER-2/NEU

Overexpression of HER-2/neu has been reported to range from 0% to 52% in squamous cell carcinomas of the esophagus

TABLE 45-2 Single-Agent Activity in Chemotherapy of Esophageal Cancer*

Drug	No. Patients	Complete Response Rate or Partial Response Rate (%)	Median Duration of Response (mo)
Cisplatin[178]	47	38	2-3
5-Fluorouracil[179]	26	15	1-5
Vindesine[180]	71	36	4
Vinorelbine[181]	29	7	2
Mitomycin C[178]	51	27	3-4
Paclitaxel[182]	52	32	4
Etoposide[183]	26	19	4
Irinotecan[184]	43	14	6
Tarceva[185]	20	15	NR
Gefitinib[186]	34	9	NR
Cetuximab[87]	35	3	NR

NR, *Not reported.*
**Response as determined by radiographic or endoscopic methods.*

TABLE 45-3 Combination-Agent Activity in Chemotherapy of Esophageal Cancer*

Combination	No. Patients	Overall Response Rate (%)
Cisplatin + bleomycin[187]	61	15
Cisplatin + vindesine + bleomycin[188]	68	53
Paclitaxel + cisplatin[189]	20	40
5-Fluorouracil + cisplatin + doxorubicin[190]	21	33
Cisplatin + etoposide[191]	73	48
5-Fluorouracil + cisplatin[192]	88	35
Bleomycin + doxorubicin[193]	16	19
Irinotecan + cisplatin[194]	35	57
Gemcitabine + cisplatin[195]	36	41
Gemcitabine + irinotecan[196]	61	NR
Bevacizumab + irinotecan + cisplatin[105]	47	65
Bevacizumab + docetaxel + cisplatin + 5-fluorouracil[105]	44	67
Bevacizumab + capecitabine/5-fluorouracil + cisplatin[197]	372	38
Sorafenib + docetaxel + cisplatin[198]	44	41
Cetuximab + epirubicin + cisplatin + 5-fluorouracil	90	58
Cetuximab + cisplatin + irinotecan	90	38
Cetuximab + leucovorin + 5-fluorouracil + oxaliplatin[199]	90	51
Cetuximab + leucovorin + 5-fluorouracil + irinotecan[91]	38	44
Panitumumab + epirubicin + oxaliplatin + capecitabine[200]	278	46
Trastuzumab + 5-fluorouracil + cisplatin[73]	594	47.3

NR, *Not reported.*
**Response as determined by radiographic or endoscopic methods.*

and 0% to 73% in adenocarcinomas.[201] The ToGa trial screened tumors from 3807 patients with advanced gastric (80%) or esophagogastric (20%) cancer, and 22.1% were found to be Her-2/neu-positive. In this trial 594 patients with Her2/neu positive cancers were randomized to receive either chemotherapy (5-fluorouracil or capecitabine and cisplatin) alone or the same chemotherapy with trastuzumab resulting in improved survival for those patients with Her-2/neu positive (IHC 2-3+ or FISH+) tumors treated with trastuzumab. Median overall survival was 16 months for those patients receiving trastuzumab with IHC 2-positive and FISH-positive or IHC 3-positive tumors compared to 11.8 months for those who did not.[73] Trastuzumab emtansine (T-DM1) is a conjugated antibody to a potent microtubule inhibitor. T-DM1 has demonstrated efficacy in esophagogastric cancer cells and xenograft models.[202] A Phase II/III trial is planned using a taxane with or without T-DM1 in patients with refractory esophagogastric cancer.

EGFR

Up to 80% of esophageal adenocarcinomas and squamous cell carcinomas demonstrate increased EGFR expression, which is associated with decreased overall survival.[82] Multiple trials with tyrosine kinase inhibitors of anti-EGFR antibodies have failed to suggest utility for these agents in advanced disease for either adenocarcinoma or squamous cell carcinoma. The potential application of these agents combined with radiotherapy is discussed in the section on combined modality therapy.

VEGF

High levels of VEGF expression have been correlated with poor overall survival rates in patients with esophageal cancer.[94,96-100] The impact of VEGF inhibition in combination with chemotherapy in patients with esophageal cancer is under evaluation, but impact on survival remains unclear. Recently reported results from Phase III studies in advanced gastric (including gastroesophageal junction) cancers have not demonstrated a survival benefit for the addition of bevacizumab to systemic chemotherapy, although improved progression-free survival was observed.[203,204]

Sorafenib is a tyrosine kinase inhibitor of VEGFR1-3, Raf-1, Braf, and PDGFR1. It has been studied in combination with docetaxel and cisplatin in advanced gastric and esophagogastric junction cancer demonstrating a 41% response rate and 13.6 month median survival.[198]

COX-2

COX-2 is another molecular target that has been shown to have significance in cancer development and progression in dysplastic lesions of the esophagus, with COX-2 level increasing in the early stages of carcinogenesis of esophageal adenocarcinoma.[63] Selective inhibition of COX-2 has been shown to alter the development and progression of cancer in clinical trials.[205] In addition, inhibition of COX-2 activity results in enhanced radiosensitization of tumor tissue but not normal tissue.[107,206] Selective COX-2 inhibition has also been shown to directly inhibit tumor neovascularization.[107,108,206,207] The combination of these effects suggests potential enhancement of selective tumor targeting by COX-2 inhibition. Studies combining COX-2 inhibition with neoadjuvant chemotherapy and radiation have demonstrated tolerability but failed to demonstrate an improvement in the pathologic response over standard neoadjuvant combined-modality treatment.[208-210]

New Targets

Hepatocyte Growth Factor/Mesenchymal Epithelial Transition Factor (Hgf/Met). cMET (mesenchymal–epithelial transition factor) and its ligand, HGF are potential therapeutic targets in esophagogastric cancer. MET tyrosine kinase activation is mediated by HGF binding and multiple downstream signal transduction pathways (Ras, mTOR, STAT3, PI3K and

NF-κB)[211,212] and can promote angiogenesis.[213,214] MET signaling is altered by receptor or ligand overexpression as well as gene amplification in some gastric and esophagogastric tumors.[213-217] MET gene mutations may be sporadic or hereditary.[213,218,219] Only 2% of esophagogastric adenocarcinomas contain the MET amplification, which is associated with advanced stage disease.[220] Crizotinib is an orally available small molecule inhibitor of MET and ALK. In a small study of patients with esophagogastric with MET amplification treated with crizotinib, a 30% response rate was observed.[220] Another strategy to target the MET pathway is Rilotumumab, a human monoclonal antibody to HGF. A randomized Phase II study has demonstrated an improved median survival with the addition of rilotumumab to epirubicin, cisplatin and capecitabine (ECX) in patients with gastric/esophagogastric disease with greater than 50% of cells staining positive for MET by immunohistochemistry.[221] MET expression is predictive of both poor overall prognosis and response to anti-HGF antibody therapy.[221] A Phase III study is planned for first-line therapy in patients with esophagogastric adenocarcinoma with high MET expressing tumors using rilotumumab.

Heat Shock Protein 90 (Hsp90). HSP90 binds to nucleotide binding sites as a chaperone protein resulting in the release of important client proteins, which include wild-type and activated signaling proteins of B-RAF, KIT, EGFR, HER-2, PDGFR, and KIT. Hsp90 inhibition results in alterations in the structure of these proteins and subsequent ubiquitination and degradation.[222] In a study of human esophageal cell lines, inhibition of Hsp90 with 17-allylamino-17-demethozygeldanamycin (17-AAG) resulted in decreased proliferation and survival, and synergistic effect with radiation.[223] A Phase II study of a small molecule inhibitor of Hsp90, STA9090, in patients with metastatic esophagogastric cancer is completed and results are pending (NCT01167114).

Radiation Therapy

Historical series reported results using external beam radiation alone for the treatment of patients with esophageal cancer, mostly those who refuse surgery or those with unresectable tumors (T4). The outcome following primary radiation therapy alone in the treatment of clinically localized esophageal cancer remains poor, with a 2-year survival rate of approximately 10% to 20% and a 5-year survival rate of approximately 5%[224-226] (Table 45-4). Several autopsy studies demonstrate that 50% to 89% of patients harbor both local and undetected distant disease.[227] Review of the literature examining patterns of failure following irradiation alone demonstrate local failure rates of 50% to 91% following doses greater than 50 Gy.[228,229] Attempts to increase total radiation dose have failed to improve outcome for these patients. In the Radiation Therapy Oncology Group (RTOG) 85-01 trial, all patients in the radiation alone arm who received 64 Gy at 2 Gy per fraction delivered with conventional techniques died of cancer within 3 years following treatment.[230,231]

Twice-a-Day Radiation

Building on the encouraging data of twice-daily radiotherapy in other tumor sites, a number of researchers have investigated its usefulness in esophageal cancer. Kikuchi et al observed an encouraging 5-year cause-specific survival rate of 31.5% for 60 patients receiving twice-a-day concomitant boost radiation therapy alone,[239] while Zhao et al reported on the feasibility of late-course accelerated hyperfractionated radiotherapy for early-stage esophageal carcinoma (41.4 Gy in 5 weeks, followed by a 2-week course of twice-daily irradiation at 1.5 Gy per fraction; cumulative dose of 67 Gy to 70 Gy). The investigators observed an encouraging 5-year local control rate of 85%.[240] Another study reported a 5-year survival rate of 33% for patients treated with definitive late-course accelerated radiotherapy alone to 68.4 Gy.[237] The addition of chemotherapy appears to improve outcome for patients treated with hyperfractionated radiation as demonstrated by Girvin et al who treated patients with twice-a-day preoperative irradiation plus concurrent 5-fluorouracil, cisplatin, and vinblastine and observed a remarkable complete response rate of 79%.[241] Data from a larger series using a similar concurrent regimen of 5-fluorouracil plus cisplatin and twice-daily irradiation did not confirm the findings of Girvin, however. In the series reported by Yu et al, a local tumor control rate of 94% was reported with an alternating schedule of cisplatin and 5-fluorouracil with twice-daily irradiation on alternating weeks (1.8 Gy to 2 Gy to 60 Gy), but the regimen was associated with significant grade-5 acute toxicity.[242] The use of twice-daily irradiation is currently restricted to clinical trials.

