Modern Approaches to Localized Cancer of the Esophagus

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Abstract
The clinical spectrum of esophageal cancer has changed dramatically over the past couple of decades. Most notably, a profound rise in esophageal adenocarcinoma and decrease in the incidence of squamous carcinomas have occurred. An understanding of the factors that influence survival for patients with localized esophageal cancer has evolved concomitantly with these changes in epidemiology. Significant advancement in endoscopic and radiographic staging allows for more selective use of treatment modalities. The treatment of localized esophageal cancer mandates a multidisciplinary approach, with treatment tailored to disease extent, location, histology, and an accurate assessment of pretreatment staging. Despite these improvements in the staging and use of multimodality therapy, only modest improvements in patient survival have been observed. This article summarizes these modern approaches to localized cancer of the esophagus. (*JNCCN* 2011;9:902–911)

Esophageal cancer is a highly lethal disease, with approximately 16,640 new cases diagnosed and 14,500 related deaths each year in the United States.[1] Despite recent decreases in the overall incidence of cancer and cancer-related deaths in the United States between 1991 and 2006, the death rate from esophageal cancer in men has increased. This is likely attributable to an overall increase in the incidence of esophageal cancer,[1] which is driven by the profound rise in the incidence of esophageal adenocarcinoma. In the 1960s, squamous cell carcinoma accounted for more than 90% of all esophageal cancers. Although the overall incidence of squamous cell carcinomas has decreased in Western nations, the incidence of adenocarcinomas has increased 15% to 42% annually, with a 20.6% annual increase seen in the United States.[2] This translates into a 463% and 335% increased incidence in white men and women, respectively, between 1975 and 2004, with 58% of all esophageal cancers being adenocarcinoma in 2007.[3]

This change in the epidemiology of esophageal cancer has contributed to the confusion and controversy in the management of localized esophageal cancer. Most clinical studies in the treatment of esophageal cancer have included both squamous and adenocarcinomas. However, it is becoming clear that these entities differ in epidemiology, pathogenesis, and tumor biology. Squamous cancers arise most commonly in the proximal and middle esophagus, result from a progression from squamous epithelial dysplasia, and are associated with dietary and nutritional factors and, more importantly, tobacco and alcohol abuse. Adenocarcinomas arise in the lower third of the esophagus, are associated with gastroesophageal reflux disease and high body mass index, and most commonly result from the progression of Barrett's metaplasia spectrum. In recognition of the potential differences between squamous cell and adenocarcinomas, the 2010 American Joint Committee on Cancer (AJCC) TNM staging distinguishes between the histopathologies (see staging table, available online, in these guidelines, at www.NCCN.org [ST-1]).[4] However, most clinical treatment algorithms, including those from NCCN,[5] are just beginning to differentiate between adenocarcinoma and squamous cancers.

If localized esophageal cancer is defined as lesions that are amenable to locoregional treatment, approximately 50% of patients who present with esophageal cancer are candidates for potentially curative treatment.[6,7] The remaining patients have distant metastatic disease, extraregional nodal disease, or T4b tumors (involvement of the heart, great vessels, trachea), or are unable to tolerate surgery or multimodality therapy because of insufficient functional status. Even with optimal locoregional treatment of localized esophageal cancer, survival remains poor, with only 17% of all patients surviving 5 years, 37% of whom with localized disease, 19% with regional nodal involvement, and 3% with distant metastasis.[8] This has led to significant recent advances in preoperative staging modalities to optimize patient selection for treatment. In addition, treatment algorithms consisting of a combination of chemotherapy, radiation therapy, and surgery have been developed to optimize treatment of patients in need of multimodality therapy for intermediate-stage lesions that are at the highest risk for failure of locoregional control. This article summarizes these modern approaches to localized cancer of the esophagus.

Factors Influencing Survival

The tumor-specific factors that most influence survival in patients diagnosed with esophageal cancer include metastatic disease, nodal involvement, and depth of tumor penetration. For patients with metastatic esophageal cancer to other organs, 5-year survival is 3% or less. Patients with liver, lung, and other distant organ involvement are best treated with palliative intent. A more complicated issue involves metastatic disease to nonregional lymph nodes, including supraclavicular nodes in the setting of distal esophageal lesions, and celiac nodes in the setting of more proximal lesions. Although previously considered metastatic or M1a disease according to the previous TNM staging manual, this distinction is not made in the current 2010 TNM staging manual, which specifies number of regional lymph nodes rather than nodal station.[4] That said, most consider nonregional lymph nodes and nodes outside of the standard locoregional treatment field to be equivalent to metastatic disease and, therefore a contraindication to locoregional measures, including surgery. Bulky multistation mediastinal lymph-

adenopathy indicates locoregional advanced disease and a poor prognosis; these patients may benefit from chemoradiation.

