Multimodality Imaging Approach, Staging and Therapy Assessment of Esophageal Cancer

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Financial disclosures:
Myrna Godoy: Siemens Healthcare
Brett Carter: Amirsys-Elsevier
Carol C. Wu: Elsevier, Inc
Objectives/Teaching Points

✓ Description of the 7th edition of the American Joint Committee on Cancer (AJCC) Staging System for esophageal cancer (EC) and proposed changes for the 8th edition.

✓ Endoscopic esophageal ultrasound (EUS) is the optimal modality to access tumor depth (T classification) and has a reported accuracy of 89%.

✓ EUS with ultrasonography-guided biopsy is the first choice for assessment of metastatic locoregional nodes (N status). The main role of CT is to identify suspicious non-locoregional lymph nodes and intrathoracic distant metastatic disease.

✓ CT of the chest and abdomen with intravenous (IV) and oral contrast is the main imaging modality used to detect distant metastasis (cM).

✓ The addition of 18F-2-deoxy-D-glucose (FDG)-positron emission tomography/computed tomography (PET/CT) improves the detection of metastases, especially with advanced cT and cN classifications. PET/CT is also used to assess response after neoadjuvant therapy.
7th Edition of AJCC for EC
Major modifications

✔ Data-driven of 13 institutions based on 4627 esophagectomy patients who had no induction or adjuvant therapy.

✔ Staging based on random forest (RF) analysis.

✔ T classification was changed for Tis and T4 cancers.
  • Tis: high grade dysplasia including all noninvasive neoplastic epithelium.
  • T4: T4a or T4b based on resectable or unresectable tumors.

✔ N: any lymph node (LN) from cervical to celiac is considered regional and staging are based on the number of cancer-positive nodes.

✔ M: MX, M1a and M1b were eliminated. Distant metastasis is M1, no distant metastasis M0.

✔ Includes cancer within the 5 cm of the stomach (cardia) that invade the esophagogastric junction (EGJ).

✔ Includes histological grade.
8th Edition of AJCC for EC
Proposed changes

✓ Expand the data analysis.

✓ Better homogeneity of stage 0 and IV.

✓ Improving homogeneity of stage IIB AC and stages IIA and IIB SCC.

✓ Adding clinical (cStage), postinduction clinical and postdefinitive nonsurgical clinical (ycStage), and post-induction pathologic (ypStage) staging recommendations.

✓ Adding nonesophagectomy survival data, endoscopic treatment in stage 0 and stage IA, and palliative therapy for stage IV.

✓ Adding other nonanatomic tumor analysis that affect survival.

✓ Adding cancer of cervical esophagus (harmonization as was done with GEJ tumors in the 7th edition).
### 7th Edition of AJCC for EC

<table>
<thead>
<tr>
<th>Tumor</th>
<th>TX: primary tumor cannot be assessed</th>
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<tbody>
<tr>
<td></td>
<td>T0: no evidence of primary tumor</td>
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<tr>
<td></td>
<td>Tis: high-grade dysplasia</td>
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<tr>
<td></td>
<td>T1a: invasion of lamina propria or muscularis mucosae</td>
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<td></td>
<td>T1b: invasion of submucosa</td>
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<td></td>
<td>T2: invasion of muscularis propria</td>
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<td></td>
<td>T3: invasion of adventitia</td>
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<td></td>
<td>T4: invasion of adjacent structures:</td>
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<tr>
<td></td>
<td>T4a: resectable (pericardium, pleura, or diaphragm)</td>
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<tr>
<td></td>
<td>T4b: unresectable (other structures such as, vertebral body, aorta, trachea, vertebral body, etc)</td>
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<tr>
<th>Regional Lymph node</th>
<th>NX: regional lymph nodes cannot be assessed</th>
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<tr>
<td></td>
<td>N0: no regional lymph node metastasis</td>
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<tr>
<td></td>
<td>N1: metastasis in 1-2 regional lymph nodes</td>
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<td>N2: metastasis in 3-6 regional lymph nodes</td>
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<td>N3: metastasis in ≥ 7 regional lymph nodes</td>
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<tr>
<th>Distant Metastasis</th>
<th>M0: no distant metastasis</th>
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<tr>
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<td>M1: distant metastasis present</td>
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<tr>
<th>Histologic grade</th>
<th>GX: grade cannot be assessed - stage grouping as G1</th>
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<tr>
<td></td>
<td>G1: well differentiated</td>
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<tr>
<td></td>
<td>G2: moderately differentiated</td>
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<tr>
<td></td>
<td>G3: poorly differentiated</td>
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<td>G4: undifferentiated – stage group as G3 squamous</td>
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*Table: 7th edition of AJCC for EC published in 2010*
T score: the primary tumor