TABLE 45-4 Results with Irradiation Alone for Definitive Treatment of Esophageal Cancer

Investigator	Years	No. Patients	5-year Survival (%)
Hussey[232]	1945-1975	69	10
Newaishy[224]	1956-1974	444	9
Van Houtte[233]	1962-1972	81	3
Appelqvist[234]	1965-1974	50	4
Lewinsky[235]	1966-1971	85	4
Petrovich[236]	1963-1986	137	2
Herskovic[230]	1986-1990	53 evaluable†	10 at 2 years
Shi[237]	1988-1990	42‡	33
Girinsky[238]	1986-1993	88*	6 at 3 years

**Some patients received chemotherapy.*
†Escalated total dose: 64 Gy in 32 fractions per fraction
‡Late course accelerated fractionation: 41.4 Gy in 23 fractions over 4 to 5 weeks then 1.8 Gy/day to 64.8 Gy total.

Combined-Modality Therapies

Combined-modality therapy has been adopted for the treatment of esophageal cancer because of the poor survival rates associated with patients treated with surgery or radiation alone and has now become standard for the treatment of non-metastatic disease, except for the earliest lesions.[243]

Surgery with Neoadjuvant or Adjuvant Chemotherapy (without Radiation)

The rationale for the use of chemotherapy before either surgery or chemoradiation includes the early treatment of subclinical distant disease while the primary tumor is also being treated, administering the drug when the patient can best tolerate the toxicities. In addition to the hope that both local and distant control rates might improve, there is also hope that this approach might identify patients who would respond to additional chemotherapy for control of minimal residual disease.

Although a number of studies evaluating preoperative chemotherapy have demonstrated good response rates, only a few randomized studies have been reported. The most robust experience comes from the Medical Research Council Oesophageal Cancer Working Group.[244] In this study, 802 previously untreated patients with resectable esophageal cancer were randomized to receive either two cycles of cisplatin plus 5-fluorouracil followed by surgery or surgery alone. The

median survival time was 16.8 months for patients randomized to chemotherapy compared with 13.3 months for patients who underwent surgery alone. The 2-year survival rate was also improved for patients randomized to chemotherapy (43%) versus surgery alone (34%) and at a median followup of 6 years, survival remained higher for those patients treated with preoperative chemotherapy (23% versus 17%).[245] Lesser improvements in median survival times have been demonstrated in other randomized studies.[191,246-248]

In striking contrast are the data from Kelsen et al from the Intergroup trial (INT 0113).[249,250] Four hundred sixty-seven patients were randomized to surgery alone versus induction chemotherapy (three cycles of cisplatin/5-fluorouracil chemotherapy) followed by surgery. With a median follow-up time of 55.4 months preoperative chemotherapy decreased the incidence of R1 resections, but produced no significant differences in survival.[250] An individual patient databased meta-analysis has demonstrated a small but significant difference (4%) in overall and disease-free survival favoring preoperative chemotherapy over surgery alone.[251] A larger meta-analysis of 1981 patients from nine randomized trial also showed a survival benefit for patients treated with preoperative chemotherapy.[252]

The utility of postoperative chemotherapy alone has also been studied in a limited fashion. A multicenter Phase II trial evaluated four cycles of adjuvant paclitaxel and cisplatin chemotherapy; the 3-year survival rate was encouraging at 42%, but most patients (76%) had failure at distant sites.[253] The Japan Clinical Oncology Group reported the results from 242 patients with squamous cell carcinoma of the esophagus who underwent transthoracic esophagectomy with lymphadenectomy and were then randomized to either observation or two courses of cisplatin plus 5-fluorouracil chemotherapy. Although an improvement in the 5-year disease-free survival rate was seen for patients receiving the adjuvant chemotherapy (55% versus 45%), a slight improvement in overall survival rate was observed (61% versus 52%).[254] These results were not different from those observed in a 205-patient Phase III trial showing no benefit with the addition of adjuvant cisplatin and vindesine chemotherapy to surgery.[255] We currently recommend that patients receive adjuvant chemotherapy only as part of a clinical trial.

There is a growing interest in perioperative chemotherapy for the treatment of resectable esophagogastric cancer. The MAGIC trial randomized 503 patients with esophageal (25%; 14% lower esophagus, and 11% esophagogastric junction) or gastric (75%) adenocarcinomas to receive pre- and postoperative chemotherapy (epirubicin, cisplatin, and 5-fluorouracil). The perioperative chemotherapy group was found to have less advanced nodal involvement (84% versus 70.5%) and a greater proportion of early stage (T1-T2) tumors (51.7% versus 36.8%) than the surgery alone group, and chemotherapy improved 5-year survival rates (36% versus 23%, respectively).[256] A similar approach was taken by the FNCLCC/FCCD trial in which patients with adenocarcinoma of the lower esophagus or esophagogastric junction (75%) or proximal stomach (25%) were treated with perioperative 5-fluorouracill and cisplatin. The 5-year disease-free (34% versus 19%) and overall survival (38% versus 24%) rates were improved for patient receiving perioperative chemotherapy.[257] These studies have established perioperative chemotherapy as a viable option for patients with resectable adenocarcinoma of the distal esophagus or esophagogastric junction.

Neoadjuvant Radiation Followed by Surgery (without Chemotherapy)

Early attempts to improve local control and survival rates combined radiation and surgery. At the Memorial Sloan Kettering Cancer Center from 1956 to 1966, 85 patients were treated with preoperative radiation and surgery, with 47 patients ultimately going on to resection. The overall crude 5-year survival rate was 6% and the median survival rate was 14 months. No tumor was seen in the surgical specimen in 7 (14%) of the tumors resected.[228] One study compared the outcomes for patients who underwent staging laparotomy, gastrostomy, and nutritional supplementation before preoperative radiation (20 Gy to 25 Gy in four to five fractions) followed by a total esophagectomy with the outcomes for patients who underwent either irradiation or surgery alone. The 3-year survival rate was 27% for patients treated with combined therapy versus 22% for those treated with surgery alone and 6% with irradiation alone,[258] but updated data showed a 5-year survival rate of 13% for the combined-modality cohort.[259] Others report a 5-year survival rate of 25% for patients receiving 50 Gy preoperatively versus 14% for patients treated with surgery alone.[260]

These studies, however, were all retrospective reviews that did not allow direct comparisons of treatments. Prospective randomized trials evaluating outcomes for patients treated with either surgery alone or preoperative irradiation demonstrated no benefit to the addition of preoperative radiotherapy; reported 5-year survival rates ranged from 9.5% to 45% for the preoperative radiation and surgery group and from 11.5% to 25% for patients treated with surgery alone.[261-264] To date, randomized trials have not demonstrated a survival advantage for either preoperative or postoperative radiation alone.[264-266] Table 45-5 summarizes the results of randomized trials comparing radiation alone followed by surgical resection to surgery alone.

Primary radiotherapy or preoperative radiation therapy should be restricted to palliation for patients who are medically unable to receive chemotherapy as part of their treatment course.

Chemoradiotherapy

Numerous single institutions and cooperative groups have investigated the use of concurrent chemotherapy and radiotherapy in the management of patients with localized esophageal cancer, either as definitive treatment or as preoperative therapy. A significant body of information suggests that chemotherapeutic agents such as 5-fluorouracil, cisplatin, mitomycin C, gemcitabine, irinotecan, oxaliplatin, and paclitaxel

TABLE 45-5 Results of Randomized Trials of Surgery Alone ± Preoperative Irradiation (No Chemotherapy)

Investigator	Year	No. Patients	Radiation Dose	5-year Survival (%)
Launois[263]	1981	67	40 Gy	9.5
		57	Control	11.5
Huang[262]	1986	83	40 Gy	45.5
		77	Control	25
Gignoux[261]	1987	102	33 Gy	16
		106	Control	10
Wang[264]	1989	104	40 Gy	35
		102	Control	30
Nygaard[267*]	1992	108	35 Gy	21
			Control	9
Arnott[268]	1992	176	20 Gy	9
			Control	17

Gy, *Gray.*
**3-year survival data.*

have a greater than additive effect when used in combination with radiation therapy. In addition, there is a growing body of evidence that incorporation of targeted therapies in to treatment regimens may enhance radiosensitization. Therefore, most studies testing multimodality therapy have used these agents in a concurrent schedule. The mechanism of the interaction between irradiation and chemotherapeutic agents is complex and not entirely understood.

Definitive Concurrent Chemotherapy and Irradiation

Table 45-6 reports the results of several nonrandomized trials employing concomitant chemotherapy and radiation therapy for the definitive treatment of esophageal cancer. Generally, the most successful treatment regimens have combined infusional 5-fluorouracil with either mitomycin C or cisplatin.

Randomized data have shown benefit in patients treated with definitive concurrent chemoradiation (Table 45-7), resulting in local control rates ranging from 24% to 67% (Tables 45-8 and 45-9).

The most important contemporary trial is that of Herskovic et al (RTOG 85-01).[230] One hundred and twenty-one patients were randomized to either 50 Gy with concurrent chemotherapy with 5-fluorouracil (1000 mg/m^2 for 4 days) and cisplatin (75 mg/m^2) versus 64 Gy alone. At 5 years, 27% of the combined-modality patients were alive versus none of the patients in the irradiation-only group.[280] The median survival time for the combined-modality arm was 14.1 months versus 9.3 months for the irradiation-alone arm.[280] These results are important because they not only demonstrate a survival advantage with combined-modality therapy but also show that the survival advantage cannot be obtained by simply substituting a higher radiation dose in place of chemotherapy.