For patients with localized esophageal cancer, the T (extent of tumor penetration of the esophageal wall) and N (nodal involvement) based on pretreatment staging are vital for determining appropriate treatment. These 2 factors are related in that the T stage usually predicts nodal stage. As tumor thickness advances from T1 (tumor invades lamina propria, muscularis mucosae, submucosa) toward T4 (tumor invades adjacent organs and structures), survival decreases. The 5-year survivals for T1, T2, T3, and T4 tumors are 69%, 51%, 17%, and 0%, respectively.[6] In recent reviews of resected esophageal cancer specimens, the 5-year survival in patients with T1a lesions (tumor invades lamina propria or muscularis mucosae) was 88% to 90% versus 47% to 62% for lesions involving the submucosa.[6,9]

The significant decrease in survival with progression of T stage beyond T1a is driven by the increase in nodal involvement beginning with T1b lesions. In a recent review of 85 resected T1 specimens, the risk of lymph node involvement was 0% for T1a lesions compared with 4% for T1b lesions with well/moderate differentiation and no lymphovascular invasion, 22% for T1b lesions with poor differentiation and no lymphovascular invasion, and 46% for T1b of any grade with lymphovascular invasion.[10] These data also validate the significance of differentiation and lymphovascular invasion in predicting survival. In a review of 99 patients with T1 lesions treated with resection, 5-year overall survival for lesions without lymphovascular invasion was 85% versus 36% with invasion ($P = .0001$). For T1b tumors without lymphovascular invasion, the survival was similar to T1a tumors (77% vs. 85%; $P = .08$) and superior to T1b tumors with lymphovascular invasion (27%; $P = .006$).[9] Furthermore, the likelihood of nodal spread increases with increasing depth of invasion thru the submucosa, with nodal involvement seen in 0% to 21% of patients with submucosa level 1 (sm1) disease, 26% to 33% for sm2 disease, 43% to 67% for sm3 disease.[11]

Nodal status seems to be the most important predictor of survival in patients with esophageal cancer. The presence of lymph nodes with metastatic disease and the overall number of involved lymph nodes correlate with survival. In patients with 1 pos-

itive lymph node, median survival decreased from 26 to 16 months.[12] Overall 5-year survival decreased from 55% in N0 patients to 31% in patients with 1 to 2 positive nodes.[6] Several recent reports have confirmed the significance of the number of positive nodes as an important negative prognostic factor. Overall 5-year survival decreased from 53% to 55% in patients with N0 disease to 27% to 31% in those with 1 to 2 positive nodes, and 6% to 7% in those with 3 or more nodes involved.[6,13] Although previously thought to be an independent predictor of poor survival, a recent series confirms that celiac nodes represent a continuum of nodal involvement rather than true metastatic or M1b disease. The 5-year survival was 45% in patients with N0 disease, 9% in those with N1 disease without celiac node involvement, and 11% in those with N1 disease with positive celiac nodes, confirming again that the number of positive nodes, not their location, correlates best with survival.[14–16] This is borne out in the current 2010 AJCC staging manual for both squamous and adenocarcinoma, in which nodal staging is based on number of positive nodes with N1 (1–2 positive nodes), N2 (3–6 positive nodes), and N3 (≥ 7 positive nodes), and final overall staging is a function of nodal involvement extent.[4] The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) and the AJCC guidelines recommend analysis of at least 15 lymph nodes in resected specimens. Both the AJCC and NCCN Guidelines include gastroesophageal junction tumors, as defined by Siewert and colleagues,[17] in the esophageal cancer staging and treatment algorithms.

Modern Staging

As the tumor thickness, nodal stage and presence of metastatic disease significantly influence outcome and, ultimately, treatment for patients with esophageal cancer. Appropriate and thorough pretreatment staging is imperative before treatment is initiated. The goal of this staging is to accurately characterize each of the AJCC TNM variables. An accurate pretreatment staging will then allow clinicians to stratify patients to treatment algorithms tailored to their disease stage.