- It is based on the depth of mural invasion of the primary tumor.
- EUS is the most accurate imaging tool for esophageal T score: differentiation of the 5 histological layers of the esophageal wall.
- 3rd layer: preservation or obliteration determines T1a or T1b disease, respectively.
- 5th layer: preservation or obliteration determines T2 or T3 disease, respectively.
- Preservation of fat plane between the aorta or left atrium and the tumor excludes T4 disease.

Layers of esophageal wall. (a) Schematic and (b) EUS image.
Important considerations:

- EUS is the optimal modality to access tumor depth (T classification) and has a reported accuracy of 89%.
- CT has poor sensitivity for depiction of the primary mass (approximately 67% compared to EUS).
- PET/CT is not useful and should not be performed in the evaluation of early stage esophageal cancer (cTis and cT1).
- PET/CT has low sensibility for detection of EGJ adenocarcinoma that secrete mucin.

T1b tumor in a 82-year-old woman. (a) Axial contrast-enhanced CT image at the level of the ventricles show a suspected small intramural mass in the lower esophagus (arrow). (b) EUS image shows smooth, eccentric wall thickening (**), with focal obliteration of the submucosa (3th layer, arrows), biopsy-proven adenocarcinoma (AC). (c) This lesion was not appreciated by fused PET/CT.
T score: the primary tumor

Stenotic esophageal AC with GEJ involvement in a 69-year-old man that presented with progressive dysphagia. (a) Axial contrast-enhanced CT image shows an eccentric distal esophageal mass (arrow). (b) Fused PET/CT image shows FDG uptake of the lesion with SUV max of 12. (c,d) EGD image shows exophytic, friable and stenotic esophageal mass. (f) EUS shows T3 tumor penetrating the adventitia (arrow). (g) EUS shows peritumoral lymph node (arrow) biopsy-proven locoregional metastatic disease.

EUS potential limitations:

- Operator-dependence, peritumoral edema (overstating), stenosis (may restrict evaluation and biopsy sampling in up to 30% of the patients).
- Blurring of the normal 5 layer wall pattern can be consistent with either post treatment inflammatory effect or tumor staging after neoadjuvant therapy secondary to fibrosis and adherence.
N score: locoregional LN

- Nodal classification allows risk stratification for overall survival after surgery and it is an independent predictor of survival in esophageal cancer.

- N score is based in the number of involved locoregional lymph nodes.

- Any paraesophageal node located from the cervical to celiac region is considered locoregional, independent of the site of the primary esophageal tumor.

- The rich lymphatic plexus surrounding the esophagus permits bidirectional tumor spread and development of “skip metastases” to nodes at other levels, without the first involvement of lymph nodes at the same level of the primary tumor, and are found in up to 20% of resected tumors.

- EUS with ultrasonography-guided biopsy is superior to both CT and PET/CT for N staging with sensitivity, specificity and accuracy of 89%, 75% and 84%, respectively.
EUS criteria for pathologic LN is based on size (>1 cm) and morphology (round with hypoechoic central echo pattern).

EUS with fine needle aspiration (FNA) biopsy permits cytologic confirmation of LN metastases. CT and PET-CT are important to show suspicious nonregional LN for FNA biopsy.

EUS image show round lymph node with hypoechoic central echo pattern (arrows) suspicious for metastatic disease in a 64 year-old woman presenting esophageal GEJ adenocarcinoma. EUS-FNA was positive for locoregional metastatic disease.
AC of the esophagus (uT3N2) in a 75-year-old man presenting dysphagia. (a,b,c) Axial contrast-enhanced CT images show enlarged right paratracheal LN (arrow); concentric thickening of the distal esophageal wall (*) with adjacent LN (arrow) and extension of the esophageal mass to the cardia (arrow), respectively. (d,e,f) Fused PET/CT images at same levels of “a”, “b”, “c”, respectively, show high FDG uptake of respective structures. (g,h,i) EUS images show enlarged, hypoechoic and round right paratracheal LN (FNA positive for locoregional metastatic disease); peritumoral LN correspondent to images “b” and “e”; and esophageal mass with obliteration of adventitia (arrows on image “i”), respectively. The patient received induction chemotherapy with minimal response (persistent GEJ tumor, not shown) and proceeded with definitive concurrent chemoradiation.
CT limitations:
✓ Criteria for pathologic LN is based on short-axis diameter only (> 1 cm).
✓ Overstaging: inflammatory LN.
✓ Understaging: LN < criteria size with microscopic metastatic foci, conglomeration of lymph nodes, LN adjacent to the esophageal mass may not be distinguish from the mass.

