

## REVIEW

# Staging of upper GI malignancy

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### Abstract

Imaging plays a vital role in the management of oesophageal cancer including diagnosis, staging and follow up. Computerised tomography (CT) is used for staging and follow up, with magnetic resonance imaging (MRI) having only a limited role. Endoscopic ultrasound (EUS) provides optimal information for tumour extent and local nodal involvement. Functional imaging using  $2\text{-}^{18}\text{F}$ fluoro-deoxyglucose positron emission tomography (FDG-PET) is increasingly being used to provide unique information and, when combined with anatomic imaging, will provide better staging information for the extent of metastases and perhaps response to treatment.

**Keywords:** *Oesophageal neoplasms; computerised tomography; magnetic resonance imaging; positron emission tomography; endoscopic ultrasound.*

### Introduction

The prevalence of oesophageal carcinoma has increased by 350–800% over the last 30 years<sup>[1]</sup>. Adenocarcinoma is now the commonest cell type in the United States. 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<sup>[2]</sup>. 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.

Gastric cancer is decreasing in incidence worldwide and can be staged in a similar way to oesophageal cancer.

### 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). Minimal invasive surgery (thoracoscopy and laparoscopy) can also be used.

### 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–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.

### EUS

The accuracy of staging using EUS is dependent on not only operator experience but also on the actual T stage, being better for T4 than for T1 tumours. In a meta-analysis of several series<sup>[3]</sup>, 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

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11% under-staged. The variation in the quoted accuracy in published studies is quite high, ranging from 75 to 82% for T1, 64 to 85% for T2, 89 to 94% for T3 and 88 to 100% for T4<sup>[4]</sup>. In a more recent study of EUS in T1–T3 tumours an accuracy of only 64% was achieved with 19% over-staged and 17% under-staged<sup>[5]</sup>. EUS is the best method for assessment of T stage.

**Table 1 Staging of oesophageal cancer—TNM system**

T0	No evidence of primary tumour		
Tis	Carcinoma <i>in situ</i>		
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		
<i>Lower oesophagus</i>			
M1a	metastases in coeliac nodes, M1b—distant metastases		
<i>Upper oesophagus</i>			
M1a	metastases in cervical nodes, M1b—distant metastases		
<i>Mid-oesophagus</i>			
M1a	not apply, M1b—non-regional nodes, distant metastases		
<i>Stage</i>			
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

### 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. 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%<sup>[6]</sup>, 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%<sup>[7]</sup>.

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.

### FDG–PET

The commonest used isotope for oncology imaging is 2-<sup>18</sup>fluoro-2-deoxy D-glucose (FDG). This glucose analogue can differentiate malignant from normal cells based on increased accumulation in malignant cells due in part to the enhanced glycolysis; thus both the primary tumour and distant metastases can be identified. 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<sup>[5]</sup>.

The poor spatial resolution means mediastinal invasion cannot be assessed accurately and PET should not be used for T staging.

### N stage

Lymphatic involvement is common, particularly with squamous cell carcinoma, where there is early spread through interconnecting lymphatics. 32% of upper third tumours will have involved abdominal nodes and in lower third tumours abdominal nodal disease is commoner 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 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 micrometastases and enlarged nodes may be reactive rather than neoplastic.

### EUS

EUS can define the size, borders and internal structure of nodes. Nodes that are greater than 1 cm, 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%<sup>[8]</sup>. A limitation of EUS is that only 30% of nodes identified at surgery will be visualised, with size an important limiting factor. EUS will identify 92% of

nodes greater than 10 mm, 53% of nodes between 5 and 9 mm and only 1% of nodes less than 5 mm<sup>[9]</sup>.

Endoluminal ultrasound overestimates lymph node disease due to 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<sup>[10]</sup>. It is also important to remember 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 reported sensitivity of 92%, specificity of 93%, PPV of 100% and NPV of 86%<sup>[11]</sup>.

### *CT*

CT has well known limitations in the accuracy of nodal staging as size is used as the only criterion. 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<sup>[12]</sup>. Consigliere<sup>[13]</sup> 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<sup>[14]</sup> 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.

### *FDG–PET*

Uptake of FDG is dependent on metabolic activity, not size of nodes, and FDG–PET will therefore identify tumour in normal size lymph nodes. 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 due to 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 reported sensitivity of 33%,

specificity 89% and accuracy 59%<sup>[5]</sup>. 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 commonest 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.

### *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).

### *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%. Sub-centimetre metastases may be missed and are better identified on laparoscopy. However characterisation 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 will be altered<sup>[15]</sup>.

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

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%<sup>[16]</sup>.

Overall, the sensitivity of CT for screening for distant metastases is 41–62%, with specificity of 69–83% and accuracy of 63–90%<sup>[5,17,18]</sup>.

### *PET*

PET is an excellent method for screening for distant metastases and is superior to CT. 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%)<sup>[17]</sup>. In this study 10 liver, four pleural, two lung and one peritoneal deposit 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 four (33%). Other studies<sup>[5]</sup> comparing FDG–PET to the combination of EUS and CT found similar results with sensitivity of 74% (CT/EUS 47%), specificity 90% (CT/EUS 78%) and accuracy 82% (CT/EUS 64%). In this study PET under-staged 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 due to the high incidence of micrometastases.

### Conclusions

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 (Tables 2 and 3).

**Table 2 Accuracy of techniques for TNM staging**  
[3,5,8,13,17]

	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

CT is readily available and is best for advanced disease. FDG–PET is best for distant metastases and regional nodal metastases. It is not widely available.

Most patients present with advanced disease; therefore the standard staging algorithm will normally 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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