Multiple Management Modalities in Esophageal Cancer: Epidemiology, Presentation and Progression, Work-up, and Surgical Approaches

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LEARNING OBJECTIVES

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

1. Describe the epidemiology, work-up, and staging of esophageal cancer.
2. Identify the disease presentation, progression, and prognostic factors for esophageal cancer.
3. Discuss the surgical approach and management of esophageal cancer.

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ABSTRACT

Annually, approximately 13,200 people in the U.S. are diagnosed with esophageal cancer and 12,500 die of this malignancy. Of new cases, 9,900 occur in men and 3,300 occur in women. In part I of this two-part series, we explore the epidemiology, presentation and progression, work-up, and surgical approaches for esophageal cancer. In the 1960s, squamous cell cancers made up greater than 90% of all esophageal tumors. The incidence of esophageal adenocarcinomas has risen considerably over the past two decades, such that they are now more prevalent than squamous cell cancer in the western hemisphere. Despite advances in therapeutic modalities for this disease, half the patients are incurable at presentation, and overall survival after diagnosis is grim. Evolving knowledge regarding the etiology of esophageal carcinoma may lead to better preventive methods and treatment options for early stage superficial cancers of the esophagus. The use of endoscopic ultrasound and the developing role of positron emission tomography have led to better diagnostic accuracy in this disease. For years, the standard of care for esophageal cancer has been surgery; there are several variants of the surgical approach. We will discuss combined modality approaches in part II of this series.

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INTRODUCTION

It has been estimated that in 2001 there were 13,200 new cases and 12,500 deaths attributable to esophageal carcinoma in the U.S. [1]. Table 1 presents new cancer cases and deaths in the U.S. for a few selected sites for comparison. We use the ratio of deaths to new cases as a rough index of the overall degree of success of treatments for various cancers. We can, thus, anticipate that, nationwide and for all presentations and all management approaches, the curative success in dealing with cancer of the esophagus is less than 10%. Cancer of the esophagus occurs much less frequently than cancers of the breast, prostate, lung, or rectum (Table 1). With reference to ratios of deaths to new cases, roughly 80% of cancers of the breast, prostate, and rectum can be treated successfully in the U.S. Lung cancer, however, resembles esophageal cancer in that less than 10% of patients in our country are treated successfully. Lung cancer occurs less commonly than breast or prostate cancers, but accounts for more cancer deaths than the other four sites combined.

There is an approximate 3:1 male predominance in esophageal cancer incidence and death. One factor in the poor results obtained for the treatment of esophageal carcinomas is that half the cases are unresectable or metastatic at presentation.

The cervical esophagus begins at the cricopharyngeus muscle at the level of the cricoid cartilage and extends 6 cm to enter the thoracic inlet. The intrathoracic esophagus extends for another 20-25 cm to the gastroesophageal junction. The American Joint Committee on Cancer (AJCC) divides the esophagus into four regions: cervical, upper thoracic, midthoracic, and lower thoracic [2].

The predominant histological types of esophageal carcinoma are squamous cell carcinoma (SCC) and adenocarcinoma (AC). Less common histologies include adenoid cystic, mucoepidermoid, adenosquamous, undifferentiated, and malignant melanoma, all of which have poor prognoses. Small cell carcinoma can also occur in the esophagus, and it has a course similar to that in the lung [3]. Non epithelial tumors in the esophagus are rare; the most common type is leiomyosarcoma and the most common metastatic source to the esophagus is the breast [4]. In the 1960s, more than 90% of all esophageal tumors were SCCs. The incidence of esophageal AC has risen considerably over the past two decades such that it is now more prevalent than SCC in the western hemisphere. The rise in esophageal AC, particularly in the distal esophagus, has been paralleled by a rise in gastric cardia AC. This leads to the concept of gastroesophageal junction AC.