As part of the initial evaluation leading to the diagnosis of esophageal cancer, most patients will have already undergone upper endoscopy with biopsy con-

firming the diagnosis of esophageal cancer. The upper endoscopy should note the location of the tumor relative to the teeth and esophagogastric junction (upper, middle, lower esophagus), length of tumor, and the extent of circumferential involvement and degree of obstruction. If present, the location, length and circumferential extent of Barrett's esophagus should be characterized and mucosal nodules carefully documented. Pathologic evaluation of the biopsy specimen should include a description of histopathologic type of tumor (squamous, adenocarcinoma) and histologic grade, because these variables influence tumor staging (see staging table, available online, in these guidelines, at www.NCCN.org [ST-1]).

After cancer is diagnosed, patients should then undergo a CT scan of the chest and abdomen to evaluate for extension of the tumor to adjacent mediastinal structures and exclude metastatic disease. Obliteration of fat planes between the esophagus and adjacent organs indicates local extension of the tumor. The presence of metastasis or direct extension into adjacent organs precludes curative treatment, except when resectable adjacent structures are involved (T4a extension), such as the pleura, pericardium, and diaphragm. CT is otherwise not useful in distinguishing across local T stage. The sensitivity and specificity of CT in detecting distant metastatic disease range from 33% to 81% and 82% to 96%, respectively.[15,16] For nodal disease, CT has a sensitivity of 47% to 84% and a specificity of 25% to 92%.

PET using fluorodeoxyglucose (FDG) is useful in staging patients with esophageal cancer. PET is especially useful for detecting occult metastatic disease, identifying metastatic foci not detected through other means in up to 15% of patients.[18] Ideally, CT should be combined with PET (PET/CT) to improve the sensitivity and specificity of the scan and the detection of metastasis.[19] Therefore, PET/CT is preferred over conventional CT in the initial staging of patients with esophageal cancer.

If the CT or PET/CT shows no evidence of metastatic disease, endoscopic ultrasound (EUS) is then performed to clarify the thickness (T) and nodal stage (N) of the lesion. The overall accuracy of EUS in predicting correct T stage is 72% to 80%.[20–22] The accuracy seems to be highest in T3 and T4 versus earlier-stage lesions. In T1 lesions, EUS can accurately predict submucosal involvement in 75% to 82% of cases.[23,24] The sensitivity of EUS in detecting

nodal metastasis is 63% to 89%, with a specificity of 75% to 81%.[16,25,26] The addition of fine needle aspiration (FNA) biopsy to EUS improves on the sensitivity, specificity, and accuracy compared with EUS alone.[27] FNA of suspicious lymph nodes should be performed if it can occur without traversing an area of primary tumor or major blood vessels, and if it will impact on treatment decisions.

With the PET/CT and EUS, an accurate pretreatment stage is established. As per NCCN Guidelines, patients are next discussed in a multidisciplinary treatment planning meeting, with input from representatives of all medical and support services involved in the care of the patient. For patients with localized esophageal cancer, this multidisciplinary review and treatment should occur at high-volume esophageal centers by experienced esophageal surgeons, endoscopists (especially when considering endoscopic mucosal resection or other ablative technologies), medical oncologists, radiation oncologists, radiologists, and pathologists. Outcomes in these high-volume centers, especially NCI-designated comprehensive cancer centers, are superior.[28,29] The remainder of this discussion focuses on management of patients with localized esophageal cancer who are medically fit to undergo treatment, including chemotherapy, radiation therapy, and surgery, as indicated. For purposes of this discussion, localized cancer is defined as esophageal cancer limited to the esophagus with or without regional nodal involvement.

Treatment of T1N0M0 Esophageal Cancer

Considerable recent changes have occurred in the management of patients with T1N0M0 esophageal cancer. These changes in treatment strategies have arisen out of a better understanding of the role of tumor progression from the mucosa (T1a) into the submucosa (T1b), and the associated risk for acquiring nodal spread in the natural history of this disease. All patients with a pretreatment T1N0M0 disease according to EUS and PET/CT should undergo endoscopic biopsy, preferably, endoscopic mucosal resection (EMR) biopsy of the lesion to evaluate for submucosal extension.

