

## SPECIAL FOCUS TOPICS

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# The value of [<sup>18</sup>F]fluorodeoxyglucose-PET/CT in oesophageal cancer

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### Abstract

[<sup>18</sup>F]Fluorodeoxyglucose-positron emission tomography/computed tomography (CT) is recognized as a useful adjunct to conventional imaging with CT and endoscopic ultrasonography for the staging of oesophageal cancer, for response assessment and identification of recurrent disease and it may provide prognostic information.

**Keywords:** *Oesophageal cancer; staging; response assessment; recurrent disease; prognosis; [<sup>18</sup>F]fluorodeoxyglucose PET/CT.*

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### Staging

The prognosis for oesophageal cancer is poor and up to 50% of patients present with advanced disease with multiple sites of nodal involvement or distant metastases. The overall 5-year survival is 10–25%, but if surgery can be undertaken the 3-year survival after radical resection and lymphadenectomy is 40–56%.

Staging uses the TNM classification and the 7th edition of the American Joint Committee on Cancer staging manual, is based on data from almost 5000 patients who underwent oesophagectomy, and there are some changes from the 6th edition<sup>[1]</sup>.

The changes in the T stage are that Tis is now high-grade dysplasia and includes non-invasive tumours previously called carcinoma in situ, and T4 tumours are subdivided into T4a, which are potentially resectable cancers invading adjacent structures such as the pleura, pericardium or diaphragm, and T4b tumours, which are unresectable and invade the aorta, spine and trachea. T1–T3 are unchanged (T1 infiltrates the lamina propria or submucosa, T2 infiltrates the muscularis propria and T3 infiltrates the adventitia).

Regional nodes now include any involved para-oesophageal node from the cervical to coeliac nodes and the number of nodes involved designates the N

stage (N0 = 0 nodes, N1 = 1–2 nodes, N2 = 3–6 nodes and N3 > 6 nodes). The loco-regional nodes for the cervical oesophagus include the scalene and supraclavicular nodes, for the thoracic oesophagus subcarinal and peri-oesophageal nodes and for the gastro-oesophageal tumours the pulmonary ligament nodes, diaphragmatic and coeliac nodes.

The previous M subclassifications of M1a and M1b have been replaced by M0 (no metastases) and M1 (distant metastases), including both organ and distant node metastases. Organ metastases have a worse prognosis than lymph node metastases and are usually in the liver, and more rarely in the lungs and bones.

The cell type, grade and the site of the tumour also influence survival, and adenocarcinoma and squamous cell cancer now have separate staging for stage 1 and 2. Increasing grade is associated with decreased survival in early stage tumours (G1 and G2 compared with G3 in adenocarcinoma and G1 compared with G2 and G3 in squamous cell carcinoma (SCC) and the location is important in SCC.

Accurate staging using the TNM classification is important to suggest the most appropriate treatment. Patients with T1 and T2 tumours can be treated by primary resection. Patients with T3 and T4a tumours may be resectable but are given chemoradiotherapy (CRT)

prior to surgery. A recent meta-analysis shows a survival advantage of neoadjuvant chemotherapy or CRT over surgery alone. A clear advantage of CRT over chemotherapy has not been demonstrated<sup>[2]</sup>. Patients with T4b disease or distant metastases are not surgical candidates and should be treated with chemoradiotherapy.

## T stage

In [<sup>18</sup>F]fluorodeoxyglucose (FDG)-positron emission tomography (PET), the expression rate of GLUT-1 and the size of tumours are important factors in identification of tumours. Both adenocarcinoma and SCC demonstrate high avidity for FDG. However, the standardized uptake value (SUV) of SCC is significantly higher than that of adenocarcinoma (13.5 versus 9.1)<sup>[3]</sup> and most SCCs are identified. The sensitivity of detection for adenocarcinoma is more variable particularly for the gastro-oesophageal junction and the proximal stomach and 17–20% may show no or little uptake partially related to the mucin content of tumours. Low uptake is found in well-differentiated tumours or those that demonstrate a diffuse growth pattern or contain large amounts of mucin.