The standard of care for esophageal cancer had been surgery alone for many years. There are several different surgical approaches in use, with various advantages and disadvantages and with differences in procedure preference in different parts of the world. We review the epidemiology, etiology, presentation and work-up, and surgical approaches for esophageal cancer in this paper.

EPIDEMIOLOGY AND ETIOLOGY

The incidence of esophageal cancer varies considerably with geographic location and also, to some extent, among ethnic groups within a common area. Some of the highest rates occur in northern China and northern Iran, where incidence exceeds 100 in 100,000 individuals; in the U.S., the incidence is less than 5 per 100,000, although rates are nearly quadruple for African Americans [4]. In Linxian, Hunan province, China, esophageal cancer is endemic and has been directly related to nitrosamines and inversely related to consumption of riboflavin, nicotinic acid, magnesium, and zinc [5]. SCC predominates in African Americans over Caucasians by a ratio of 6:1, and AC has the opposite preponderance, occurring in Caucasians over African Americans at a ratio of 4:1 [6]. Nearly 30 years ago, AC accounted for only 15% of cases of esophageal cancer, but the incidence of AC has increased more than 350% since 1970, surpassing SCC since 1990; this increase is also seen, to a lesser extent, in African Americans [7, 8]. In the Far East, no increase in AC has been observed, and SCC continues to be the more common histology [9]. In the western world, there is less impact from dietary factors, such as nitrosamines, due to different food preservation techniques, and the primary etiology of esophageal cancer is the use of tobacco and alcohol, which have a synergistic effect; there are very strong risk factors for SCC and moderate risk factors for AC [10]. Tobacco exposure has been linked to a tenfold higher risk for esophageal SCC in heavy smokers relative to nonsmokers, and the risk is directly related to the duration of exposure [7, 11]. In contrast, smoking has been linked to only a twofold greater risk for esophageal AC in smokers relative to nonsmokers [8, 12]. There is a greater than multiplicative effect between smoking and alcohol consumption that occurs in SCC; for AC, the effect...
is only additive [13]. The exception to this may be the consumption of hard liquor, which has been found to have a stronger association with AC than with SCC [14]. The relative risk of esophageal AC remains high up to 30 years after smoking cessation, in contrast to the significant decline in risk of SCC within a decade of smoking cessation [15].

Several studies have linked obesity to the risk for esophageal AC. Increasing body mass index (obesity) correlates with increasing risk for esophageal AC, but decreasing risk for esophageal SCC [4]. Obesity promotes gastroesophageal reflux disease (GERD) by increasing intra-abdominal pressure; GERD, in turn, promotes the formation of Barrett’s esophagus (BE)—a metaplastic precursor of AC [16, 17]. Multiple studies have shown that the bacterium Helicobacter pylori has an inverse relationship with the risk for esophageal cancer but causes a greater risk for gastric cancer [18]. H. pylori is thought to protect against the risk of esophageal AC because it promotes achlorhydria, implying lower acid production and reflux [15]. As rates of H. pylori infection have decreased in the U.S. and Europe, there has been a parallel rise in the incidence of GERD (an independent risk factor for esophageal AC) and BE [9]. Prior aerodigestive tract malignancies predispose to a higher risk for esophageal cancer, primarily through field carcinization. Ten percent of second primary cancers in patients with prior oropharyngeal cancer or lung cancer occur in the esophagus [19, 20]. Chronic inflammation and stasis, which occur with strictures caused by caustic injury and achalasia, are long-term risks for esophageal SCC; in addition, patients with taylorosis, which is inherited in an autosomal dominant fashion, and Plummer Vinson syndrome have a definite greater risk for esophageal SCC [21].