There was a suggestion of a radiotherapy dose-response relationship from early (nonrandomized) studies at Wayne State University, as patients treated to 5000 cGy (concurrent with a 5-fluorouracil plus cisplatin regimen) appeared to have longer median survival than patients treated to 3000 cGy with the same chemotherapy (see Table 45-6).[274] INT 0123,

TABLE 45-6 Results from Definitive Chemoradiotherapy for Esophageal Cancer

Investigator	No. Patients	Irradiation Dose	Chemotherapy Agents	Median Survival Time (mo)	2-year Survival (%)
Kavanagh[269]	45	60 Gy-64 Gy	5-FU or etoposide, cisplatin or carboplatin	18	27
Seitz[270]	35	40 Gy	5-FU, cisplatin	17	45
Keane[271]	35	45 Gy-50 Gy	5-FU, mitomycin C	NR	28
Hukku[272]	34	30 Gy	5-FU, cisplatin	NR	38
John[229]	30	41 Gy-50 Gy	5-FU, cisplatin, mitomycin C	11	29
Herskovic[273]	22	50 Gy	5-FU, cisplatin	19.5	36
	39	30 Gy	5-FU, cisplatin	9.8	20
Minsky[274]	109	64.8 Gy	5-FU, cisplatin	13 NS	31 NS
	109	50.4 Gy	5-FU, cisplatin	18 NS	40 NS

5-FU, *5-Fluorouracil;* Gy, *Gray;* NR, *not reported;* NS, *not significant.*

TABLE 45-7 Randomized Studies Comparing Definitive Irradiation Alone with Chemoradiotherapy

Investigator	No. Patients	Irradiation Dose	Chemotherapy Agents	2-year Survival (%)
Araujo[275]	28	50 Gy	Control	22
	31	50 Gy	5-FU, mitomycin C, bleomycin	38
Sischy[276*]	62	60 Gy	Control	12
	65	60 Gy	Mitomycin C, 5-FU	30
Roussel[277]	69	45 Gy	Control	31 at 1 year
	75	56 Gy	Methotrexate	35 at 1 year
Herskovic[230]	60	64 Gy	Control	10
	61	50 Gy	5-FU, cisplatin	38

5-FU, *5-Fluorouracil;* Gy, *Gray.*
**Some patients went to resection.*

TABLE 45-8 Patterns of Failure Following Definitive Concurrent Chemoradiotherapy

Investigator	No. Patients	Local Control Rate (%)	Local Plus Distant Control Rate (%)	Distant Control Rate (%)
Kavanagh[269]	45	24	20	18
Chan[278]	21	24	18	43
Coia[279]	57	25	23	16
Herskovic[273]	22	32 (50 Gy)	18	23
	39	67 (30 Gy)	18	3
Minsky[274]	109	44 (64.8 Gy)	50	91
	109	48 (50.4 Gy)	45	84

Gy, *Gray.*

TABLE 45-9 Patterns of Failure from Randomized Studies of Definitive Chemoradiotherapy versus Radiation Alone

Investigator	No. Patients	Therapy	Local Control Rate (%)	Distant Control Rate (%)
Herskovic[230]	121	Radiation therapy	64	70
		Radiation therapy + chemotherapy	44	25
Araujo[275]	59	Radiation therapy	74	13
		Radiation therapy + chemotherapy	46.5	18
Minsky[274]	218	50.4 Gy + chemotherapy	52	16
		64.8 Gy + chemotherapy	56	9

Gy, *Gray*.

randomized patients with unresectable esophageal cancer to receive the same chemotherapy (5-fluorouracil and cisplatin) with either 64.8 Gy or 50.4 Gy. In this study there was no significant difference in median survival times (13 months versus 18.1 months), 2-year survival rate (31% versus 40%), or locoregional failure rate (56% versus 52%) between the high-dose and standard-dose treatment arms, respectively; however there was a higher treatment-related mortality rate (10% versus 3%) in the patients assigned to the high-dose radiation arm, which did not seem to be related to the higher radiation dose.[274] The trial was stopped after an interim analysis. The reason for the lack of benefit in the high-dose arm is unclear, but there was a significant prolongation of the treatment time because of toxicity breaks when correcting for the number of radiation treatments as well as a significantly lower 5-fluorouracil dose delivered when compared with the low-dose arm.[274] Results of these studies have established 50.4 Gy as the standard dose for definitive chemoradiation in esophageal cancer.

The improvement in survival rates in the combination trials seems related at least in part to an improvement in local control rates. Tables 45-8 and 45-9 show the crude patterns of failure from several definitive chemoradiation trials. These data suggest that combined-modality therapy produced a shift in the pattern of failure, from a local failure rate of 50% to 90% for irradiation alone to 20% to 50% with combined-modality therapy. RTOG 85-01 reported a crude local persistence or recurrence rate of 44% for patients treated with chemoradiation versus 64% for the irradiation alone group. The 2-year actuarial local failure rate was reduced from 68% to 43% and the rate of distant metastases was reduced from 70% to 25% with combined-modality therapy.[230]

Many chemotherapy agents have been investigated in an attempt to improve outcomes. RTOG 0113 was a randomized Phase II study for patients who were unwilling to have surgery or were medically unfit for surgery, who were randomly assigned to receive either induction treatment with 5-fluorouracil, cisplatin, and paclitaxel and then 5-fluorouracil plus paclitaxel with 50.4 Gy of irradiation or induction with paclitaxel plus cisplatin and then the same chemotherapy with 50.4 Gy of irradiation. Unfortunately, both arms were associated with high morbidity rates, and the study did not meet its 1-year survival end point.[281] Others have demonstrated efficacy of carboplatin and paclitaxel with concurrent definitive chemoradiation in esophageal cancer.[282,283] Definitive chemoradiation with cisplatin and docetaxel has been shown to result in a high response (98%), local control (60%), and 3-year survival (37%) rates in patients with squamous cell carcinoma.[204] A recent Phase II trial randomized patients to either FOLFOX (leucovorin, 5-fluorouracil, oxaliplatin) or 5-fluorouracil and cisplatin with concurrent definitive radiation resulting in improved outcome for those treated with FOLFOX (3-year OS 18.2 months versus 17.4 months; median OS 20.2 months versus 17.5 months, respectively).[284] An optimum regimen for concurrent chemoradiation has not been established, though active cooperative group prospective trials have adopted paclitaxel and carboplatin or FOLFOX-based regimens as standard therapy concurrent with radiotherapy.

A number of targeted agents have been incorporated into chemoradiation trials with attempt to improve outcome. Trastuzumab in addition to cisplatin, paclitaxel, and concurrent radiation followed by maintenance trastuzumab has demonstrated safety and a promising 3-year survival rate of 47% for patients with esophageal adenocarcinomas that overexpress HER-2.[285] Based on this encouraging safety and efficacy data, RTOG 1010 (NCT01196390) is studying the addition of trastuzumab to chemoradiation in patients with HER2-positive operable locally advanced adenocarcinoma of the esophagus and esophagogastric junction. Results of a randomized Phase III trial (RTOG 0436; NCT00655876) of cisplatin, paclitaxel, and radiation therapy with or without cetuximab in locally advanced, nonsurgically treated esophageal cancer were recently presented, and the addition of cetuximab did not improve OS regardless of histology.[286] A smaller prospective study (SWOG 0414) evaluating cetuximab with concurrent cisplatin, irinotecan, and radiation demonstrated poor tolerability of the regimen with treatment-related mortality approaching 10% resulting in early study closure.[287] The SCOPE1 study (NCT00509561) randomized Phase II/III study showed the addition of cetuximab to chemoradiotherapy resulted in both greater toxicity and worse survival.[288] These results give caution to the use of targeted agents outside of a clinical trial.

An important concern regarding the use of combined-modality therapy is treatment toxicity. In the Wayne State University series, 5 of 20 patients required hospitalization for intravenous hydration and nutritional support, and 38% developed pulmonary compromise (thought to be secondary to receiving bleomycin plus irradiation) that required corticosteroids.[273] The overall irradiation dose appears to be important, as has been reflected in data from Sauter et al.[289] In a study of 30 patients receiving concurrent chemotherapy and irradiation (60 Gy), only 67% of patients were able to complete the irradiation schedule as planned and only 18 of the 30 patients were able to proceed to resection.[289] Coia et al[279,290] reported a 56% incidence of moderate to severe acute toxicities, whereas the researchers of RTOG 85-01 found that side effects were severe in 44% of patients and life-threatening in 20% of patients in the combined-modality arm versus 25% and 3% in the radiation only group, respectively.[230] Most of the toxicity was hematologic, along with significant esophagitis and stomatitis. Although only 1 of 61 patients in the combined-modality group died of acute toxicity, only 50% of patients completed all four cycles of chemotherapy.[230]

Definitive Sequential Chemotherapy and Irradiation

The usefulness of sequential chemotherapy followed by a course of definitive radiation therapy alone has been

evaluated on a limited scale. One study evaluated patients treated with sequential cisplatin/bleomycin chemotherapy for three courses followed by definitive thoracic irradiation and resulting in a partial response rate of 52% and a complete response rate of 16% as determined by CT scanning and endoscopy, with 1-year and 4-year survival rates disappointing at 20% and 8%, respectively.[291] Similarly, patients treated with two cycles of induction cisplatin-vindesine-bleomycin chemotherapy followed by definitive radiotherapy results in a discouraging 15% OS rate at 5 years.[292] A more recent Phase II sequential study reported by Sharma et al,[293] testing multiple cycles of 5-fluorouracil plus cisplatin followed by a definitive course of irradiation (60 Gy), was equally disappointing, with a median survival time of 39 weeks. This approach has generated relatively little interest as it does not take advantage of the probable benefit of concurrent chemoradiotherapy.

Definitive Induction and Concurrent Chemotherapy and Irradiation

A number of investigators have tested induction chemotherapy followed by definitive irradiation and concurrent chemotherapy, mostly in the preoperative setting.[294-301] One report in the nonoperative setting evaluated 45 patients with locally advanced disease treated with three cycles of induction 5-fluorouracil and cisplatin followed by two additional cycles of chemotherapy delivered concurrently with irradiation to 64.8 Gy. Although the median survival time was an encouraging 20 months, six patients died from treatment-related toxicity.[302,303] The impact of induction chemotherapy on the therapeutic ratio for patients receiving definitive concurrent chemoradiotherapy has not been well studied.