False-positives will occur with oesophagitis, either peptic or infective, and with patients with strictures that have been dilated. False-negatives occur in small tumours, less than 8 mm, and the sensitivity for detection of T1 tumours may be as low as 43%. FDG-PET is certainly unable to differentiate the layers of the oesophagus and the SUV<sub>max</sub> is lower in T1 compared with T2/3 tumours; however, when tumours invade deeper the SUV does not predict depth of invasion so T4 cannot be differentiated from T2/3 tumours<sup>[4]</sup>.

Computed tomography (CT) cannot identify the different layers of the oesophageal wall or differentiate between T1, T2 and T3; however, with multiplanar techniques the length of the tumour can be assessed and CT has a complementary role to endoscopic ultrasonography (EUS) particularly for excluding T4b disease.

Endoscopic ultrasound remains the best modality for the assessment of the T stage with a high pooled sensitivity for tumour invasion (81–90%), especially for T4 disease (92.4%), and the specificity is 99%<sup>[5]</sup> although it may both overstage and understage patients.

## N stage

The higher the T stage the more likely there is to be nodal disease. Nodal staging provides important prognostic information with the 5-year survival for node-negative patients of 40% and 3% for node-positive patients; the number of nodes is now required for staging. The non-invasive techniques have limitations. CT, depending only on size, is of limited sensitivity and specificity (30–60% and 60–80%, respectively). EUS is more sensitive and the addition of fine-needle aspiration cytology (FNAC) increases the specificity<sup>[6]</sup> but is operator dependent.

The accuracy of a combination of CT and EUS is reported to be greater than each technique alone.

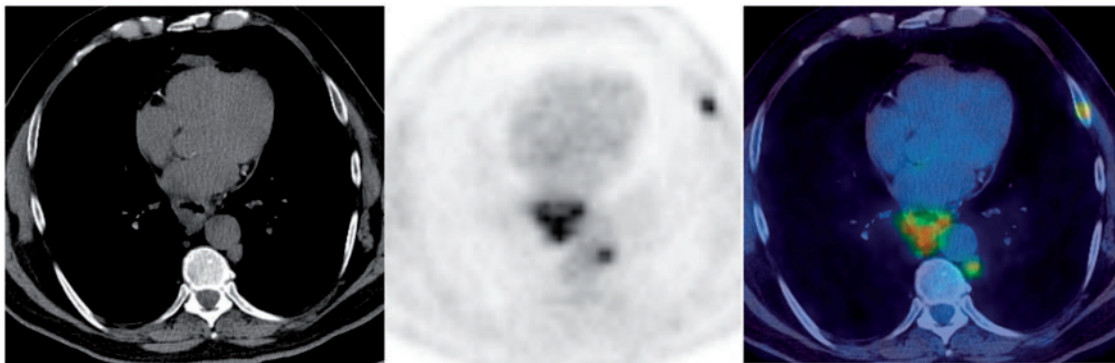
FDG-PET can identify tumour in normal size nodes and has been shown to have improved diagnostic sensitivity, specificity and accuracy compared with CT. The false-negatives in PET are in micrometastases and in small nodes close to the primary tumour that cannot be separated from it. The false-positives include calling reactive nodes positive in patients with chronic lung disease. Lerut et al.<sup>[7]</sup> looking at a group with both SCC and adenocarcinoma found CT/EUS was more sensitive but less specific than PET for loco-regional nodes (EUS/CT sensitivity 83%, specificity 45%, accuracy 69% vs 22%, 91% and 48% for PET). The advent of integrated PET/CT has improved results and Yuan et al.<sup>[8]</sup> found there was an increase in sensitivity, specificity and accuracy with PET/CT for nodal staging compared with PET alone (sensitivity 81%, specificity 87%, accuracy 86% for PET vs 93%, 92% and 92% for PET/CT). There has been considerable variation in the reported accuracy of PET/CT for nodal staging. Yen et al.<sup>[9]</sup> found PET/CT and EUS were similar in accuracy (EUS 55.6% and PET/CT 54.%), whereas Walker et al.<sup>[6]</sup> reported an accuracy for PET/CT of 35.8% compared with EUS accuracy of 60.5%. Van Vliet et al.<sup>[10]</sup> in a meta-analysis found no significant difference in diagnostic performance between EUS, CT and FDG-PET; although the sensitivity for CT and PET was significantly lower than EUS, the specificity was significantly higher.

