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REVIEW

Staging of oesophageal cancer

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Introduction

The prevalence of oesophageal carcinoma has increased dramatically in the last 30 years with reported increases of 350–800%.[1] Adenocarcinoma is now the most common cell type in the United States, and although the disease may present late it should not be considered an entity with a uniformly poor prognosis. The overall 5-year survival is 25%, increasing to 85% if the nodes are disease-free at presentation. Unfortunately, approximately 75% of patients will have evidence of nodal disease at presentation and 18% will have distant metastases.[2] Appropriate staging is important for assessment of prognosis and deciding the most appropriate therapy. Treatment options include curative and palliative surgery, chemo-radiotherapy and stent insertion.

Staging

Staging is based on depth of tumour invasion (T stage), regional node involvement (N stage) and the presence of metastases (M stage). The TNM classification and the stage groupings are shown in Table 1.

Non-invasive methods of staging include computerised tomography (CT), endoscopic ultrasound (EUS) and positron emission tomography (PET). Magnetic resonance imaging (MRI) has no real advantage over CT, is not commonly used and will not be included in this review.

Table 1 Staging of oesophageal cancer — TNM system

T0	No evidence of primary tumour
Tis	Carcinoma *in situ*
T1	Tumour invades lamina propria or submucosa
T2	Tumour invades muscularis propria
T3	Tumour invades adventitia
T4	Tumour invades adjacent structures
N0	No regional nodes
N1	Regional nodal metastases — cervical, mediastinal and perigastric
M0	No distant spread
M1	Distant spread

Lower oesophagus
M1a — metastases in coeliac nodes, M1b — distant metastases

Upper oesophagus
M1a — metastases in cervical nodes, M1b — distant metastases

Mid-oesophagus
M1a — not apply, M1b — non regional nodes, distant metastases

Stage

0	Tis	N0	M0
1	T1	N0	M0
11A	T2	N0	M0
	T3	N0	M0
11B	T1	N1	M0
	T2	N1	M0
111	T3	N1	M0
	T4	N0/1	M0
IV	T1-4	N0/1	M1

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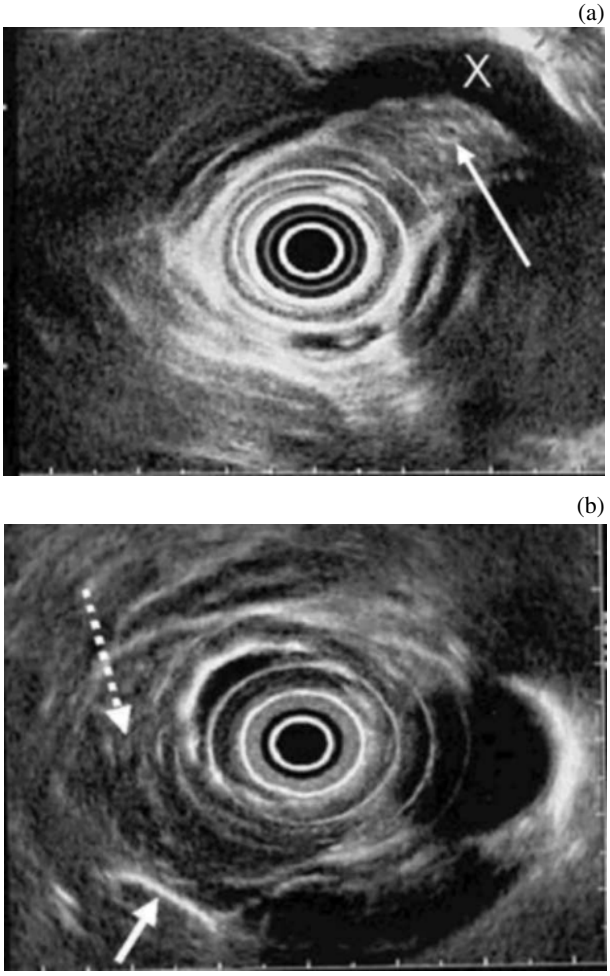