For patients with a T1aN0M0 tumor, treatment options include EMR with negative pathologic margins and ablation of at-risk adjacent mucosa or esophagectomy. The specific lesion characteristics that influence the outcome of EMR as a primary treatment modality for early-stage tumors are summarized in Table 1.[30] The rationale for endoscopic therapy of T1a lesions is based on the observation that these lesions almost never spread to regional lymph nodes and are, therefore, truly localized tumors. The results of EMR for T1a have been encouraging, with 93% to 99% local disease control.[31–34] Local recurrence after initial treatment is seen in 11% to 26% of patients and is almost uniformly managed with repeat EMR unless submucosal involvement is identified, at which point patients should undergo esophagectomy. EMR for T1a lesions has an 84% to 98% 5-year disease-free survival rate. Early severe morbidity is rare and includes bleeding and perforation in 1% of patients. Late complications, most notably stricture requiring endoscopic treatment, occur in 23% to 49% of patients, particularly in those who have undergone full circumferential EMR or circumferential ablation of long segments of Barrett's esophagus. No randomized studies have compared EMR with esophagectomy for T1a disease. Most therapeutic endoscopists endorse ablation of at-risk adjacent mucosa, including Barrett's metaplasia or squamous dysplasia. Proven methods of local endoscopic mucosal ablation include radiofrequency ablation, cryoablation, argon plasma coagulation, and photodynamic therapy. Figure 1 shows a successful EMR with radiofrequency ablation for a T1a esophageal adenocarcinoma in

Table 1	Risk Stratification for Endoscopic Therapy in Early Esophageal Cancer	
Low Risk	**High Risk**
ACA mucosal invasion (m1–sm1)	ACA submucosal invasion (sm2–sm3)
SCC mucosal invasion (m1–m2)	SCC submucosal invasion (m3–sm3)
No lymphovascular invasion	Lymphovascular invasion
Well or moderate differentiation	Poor differentiation
Size < 3 cm	Size ≥ 3 cm
No neural invasion	Neural invasion
High lymphocyte infiltration	Low lymphocyte infiltration

Abbreviations: ACA, adenocarcinoma; m1/2/3, mucosa layers 1, 2, and 3; SCC, squamous cell carcinoma; sm1/2/3, submucosa layers 1, 2, and 3.
Data from Ancona E, Rampado S, Cassaro M, et al. Prediction of lymph node status in superficial esophageal carcinoma. Ann Surg Oncol 2008;15:3278–3288.

Barrett's esophagus. After successful EMR treatment, patients should undergo surveillance endoscopy with biopsy every 3 months for 1 year, and then annually.

If the patient is medically fit, the other option for treating T1a disease is to proceed directly to esophagectomy. This approach has the advantage of eliminating all at-risk tissue, and the main disadvantage of the morbidity and mortality of esophagectomy. In experienced centers, the current mortality of esophagectomy is 4% to 10%, with a 26% to 41% overall morbidity.[35–37] No specific surgical approach to esophagectomy has proven superior to the others when comparing oncologic outcomes, including survival. Surgical approaches currently endorsed for esophagectomy are summarized in Table 2. Surgery should only be performed with curative intent. The goal of surgical resection is to remove all disease intrinsic to the esophagus and surrounding regional lymph nodes. The minimal proximal margin should be 10 cm.[38] The distal margin should be at least 5 cm from the closest palpable disease.[39] Therefore, lesions less than 5 cm from the cricopharyngeus muscle should be treated with definitive chemoradiation.

Two recent large population studies using the SEER database and the Worldwide Esophageal Cancer Collaboration database have shown improved overall and disease-free survivals with more extensive lymphadencectomy.[40,41] As per NCCN Guidelines, at least 15 regional lymph nodes should be retrieved and analyzed to optimize therapeutic benefit to the patient and ensure adequate nodal tissue for accurate staging. Reconstruction with a gastric interposition conduit via the posterior mediastinal esophageal bed is preferred.

Colonic interposition affords a good functional outcome but with significantly elevated perioperative risk.

For patients with T1bN0M0 disease, the increased risk of actual nodal involvement is significantly increased. For this reason, patients with T1bN0M0 tumors who are medically fit should undergo esophagectomy. Patients who are medically unfit for surgery should be considered for chemoradiation or palliative measures. Patients with T1bN1M0 disease should be treated with multimodality therapy, as is the case with more advanced localized tumors.

