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Review

Esophageal cancer: An update

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ABSTRACT

Esophageal cancer continues to be a lethal disease with the majority of patients presenting at an advanced stage. The incidence of adenocarcinoma is rising. Although Barrett's esophagus has been well characterized, specific pathways to the development of adenocarcinoma remain undefined. Current treatments for locoregional esophageal cancer include surgery, chemotherapy, radiation therapy, or a combination of these modalities. Optimal surgical treatment strategies include appropriate patient selection, accurate staging and risk assessment, selection of an appropriate surgical approach, and the use of multimodality treatment. This article provides an update on the myriad of options for managing esophageal cancer and outlines the surgical technique for minimally invasive esophagectomy used at our center.

1. Introduction

Esophageal cancer continues to be a fatal disease throughout the world. The rate of increase in the incidence of esophageal adenocarcinoma (EAC) has been higher than any other cancer in the United States.[1] This rise parallels the increased prevalence of both gastroesophageal reflux disease (GERD) and obesity.[1] Historically, squamous cell carcinoma of the esophagus (SCC) was the most common esophageal malignancy internationally, accounting for more than 90% of esophageal cancers.[2] However, in the last three decades, there has been a rapid rise in the incidence of EAC with reported increase in white males of 463% (from 1.01 per 100 000 person-years in 1975–1979 to 5.69 per 100 000 person-years in 2000–2004).[1] A similar rapid increase was also apparent among white women, in whom the adenocarcinoma rate increased 335% (from 0.17 to 0.74 per 100 000 person-years, over the same time period).[1,2] EAC is now the predominant esophageal cancer in the Western world.[2,3] The National Cancer Institute reported 13 900 new cases and 13 000 deaths from esophageal adenocarcinoma in 2003 and anticipated 16 470 new cases and 14, 539 deaths in 2009.[3]

The American Cancer Society Cancer 2009 statistics state that the 5-year survival rate for all patients with esophageal cancer is only 17%, with better survival for local (33.7%) or regional (16.9%) compared to distant (2.9%) disease at presentation.[2] When patients are identified with *in situ* cancer (high-grade dysplasia) and T1 (mucosal or submucosal invasion) lesions, 5-year survival improves to 95–100%.[4] Recent advances in the diagnosis, staging, and treatment of this neoplastic condition have led to small but significant improvements in survival.[5]

2. Barrett's esophagus

Barrett's esophagus (BE) is characterized by replacement of squamous epithelium of distal esophagus with specialized columnar epithelium with goblet cells. It develops in 5–8% of patients with GERD.[6] Esophageal adenocarcinoma develops in approximately 0.5% of patients with BE per year and GERD is the main recognized risk factor.[7] However, in 10–30% of patients with EAC, BE is not found.[7] It is now generally accepted that Barrett's epithelium can progress through a metaplasia-dysplasia-carcinoma progression but the natural history of dysplasia in Barrett's esophagus is not well defined. Identification of high-grade dysplasia (HGD) has been considered an indication for esophagectomy or aggressive endoscopic treatment, since occult invasive caner has frequently been identified at the time of resection. Without treatment, invasive cancer develops within 3 years in up to half of patients with HGD.[8]

3. Staging

The TNM classification system is traditionally used to stage esophageal carcinoma (Table 1). T1a lesions have less chance of nodal spread with most series showing less than an incidence of

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Table 1
TNM classification for staging of esophageal carcinomas.

T	*Primary tumor*		
TX	Tumor cannot be assessed		
T0	No evidence of tumor		
Tis	High-grade dysplasia		
T1	Tumor invades the lamina propria, muscularis mucosae, or submucosa.		
T1a	Tumor invades lamina propria or muscularis mucosae		
T1b	Tumor invades submucosa		
T2	Tumor invades into, but not beyond, the muscularis propria		
T3	Tumor invades the paraesophageal tissue but does not invade adjacent structures		
T4	Tumor invades adjacent structures		
N	*Regional lymph nodes*		
NX	Regional lymph nodes cannot be assessed		
NO	No regional lymph node metastases		
N1	Regional lymph node metastases		
N2	Metastasis in 1–2 regional lymph nodes		
N3	Metastasis in 7 or more regional lymph nodes		
M	*Distant metastasis*		
MX	Distant metastases cannot be assessed		
M0	No distant metastasis		
M1	Distant metastasis		
Stage groupings			
Stage 0	Tis	N0	M0
Stage IA. Grade 1–2, X	T1	N0	M0
Stage IB. Grade 3	T1	N0	M0
Grade 1–2, X	T2	N0	M0
Stage IIA. Grade 3	T2	N0	M0
Stage IIB	T3	N0	M0
	T1	N1	M0
	T2	N1	M0
Stage IIIA	T1	N2	M0
	T2	N2	M0
	T3	N1	M0
	T4a	N0	M0
Stage IIIB	T3	N2	M0
Stage IIIC	T4a	N1	M0
	T4a	N2	M0
	T4b	Any N	M0
	Any T	N3	M0
Stage IV	Any T	Any N	M1