Figure 1 **Endoscopic ultrasound of patients with oesophageal cancer with mediastinal invasion. (a) Oesophageal tumour (T4): the tumour (white arrow) is adherent to the left pulmonary vein (white cross) with loss of the intervening plane. (b) Oesophageal tumour (T4): the tumour (broken white arrow) has breached the pleura (white arrow) to invade the right lung.**

T Stage

This is defined as the depth of tumour invasion through the oesophageal wall and adequate T staging requires identification of the individual layers of the wall. T1 to T3 tumours are confined to the oesophagus and may be suitable for surgical resection, while T4 tumours extend beyond the oesophageal wall into adjacent structures and are not suitable for surgical intervention.

Endoscopic ultrasound (EUS)

The oesophageal wall can be resolved into individual layers and is seen as five layers of alternating echogenicity. This definition allows accurate determination of the depth of tumour invasion depending on which layer is infiltrated.[3]

The tumour usually appears as circumferential thickening of the wall of hypoechoic or mixed echo pattern with distortion of the layers. Accurate assessment of the depth of invasion through the mucosa, submucosa and muscularis propria can be made. T1 and T2 tumours can be differentiated and extension of tumour through the oesophageal wall and invasion into the surrounding structures identified (Fig. 1).

The accuracy of staging using EUS is dependent not only on operator experience but also on the actual T stage, being better for T4 than for T1 tumours. In a meta-analysis of several series,[4] the overall accuracy was 84%. For T1 tumours it was 83.5% with 16.5% over-staged; for T2 tumours 73% with 10% under-staged and 17% over-staged; for T3 tumours 89% with 5% under-staged and 6% over-staged and for T4 tumours 89% with 11% under-staged. The variation in the quoted accuracy in published studies is quite high, ranging from 75–82% for T1, 64–85% for T2, 89–94% for T3 and 88–100% for T4.[5] In a more recent study of EUS in T1 to T3 tumours an accuracy of only 64% was achieved with 19% over-staged and 17% under-staged.[6]

A limitation of EUS is that oesophageal stenosis can prevent complete staging in 19 to 63% of tumours,[7] although this problem may be overcome by use of miniature ultrasound probes or by attempted dilatation of the stricture.

EUS is the best method for assessment of T stage.

Computerised tomography (CT)

The normal oesophageal wall is less than 3 mm on CT, and individual layers cannot be identified, so T1 and T2 tumours cannot be differentiated. Invasion of the peri-oesophageal fat may be seen as ill-defined soft tissue stranding but T3 tumours cannot be accurately assessed. T4 tumours are inferred by the loss of fat planes between the tumour and adjacent structures, although this may be difficult in very thin patients (Fig. 2). Aortic invasion, which is found in only 6% of patients at post mortem, is diagnosed if the angle of contact between the tumour and aorta is greater than 90°, if the angle of contact is less than 45° there is no invasion. Using this criterion produces a large number of indeterminate results and an overall accuracy of 55%,[8] and loss of the triangular fat space between the oesophagus, aorta and spine is a better sign of invasion with an improved accuracy of 86%.[9]

Bowing of the posterior wall of the trachea or left main stem bronchus suggests airway invasion (sensitivity = 71%, specificity = 91%, and accuracy = 88%); this requires bronchoscopy for confirmation.

The main value of CT in T staging is to exclude T4 tumours, which will preclude surgery.