Preoperative Chemoradiation

Preoperative chemoradiation followed by surgery is the most commonly used treatment approach for patients with esophageal carcinoma. The Southwestern Oncology Group (SWOG) and the Radiation Therapy Oncology Group (RTOG), based on pilot data from Wayne State University, performed two similar Phase II trials using concurrent chemotherapy and irradiation followed by planned resection in patients with squamous cell carcinoma of the esophagus. In the SWOG study, 113 patients with initially resectable tumors received treatment with infusional 5-fluorouracil plus cisplatin with concurrent irradiation to a dose of 30 Gy. The overall operability rate was 63%, and the overall resectability rate was 49%. The median survival time was 12 months, with 16% of patients alive at 3 years.[304] Of the 41 patients entered in the RTOG preoperative trial of concurrent irradiation plus 5-fluorouracil and cisplatin, 7.5% were alive at 3 years.[305] For patients with esophageal adenocarcinoma, preoperative chemoradiation followed by surgery has been the subject of numerous clinical trials. Data from the University of Michigan and Duke University report 5-year survival rates of 34% and 27%, respectively.[269,306]

Although chemotherapy before preoperative chemoradiation has been included in several regimens, there are no randomized clinical trials at this time that demonstrate benefit over concurrent chemoradiation without induction chemotherapy. A renewed interest in this approach has come about recently with exploration of early PET scans to assess the response.[307,308] Currently, the CALGB is evaluating a response-adapted strategy using induction chemotherapy with early FDG-PET imaging followed by chemoradiation, with concurrent chemotherapy selection based on the response to initial chemotherapy (CALGB 80803—NCT01333033). In this study patients receive either modified FOLFOX (leucovorin, 5-fluorouracil and oxaliplatin) for three 14-day courses or carboplatin and paclitaxel for two 21-day courses. Patients then undergo PET/CT scan. Patients with responsive disease (tumor metabolic activity decreased by ≥35%) receive three additional courses of FOLFOX and concurrent radiotherapy or weekly radiosensitizing doses of concurrent carboplatin/paclitaxel with concurrent radiotherapy. The primary endpoint of this study is pathologic complete response rate of PET/CT nonresponders within each treatment group.

The next generations of chemoradiation trials attempted to incorporate more novel chemotherapeutic agents. The results of a 46-patient Phase II study of irradiation and concurrent cisplatin, 5-fluorouracil, and paclitaxel demonstrated a pathologic complete response rate of 45% for the 40 patients able to undergo resection. The overall median survival time was 34 months, with 37% of patients alive at 5 years.[309] Urba et al reported results from a Phase II trial using preoperative cisplatin, paclitaxel, and twice-daily irradiation, with 90% of patients able to undergo surgery and a 19% complete pathologic response rate. Survival data compared favorably with other previously reported combinations, with a median survival time of 24 months.[310] Oxaliplatin has also been evaluated in combination with 5-fluorouracil–based chemotherapy with or without irradiation in the neoadjuvant setting. Data suggest that a course of preoperative oxaliplatin and concurrent chemotherapy with protracted venous infusion of 5-fluorouracil with irradiation (50.4 Gy) is an active regimen in locally advanced esophageal cancer, resulting in rates of 81% for complete radiologic response and 38% for complete pathologic response.[311] More recent studies demonstrated promising complete pathologic response rates of up to 63%,[312] but excessive treatment-related deaths were encountered. Currently, it is thought that concurrent irradiation and containing-containing regimens are not acceptable because of excess toxicity.[312,313]

The addition of targeted agents to chemoradiation in the neoadjuvant setting is under investigation. One treatment strategy evaluated the benefit of the addition of bevacizumab to preoperative chemoradiation using carboplatin, paclitaxel, and 5-flurouracil in stages I to III esophageal or esophagogastric junction cancer (95% adenocarcinomas). A pathologic complete response rate of 29% was observed, similar to regimens not containing bevacizumab.[314] Ilson et al evaluated the efficacy chemoradiation with bevacizumab in patients with Siewert I/II adenocarcinoma of the esophagus. The treatment regimen consisted of induction chemotherapy with cisplatin, irinotecan, and bevacizumab followed by concurrent chemotherapy with cisplatin, irinotecan, and bevacizumab concurrent with radiation therapy. Surgery was followed by adjuvant bevacizumab. A pathologic complete response was observed in only 12% and progression-free and OS were 14 and 30 months, respectively.[315] Given the lack of improvement in the pathologic complete response rate in these Phase II compared with historical controls, there is no role for bevacizumab with chemoradiation for esophageal cancer outside of clinical trials.

Chemoradiation with cetuximab has been extensively studied in the Phase II setting. The Swiss Group for Clinical Cancer Research (SAKK) 75/06 trial evaluated treatment with induction cisplatin, docetaxel, and cetuximab followed by radiation therapy with concurrent cisplatin and cetuximab in 28 patients with operable esophageal cancer resulting in a pathologic complete response rate of 32%.[316] Another study evaluated cetuximab, paclitaxel, and cisplatin in combination with radiation therapy in 60 patients and a pathologic complete response rate of 27% was observed.[317] These studies were not associated with unacceptable toxicity. In contrast, ECOG 2205 evaluated a neoadjuvant regimen of cetuximab combined with 5-fluorouracil, oxaliplatin, and radiation but because of an excess of acute respiratory deaths (ARDS), the study was closed.[318]

TABLE 45-10 Results from Preoperative Chemoradiotherapy and Chemoradiotherapy with Targeted Agents Followed by Surgery

Investigator	No. Patients	Irradiation Dose	Chemotherapy Agents	2-year Survival (%)	Median Survival
Bates[319]	35	45 Gy	5-FU, cisplatin	47	22 mo
Forastiere[320]	47	44 Gy	5-FU, cisplatin	58	31.3 mo
Kavanagh[269]	58	45 Gy	5-FU or etoposide, cisplatin or carboplatin	37	18 mo
Gignoux[261]	119	37.5 Gy	Cisplatin	56.5 (18 mo)	NR
Bidolo[321]	34	30 Gy	5-FU, cisplatin	38	NR
Seydel[305]	41	30 Gy	5-FU, cisplatin	15	13 mo
Poplin[304]	71	30 Gy	5-FU, cisplatin	28	NR
Stewart[322]	68	30 Gy	5-FU, cisplatin, etoposide, leucovorin	76	26 mo
Urba[310]	69	45 Gy twice daily	Paclitaxel, cisplatin	50	24 mo
Meluch[323]	129	44 Gy	Paclitaxel, 5-FU, carboplatin	47	22 mo
Choi[309]	46	58.5 Gy concomitant boost	Paclitaxel, 5-FU, cisplatin	57	34 mo
Ruhstaller[299]	66	45 Gy	Cisplatin, docetaxel	66	NR
Ajani[295]	43	45 Gy	Irinotecan, cisplatin	42	22.1 mo
Ilson[308]	19	50.4 Gy	Irinotecan, cisplatin	NR	31.7 mo
Khushalani[311]	38	50.4 Gy	Oxaliplatin, 5-FU	NR	NR
Ruhstaller[324]	28	45 Gy	Cisplatin, docetaxel, cetuximab	NR	16 mo
Kleinberg[318]	22	45 Gy	Oxaliplatin, 5-FU, cetuximab	NR	NR*
Suntharalingam[286]	344	50.4 Gy	Cisplatin, paclitaxel, cetuximab Cisplatin, paclitaxel	41 42	NR
Ilson[315]	33	50.4 Gy	Irinotecan, cisplatin, bevacizumab	NR	30 mo
Bendell[314]	62	45 Gy	Paclitaxel, carboplatin, bevacizumab	NR	NR†

5-FU, *5-Fluorouracil;* Gy, *Gray;* mo, *months;* NR, *not reported.*
**Closed early because of unacceptable pulmonary toxicity resulting in early deaths.*
†*Pathologic complete response 30%.*

Results from several nonrandomized trials employing using various chemotherapeutic and targeted therapies in the setting of preoperative chemoradiation are shown in Table 45-10.

The question of whether combined preoperative radiotherapy and chemotherapy is superior to preoperative chemotherapy was addressed in a Phase III study in patients with locally advanced esophagogastric junction adenocarcinomas. A higher pathological complete response rate and uninvolved lymph node rate was observed in those patients treated with combined modality therapy compared to those receiving only chemotherapy (15% versus 2% and 64% versus 37%, respectively). Although the study was closed early because of poor accrual, there was a trend for 3-year survival rate in favor of the combined-modality group (47% versus 27%, $p = 0.7$).[300]

Preoperative Chemoradiation versus Surgery Alone

Preoperative chemoradiation is the most common treatment approach for patients with esophageal carcinoma and is currently considered standard of care. Although earlier randomized trials comparing surgery alone with chemoradiation followed by surgery for the treatment of resectable esophageal cancer have shown conflicting results[325-330] four meta-analyses have demonstrated that chemoradiation results in improved survival[252,331-333] and decreased local recurrence compared to surgery alone.[331,333] In addition, preoperative chemoradiation has been reported to result in increased pathologic response rates compared with preoperative chemotherapy without radiation (28% versus 4%, respectively) in patients with locally advanced esophageal cancer,[334] while pathologic complete response to neoadjuvant therapy has been associated with an improvement in overall survival in some series[334] but not in others.[335]

In a nonrandomized study of preoperative chemoradiation and surgery versus surgery alone, Vogel et al[336] reported an OS advantage for patients receiving multimodality therapy, with 36% alive at 5 years versus 11% for surgery alone. Urba et al also reported a 3-year survival advantage for those patients receiving preoperative concurrent chemoradiation compared with surgery alone (30% versus 16%, respectively), although not nonstatistically significant.[208] Walsh et al conducted a randomized study of patients treated with two 5-day courses of 5-fluorouracil given on weeks 1 and 6 and cisplatin with concurrent (40 Gy) irradiation, delivered before surgery compared with patients who underwent surgery alone. The reported (actuarial) survival rates favored patients receiving combined-modality therapy, with 32% alive at 3 years versus 6% who underwent surgery only[330]; however, this trial has been criticized for the unusually low survival rate in the surgical arm. In contrast, no survival advantage was observed for patients receiving preoperative chemoradiation versus surgery alone in a randomized study reported by Bosset.[325] This study, however, used a unique irradiation and chemotherapy schedule: irradiation was delivered via a split course, and over the span of 2 weeks, a total dose of 37 Gy in 3.7-Gy daily fractions was delivered. The chemotherapy consisted of cisplatin given prior to each week of irradiation. Patients were taken to surgery 2 to 4 weeks after completing the preoperative regimen.[325] The lack of benefit and increased toxicity observed for the combined-modality arm may have been predicted with the application of large radiation fractions, the inclusion of a planned treatment break, an inadequate recovery period between the preoperative therapy and surgery, and the use of single-agent chemotherapy.