T4a = resectable tumor invading pleura, pericardium, or diaphragm.
T4b = Unresectable tumor invading other adjacent structures.
Adapted from Edge SB et al (eds): Esophagus and Esophagogastric Junction. In AJCC Cancer Staging Manual, 7th ed. New York, Springer, 2010, pp 103–11.

nodal metastases of <10%, while about 30% of T1b lesions will have nodal metastases. In addition, the number of lymph nodes involved, histology, degree of differentiation, and location seem to have an impact on survival of patients with esophageal cancer.[9] Overall, more than 50 percent of patients have unresectable or metastatic disease at the time of presentation.

4. Dignosis

4.1. Upper endoscopy

Upper endoscopy is the gold standard for the diagnosis of esophageal carcinoma. While the presence of a mass or a nodule is diagnosed via an upper endoscopy (and presence of cancer proven by biopsy), the depth of the tumor and lymph node involvement cannot be assessed with this modality. *Computed tomography scan:* The sensitivity and specificity of computed tomography (CT) scan in diagnosing locoregional nodal involvement are 84% and 67%, respectively. For distant organ metastases, the sensitivity is 81% and the specificity is 82%.[10]

4.2. ^{18}F-fluoro-2- deoxy-D-glucose positron emission tomography

18F-fluoro-2-deoxy-D-glucose positron emission tomography (FDG-PET) scanning has recently been introduced into esophageal cancer staging and is more accurate than conventional CT imaging, particularly in the detection of distant metastases. A systematic review has shown a moderate sensitivity and specificity of 51% and 0.84%, respectively, for the detection of locoregional lymph node metastases, and a sensitivity and specificity of 67% and 97%, respectively, for detection of distant metastases.[11]

4.3. Endoscopic ultrasound

Endoscopic ultrasound (EUS) is the most accurate noninvasive test for locoregional staging of esophageal cancer (T and N classification), though distinguishing between early lesions (T1a or T1b) remains problematic. The overall accuracy of EUS for T classification is 84%.[11] Rounded, sharply demarcated, homogeneous, and hypoechoic features of a lymph node on EUS indicate malignancy. The overall accuracy of EUS staging of locoregional nodal disease is 77%. The addition of fine needle aspiration (FNA) to EUS further refines the staging of nodal disease, bringing the accuracy up to 85%.[12]

4.4. Diagnostic endoscopic mucosal resection

Endoscopic mucosal resection (EMR) is the best method to differentiate mucosal (T1a) tumors from submucosal (T1b) tumors. The use of EMR has increased both as a diagnostic modality and as a therapeutic modality. In patients who are not fit to undergo esophagectomy, EMR is used as a therapeutic modality, in combination with ablative therapies for superficial esophageal cancer.[13]

4.5. Minimally invasive staging

The use of minimally invasive staging (laparoscopy or thoracoscopy) is not widely practiced, given the improving accuracies of noninvasive methods.[14] Staging laparoscopy can also be performed prior to performing a minimally invasive esophagectomy (MIE) or definitive resection. Laparoscopy is useful for detecting and confirming nodal involvement and distant metastatic disease that potentially would alter treatment and prognosis in patients with esophageal cancer. Laparoscopy was reported to change the planned therapeutic approach in 10%–17% of patients.[14]

5. Treatment

Esophageal cancer is treated with multimodal approaches. Surgery remains the main stay of treatment for local and locally advanced disease. Recently, the combination of EMR for superficial esophageal cancer arising in the background of BE and ablation of BE has shown promising results in selected patients.

Historically the outcomes of patients undergoing esophagectomy for cancer have been dismal. Five year survival ranged from 15 to 27%.[15] This lead to the use of a combination of modalities for the treatment of esophageal cancer including chemotherapy or radiation therapy alone or in combination, followed by surgery with or without postoperative chemotherapy, with varying outcomes.

6. Neoadjuvant chemotherapy

Preoperative (neoadjuvant) chemotherapy (Table 2) has the potential benefits of shrinking the primary tumor and killing micrometastases (both in local nodes and systemically). In 2002, the Medical Research Council (MRC) reported the results of a randomized study using cisplatin and 5-flurouracil (5-FU),