The definition of BE has evolved from simply a columnar-lined esophagus to at least 3 cm of columnar lining or metaplasia in the esophagus [21, 22]. Approximately 0.5%–2% of adults in the western world have BE, with prevalences greater in Caucasians and men and with increasing age until the eighth decade of life [23, 24]. In a review of 51,311 patients at the Mayo Clinic, the length of BE epithelium did not increase significantly with age, suggesting that BE does not progress with age and is latent for several years before being discovered [24]. GERD affects up to 44% of the general population in the U.S., but only 10% of people with GERD develop BE [25, 26]. Recurrent symptoms of reflux have been associated with a 7.7 times greater risk for esophageal AC, with more frequent, more severe, and longer-lasting reflux resulting in a 43.5 times higher risk for esophageal AC [26]. Patients with BE have a 40-fold greater risk or 0.5% risk per patient year of developing esophageal AC [27]. A middle-aged patient who develops BE has a 10%–15% risk of developing esophageal AC during his lifetime [28]. Specific risk factors that predispose for the progression of BE to AC include hiatal hernia of at least 3 cm in length, length of BE, and the presence of dysplasia [29]. In addition, increased bile acid exposure is thought to exacerbate esophageal mucosal injury and to promote the neoplastic process [23, 30].

Esophageal cancers, both SCC and AC, typically have aberrant cell-cycle regulation. Mutations occur in oncoproteins such as EGFR, erbB-2, and cyclin D1, and in tumor suppressors such as 3p(FHIT), Rb, p53, p16, p14ARF, and telomerase, which affect the G1 restriction point. Cyclin D1 directly regulates phosphorylation of the Rb protein at the G1 restriction point facilitating G1/S transit. About 40%–60% of esophageal carcinomas and 30% of premalignant lesions overexpress cyclin D1. Cancers that retain normal Rb expression typically overexpress cyclin D1, whereas those that lack normal Rb have normal cyclin D1 levels. The p53 gene product regulates cell-cycle progression, DNA repair, neovascularization, and apoptosis; 50%–80% of esophageal carcinomas have p53 mutations. Malignancy is facilitated by inactivation of the growth constraints imposed by the Rb and p53 suppressor pathways, but also requires activation of telomerase, a ribonucleoprotein that adds hexamer DNA repeats to the ends of chromosomes to prevent loss of telomere length in DNA replication. Elevated telomerase expression is found in high-grade dysplasia as well as virtually all esophageal carcinomas. Several of the individual aforementioned factors have been shown to carry prognostic significance [21].

Part of the problem in dealing with esophageal carcinomas is that half the patients present with unresectable or metastatic cancers; if a screening program could detect disease at an earlier stage, there could be a greater possibility of cure. In comparison, there is considerable evidence that the combination of physical examination with mammography used as a screening tool decreases the death rate from breast cancer [31]. However, several studies have failed to demonstrate the benefit of a decreased death rate due to lung cancer from screening chest x-rays and physical examinations [32]. Unfortunately, the value and cost-effectiveness of endoscopic surveillance for esophageal cancers has not been demonstrated. In 11 screening studies with 1,127 patients with BE, only 3.5% actually progressed to cancer [33]. To date, there is no solid evidence that screening reduces the esophageal AC death rate [34].

Proponents argue that screening, to be productive, should be focused on patients with multiple risk factors: GERD, Caucasian race, male gender, age greater than 50 years, and long duration of symptoms. Small studies have suggested that surveillance can identify neoplasms that are at an earlier stage and, thus, potentially curable [35-38]. However,
these hopeful results may be confounded by lead time bias, length time bias, and pseudodisease [37]. Furthermore, even if surveillance were effective, it is unlikely to impact mortality soon because few patients with esophageal cancer are diagnosed via surveillance programs. Less than 5% of patients with esophageal cancer were known to have had BE before they sought help for symptoms of cancer, and up to 40% had no prior history of GERD [39, 40]. Most patients with BE die from unrelated causes, and the presence of BE does not change life expectancy or overall survival [41, 42]. Currently, the American College of Gastroenterology recommends that surveillance endoscopy for BE be guided by the presence of dysplasia. If dysplasia is not present, endoscopy is recommended every 3 years, and if low-grade dysplasia is present, it is recommended that endoscopy be done every 6 months for 1 year and yearly thereafter if no progression is seen [43]. If high-grade dysplasia is present, this finding should be confirmed by an experienced pathologist and the patient should be offered either esophagectomy or intensive surveillance (endoscopy every 3 months) [43]. The technique of four-quadrant biopsies taken every 2 cm of BE segment during endoscopy is optimal [44]. Dysplasia is currently the best pathological predictor of cancer development.