The U.S. Gastrointestinal Intergroup trial attempted to further evaluate the role of preoperative chemoradiation therapy compared to surgery alone but was stopped before completion because of poor accrual. Nonetheless, Tepper et al[327] reported the results from this trial (CALGB 9781) for the 56 patients who were enrolled before the trial closed. A median survival time of 4.48 years versus 1.79 years in favor of trimodality therapy and a 5-year survival rate of 39% versus 16% in favor of trimodality therapy were demonstrated on an intent-to-treat analysis.[327] Despite the low accrual rate, the observed difference supportive trimodality therapy as an appropriate standard for resectable esophageal cancer.

The Phase III CROSS trial randomized patients with resectable esophageal cancer (75% adenocarcinomas) to preoperative weekly radiosensitizing carboplatin and paclitaxel with concurrent radiation (41.4 Gy at 1.8 Gy per fraction) or surgery alone and demonstrated improved median and 5-year survival in the chemoradiation arm compared to the surgery arm (49 months versus 24 months, and 47% versus 34%, respectively). The pathologic complete response rate was higher for squamous cell carcinomas compared to adenocarcinomas, but histology was not prognostic for survival. The study included 368 patients (23% squamous cell; 75% adenocarcinoma; and 2% undifferentiated) with 178 patients randomized to neoadjuvant chemoradiation. R0 resection was achieved in 92% of the patients receiving neoadjuvant chemoradiation compared with 69% of those who proceeded directly to surgery. A pathological complete response was achieved in 47 of 161 patients (29%) who underwent resection after preoperative therapy. The results of this trial were statistically significant and present convincing data supporting trimodality therapy for patients with resectable esophageal cancer.[329]

A recently reported meta-analysis of more than 1000 patients enrolled in nine randomized trials evaluating preoperative chemoradiation versus surgery alone revealed a 0.66 survival odds ratio at 3 years in favor of patients receiving preoperative therapy.[333] Three other meta-analysis also demonstrate a similar survival advantage to trimodality therapy compared to surgery alone.[252,331,332] Table 45-11 summarizes the randomized trials comparing the results of preoperative chemoradiation followed by surgery to surgery alone.

Preoperative Chemoradiation versus Definitive Chemoradiation

Bedenne et al[337] have reported the results of a study comparing preoperative chemoradiation followed by surgery versus definitive chemoradiation. In this randomized Phase III trial, patients with locally advanced esophageal cancer received two cycles of induction 5-fluorouracil plus cisplatin with radiotherapy, either delivered via standard fractionation (46 Gy in 4.5 weeks) or over a split course. Patients were then randomized between surgical resection versus completion of definitive chemoradiation to 61 Gy. The 2-year survival rates and median survival times were not different, at 34% and 17.7 months for patients in the preoperative arm versus 40% and 19.3 months for patients randomized to definitive chemoradiation ($p = 0.56$).[337] In a related German study, patients with locally advanced squamous carcinoma of the esophagus received induction chemotherapy followed by a randomization to either chemoradiotherapy (40 Gy) followed by surgery or definitive chemoradiotherapy. The analysis of the 172 randomized patients showed the overall survival rates to be equivalent; the survival rate at 3 years was 31% for patients randomized to combined-modality therapy versus 24% for patients treated with definitive chemoradiation.[338]

A study from the Minnie Pearl Cancer Research Network reflects the difficulties associated with studies that randomize patients away from a surgical intervention. In this study, patients with locally advanced esophageal cancer were to receive a course of preoperative chemoradiation followed either by surgery or by completion of the definitive chemoradiation regimen. One-hundred and ninety-four patients were entered, but only 57 patients actually proceeded with the treatment to which they were randomized. When all patients were considered, the survival rates were similar; the 3-year survival rate for patients undergoing resection was 35% versus 31% for patients receiving definitive chemoradiation.[323]

The data, taken in aggregate, suggest that the results with definitive chemoradiation are comparable to those observed with treatment strategies that incorporate preoperative chemoradiation and surgery. However, compared to data from historical control patients undergoing planned esophagectomy 4 to 6 weeks after completion of chemoradiation, patients undergoing salvage esophagectomy following definitive chemoradiation experienced increased rates of operative death and complications, including the need for prolonged intubation or longer stays in the intensive care unit and hospital and increased anastomotic leaks. Salvage esophagectomy, nonetheless, has demonstrated a 25% 5-year survival rate in a subset of patients with stage T1-T2, N0 tumors, who undergo R0 resection, and those with a prolonged time to recurrence.[339]

TABLE 45-11 Randomized Trials of Chemoradiotherapy Plus Surgery versus Surgery Alone

Investigator	No. Patients	Treatment	Median Survival Time (mo)	3-year Survival Rate (%)	*p* Value
Urba[328]	50	Surgery	NR	16	0.15
	50	Chemoradiation plus surgery	NR	30	
Walsh[330]	55	Surgery	NR	6	0.01
	58	Chemoradiation plus surgery	NR	32	
Bosset[325]	139	Surgery	NR	37*	0.78
	143	Chemoradiation plus surgery	NR	39*	
Burmeister[326]	256	Surgery	19	NR	0.38
		Chemoradiation plus surgery	22	NR	
Tepper[327]	475	Surgery	21	NR	0.002
		Chemoradiation plus surgery	54	NR	
Van Hagen[329]	366	Surgery	24	44	0.003
		Chemoradiation plus surgery	49	58	

Mo, *Months;* NR, *not reported.*

**Approximate 3-year survival rate or time determined from survival curve.*

Postoperative Chemoradiation

Prospective and retrospective analyses have demonstrated a survival benefit to the addition of postoperative chemoradiation in patients with node-positive esophageal cancer who have undergone esophagectomy.[340-342] SWOG 9008/INT-0116[341] reported a 3-year disease-free survival of 37% for patients with node-positive disease receiving postoperative chemoradiation compared to 24% for patient who did not. SWOG 9008/INT-0116 investigated the benefit of postoperative chemoradiation following surgery in patients with stage Ib-IV, M0 resectable adenocarcinoma of the esophagogastric junction or stomach in a prospective randomized trial. In this trial 556 patients (20% esophagogastric junction) were randomized to receive surgery alone or surgery followed by postoperative chemoradiation (5-fluorouracil plus leucovorin for one cycle followed by concurrent chemoradiation during cycles two and three, followed adjuvant 5-fluorouracil plus leucovorin following completion of chemoradiation). Patients treated on the postoperative chemoradiation arm experienced improved 3-year overall survival (50% versus 41%) and relapse-free survival (48% versus 31%) rates compared to those treated with surgery alone. There was also a decrease in local failure observed in this group (19% versus 29%). However, high rates of hematologic and gastrointestinal toxicities were associated with this treatment regimen resulting in 17% discontinuation of treatment. Despite the significant number of patients who did not complete the treatment, survival benefits have persisted after more than 10 years of followup and the results of INT-0116 have established postoperative chemoradiation as a standard of care for patients with completely resected adenocarcinoma of the esophagogastric junction or stomach.[341] Based on these results, postoperative chemoradiation is considered an acceptable treatment strategy for patients with stage Ib-IV, M0 distal esophageal and esophagogastric junction tumors who undergo resection.

The Significance of Pathologic Complete Response to Neoadjuvant Chemoradiation

Compared with historical unimodality series, failures locally and distantly have markedly decreased with the advent of multimodality therapy (Table 45-12). In general, preoperative irradiation and chemotherapy produce complete pathologic response rates of 20% to 50% (an average of approximately 30%) (Table 45-13). Pathologic complete response to neoadjuvant therapy has been associated with an improvement in OS in some series,[334] but not in others.[335] In the SWOG study, patients who had no evidence of disease at the time of surgery, when compared with all patients who had resection, had a projected 3-year survival rate of 45% versus 14%, and a median survival time of 32 months versus 14 months, respectively.[304]

TABLE 45-12 Patterns of Failure for Concurrent Chemoradiotherapy Followed by Surgical Resection

Investigator	No. Patients	Local Control Rate (%)	Local Plus Distant Control Rate (%)	Distant Control Rate (%)
Herskovic[273]	50	36	38	16
MacFarlane[345]	22	0	38	16
Forastiere[343]	43	2	5	28
Kavanagh[269]	57	14	10	29

TABLE 45-13 Pathologic Findings after Preoperative Chemoradiotherapy

Investigator	No. Patients	Pathologic Complete Response Rate (%)	Radiation Therapy Dose	Chemotherapy Agents
Parker[346]	33	33	30 Gy	5-FU, mitomycin C
Seydel[305]	41	19.6	30 Gy	5-FU, cisplatin
Herskovic[273]	50	24	30 Gy	5-FU, cisplatin
Gignoux[261]	101	24	37.5 Gy	Cisplatin
Forastiere[343]	43	24	37.5 Gy-45 Gy	5-FU, cisplatin, vinblastine
Bates[319]	32	50	45 Gy	5-FU, cisplatin
Kavanagh[269]	72	42	45 Gy	5-FU or etoposide, cisplatin or carboplatin
Hoff[347]	51	21	30 Gy	5-FU, cisplatin, etoposide, leucovorin
Van Hagen[329]	178	29	41.4 Gy	Paclitaxel, carboplatin
Urba[310]	69	19	45 Gy twice daily	Paclitaxel, cisplatin
Bains[348]	41	26	50.4 Gy	Paclitaxel, cisplatin
Meluch[323]	129	46	44 Gy	Paclitaxel, 5-FU, carboplatin
Choi[309]	46	45	58.5 Gy concomitant boost	Paclitaxel, 5-FU, cisplatin
Ruhstaller[299]	66	23	45 Gy	Cisplatin, docetaxel
Ajani[295]	43	41	45 Gy	Irinotecan, cisplatin
Ilson[308]	19	16	50.4 Gy	Irinotecan, cisplatin
Khushalani[311]	38	38	50.4 Gy	Oxaliplatin, 5-FU
Ruhstaller[324]	28	68	45 Gy	Cisplatin, docetaxel, cetuximab
Ilson[315]	33	15	50.4 Gy	Irinotecan, cisplatin, bevacizumab
Bendell[314]	62	30	45 Gy	Paclitaxel, carboplatin, bevacizumab