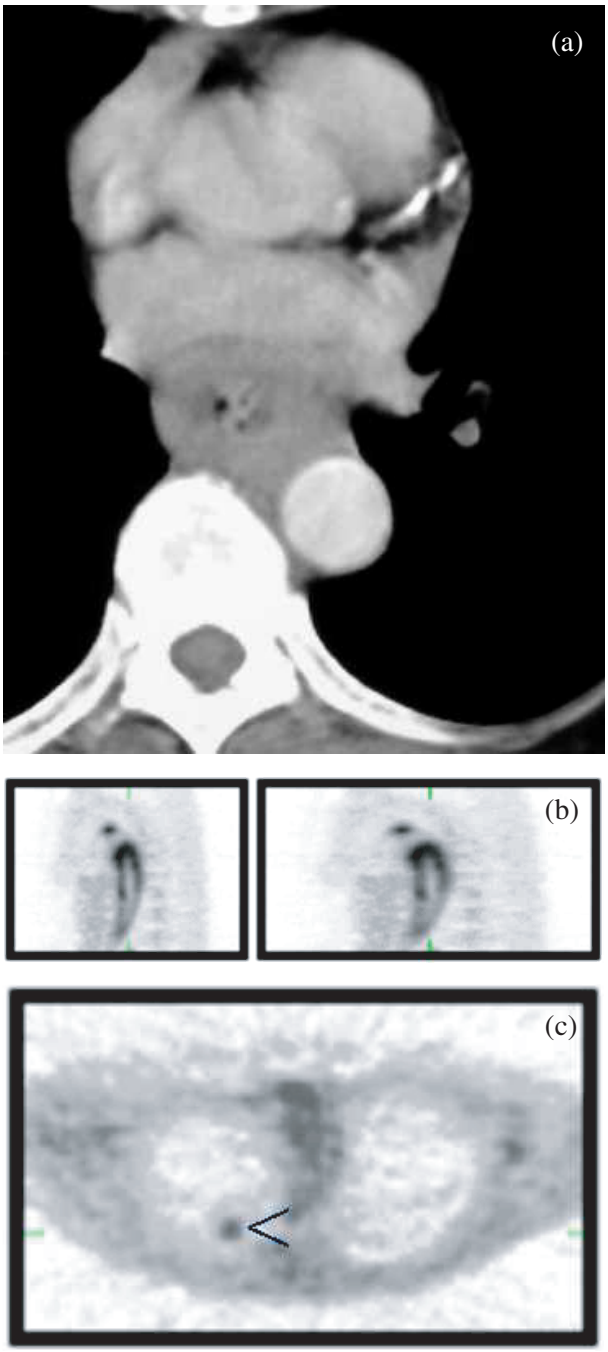


Figure 2 **(a) CT scan of patient with oesophageal cancer showing infiltration into the mediastinum with aortic invasion (T4 tumour). (b) PET scan of the same patient showing oesophageal uptake but the extent of mediastinal invasion is not clearly identified. (c) PET scan of the same patient with uptake in lung metastasis (arrow) not seen on the CT.**

Positron emission tomography (PET)

The most commonly used isotope for oncology imaging is 2-^{18}fluoro-2-deoxy-D-glucose (FDG). This glucose analogue can differentiate malignant from normal cells based on the increased accumulation in malignant cells partly as a result of the enhanced glycolysis; thus both the the primary tumour and distant metastases can be identified.[10] Both adenocarcinoma and squamous carcinoma of the oesophagus demonstrate increased FDG uptake. The reported sensitivity for detecting the primary tumour is 91–100%, but increased uptake may also be seen in oesophagitis. False-negative results may occur in very small T1 tumours.[6]

PET has the advantage of being a whole body imaging method, however, the spatial resolution is relatively poor (5 mm) when compared with CT, and image registration may be required to improve anatomic localization. The poor spatial resolution means mediastinal invasion cannot be assessed accurately and PET should not be used for T staging (see Fig. 2).

N Stage

Lymphatic involvement is common, particularly with squamous cell carcinoma, where there is early spread through interconnecting lymphatics, so that the site of the primary lesion does not indicate which lymph nodes will be involved. Thirty-two per cent of upper third tumours will have involved abdominal nodes and in lower third tumours abdominal nodal disease is more common than mediastinal.

Nodal staging is based on infiltration of local nodes only, however, the number of nodes involved is an important prognostic indicator (more than four nodes or greater than 10% of nodes involved carries a poor prognosis). The presence of metastases in the peri-oesophageal nodes does not preclude surgery, as they will be removed *en bloc* at the time of resection. The normal size used for supraclavicular nodes is less than 5 mm, mediastinal nodes less than 1 cm in short axis, 6 mm for retro-crural nodes and 6–8 mm for left gastric nodes. Using size as a criterion has limitations as normal-sized nodes may contain micro-metastases and enlarged nodes may be reactive rather than neoplastic.

