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Esophageal Cancer: Role of Imaging in Primary Staging and Response Assessment Post Neoadjuvant Therapy

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Advances in the early detection and treatment of esophageal cancer have meant improved survival rates for patients with esophageal cancer. Accurate pretreatment and post–neoadjuvant treatment staging of esophageal cancer is essential for assessing operability and determining the optimum treatment plan. This article reviews the multimodality imaging approach in the diagnosis, staging, and assessment of treatment response in esophageal cancer.
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Introduction

Esophageal cancer is the eighth most common malignancy worldwide with 456,000 new cases diagnosed in 2012.[1] Rates have risen by 65% in men and 14% in women since the mid 1970s. In the UK, the incidence rate is the second highest in Europe for men and the highest for women. Although it is a leading cause of mortality (sixth most fatal cancer globally), survival rates have been improving with now approximately 20% surviving at least 5 years after diagnosis for all stages of esophageal cancer.[1]

Precise pretreatment staging of esophageal cancer is essential to determine which patients are suitable for surgery and to help formulate the optimal treatment plan. This minimizes inappropriate treatment and results in better clinical outcome. Computed tomography (CT), endoscopic ultrasound (EUS), and positron emission tomography-computed tomography (PET-CT) are all considered complementary modalities in the preoperative staging and therapeutic monitoring of esophageal cancer. This article reviews their clinical utility and relative strengths and weaknesses.

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Histologic Types of Esophageal Cancer

More than 90% of esophageal cancers are either squamous cell carcinomas (SCCs) or adenocarcinomas. SCCs are linked to tobacco and alcohol abuse, whereas adenocarcinomas are highly associated with obesity and gastroesophageal reflux disease. SCC has historically been more prevalent than adenocarcinoma. However, over the last few decades, there has been an unexplained shift in histologic type and primary tumor location with a dramatic rise in rates of adenocarcinoma in the United States and Western Europe, especially in white men. Adenocarcinoma originates from metaplastic epithelial cells in the esophagogastric junction that transform into an intestinal-type columnar epithelium through irritation by gastric secretions. This columnar epithelium, known as Barrett esophagus is better suited to withstand gastric acid erosive contents from gastroesophageal reflux but increases the risk of dysplasia 7-fold with Barrett esophagus transforming into adenocarcinoma at a rate of 1% per year.[2] Most adenocarcinomas are located in the distal third of the esophagus and gastroesophageal junction (GOJ), unlike SCC that is more evenly distributed throughout the mid and distal esophagus.[3-5] Esophageal adenocarcinoma has a better long-term prognosis after resection than SCC. In a study of 1059 patients who had undergone resection, the overall 5-year survival rate was only 37% for the SCC group compared with 47% for the adenocarcinoma group.[6]

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Table 1 T, N, and M Definitions for Esophagus and Esophagogastric Junction Cancer in the Seventh Edition of the AJCC Cancer Staging Manual

	Definition
T status	
Tis	High-grade dysplasia
T1	Invasion into the lamina propria (T1a), muscularis mucosae (T1a), or submucosa (T1b)
T2	Invasion into muscularis propria
T3	Invasion into adventitia
T4a	Invades resectable adjacent structures (pleura, pericardium, and diaphragm)
T4b	Invades unresectable adjacent structures (aorta, vertebral body, and trachea)
N status	
N0	No regional lymph node metastases
N1	1-2 positive regional lymph nodes
N2	3-6 positive regional lymph nodes
N3	7 or more positive regional lymph nodes
M status	
M0	No distant metastases
M1	Distant metastases

TNM Staging of Esophageal Cancer

Accurate staging of esophageal cancer requires an innate understanding of the pattern of tumor spread. Radiologists need to be familiar with the seventh edition of the TNM staging system (Table 1) as developed by American Joint Committee on Cancer (AJCC) and the Union for International Cancer Control (UICC).[7] This has made significant changes to the sixth edition with new definitions for the anatomical classifications of Tis, T4, N (regional lymph node), and M (distant metastasis) together with inclusion of nonanatomical characteristics such as histologic grade, cell type, and cancer location to define prognostic stage groupings. The prognostic groupings (Tables 2 and 3) are different for adenocarcinoma and SCC. The prognosis correlates with the extent of disease at diagnosis.