5-FU, *5-fluorouracil;* Gy, *Gray.*

A similar survival advantage was demonstrated by investigators from the University of North Carolina where median survival time for patients with no evidence of disease at resection was 37 months compared to 13 months for patients with residual tumor.[319] Similarly, in the University of Michigan series, the median survival time was improved for patients without evidence of residual disease at the time of surgery compared to the entire cohort (70 versus 29 months, respectively).[343] Although survival rates were higher in patients who had no disease in the surgical specimen in the University of Michigan and University of North Carolina series, there were long-term survivors among patients with residual disease, suggesting that the addition of surgery, at least in a subset of patients, can produce additional cures after chemoradiation therapy. A retrospective review was performed using a recursive partitioning analysis for 276 patients who received chemoradiation before esophagectomy. These results supported the idea that a pathologic complete response predicted for improved survival rates compared with patients with residual disease, but was less prognostic than the presence of nodal disease and metastases.[344]

Nodal status following neoadjuvant chemoradiation has also been demonstrated to be a predictive factor for survival rates. Gaca et al[349] performed a retrospective analysis of 28 patients with a complete pathologic response and found that patients who were node-negative, regardless of T stage, experienced improved median disease-free survival rates compared with patients with stage N1 nodes. They also found that preoperative tumor stage, patient age, tumor location, or the presence of Barrett's esophagus did not independently predict OS on univariate analysis. Multivariate analysis showed that only posttreatment nodal status, and not posttreatment tumor status, predicted disease-free survival.[349]

Assessing Residual Disease Following Neoadjuvant Chemoradiation

There are no reliable methods to predict pathologic complete responders following neoadjuvant. The use of preresection endoscopy was not useful for determining the tumor response; although 77% of patients were reported to have had a clinical complete response (by endoscopy) preoperatively, 41% of these patients had residual tumor in the pathologic specimen.[319] The inaccuracy of endoscopy in discerning the response after preoperative chemoradiation has been further confirmed in a study from Roswell Park and is important because it suggests that a strategy of initial chemotherapy plus radiation therapy with surgery saved for patients with incomplete clinical response may not be successful.[350]

FDG-PET as an indicator of complete response has also been evaluated.[297,351-353] Tumors with low pretreatment standard uptake unit values, defined as less than 4.5, are less likely to show evidence of treatment response after chemoradiation. A higher likelihood of nodal and pathologic complete response has been demonstrated in tumors with pretreatment SUV_{max} values greater than 4.5. Patients with tumors in both low and high pretreatment SUV_{max} groups demonstrate similar survival rates.[353]

PALLIATION

Oncologists can produce palliation with irradiation alone by using external beam radiation doses ranging from 30 Gy in 2 weeks to 50 Gy to 60 Gy over 6 weeks (Table 45-14). Wara et al[354] reported on 103 patients who completed therapy with 50 Gy to 60 Gy, with 89% having symptomatic improvement and 66% maintaining relief for 2 months or more. The average duration of palliation was 6 months. The dysphagia usually improved near the end of therapy, and almost all patients reported an arrest of their previous symptom progression.[354] Similar data report a 60% to 88% improvement in dysphagia with radiation doses of 50 Gy or higher.[355,356] Concurrent chemoradiation may also be used for palliation of dysphagia (Table 45-14). Studies demonstrate a rate of up to 88% improvement in swallowing, with the median time to improvement being 2 weeks with durable relief of symptoms.[290] Aggressive concurrent irradiation potentially increases complications in patients with incurable disease and a limited life span, but it may offer a more effective means of palliation.

When considering brachytherapy in esophageal cancer, one must keep in mind both the biologic characteristics of the disease and the physics of brachytherapy. Esophageal tumors are rarely confined to the mucosa or the muscular wall, and they generally extend outside the walls of the esophagus and have a high incidence of nodal spread. The physics of brachytherapy are such that the dose is primarily delivered within a radius of approximately 1 cm from the applicator. Therefore, it is quite unlikely that this approach will be effective for curative therapy of most esophageal carcinomas because of inadequate therapy to much of the tumor. It may, however, be useful for palliation where the central disease is producing the symptoms and can be effectively treated with brachytherapy. Several small series have demonstrated that intracavitary irradiation in the appropriately selected patient is a safe and

TABLE 45-14 Palliative Impact of Radiation Therapy with and without Chemotherapy

Investigator	No. Patients	Radiation Therapy Dose	Chemotherapy Agents	Palliation of Dysphagia (%)
Albertsson[357]	67	<45 Gy	None	55
	43	>45 Gy	None	65
Wara[354]	169	50 Gy-60 Gy	None	67
Petrovich[236]	133	55 Gy	None	52
Whittington[358]	165	50 Gy-60 Gy	5-FU, mitomycin C	87
Kavanagh[269]	143	44 Gy-60 Gy	Cisplatin, carboplatin, etoposide, 5-FU	71
RANDOMIZED TRIALS				
Herskovic[230]	121	64 Gy	None	66
		50 Gy	5-FU, cisplatin	58
Roussel[277]	170	56.2 Gy	None	78
		56.2 Gy	Methotrexate	71

5-FU, *5-fluorouracil;* Gy, *Gray.*

effective method of palliation resulting in local control rates of 25% to 35%. Harvey et al reviewed 22 patients treated with either 20 Gy in three fractions of low-dose-rate brachytherapy versus 12.5 Gy in one fraction of high-dose-rate brachytherapy and found that both modalities resulted in equally effective palliation of dysphagia.[359] Accelerated treatments are especially suitable for patients in poor physical condition or with a short life expectancy; however, the incidence of stricture and fistula formation increased with the brachytherapy fraction size (9.5% for fractions <500 cGy, 20% for fractions between 500 cGy and 800 cGy, and 38% for fractions >800 cGy). In a randomized trial by Sur et al, there was no reported difference in local control or survival between palliative external beam radiotherapy or high-dose rate brachytherapy.[360] Brachytherapy as an intraluminal boost has also been evaluated in RTOG 85-01 in which patients with unresectable esophageal cancer received 50 Gy with concurrent cisplatin and 5-fluorouracil followed by a brachytherapy intraluminal boost. Although the local failure rate was 27%, there were a significant number of grade-3 to grade-5 toxicities, and the cumulative incidence of fistulas was 18% per year.[361] The benefit of brachytherapy added to chemoradiation or external beam radiation alone remains unclear.

TOXICITY FROM IRRADIATION

Benign Strictures Resulting from Irradiation

Unfortunately, benign strictures can result from irradiation of esophageal cancers, causing a worsening of symptoms. The incidence of benign stricture is estimated at 12% to 30% in patients treated with irradiation alone. Strictures usually develop 4 to 6 weeks after therapy.[290,362,363] In 25 patients treated with concurrent irradiation and chemotherapy, Coia et al observed a 12% incidence of benign strictures that responded to one or two dilations.[290]

Tracheoesophageal Fistula

The development of a malignant fistulous tract between the esophagus and airway (trachea or bronchus) is not uncommon in midesophageal lesions because of the anatomic location of the two structures. Most fistulae involve the trachea, but they can also involve either a main stem, lobar, or segmental bronchus. Involvement of the trachea with tumor can lead to fistula formation during irradiation because of necrosis of the tumor or the natural progression of the disease. It is estimated that the incidence of this complication is 5% to 10% of patients with esophageal cancer. In general, excision, bypass, or intubation has been recommended in an attempt to prevent further contamination of the airway. The median survival time following these limited measures can be as brief as 6 to 10 weeks, with the procedures themselves resulting in a mortality rate of 10% to 32%.[364]

Many oncologists accept the fact that irradiation of a fistula worsens the condition because healing may be compromised by irradiation. However, Burt et al found that the survival rate for patients with an untreated fistulous tract was 4% at 6 months and 1% at 1 year compared to 15% and 5% in patients treated with irradiation, respectively.[365] Treatment of radiation-induced fistulae can be challenging. Yamado et al reported on 14 patients with fistulae secondary to esophageal cancer who were treated with primary irradiation. Closure of the fistula occurred in 5 of 8 patients whose fistulae developed before or during irradiation. In two of these cases, the closure lasted over the long term, but for patients who developed fistulae during irradiation, resolution was less likely.[366] Gschossmann reported on a 10-patient series from the Mayo Clinic with fistulae developing during treatment and observed that the severity of the fistulae did not increase with therapy and the median survival time was 4.8 months.[367]

Although it has been speculated that development of radiation-induced fistulae may impact patient outcome, there is also a growing body of evidence supporting the safe use of chemotherapy with or without irradiation in managing patients with a tracheoesophageal fistula. Malik et al observed an objective response and closure of the fistulae in two patients treated with chemoradiation and concluded that the presence of a fistula should not exclude a patient from receiving combined-modality therapy.[368] At present, it is difficult to determine whether aggressive combined-modality therapy will increase treatment-related morbidity in patients who present with airway or esophageal fistulae or develop them shortly after starting therapy. Once the diagnosis of a fistulous tract into the airway is documented and the process is stabilized, planned curative therapy for selected patients with localized disease is recommended, especially if the fistula is relatively small.