Endoscopic ultrasound (EUS)

EUS can define the size, borders and internal structure of nodes. Nodes greater than 1 cm, that are round, hypoechoic, non-homogeneous and well defined are more likely to be malignant. Small, oval, hyperechoic, homogeneous nodes with indistinct borders are more likely to be benign. In one study the sensitivity of EUS was 89%, specificity 75% and accuracy 84% with a positive predictive value (PPV) for N1 disease of 86% and a negative predictive value (NPV) of 79%. If all the malignant features were identified the accuracy increased to 100%.[11] A limitation of EUS is that only 30% of nodes identified at surgery will be visualized, with size an important limiting factor. EUS will identify 92% of nodes

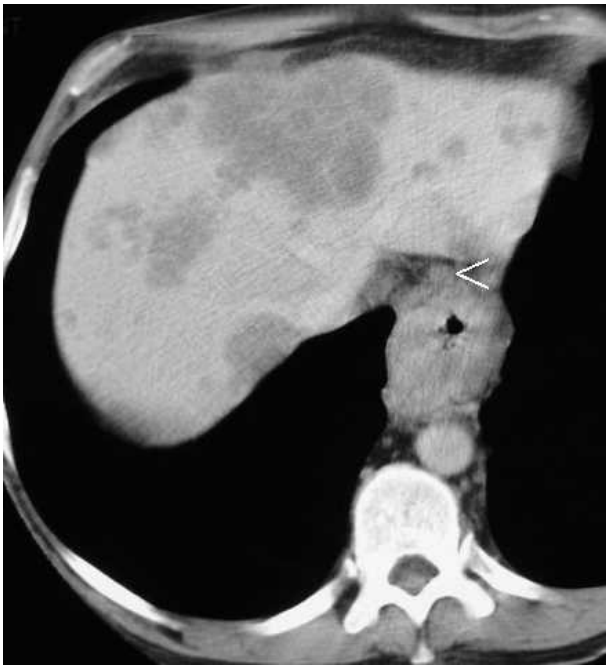


Figure 3 **CT of patient with oesophageal cancer and liver metastases and peri-oesophageal lymph node (arrowhead).**

greater than 10 mm, 53% of nodes between 5 and 9 mm and only 1% of nodes less than 5 mm.[12] The accuracy for assessment of lymph nodes in non-traversable strictures may be as low as 10%.

Endoluminal ultrasound overestimates lymph node disease because of difficulties in differentiating between infiltration and inflammation and thus has a limited specificity. Generally, EUS is better at diagnosing malignant nodes rather than benign nodes (accuracy 89% for N1 and 69% for N0 disease).

Accuracy is highest for peri-oesophageal nodes and varies inversely with the axial distance of the nodes from the oesophageal axis.[13] It is also important to remember that the incidence of nodal disease depends on the T stage of the tumour ranging from 17% for T1 tumours to 88% for T4 tumours.

EUS can also be used in association with fine needle aspiration to produce excellent results with a reported sensitivity of 92%, specificity of 93%, PPV of 100% and negative predictive value (NPV) of 86%.[14]

Computerised tomography (CT)

CT has well-known limitations in the accuracy of nodal staging as size is used as the only criterion. Small lymph nodes containing metastases, particularly the peri-oesophageal nodes, will not be diagnosed as infiltrated and the patient will be under-staged (Fig. 3). False-positive examinations are due to enlarged inflammatory nodes being called malignant, and, as it is important not to over-stage patients and deprive them of potentially curative surgery, any enlarged node on CT should have tissue confirmation if this CT finding alone would change therapy. If mediastinal lymph nodes with a short axis greater than 10 mm are considered abnormal, the accuracy for CT diagnosis of node involvement is 51–70%. In one series the sensitivity was 19% with a PPV of 33% and in this series only 28% of the metastatic nodes were greater than 10 mm in size, 35% were 5–9 mm and 36% were less than 5 mm.[15] Consigliere[16] found that CT had an overall accuracy of 69% for detection of nodal enlargement, however, only 38% of the identified enlarged nodes were malignant and 57% of unidentified normal-sized nodes contained tumour.