PET/CT limitations:
✓ Understaging: FDG uptake of primary tumor not distinguished from locoregional LN (“Bloom effect”).
✓ Overstaging: inflammatory LN.

Surveillance of distal EC status post-chemoradiation in a 61-year-old man. (a) EUS image shows irregular thickening of the distal esophagus with blurring of the normal 5 layer wall pattern consistent with either post treatment inflammatory effect or tumor (arrows). (b) Fused PET/CT image at same level of “a” shows FDG metabolic activity with [SUV max] = 3.91 that may be related with primary neoplasm and/or treatment-related changes (arrow). Endoscopic FNA revealed recurrent AC.
CT of the chest and abdomen with IV and oral contrast is the main imaging modality used to detect distant metastasis (cM).

T4B: CT provides evaluation of extension within aorta and trachea in staging T4B (non resectable).

The addition of FDG PET/CT improves the detection of metastases, especially with advanced cT and cN classifications. PET/CT is also used to assess response after neoadjuvant therapy.

Metastatic esophageal AC of the GEJ in a 70-year-old men with right shoulder pain. (a) Axial contrast-enhanced CT at the level of the shoulders shows no abnormalities. (b) Fused PET/CT at same level of “a” shows high FDG uptake in the subscapularis muscle (arrow). FNA was positive for metastatic tumor. The patient underwent chemoradiation therapy (CRT).
Metastatic esophageal adenocarcinoma of the GEJ with peritoneal carcinomatosis in a 58-year-old men. (a,b) Axial contrast-enhanced CT and fused PET/CT image at same level show distal esophageal wall thickening with high FDG uptake (SUV max of 22.3), extending into the stomach along the lesser curvature (arrow), compatible with a gastroesophageal malignancy. Note mesenteric and peritoneal soft-tissue nodules consistent peritoneal carcinomatosis (*) in “a”. (c,d) Fused PET/CT images show signs of left lower paratracheal, paraaortic and subcarinal nodal metastatic disease presented with high FDG uptake. (e) Whole-body anterior maximal intensity projection image of PET/CT shows extensive metastatic abdominal disease.
Metastatic esophageal adenocarcinoma (cT3N2M1) in a 73-year-old woman with progressive dysphagia and weight loss. (a,b) Axial contrast-enhanced CT and fused PET/CT images show circumferential distal esophageal wall thickening (arrows) with high FDG uptake (SUVmax of 28). (c,d) Axial contrast-enhanced CT and PET/CT images show distal extension of the mass towards the proximal aspect of the stomach with high FDG uptake (arrows). (e,f) Axial contrast-enhanced CT and fused PET/CT images of an enlarged LN adjacent to the left carotid and left subclavian arteries with high FDG uptake with a SUVmax of 21.2. (g,h) Axial contrast-enhanced CT and fused PET/CT images show distal retroperitoneal lymph node with high FDG uptake with a SUVmax of 32.2.
The most common histological types of esophageal cancer are the squamous cell carcinoma (SCC) and adenocarcinoma (AC), which together represented more than 90% of malignant esophageal tumors.

AC has a better prognosis than SCC independent of staging (5-year survival rate after resection of 42% compared with 30% for SCC).