Hsu et al.<sup>[4]</sup> investigated the value of PET/CT for the new nodal staging, where the number of involved lymph nodes is required and this may be difficult to assess prior to surgery using EUS. These authors found that the SUV<sub>max</sub> of extra tumour uptake (but not the main tumour) was associated with N status. In patients where the SUV<sub>max</sub> was >4.9, 61% had N2/3 disease, whereas only 17.2% had N2/3 disease if the SUV<sub>max</sub> was <4.9 and using an SUV<sub>max</sub> of 4.9 the prediction of N2/3 status had sensitivity of 52.4%, specificity of 87.3% and accuracy of 77.6%.

## M staging

Patients with distant metastases either in lymph nodes or solid organs have a very poor outcome and should not undergo surgical resection. Patients with only local disease have a 30-month survival of 60%, whereas if distant metastases are present it is only 20%. Metastases are found in 20–30% of patients at presentation with the commonest sites of metastatic disease being non-regional lymph nodes, liver and more rarely lung and bone (Fig. 1). These sites are not assessable by EUS.

FDG-PET has been reported to be superior to CT in the detection of non-regional lymph nodes and distant organ metastases. The sensitivity of PET decreases with decreasing size, with lesions less than 1 cm often difficult to visualize. Luketich et al.<sup>[11]</sup> found PET was superior to



**Figure 1.** Staging oesophageal cancer with high uptake in the primary and the loco-regional nodes with an unsuspected rib metastasis.

CT and identified 69% of lesions, missing lung, liver and peritoneal metastases all less than 1 cm, giving a diagnostic accuracy of 84% (CT was 46% sensitive with an overall accuracy of 63%). The meta-analysis by Van Vliet et al.<sup>[10]</sup> reported a pooled sensitivity of 71% and specificity of 93% of PET for metastases.

PET/CT is superior to PET alone and is also better than CT for distant metastases. In a large study, PET upstaged only 4% of patients compared with conventional imaging and these authors suggested it should not be routinely undertaken<sup>[12]</sup>. However, Gillies et al.<sup>[3]</sup> found PET/CT provided additional information in 18.5% and altered management in 17% with 11% upstaged and 7.5% downstaged compared with conventional imaging and recommended its routine use in staging.

### Staging strategy

Most institutions use EUS for T and N staging with CT used to exclude T4b disease and for distant metastases. PET/CT is used to exclude distant metastases leading to a change in therapy in 11–17%<sup>[3]</sup>. Wallace et al.<sup>[13]</sup> have compared the effectiveness of different strategies for the pre-operative assessment, including life expectancy and cost effectiveness. These authors concluded that the combination of PET with EUS with fine-needle aspiration is the most effective strategy.

However, a recent study of staging sequences<sup>[14]</sup> using logistical regression suggests that PET/CT should be performed first, with EUS used in limited cases for patients with curable disease. This differs from many strategies and these authors suggest this is because, apart from T4b disease, the tumour depth and loco-nodal disease are not contraindications to surgery.

### Response assessment

The prognosis for oesophageal cancer is poor with a median survival of 3–5 months and recurrences are

frequent. The best chance of cure is successful surgery and preoperative chemoradiotherapy is used to improve outcomes with the aim of eradicating lymphatic and haematogenous metastases, not only to improve survival and decrease recurrences, but also to shrink the primary tumour<sup>[2]</sup>.

However, patients may not respond or may progress during therapy and could benefit from early surgical intervention and non-responding patients do worse following surgery even if there is a complete resection, than those who undergo surgery alone. It is therefore very important to differentiate responders from non-responders. Clinical parameters such as weight gain and improvement in swallowing can be assessed but imaging is used in an attempt to improve outcomes but has rather variable results.

EUS is the most accurate method for staging the primary tumour and local lymph nodes at diagnosis but has limitations following chemoradiotherapy as EUS cannot differentiate between fibrosis and residual disease and the accuracy of T and N staging after chemoradiotherapy can be as low as 34.9% and 39.8%, respectively<sup>[9]</sup>.