DISEASE PRESENTATION, PROGRESSION, AND PROGNOSTIC FACTORS

The most common presenting symptoms of esophageal cancer are dysphagia and weight loss. Less common symptoms include odynophagia, cachexia, melena, retrosternal pain, and hoarseness [45]. Cancers of the esophagus must involve at least 75% of the circumference before the sensation of food “sticking” or blockage is experienced. As noted above, about one-half of esophageal cancer patients present with locally advanced unresectable disease or distant metastasis. The extent of wall penetration and lymph node metastases are more important prognosticators of survival than tumor length or functional obstruction [21].

Esophageal AC spreads via transverse penetration through the full thickness of the wall, whereas SCC tends to spread linearly in a submucosal fashion [46]. Esophageal cancer spreads through extensive lymphatic channels with an erratic pattern including “skip metastases” being observed in autopsy specimens; in addition, up to 71% of frozen tissue sections classified as tumor free by conventional histopathology have been positive for lymphatic micrometastases when tested by immunohistochemistry [47]. This micrometastatic disease has been shown to be a significant independent adverse prognostic factor for relapse-free survival and overall survival [48]. Routine use of immunohistochemistry in conjunction with extensive lymph node sampling has been advocated as an advance over the traditional staging work-up.

Histologic tumor type is an independent prognostic factor in esophageal cancer patients who have had surgical treatment. Siewert et al. analyzed 1,059 patients who had undergone resection and found that overall survival at 5 years was 46.8% for the AC group versus 37.4% for the SCC group; patients with early-stage AC had a much lower incidence of lymph node involvement than their SCC counterparts, and it was hypothesized this was due to occlusion of lymphatic channels secondary to the inflammatory changes of GERD in AC [49]. Tumor size less than 5 cm, upper third esophageal location, female sex, and age less than 65 years have all been noted to positively influence outcome [50, 51]. Conversely, weight loss, low Karnofsky performance status, deep ulceration of tumor, sinuses tract formation, and fistula formation have all been found to be poor prognostic factors [21, 50].

STAGING AND WORK-UP

The AJCC has established a staging system for esophageal cancer that is based on the tumor-node-metastasis (TNM) system and is, in essence, a pathological staging system [2]. Table 2 illustrates the AJCC staging classification of esophageal cancer. Only the depth of penetration is taken into account for the T staging, not the length of the tumor, extent of involved circumference, or degree of lumen narrowing. Clinical staging takes into account the amount of disease that is present before treatment and is based on history, physical examination, biopsy, laboratory studies, endoscopic examination, and imaging such as endoscopic ultrasound (EUS), computed tomography (CT) scan and positron emission tomography (PET) scan. Pathologic staging is based on examination of the surgically resected esophagus and lymph nodes. Spread to the celiac lymph nodes is considered a site of distant metastasis, as are cervical nodes occurring with an esophageal primary elsewhere than in the cervical esophagus [2].

The appropriate work-up for a patient suspected of having esophageal cancer should include a thorough history and physical exam with special attention to the supraclavicular and cervical lymph nodes. Fine-needle aspiration should be performed on any palpable cervical lymph node to rule out extrathoracic spread of disease. Blood tests, a chest x-ray, and a double-contrast barium swallow should follow. CT scans of the chest and upper abdomen should be obtained to further characterize the lesion and evaluate for metastatic disease. Esophagoscopy, with the intent of tissue biopsy and detailed characterization of the lesion, should be pursued with an emphasis on how far the lesion is from the incisors and the squamocolumnar junction; in addition, the presence of esophagitis or BE should be noted [21]. Brushings should be obtained before biopsy, and these two procedures together
Esophageal Carcinomas