A recent study[17] using thin section (5 mm) spiral CT in gastro-oesophageal adenocarcinoma found that CT detected only 21% of all the nodes identified at surgery irrespective of histology. Detection was dependent on the size of the nodes with only 1% of nodes measuring less than 4 mm identified, 45% of nodes measuring less than 5–9 mm, and 72% of nodes greater than 9 mm in size.

2-^{18}fluoro-2-deoxy-D-glucose positron emission tomography (FDG PET)

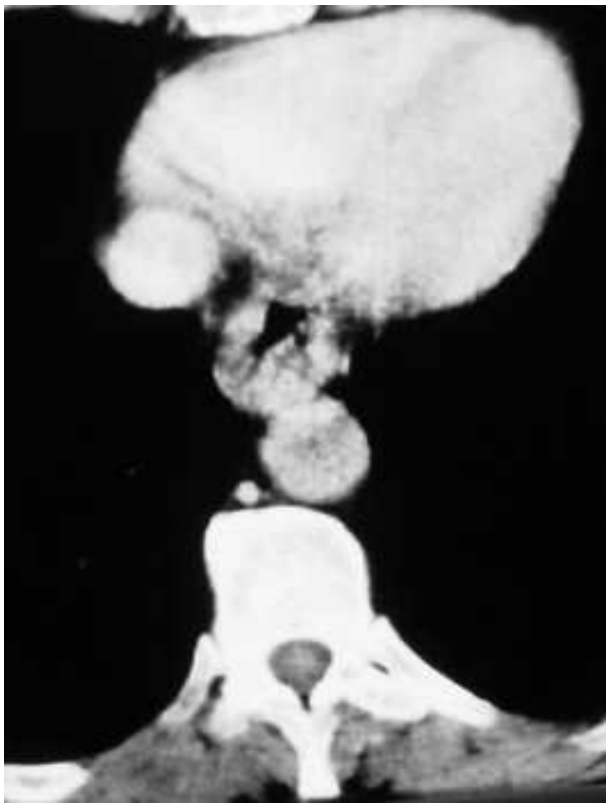
Uptake of FDG is dependent on metabolic activity not size of nodes and therefore FDG PET will identify tumour in normal size lymph nodes (Fig. 4). A limitation in local nodal staging is the poor spatial resolution. False-negative studies occur with nodes situated very close to the primary that may not be identified as separate from it and in very small nodes or nodes containing micrometastases. False-positive results are a result of uptake of FDG PET in non-malignant inflammatory nodes such as those involved with tuberculosis or sarcoidosis. Positive nodes on PET should therefore be sampled if management will be altered. Nevertheless, the results appear to be promising with a reported sensitivity of 33%, specificity 89% and accuracy 59%.[6] In this study the low sensitivity for local nodes on FDG PET contrasted with the results of EUS which had a sensitivity of 81%, with specificity of 67% and accuracy of 74%.

M Stage

Distant metastases are common and approximately 18% of patients will have metastases at presentation. The most common sites are abdominal lymph nodes (45%), liver (35%), lung (20%) supraclavicular nodes (18%), bone (9%), and adrenals (5%); other sites including the brain, peritoneum and pericardium are rarely involved.

The M stage has been modified for tumours of the upper and lower oesophagus to differentiate non-regional nodal metastases from other metastatic sites (Table 1).

(a)



(b)

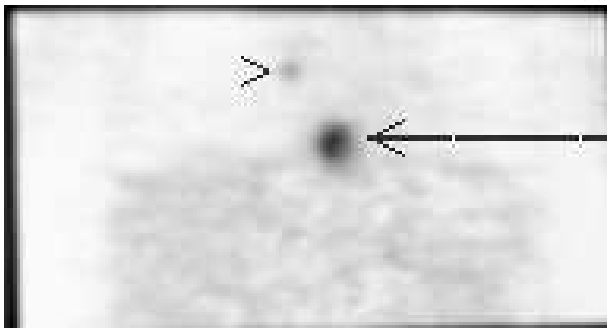


Figure 4 **(a) CT scan of patient with oesophageal cancer. No evidence of mediastinal invasion. (b) Coronal PET scan of same patient showing uptake in tumour (arrow) and also in mediastinal node (arrowhead) not seen on CT.**