IRRADIATION TECHNIQUES

The recommended dose for preoperative therapy is 41.4 Gy to 50.4 Gy delivered over 4 to 5 weeks, using 1.8-Gy to 2-Gy daily fractions. The recommended dose for postoperative radiation 45 Gy to 50.4 Gy is recommended. When definitive irradiation is used concurrently with sensitizing chemotherapy without surgery, a total dose of approximately 50 Gy to 54 Gy is recommended as lower doses may not be adequate. For inoperable tumors of the cervical esophagus, 60 Gy to 66 Gy may be appropriate.

The irradiation of esophageal cancer presents a challenge to radiation oncologists because these tumors are situated deeply in the mediastinum and are surrounded by several vital structures. The mucosa of the esophagus is mostly squamous epithelium, and the acute mucosal reaction can be substantial. Acute odynophagia and dysphagia are common, usually developing 10 to 14 days after the initiation of therapy. The esophagitis is self-limiting, but without nutritional support, the acute mucosal reaction may force a delay in completing treatment. Patients should be closely monitored and aggressive supportive care should be provided for the management of radiation-induced acute toxicities to avoid unnecessary treatment interruptions. Consideration of feeding jejunostomy, nasogastric feeding tube, or intravenous hydration should occur in case of inadequate caloric intake or dehydration.

Portions of the upper airway, trachea, bronchi, lung parenchyma, and pleura are unavoidably irradiated during therapy. The pulmonary parenchyma is highly susceptible to radiation injury, with clinical lung damage reported at total fractionated doses in the range of 20 Gy. However, the likelihood of clinical injury relates strongly to the baseline pulmonary status of the patient, as well as the amount of lung in the irradiation field. It is not uncommon for patients with esophageal cancer to have chronic obstructive lung disease, which affects the amount of normal lung that can be safely irradiated. The risks of permanent lung injury and late pneumonitis are also volume-related.

If the heart is irradiated, complications involving the pericardium and myocardium can result. Irradiation of the pericardium can result in both acute and chronic pericarditis. The former is an uncommon complication of thoracic irradiation that usually develops within the first posttreatment year. It is often associated with viral infections, which makes diagnosis difficult. Although it has been reported at doses in the range of 20 Gy to 40 Gy, acute pericarditis generally occurs with

substantially higher doses. Chronic pericarditis typically develops more than 1 year after treatment and is related to volume treated.

Irradiation of the myocardium can result in an interstitial fibrosis that decreases cardiac function. This phenomenon is also related to the volume of irradiated heart and a total dose that exceeds 40 Gy. Data have associated irradiation of the myocardium with an acceleration of coronary arteriosclerosis and sudden cardiac death in young persons. Because the vast majority of patients with esophageal cancer are older and have a limited prognosis, myocardial injury is not a significant clinical problem at present time.

Other rare complications of esophageal irradiation include the risk of rib fractures, damage to the brachial plexus, and spinal cord injury, which is potentially the most devastating side effect. In general, it is safe to treat the spinal cord with irradiation alone to a cumulative dose of 45 Gy to 50 Gy delivered in standard single daily fractions of 180 cGy to 200 cGy.

The difficulty in controlling esophageal tumors with irradiation relates to the frequent extension of tumor through the thin esophageal wall, the involvement of vital mediastinal structures, including large vessels and the trachea, and the threat of perforation; the frequent spread of tumor through submucosal lymphatics, ultimately involving long segments of the esophagus; the spread of tumor to regional lymph nodes; the presence of metastatic disease in a high percentage of patients (either occult or clinically apparent disease); and the generally poor nutritional status of patients at presentation. Esophageal tumors can extend submucosally in the cephalo-caudad direction for a significant distance from the primary tumor. In 1962, Miller[369] reported a 15% incidence of longitudinal microscopic tumor spread at greater than 6 cm from the primary lesion and an incidence of regional nodal involvement of 40% to 70%.

For lesions of the cervical esophagus, irradiation fields must take into account tumor spread into mediastinal, supraclavicular, and low anterior cervical lymph nodes. The supraclavicular nodes are generally electively treated in patients with high thoracic tumors but not in those with middle or distal thoracic tumors. Although there is a significant incidence of involvement of the celiac axis lymph nodes, little information supports routine treatment of this nodal group for patients without evidence of tumor involvement, especially if this necessitates a substantial extension of the irradiation field.

The typical irradiation field extends approximately 4 cm to 5 cm above and below gross tumor, with a field width of approximately 8 cm. The size of the tumor dictates the exact field width needed to obtain adequate mediastinal nodal coverage and to adequately cover the primary tumor mass. CT simulation and three-dimensional treatment planning techniques are recommended. When four-dimensional CT planning or other motion management is available, margins may be reduced to account for motion control. Intravenous or oral contrast should be used to facilitate target and normal tissue localization. The gross tumor volume (GTV) includes the primary tumor and the involved regional nodes as identified by CT, PET/CT, barium swallow, or EUS. The clinical tumor volume (CTV) includes areas at risk for microscopic spread and elective node regions depending on the location of the primary tumor. The planning target volume (PTV) includes the tumor plus a cephalo-caudad margin of 4 cm to 5 cm and a radial margin of 2 cm. Efforts to reduce radiation dose to surrounding normal tissue should be made.

If conventional two-dimensional radiation planning is used, patients are initially treated with anterior-posterior treatment fields to 36 Gy to 40 Gy in 1.8 Gy to 2 Gy daily fractions to limit the dose to the heart and spinal cord. The treatments then continue, avoiding the spinal cord, with either oblique or lateral fields, to a total dose of 45 Gy to 50 Gy. An alternative approach is to treat through the entire course with multiple fields that limit the dose to the spinal cord to a total dose of 45 Gy to 50 Gy.

The use of three-dimensional conformal radiation is recommended and dose volume histograms (DVH) should be generated and used as predictors of normal tissue complications. Custom blocking may be used to limit the volume of normal tissue receiving radiation. Recommended normal tissue constraints for treatment planning purposes included liver (no greater than 60% volume should receive more than 30 Gy), kidneys (no greater than 60% of one kidney should receive more than 20 Gy), spinal cord (maximum dose 45 Gy), heart (efforts to keep minimal dose to the left ventricle), and lungs (no greater than 20% volume should receive more than 20 Gy and 40% volume greater than 10 Gy). Figure 45-1 represents a three-dimensional CT-based plan demonstrating radiation treatment for a distal esophageal tumor.

Intensity-modulated radiation therapy (IMRT) may be appropriate in selected cases and has the potential of reducing the amount of radiation delivered to surrounding normal tissues. Wu et al[370] compared IMRT plans with forward and inverse three-dimensional conformal irradiation plans for 15 patients with midesophageal cancers and demonstrated that the IMRT plans generated the most conformal high-dose distribution around the planning target volume while delivering a lower mean lung dose and mean heart dose. Others have demonstrated similar findings comparing the ability of three-dimensional therapy and IMRT to deliver simultaneous integrated boost, dose-escalation in upper esophageal locations. Lower V20 and V30 volumes in the lung were consistently demonstrated in the IMRT plans.[371] An additional study explored the potential advantage of IMRT in distal esophageal cancers, resulting in a significant reduction in the mean lung dose, V10, and V20, without a significant reduction in the cardiac dose from the three-dimensional conformal plans.[372] Because the actual use of IMRT plans has not been well studied, care needs to be taken to avoid the risk of unexpected normal tissue toxicities resulting from the low-dose regions, especially in the lungs, being widely spread into normal tissue. Figure 45-2 represents an IMRT CT-based plan demonstrating radiation treatment for a distal esophageal tumor. Figure 45-3 is a dose-volume histogram showing the dose distribution differences for surrounding normal structures between a three-dimensional treatment plan and an IMRT treatment plan for the same patient. Considerations of tumor/target motion are of particular importance when IMRT is used. A full discussion of motion management considerations is found in the chapter on non–small cell lung cancer.

Proton beam therapy (PBT) is a promising modality for the management of thoracic malignancies, including esophageal cancer. A series of 62 patients treated with PBT and concurrent chemotherapy either definitively or preoperatively at M. D. Anderson Cancer Center from 2006 to 2010 evaluated toxicity associated with this treatment approach. With a median radiation dose of 50.4 Gy (range 36 Gy to 57.6 Gy), few toxicities were observed. The most common acute toxicities encountered were grade-2 to grade-3 esophagitis (46.8%), fatigue (43.6%), nausea (33.9%), anorexia (30.1%), and radiation dermatitis (16.1%). Two cases of grade-2 and grade-3 radiation pneumonitis occurred. There was no apparent impact on subsequent surgery in the preoperative cohort. There were significantly fewer local regional recurrences in the preoperative group (3 of 29) than in the definitive group but there were no differences in distant metastases or OS between the two groups.[373] Although the clinical outcomes are encouraging, a prospective comparison with traditional radiation techniques is warranted.

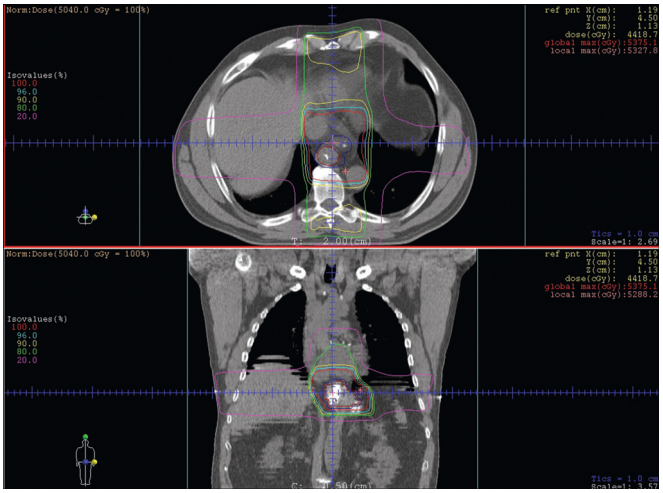

Figure 45-1 Three-dimensional treatment planning for a patient with distal gastroesophageal junction cancer. Axial and sagittal representations illustrate the dose distribution when the initial clinical target volume encompassing 5 cm of esophagus proximal to the tumor and 2 cm distal into the stomach is treated to 45 Gy using an AP/PA technique. An opposed lateral technique is used to boost the tumor and 2-cm margins to 50.4 Gy.