Table 2. AJCC staging classification of esophageal cancer

<table>
<thead>
<tr>
<th>Primary tumor (T)</th>
<th>Regional lymph nodes</th>
<th>Distant metastasis (M)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TX: Primary tumor cannot be assessed</td>
<td>NX: Regional lymph nodes cannot be assessed</td>
<td>MX: Presence of distant metastasis cannot be assessed</td>
</tr>
<tr>
<td>T0: No evidence of primary tumor</td>
<td>N0: No regional lymph node metastasis</td>
<td>M0: No distant metastasis</td>
</tr>
<tr>
<td>Tis: Carcinoma in situ</td>
<td>N1: Regional lymph node metastasis</td>
<td>M1: Distant metastasis</td>
</tr>
<tr>
<td>T1: Tumor invades lamina</td>
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<td></td>
</tr>
<tr>
<td>T2: Tumor invades muscularis propria</td>
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<td></td>
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<tr>
<td>T3: Tumor invades adventitia</td>
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<tr>
<td>T4: Tumor invades adjacent structures</td>
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Stage grouping

Stage I: T1N0M0
Stage IIA: T2N0M0; T3N0M0
Stage IIB: T1N1M0; T2N1M0
Stage III: T3N1M0; T4, any N, M0
Stage IV: Any T, any N, M1
Stage IVA: Any T, any N, M1a
Stage IVB: Any T, any N, M1b

For the cervical esophagus, the cervical nodes (including the supraclavicular nodes) are considered regional; for the intrathoracic esophagus, the mediastinal and perigastric lymph nodes (excluding the celiac nodes) are considered regional.

T1 has been further subdivided into T1M, cancer confirmed to the mucosa, and T1Sm, cancer invading the submucosa.

achieve a diagnostic accuracy of 99% [52]. In lesions that appear borderline for the endoscopist, the use of Lugol’s iodine can help distinguish normal mucosa by selectively staining it and leaving the abnormal mucosa identifiable for biopsy [53]. Finally, patients with upper- or middle-third esophageal cancers or symptoms of hoarseness or hemoptysis should have a bronchoscopy to rule out laryngeal nerve involvement or tracheobronchial fistula [21].

Conventional CT scans can accurately determine resectability 65%–88% of the time [54, 55]. CT accurately predicts T stage in 70% of cases and N stage in about 50%–70% of cases [54-56]. Secondary to poor sensitivity, CT may not be the optimal modality to evaluate celiac lymph nodes and T4 disease or response to neoadjuvant chemoradiotherapy. The sensitivity and specificity of CT for pathologically positive celiac lymph nodes are 30% and 93%, respectively, and for T4 disease, are 25% and 94%, respectively [57, 58]. With respect to assessing response after chemoradiation, no correlation has been found between tumor volume reduction on serial CT examinations and pathological assessment of tumor response or patient survival [55].

EUS has improved the preoperative staging of esophageal cancer, particularly in regard to T and N staging [59]. In a meta-analysis of 27 studies, the accuracy of EUS for T staging was 90% and for N staging was 80%, and a further review of the literature supports an overall accuracy for EUS of approximately 85% for T staging and 75% for N staging [59-61]. However, the utility of EUS in detecting distant metastases other than celiac metastases is low, secondary to limited depth of penetration, and therefore, CT is still a necessary and complementary part of the staging work-up [62]. EUS detection of celiac lymph node disease correlates with overall survival and has a sensitivity of 70%–80% and a specificity of 97% [57, 63-65]. EUS also has been useful in evaluating recurrence after resection; in a study evaluating 40 patients with suspected recurrence, the sensitivity and specificity of EUS were found to be 95% and 80%, respectively [66]. One problem with EUS specificity in that study of possible recurrences were the false positives reported for anastomotic thickening because of inflammation. Other limitations to EUS include its decreased sensitivity in the presence of stenosis and its unreliability in assessment of the response to neoadjuvant therapy [67, 68]. In three studies involving 196 patients, the accuracy of EUS after neoadjuvant therapy ranged from 27%–48% for T staging and 38%–71% for N staging [68-70]. This significantly lower accuracy is attributable to the failure of EUS to distinguish between tumor and postradiation fibrosis and inflammation.