<table>
<thead>
<tr>
<th>Squamous cell carcinoma</th>
<th>Adenocarcinoma</th>
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<tr>
<td>SCC arises from progression of a dysplastic epithelium.</td>
<td>Malignant degeneration of underlying Barrett’s epithelium.</td>
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<td>The incidence is three times higher in African Americans than Caucasians, and increases with age, peaking in the 7th decade.</td>
<td>It shows increased incidence most notably among white males.</td>
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<td>In up to 65% of the cases, SCC arises above the level of the carina.</td>
<td>Three-fourths of the cases are seen at the distal esophagus.</td>
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<td>Risk factors: moderate to heavy alcohol consumption, tobacco use, lower socioeconomic status, tylosis (autosomal-dominant syndrome characterized by oral precursor lesions, palmoplantar keratoderma and high risk of EC).</td>
<td>The majority of cases are linked with Barrett's esophagus (substitution of stratified squamous epithelium by columnar epithelium). Obesity has been attributed as a risk factor (gastroesophageal reflux secondary to the increase of abdominal girth).</td>
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Signet ring cell (SRC) carcinoma:

- Distinct histologic subtype of AC with predominant component (> 50% of the tumor) composed of SRC in the stroma.

- SRC carcinoma of the esophagus or GEJ is associated with an advanced stage at presentation, respond less well to induction therapy and presents decreased overall survival when compared with non-SRC histopathology.

A hematoxylin and eosin–stained slide of esophageal adenocarcinoma with signet ring cell features (arrows). (Original magnification ×400.) (Credit: Enlow JM et al, Ann Thorac Surg, 2013)
Synchronous SCC of the esophagus (T3N2M0) in a 63-year-old woman with a history of progressive weight loss and dysphagia. (a,b) Axial contrast-enhanced CT images show concentric thickening of the distal esophageal wall and a smaller mural mass at proximal esophagus (arrows), respectively. (c,d) Fused PET/CT images at same levels show high FDG uptake of the distal esophageal wall (SUVmax 15.9) and proximal esophageal wall (SUVmax 4.2). (e) EUS shows upper paratracheal lymph node. Fine needle aspiration (FNA) was consistent with metastatic locoregional SCC. (f) EUS shows T3 staging at level of distal esophageal mass, with the obliteration of the adventitia (arrow). No evidence of distant metastatic disease.
EC treatment

- Tumor staging, comorbidities and age should be taken in consideration to define the best therapy assessment.
- **Esophagectomy** remains the primary treatment for EC when the tumor is resectable and clinical conditions permits.
- T1a (high grade dysplasia and intramucosal cancer limited to the muscularis mucosa) have low risk of LN involvement, estimated between 0 to 2%, and can be management with endoscopic therapy [endoscopic submucosal resection (EMR) and radiofrequency ablation in selected cases]. Indications for esophagectomy are incomplete EMR or failure of endoscopic treatment.
- T1b and T2 have increased risk of lymph node metastases compared with T1a secondary to the muscularis mucosa invasion. Esophagectomy is indicated if clinical condition permits.
- Locally advanced EC can be managed with combined modality treatment, including definitive chemoradiation therapy (CRT) and neoadjuvant chemotherapy and radiotherapy and esophagectomy.
- Surgical resection or definitive CRT should still be offered to patients with complete metabolic response on PET/CT since residual microscopic tumor cannot be detected.
- Supportive care treatment for nonsurgical patients includes esophageal stent placement, percutaneous gastrostomy, chemotherapy, radiotherapy.
Esophageal SCC in situ/high grade squamous dysplasia (Tis) in a 46-year-old man, discovered during evaluation of esophageal FDG uptake on PET/CT for surveillance of Hodgkin’s lymphoma. (a,b) Fused PET/CT images within 2 months interval show increased FDG uptake area in the esophageal wall (from SUVmax of 4.05 on image “a” to SUV max of 6.34 on image “b”). (c) EUS image at this time with no abnormal findings. FNA biopsy was performed and was positive for in situ/high grade squamous dysplasia (Tis). (d) EGD using staining chromoscopy with Lugol’s solution reveals some areas of decreased uptake on the esophageal wall without mucosal irregularity or nodularity (arrows) that was treated with radiofrequency (RFA) ablation. Follow-up PET/CT after RFA showed no FDG activity at the treated location (not shown).
Stenotic esophageal SCC T4N2 after chemoradiation in a 72-year-old man with dementia who underwent supportive care. (a) Axial contrast-enhanced CT image shows 5.4 cm soft tissue mass involving the distal esophagus (arrows). (b) Coronal contrast-enhanced CT image shows the longitudinal extension of the esophageal mass. (c) Fused PET/CT image shows high FDG uptake with SUVmax of 11.7 at same level of “a”. (d) Axial contrast-enhanced CT image shows interval placement of esophageal stent (arrows) for palliative care. Patient posteriorly underwent gastrostomy.
T3 tumor in a 68-year-old man who underwent Ivor-Lewis esophagectomy 8 years earlier and presented with pathology concerning for positive proximal margin. EGD follow-up (not shown) demonstrated nonbleeding ulcer at the level of the anastomosis. (a) Axial contrast-enhanced CT image does not show definite abnormality at the esophagogastrostomy anastomosis (arrow). (b) Fused PET/CT image at same level of “a” shows focal metabolic activity with SUVmax of 4.1, suspicious for residual/recurrent disease (arrow). (c) EUS image shows an eccentric mass (**), with focal obliteration of the adventitia (5th layer, arrow), biopsy-proven recurrence of adenocarcinoma at the corresponding area.
Therapy assessment of EC
Response evaluation