The degree of primary tumor invasion is represented by the T classification. The higher the T staging the greater is the risk of nodal involvement.[8,9] Tis classification is defined as high-grade dysplasia and includes all noninvasive neoplastic epithelium (previously carcinoma in situ). Tumors confined to the lamina propria or submucosa (T1) are considered stage I. Involvement of the muscle layer of the esophagus (T2) is stage II. Tumor extension into the adventitia (T3) is considered stage IIa or stage III disease, depending on the absence or presence of regional lymph node involvement. The T4a tumors are resectable cancers that invade adjacent structures such as the diaphragm, pericardium, and pleura or peritoneum. The T4b tumors are unresectable cancers that invade other adjacent structures such as the aorta, carotid vessels, azygos vein, vertebral body, trachea, and left main bronchus. Invasion into adjacent structures is also stage III, regardless of regional lymph node involvement.

There is an extensive submucosal lymphatic network that allows early regional lymph node metastases from esophageal cancer by longitudinal spread. The flow of lymph in the upper two-thirds of the esophagus tends to be upward compared to that in the distal third that tends to be downward. However, the lymphatic channels intercommunicate and there is bidirectional flow at the tracheal bifurcation. Patients without nodal involvement have a better prognosis than those with nodal involvement.[10] The revised manual defines regional nodes as any paraesophageal node, including cervical or celiac nodes. Supraclavicular fossa nodes, however, are considered nonregional. The N0 indicates no cancer-positive nodes, N1 is 1 or 2 cancer-positive nodes, N2 is 3-6 cancer-positive nodes, and N3 is 7 or more cancer-positive nodes. Cervical and celiac axis nodal disease is no longer classified as metastatic. Lymphatic metastasis or satellite tumor nodules from the esophageal

Table 2 Prognostic Stage Grouping for Squamous Cell Carcinoma

Stage	T	N	M	Grade	Tumor Location
0	Tis (HGD)	N0	M0	1, X	Any
IA	T1	N0	M0	1, X	Any
IB	T1	N0	M0	2-3	Any
	T2-3	N0	M0	1, X	Lower, X
IIA	T2-3	N0	M0	1, X	Upper, middle
	T2-3	N0	M0	2-3	Lower, X
IIB	T2-3	N0	M0	2-3	Upper, middle
	T1-2	N1	M0	Any	Any
IIIA	T1-2	N2	M0	Any	Any
	T3	N1	M0	Any	Any
	T4a	N0	M0	Any	Any
IIIB	T3	N2	M0	Any	Any
IIIC	T4a	N1-2	M0	Any	Any
	T4b	Any	M0	Any	Any
	Any	N3	M0	Any	Any
IV	Any	Any	M1	Any	Any

X—inability to determine grade or location.
HGD, high-grade dysplasia.

Table 3 Prognostic Stage Grouping for Adenocarcinoma

Stage	T	N	M	Grade
0	Tis (HGD)	N0	M0	1, X
IA	T1	N0	M0	1-2, X
IB	T1	N0	M0	3
	T2	N0	M0	1-2, X
IIA	T2	N0	M0	3
IIB	T3	N0	M0	Any
	T1-2	N1	M0	Any
IIIA	T1-2	N2	M0	Any
	T3	N1	M0	Any
	T4a	N0	M0	Any
IIIB	T3	N2	M0	Any
IIIC	T4a	N1-2	M0	Any
	T4b	Any	M0	Any
	Any	N3	M0	Any
IV	Any	Any	M1	Any

X—inability to determine grade or location.
HGD, high-grade dysplasia.