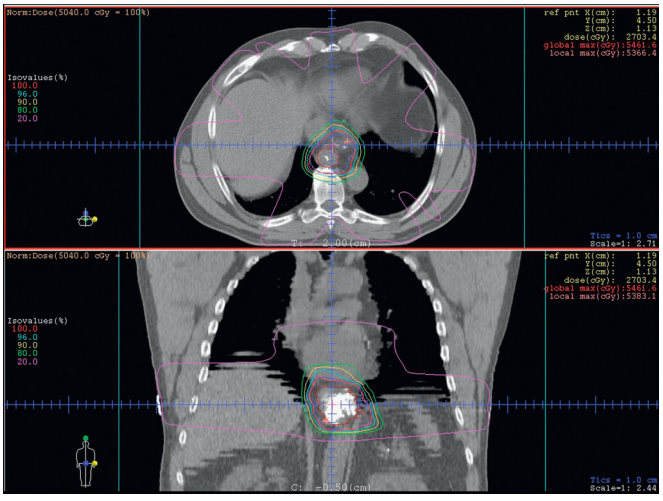

Figure 45-2 Intensity-modulated radiation treatment planning for a patient with distal gastroesophageal junction cancer. Axial and sagittal representations illustrate the dose distribution when the initial clinical target volume encompassing 5 cm of esophagus proximal to the tumor and 2 cm distal into the stomach is treated to 45 Gy to initial clinical target volume, followed by a boost to the tumor plus 2 cm to 50.4 Gy.

Other changes in treatment planning are being pursued with improved tumor localization. One study compared CT-based tumor volumes to PET/CT-based tumor volumes and demonstrated a change in target volumes for 84% of patients, with 48% with minor differences and 36% with major differences. These discrepancies were mostly in celiac or distant mediastinal lymph node involvement, resulting in a change in length of the tumor volume in 56% percent of patients.[374] It should be recognized that significant changes in treatment volumes may also increase treatment-related toxicity. Caution should be exercised in determining the exact size of a tumor from a PET/CT scan because the apparent size is determined heavily by the settings on the computer. FDG-PET

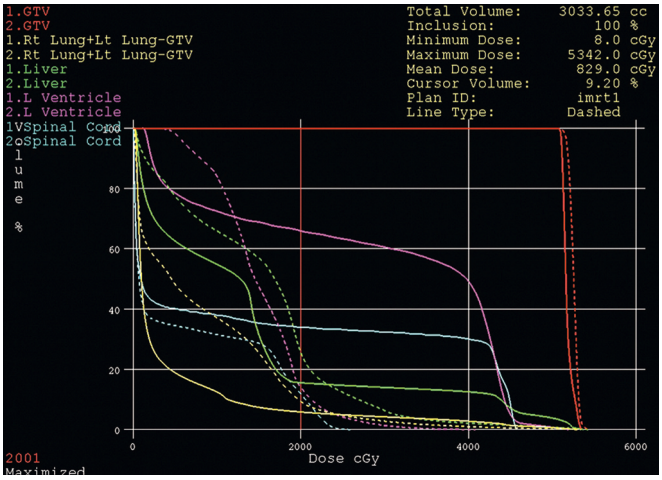

Figure 45-3 Dose-volume histograms compare dose delivered to surrounding normal tissues resulting from the three-dimensional treatment plan illustrated in Figure 45-1 *(solid lines)* and a seven-field intensity-modulated radiation therapy (IMRT) treatment plan *(dashed lines)* designed to treat the same volumes to the same dose (45 Gy to the initial clinical target volume, followed by a boost to the tumor plus 2 cm to 50.4 Gy). Note that mean doses of normal tissue are reduced, whereas the volumes of normal tissue receiving lower radiation doses (V10) increase for the IMRT plan compared with the three-dimensional conformal plan for all structures.

is perhaps most useful in finding areas of unexpected disease and determining the precise location of known lesions.

TREATMENT ALGORITHM, CONTROVERSIES, AND FUTURE POSSIBILITIES

Although surgery alone remains the standard of care in the management of early-stage localized esophageal cancer, combined-modality approaches have an important role for the typical patient with a locally advanced tumor. Figure 45-4 describes an algorithm for the treatment of esophageal cancer.

Today, the treatment of this disease requires a multimodality approach by the surgeon, radiation oncologist, and medical oncologist and a clear understanding of the interactions and toxicities associated with these modalities. Combined chemoradiation either as definitive therapy or in the preoperative setting is considered standard of care. The complications associated with multimodality therapy are significant and must be considered. Data supporting alternative treatment strategies including perioperative chemotherapy and preoperative chemotherapy followed by selective use of chemoradiation are emerging. Minimally invasive surgical techniques are promising options in selected patients. IMRT and improved tumor targeting may assist in reducing treatment-related morbidity. The use of FDG-PET response to direct therapy may be further explored depending on the results of the ongoing CALGB 80803 trial (NCT01333033) evaluating a response-adapted strategy using early FDG-PET imaging for treatment selection. We continue to evaluate novel treatment strategies using new systemic therapies, targeted agents, and radiation techniques to improve patient outcomes. We await the results of RTOG 1010 evaluating the addition of trastuzumab to chemoradiation in patients with operable, locally advanced adenocarcinoma of the esophagus and esophagogastric junction with HER2 positivity (NCT01196390).

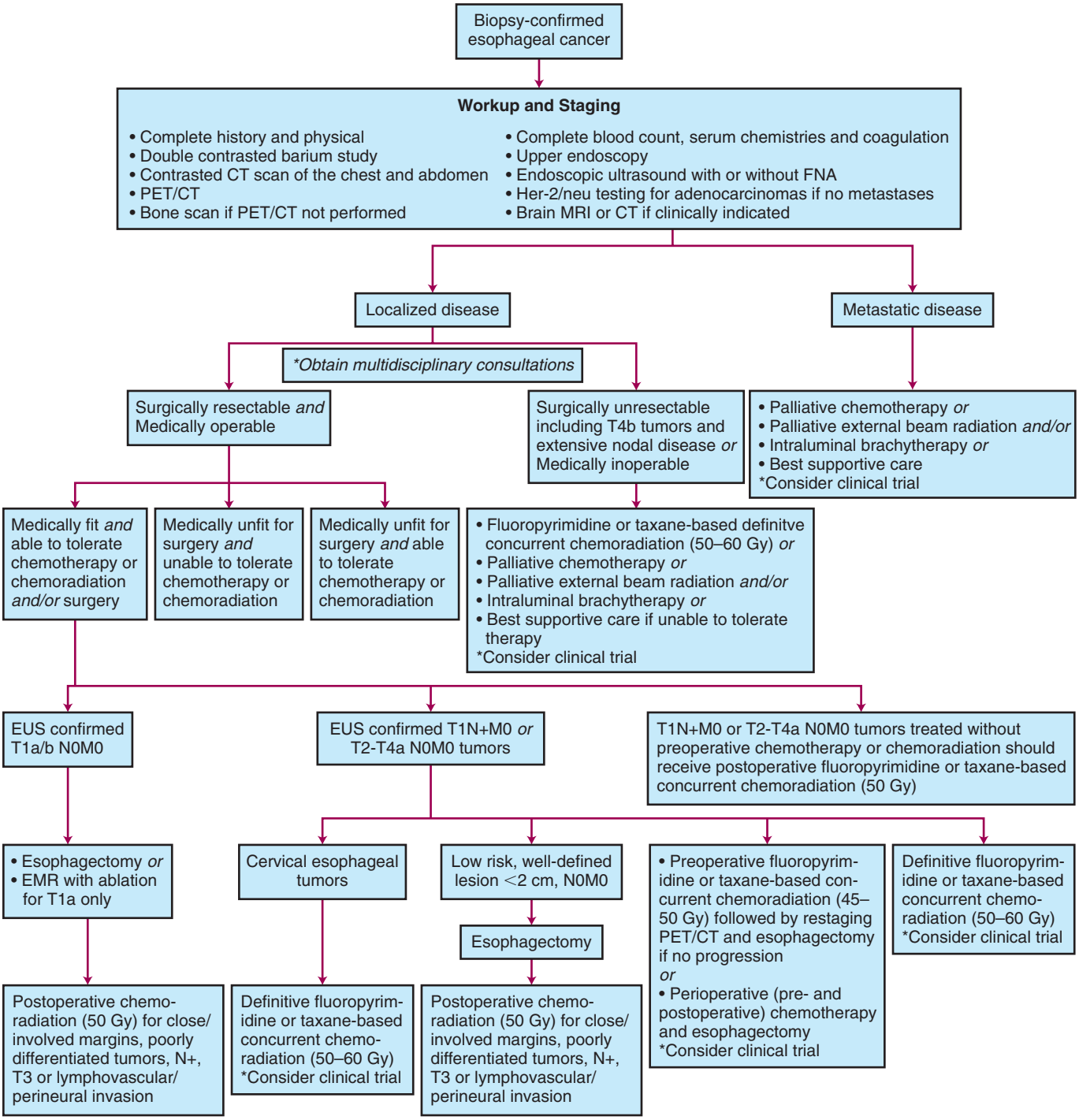

Figure 45-4 Treatment algorithm for newly diagnosed esophageal cancer. Treatment options for esophageal cancer are based in location and stage of the tumor, as well as surgical resectability and medical fitness of the patient. A multidisciplinary approach to the treatment of cancer usually includes combination therapy consisting of surgery and perioperative chemotherapy or chemoradiation, except in early stage, node-negative disease. Standard of care chemotherapy consists of fluoropyrimidine-or taxane- based regimens. Other chemotherapeutic regimens and/or targeted therapies should be considered on clinical trial. *CT,* Computed tomography; *EMR,* endomucosal resection; *EUS,* endoscopic ultrasound; *FNA,* fine-needle aspiration; *MRI,* magnetic resonance imaging; *PET,* positron emission tomography.

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