Treatment of T1b–3, N1–3, M0 Esophageal Cancer

Medically fit patients with T1b–3, N1–3, M0 disease and patients with T4a (involvement of pleura, pericardium, and diaphragm) should be considered for multimodality therapy, including chemotherapy, radiation therapy, or surgery. Options for treatment include definitive chemoradiation with salvage esophagogastrectomy, preoperative chemoradiation followed by esophagogastrectomy, preoperative chemotherapy followed by surgery and additional chemotherapy (for distal adenocarcinoma only), and esophagogastrectomy with adjuvant chemoradiation as indicated. Treatment of intermediate-stage localized tumors with radiation, chemotherapy, or surgery alone has proven less effective than multimodality therapies.

Because of poor outcomes in patients with localized intermediate-stage disease treated with surgery alone, chemoradiation as definitive treatment or used in a neoadjuvant approach followed by surgery
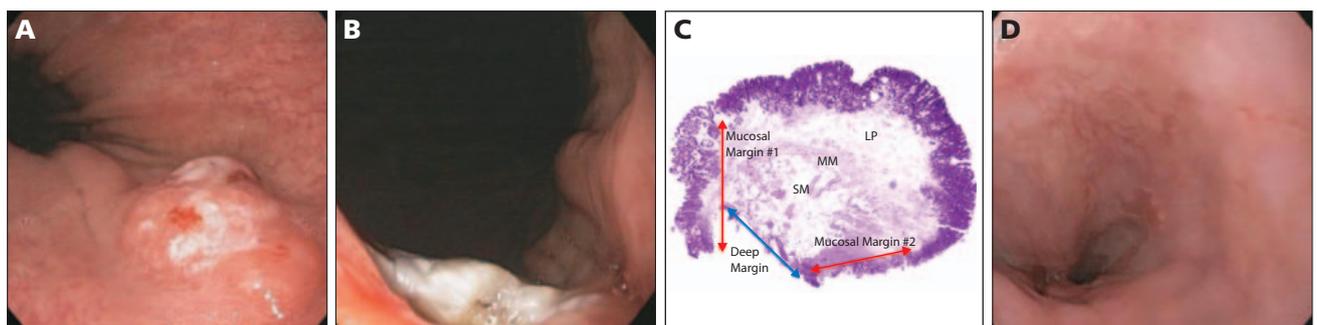
Figure 1   A) A 46-year-old man with Barrett's esophagus with nodule in a background of high-grade dysplasia. Endoscopic ultrasound shows a T1N0 nodule. B) Endoscopic mucosal resection of nodule. C) T1a moderately differentiated adenocarcinoma with no lymphovascular invasion nor invasive of the lamina propria and negative surgical margins. D) Endoscopy after radiofrequency ablation of the Barrett's esophagus showed no evidence of disease at 1 year.
Abbreviations: LP, lamina propria; MM, muscularis mucosae; SM, submucosa.

Table 2 Operative Approaches for Resectable Esophageal or Gastroesophageal Junction Cancer

Operation Name	Incision Location	Anastomosis Location
Ivor Lewis esophagogastrectomy	Laparotomy, right thoracotomy	Right chest
Transhiatal esophagogastrectomy	Laparotomy, cervical	Left neck
McKeown esophagogastrectomy	Laparotomy, right thoracotomy, cervical	Left neck
Minimally invasive Ivor Lewis	Laparoscopy, limited right thoracotomy or thoracoscopy*	Right chest
Minimally invasive McKeown	Laparoscopy, right thoracoscopy, cervical*	Left neck
Robotic minimally invasive		Variable (as above)
Left transthoracic or thoracoabdominal†		Left chest or neck

*For minimally invasive approaches, laparoscopy and/or a limited laparotomy may be used.
†For distal esophageal or gastroesophageal junction tumors only.

are the most widely used treatment strategies. The principles of systemic treatment for localized esophageal cancer are summarized in Table 3 and those for radiation treatment are summarized in Table 4. Of these approaches, preoperative chemoradiation with 4500 to 5040 cGy of radiation and concurrent chemotherapy is most commonly used. Recent meta-analyses support this recommendation, with improved 3-year mortality and reduced locoregional recurrence.[42–44]