Endoscopic ultrasound (EUS)

EUS has a role in assessing the non-regional lymph node groups, particularly the peri-gastric and coeliac nodes (sensitivity = 83%, specificity = 98%, accuracy = 95%, PPV = 91%, NPV = 97%), therefore staging M1a disease, but has a limited role for M1b disease. EUS will not depict organ metastases unless the organ is in direct contact with the upper GI tract (e.g. left lobe of the liver).

Computerised tomography (CT)

Liver metastases greater than 2 cm are well demonstrated on CT using contrast-enhanced portal phase imaging with overlapping reconstruction, with reported sensitivities of 70–80% (see Fig. 3). Sub-centimetre metastases may be missed and are better identified on laparoscopy. However, characterization of small lesions, less than 1.5 cm, is difficult and as up to 50% of small lesions, particularly if solitary, may be benign biopsy proof is important, especially if management would be altered.[18,19]

CT is poor at diagnosing peritoneal deposits that occur with adenocarcinoma but not squamous cell carcinoma, with a reported sensitivity of 21% compared with 96% for laparoscopy. CT is also sensitive for the detection of lung metastases although benign granulomatous lesions are difficult to differentiate from metastases.[20]

The diagnosis of abdominal lymph node involvement has the same problems as elsewhere in the body with a reported sensitivity for left gastric node involvement of 48%, specificity of 93% and accuracy of 79%.[21]

Overall, the sensitivity of CT for screening for distant metastases is 41–62%, with specificity of 69–83% and accuracy of 63–90%.[6,22,23]

Positron emission tomography (PET)

PET is an excellent method for screening for distant metastases and is superior to CT (see Fig. 2). In a study of 91 patients, 70 metastatic sites were confirmed on biopsy. The sensitivity for FDG PET was 69% (CT 46%), specificity 93% (CT 74%) and accuracy 84% (CT 63%).[22] In this study 10 liver, 4 pleural, 2 lung and 1 peritoneal deposits were missed, all lesions being less than 1 cm in size. In the 21 false-negative CT scans the PET was positive in 11 (62%) and in the 12 false-negative PET scans the CT was positive in 4 (33%). Other studies[6] comparing FDG-PET to the combination of EUS and CT found similar results with a sensitivity of 74% (CT/EUS 47%), specificity 90% (CT/EUS 78%) and accuracy 82% (CT/EUS 64%). In this study PET understaged the extent of nodal disease in 19 (49%), whereas the CT/EUS combination over-staged the nodal stage in 14 (36%). The high false-negative rate for PET may be a result of the high incidence of micrometastases.

Conclusions (Tables 2 and 3)

EUS is the best method for the T stage; it is also the most sensitive method for the assessment of local nodes but has limited specificity. CT is readily available and is best for advanced disease. FDG PET is best for distant metastases and regional nodal metastases, although is not widely available.

Table 2 Accuracy of techniques for TNM staging [4,6,11,16,22]

	T stage	N stage (%)	M stage
EUS	84%	84	N/A
CT	N/A	69	63%
FDG-PET	N/A	59	84%

Table 3 Comparison of techniques

	Good for	Poor for
CT	Advanced mediastinal disease Tracheo-bronchial invasion Distant metastases — liver — lung — para-aortic nodes	Differentiating T stage Identifying involved lymph nodes
EUS	T stage Local nodal involvement	Distant metastases Tracheo-bronchial invasion Tumour stenosis limits use in advanced disease
PET	Distant metastases Regional nodes Response to treatment	T stage and local invasion Local nodes

Most patients present with advanced disease, therefore the standard staging algorithm will often be an initial CT. In those patients considered suitable for resection EUS is then performed for accurate local staging and FDG PET should be used if the previous studies suggest locally resectable disease, to exclude distant metastases undetected by CT.

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