- PET-CT has an important role in the evaluation of residual tumor tissue after CRT to predictive EC outcome and prevent futile surgery when interval metastases are detected.

- PET-CT study should be done before endoscopic biopsy and 3 weeks after the end of CRT to avoid false-positive study due to inflammatory changes.

- Decrease in SUV max of 35% - 60% between baseline staging and post CRT imaging correlate to pathologic response within the esophageal tumor.

- Persistent FDG uptake $\geq 4$ correlate to persistent viable macroscopic malignancy and poor outcome.

- CT cannot evaluate presence of residual tumor after CRT and EUS-FNA have limitations related with fibrosis, treatment-related inflammation and stenosis.

- Surgical resection or definitive CRT should still be offered to patients with complete metabolic response on PET-CT since residual microscopic tumor cannot be detected.
Therapy assessment of EC
Response evaluation

Esophageal adenocarcinoma in a 59-year-old men (T3N2) presented with progressive weight loss. (a,b) Fused PET/CT images show distal esophageal mass (SUVmax of 7.0) and 2.0 cm left gastric LN with FDG uptake (SUVmax of 3.5), respectively (arrows). FNA of left gastric LN showed poorly differentiated AC. Patient completed induction chemotherapy followed by chemoradiation. (c) Restaging fused PET/CT image shows decrease in FDG uptake of the esophageal mass with SUVmax of 3.2, demonstrating metabolic response of the tumor. The previously biopsied LN resolved (not shown). Patient underwent esophagectomy with complete pathologic response. (d,e) Axial CT-enhanced image after 12 and 18 months, respectively, show subsolid nodule in the left upper lobe that has increase in size and attenuation, biopsy-proven metastatic adenocarcinoma.
Therapy assessment of EC
Response evaluation

Esophageal AC in a 64-year-old woman (T3N0). (a) Fused PET/CT image shows high FDG uptake on the distal esophagus with SUVmax of 23.6 (arrow). (b) Restaging fused PET/CT image post neoadjuvant chemoradiation with docetaxel and 5-fluorouracil shows decreased FDG uptake (SUVmax of 6.2), possibly related to residual disease or inflammatory changes related to therapy. Endoscopic esophageal biopsy was negative at this time and minimally invasive esophagectomy was performed. Surgical pathology revealed 40% viable tumor with no nodal involvement (pT3N0) (c,d) Restaging fused PET/CT images after 2 years show high FDG uptake characterizing distant metastatic disease to the right shoulder and liver, respectively (arrows).
Future Trends: Biomarkers

- The RNA expression of thymidylate synthase (TS) in the blood is a potential bad prognostic marker in patients with neoadjuvant-treated EC. Patients with TS expression above 0.78 had a median survival of 1.1 years compared to 2.6 years in patients with TS expression lower than 0.78 ($p=0.031$, log rank test).

- Periostin is an extracellular matrix protein that participates in motility and cell adhesion in the tumor microenvironment. Preclinical models using evaluating probes have demonstrated that specific imaging of periostin in esophageal SCC is feasible using a target PET tracer. This probe could play a role in the future for early detection, post-surgical follow up and with in situ characterization of primary and metastatic lesions using PET/CT images.

- The biomarker TP53 divides EC patients into 2 categories with markedly different outcomes: patients with a normal TP53 marker status may experience notable benefits from neoadjuvant chemotherapy with cisplatin/fluorouracil, whereas those with a mutant TP53 marker status appear to be at risk for lack of response.
References


Thank you!

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