Data from the recent CROSS trial conducted in the Netherlands strongly support the use of preoperative chemoradiotherapy over surgery alone in esophageal and gastroesophageal junction adenocarcinoma and squamous cancer.[45] This trial also used a more contemporary chemotherapy regimen: weekly carboplatin plus paclitaxel. Preoperative therapy conferred a median 2-year survival benefit compared with surgery alone. Pathologic complete response was reported in 30% of patients, and R0 resection was improved by 25% to 92% with preoperative therapy. Based on these results, proceeding directly to esophagectomy without preoperative treatment is an inferior option for patients with nodal or T3 disease. Clouding the interpretation of these analyses is the fact that most of the previous studies included both adenocarcinoma and squamous cell carcinoma, had variation in clinical staging, and had differences in the chemotherapy and radiation protocols.

Recent data showed that patients who underwent definitive chemoradiation for squamous cell carcinoma of the esophagus had equivalent outcomes to those who underwent neoadjuvant chemoradiation followed by esophagectomy.[46,47] With this in mind, a strategy of definitive chemoradiation with

careful endoscopic and radiographic assessment of response has gained acceptance for squamous cell carcinoma, because these patients who have experienced an endoscopic complete response are more likely to have a pathologic complete response with esophagectomy than those who have adenocarcinoma. The added value of surgery after chemoradiation in the setting of localized esophageal squamous cell cancer remains unclear.

Data supporting this approach for adenocarcinoma of the esophagus or gastroesophageal junction are lacking, and most favor resection in the setting of adenocarcinoma. Whether chemoradiation is used as a primary treatment strategy or a preoperative approach, posttreatment evaluation with follow-up CT scan, or preferably PET/CT, and upper endoscopy with biopsy are imperative among candidates for surgical resection. For patients in whom a neoadjuvant approach was planned, esophagectomy is the preferred next step in patients with either no evidence of disease or persistent localized disease. Alternatively, patients may undergo observation if neither PET/CT nor endoscopy with biopsy shows residual disease.

For definitive chemoradiation, the same follow-up algorithm is used, except that patients showing no disease after treatment undergo planned observation. In these patients, a history and physical are performed every 3 to 6 months for 1 to 2 years, every 6 to 12 months for 3 to 5 years, and then annually thereafter. Repeat radiographic imaging and endoscopy with biopsy are performed as clinically indicated by symptoms. For patients with localized recurrence, salvage esophagectomy is recommended, as is palliative systemic treatment or supportive mea-

sures in the case of metastatic or locally unresectable disease. Dosing of radiotherapy should be similar for preoperative versus definitive chemoradiotherapy, with doses of 5000 to 5040 cGy. Escalating the dose of radiotherapy to 6480 cGy in the recent INT 0123 failed to improve outcomes compared with conventional-dose radiation therapy.[48]

In patients with localized distal esophageal adenocarcinoma (a small fraction of the total study population in the MAGIC trial), a strategy of perioperative chemotherapy has shown a survival advantage over surgery alone.[49,50] In this approach, patients receive 3 cycles of ECF (epirubicin, cisplatin, and 5-FU) or modifications followed by surgery, and then an additional 3 cycles of chemotherapy. These data are derived from the British Medical Research Council (MAGIC) trial, which was a phase III trial involving patients with gastric, gastroesophageal junction, and distal esophageal cancers, only 26% of whom had distal esophageal adenocarcinoma. The usefulness of this strategy in treating more proximal tumors and squamous cell histology is not established. Preoperative chemotherapy has shown mixed results in trials involving esophageal squamous cancers, including negative results from INT 113 and positive results from OEO2, with both trials using 2 to 3 cycles of preoperative 5-FU and cisplatin.[51,52]

Although patients with T1bN1 or T2 or higher with any regional node involvement are best treated with multimodality therapy, proceeding directly to esophagectomy once localized esophageal cancer is diagnosed is acceptable. Further treatment depends on the surgical margins, nodal status, and histology. In patients undergoing complete resection (R0 resection) with squamous cell carcinoma, no further treatment is indicated. If a locoregional recurrence is observed during follow-up clinical examination, CT or PET/CT, or endoscopy with biopsy, patients should then be offered concurrent chemoradiation, chemotherapy, or best supportive care (Table 3). In patients with localized esophageal adenocarcinoma who have undergone R0 resection as primary treatment, observation is indicated for T1 or T2 and N0 tumors. In patients with high-risk T2N0 tumors (poorly differentiated histology, lymphovascular or neurovascular invasion, younger age), T3N0, or any tumor with positive regional lymph node involvement (N1–3), postoperative chemoradiation is indicated.[53] In patients with microscopic (R1) or mac-

roscopic (R2) residual adenocarcinoma or squamous cell carcinoma after primary surgical treatment, chemoradiation is indicated.