Fluorodeoxyglucose (FDG)-PET is rapidly evolving as an important tool in the noninvasive staging of patients with esophageal cancer. Kole et al. prospectively evaluated 26 patients and found the diagnostic accuracies in determining
resectability to be 65% for CT and 88% for PET; for CT and PET together, an accuracy of 92% was achieved [54]. The accuracy of PET in detecting primary tumors is 78%; nodal metastases are visualized by PET in 86% of cases [71, 72]. A particular advantage of FDG-PET has been its greater accuracy in detecting distant metastatic disease than CT alone or combined with EUS (86% versus 62%), but it has a lower accuracy in detecting local nodal disease than CT alone or combined with EUS (48% versus 69%) [73-75]. FDG-PET has also demonstrated greater accuracy than other methods in detecting recurrences other than perianastomotic recurrences [76]. The quantitative decrease in FDG uptake seen after neoadjuvant therapy has been correlated with histopathologic assessment of viable tumor cells, time to disease progression, and overall survival [77-79]. FDG-PET may assist in determining response to neoadjuvant therapy, which subsequently could aid in the selection of patients who will benefit from surgery and avoid excess morbidity and mortality in those who are unlikely to respond [80]. Minimally invasive staging, including thorascopic and laparoscopic methods, remains the most accurate method to detect distant metastases and determine resectability. Although PET had a better accuracy than CT in detecting distant metastases (84% versus 63%), minimally invasive staging was even better, determining resectability with an accuracy of 97%, compared with only 61% with EUS and CT [81, 82].

SURGERY

Esophagectomy remains the standard of care for the treatment of early-stage tumors confined to the esophagus and paraesophageal region. There is controversy about whether en bloc resection with extended lymph node dissection confers any advantage in curative management. The two most common approaches for definitive resection are the transthoracic esophagectomy (TTE) and the transhiatal esophagectomy (THE). TTE is the most common approach used worldwide, whereas THE is more common in the western world. Advantages of TTE include better visualization, access, and resection of the upper two-thirds of the esophagus and mediastinal disease and avoidance of blind blunt dissection with tumors of the midthoracic esophagus [21]. The rate of resectability of esophageal cancer is reported to range from 60%-90%, hospital mortality after resection ranges from 1.4%-23%, and the resulting 5-year overall survival rate ranges from 10%-25% [83-86]. Five-year survival rates reported for stage I esophageal cancer range from 80%-94% and, for stage III, rates range from 10%-14% [83, 84]. Advantages of THE include the avoidance of morbidity, including the respiratory compromise associated with thoracotomy, and the fact that if a leak does occur it will be in the neck where it is more accessible [82]. Operative mortality has ranged from 1% to 4%, and the 5-year survival rate has ranged from 20%-25% overall, with that of stage I as high as 65% and that of stage III as low as 10% [87-91]. Two randomized trials and a meta-analysis concluded that there were no significant differences between TTE and THE with respect to overall morbidity, operative mortality, and long-term survival [87, 92].