This discussion is predicated on patients with localized disease who are medically fit for surgery. In patients who are medically fit but do not elect sur-

Table 3	Chemotherapy Options for Localized Esophageal Cancer
Treatment Regimen	Evidence Level
Preoperative Chemoradiation	
Paclitaxel and carboplatin	1[54–56]
Cisplatin and fluoropyrimidine (5-FU or capecitabine)	1[47,57]
Oxaliplatin and fluoropyrimidine (5-FU or capecitabine)	2A[58]
Paclitaxel or docetaxel and cisplatin	2A
Carboplatin and 5-FU	2B
Irinotecan and cisplatin	2B[54,59]
Docetaxel or paclitaxel and fluoropyrimidine (5-FU, capecitabine)	2B[60]
Oxaliplatin, docetaxel, and capecitabine	2B
Definitive Chemoradiation	
Cisplatin and fluoropyrimidine (5-FU or capecitabine)	1[48,61]
Oxaliplatin and fluoropyrimidine (5-FU or capecitabine)	2A[62]
Paclitaxel or docetaxel and cisplatin	2A
Paclitaxel and carboplatin	2B
Irinotecan and cisplatin	2B
Docetaxel or paclitaxel and fluoropyrimidine (5-FU, capecitabine)	2B
Oxaliplatin, docetaxel, and capecitabine	2B
*Perioperative Chemotherapy**	
ECF (epirubicin, cisplatin, and 5-FU)	1[49]
ECF modifications	1[49,50]
Postoperative Chemoradiation†	
5-FU (bolus) and leucovorin	1[63]
LV5FU2 before and after infusion 5-FU or capecitabine	2A
Paclitaxel and 5-FU	2B[64]

*Only for adenocarcinoma of the distal esophagus or esophagogastric junction.
†Only for adenocarcinoma.

Table 4 Principles of Radiation Treatment for Localized Esophageal Cancer

Simulation	CT simulation
	Three-dimensional treatment planning
Treatment Planning and Delivery	
Gross tumor volume	Primary tumor and involved regional lymph nodes
Clinical tumor volume	Area at risk for microscopic disease
Planning target volume	5 cm cephalad 5 cm caudad 1.5–2 cm radial margin
Dose	4500–5040 cGy (1800–2000 cGy/d)[48]
Blocking (Normal Structure Dose Limits)	
Lung	Normal lung > 2 cm outside of target volume < 40 Gy
	≥ 20 Gy to < 20% of total lung ≥ 10 Gy to < 40% of total lung
Liver	60% of liver < 30 Gy
Spinal cord	Maximum < 45 Gy
Heart	One-third of heart < 50 Gy
Kidney	Two-thirds of one kidney < 20 Gy

gery, definitive concurrent chemoradiation is the optimal approach. In unfit patients, definitive chemoradiation, chemotherapy, radiation, or best supportive care are the options for treatment depending on the patient's performance status and ability to tolerate the toxicity of chemotherapy or radiation.

Conclusions

Esophageal cancer is a heterogeneous disease with 2 distinct histologies that span a wide spectrum of clinical stages at presentation. Therefore, the ideal treatment for these patients can vary. For patients with truly localized disease confined to the lamina propria or muscularis mucosae, truly localized treatment in the form of endoscopic mucosal resection is sufficient and appropriate. Beyond this earliest of stages, however, the risk of metastatic disease to regional lymph nodes and the deleterious consequences of nodal spread in terms of patient survival mandate multimodality therapy. For patients with these intermediate-stage localized lesions, a careful multidisciplinary treatment planning discussion should occur to optimize use of chemotherapy, radiation therapy, or surgery in the treatment of these pa-

tients. Treatment should be tailored to the patient's histology and TNM stage. However, even with current optimal multidisciplinary management of these patients, survival remains poor.

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