For tumors below the tracheal bifurcation, radical en bloc esophagectomy or two-field dissection has been recommended [93, 94]. The surgical objective is to achieve extensive margins, with removal of the upper abdominal, retroperitoneal, and mediastinal lymph nodes, the pericardium, periaortic tissue, bilateral pleura, ayzyous vein, and thoracic duct [93, 95]. Proponents of this radical operation argue that the technique is a better attempt to obtain the benefits of a resection with no residual disease (R0). Achievement of R0 status has been reported to be a prognostic factor for long-term survival [96, 97]. In a study of 500 patients undergoing TTE, patients with an R0 resection had a 5-year survival rate of 29% in contrast to those with microscopic residual (R1) or macroscopic residual (R2) disease, none of whom survived 5 years [84]. Some have doubted the value of the en bloc approach, theorizing that esophageal cancer systemically spreads at onset and lymphatic dissection is, therefore, palliative rather than curative [98]. The counter argument from those viewing the disease progression as sequential, from primary site to lymph nodes and then to distant sites, is that dramatically low rates of local recurrence are better achieved with en bloc resection, which results in better long-term survival [94, 99, 100]. Local recurrence rates after en bloc resection have ranged from 1%-8%, operative mortality rates have ranged from 3%-6%, and the 5-year overall survival rate has ranged from 30%-52% [98, 100, 101]. A survival advantage for patients with advanced primary and nodal disease with en bloc resection has been claimed in small retrospective studies [94, 101, 102]. The superior survival evinced in node-positive patients lends credence to the theory that disease progression is sequential and that removal of the involved nodal groups is therapeutic and potentially curative. Reservations in asserting a superiority for the en bloc resection include dependence on retrospective rather than randomized study data, with selection bias and stage migration as a result of more accurate staging (Will Rogers effect). In a study by Hagen et al., patients selected to undergo en bloc resection were chosen based on the presence of limited disease and “good general health,” while those with “poor physiologic reserve” and more advanced disease underwent THE, clearly a selection bias [102]. The selection of young patients with limited disease and excellent performance statuses for en bloc resection has been corroborated by others [103].
Japanese surgeons routinely extend the en bloc or two-field dissection into the neck, mediastinum, and upper abdomen, creating a three-field dissection. This is based on the finding that cervical nodal metastases occur in up to 46.3% of upper-third tumors and in up to 27% of lower-third tumors in patients undergoing three-field lymph node dissection [104]. Two randomized trials have been done in Japan comparing three-field radical surgery with two-field radical surgery. In one study, the 5-year survival rate was significantly better with the three-field procedure (48% versus 33%) and, in the other study, a survival difference was not noted; however, in both studies, there was a selection bias toward younger, earlier stage patients being allocated to three-field radical surgery [105, 106]. In the western world, three-field surgery has also been investigated in the institutional setting. Lerut et al. analyzed 37 patients undergoing three-field radical resection and found that the extended field improved staging accuracy (30% of patients had pathologic cervical nodes and 17% of gastroesophageal junction tumors had positive cervical nodes) but did not change overall survival [107]. Altorki et al., in the largest western study of three-field radical resection, prospectively analyzed 80 patients undergoing the procedure and found an operative mortality of 5%, cervical nodal involvement of 36%, and a 5-year survival rate of 51% (88% in node-negative patients and 25% in node-positive patients) [108]. Differences in dissection technique around the recurrent laryngeal nerve may account for the low rates of recurrent laryngeal nerve injury, only 6% in that study, dramatically lower than the up to 70% observed in Japanese reports [96, 108].

An impairment to quality of life with respect to speech and swallowing has been chronicled in up to 20% of patients for up to 5 years postoperatively and must also be a serious consideration. Both en bloc dissection and three-field resection may offer a survival benefit but, before these techniques can be widely adopted, we need more experience and randomized studies to substantiate the benefit of such radical surgery.

**CONCLUSIONS**

The overall results of treatment for esophageal cancer in our country continue to be poor, with over 90% of the new cases each year eventually succumbing to this disease. In part I of this two-part series we have covered the issues of epidemiology, work-up and staging, prognostic factors, and surgical treatment. More radical surgical approaches may have the potential of gaining an advantage in local-regional control, and perhaps ultimately survival, although perhaps at a cost in terms of the morbidity of the procedure. In part II we will explore the integration of chemotherapy and radiation therapy into multimodal management approaches to the disease.

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