The use of CT is limited for both T and N staging with a reported sensitivity after treatment of 33–55%, and a specificity ranging from 50% to 70%<sup>[15]</sup>.

FDG-PET appears to be the best method for identifying responders in oesophageal cancer. Weber et al.<sup>[16]</sup> assessed early response to therapy within 14 days of commencement of chemoradiotherapy for adenocarcinoma and found that a decrease in SUV of greater than 35% indicated a major pathological response with a 3-year survival of 70%, compared with a 3-year survival of only 35% in the non-responders. In patients with SCC, Wieder et al.<sup>[17]</sup> found FDG-PET was both sensitive and specific (93% and 88%) in identifying a major response in SCC using an SUV reduction of 30%. Swisher et al.<sup>[18]</sup> compared EUS, CT and FDG-PET and found FDG-PET was more accurate (70%) than EUS (68%) or CT (62%). In another study comparing EUS and PET/CT, EUS

identified only 5.9% of the complete pathologic responders, whereas PET/CT identified 70.6%<sup>[19]</sup>.

However, more recent studies have produced variable results. In patients with adenocarcinoma and using an SUV reduction of 24%, Malik et al.<sup>[19]</sup> found the sensitivity was 62.5%, specificity 71.4% and accuracy of 67.4% in separating responders from non-responders but did not predict survival.

Klaeser et al.<sup>[20]</sup> performing PET after chemotherapy but before radiotherapy found, using an SUV reduction of 40%, that PET could identify responders but it could not reliably predict non-responders and so define which patients should proceed to immediate surgery without radiotherapy. However, Thureau et al.<sup>[21]</sup> in patients with both adenocarcinoma and SCC found complete responders had SUV reduction of >50% and responders had a significant survival advantage. They suggested the cutoff SUV used depended on cell type, chemotherapy regimen and when the PET/CT is performed in related to either chemotherapy or radiotherapy and further studies are required.

In a meta-analysis using PET for tumour response, Kwee<sup>[22]</sup> found a pooled sensitivity of 67% and specificity of 68% and concluded that PET should not yet be used routinely to guide neoadjuvant therapy decisions.

## Recurrent disease

The disease-free survival for oesophageal cancer is poor with a 5-year survival after apparently curative surgery of 30–50%. Recurrence is often systemic (60%) or loco-regional (30%) or both in 10%. Approximately 60% occur within the first year and nearly all occur within 2 years after initial therapy. Patients with recurrent disease have a poor prognosis but early detection of recurrent disease may allow further treatment to prolong survival. EUS, magnetic resonance imaging (MRI) and CT may be of limited value as there is considerable fibrosis, oedema or scarring, which limits diagnosis by these methods, and FDG PET/CT has advantages. In a study by Teyton et al.<sup>[23]</sup> routine follow-up using EUS, CT and PET every 6 months was undertaken in asymptomatic patients. PET was more accurate than CT (91% vs 81%) for the detection of all recurrences (sensitivity 100% vs 65% and specificity 85% vs 91%). It was more accurate for loco-regional recurrence (96.2% vs 88.9%) and distant metastases (92.5% vs 84.9%), especially bone and liver, but less sensitive in the detection of early lung metastases. In a study of SCC<sup>[24]</sup>, PET/CT has an overall sensitivity of 93%, specificity of 75% and accuracy of 87% for recurrent disease. For local recurrence, although the sensitivity was high (96%), the specificity was only 50% because of false-positives at the anastomosis, and EUS and CT are more appropriate for the detection of anastomotic recurrence. False-negatives occurred in small lesions and in areas of previous irradiation. In this study, patients with a higher SUV or

systemic disease on PET had a poorer prognosis (mean SUV of survivors 6.62 vs 11.24 for those who died).

## Prognosis

The TNM staging does appear to be able to predict prognosis in those patients who undergo curative surgery without chemoradiotherapy with the number and location of nodes and whether there is extracapsular spread influencing survival. In those patients who receive preoperative chemoradiotherapy, the post-treatment staging, particularly the number of nodes and the size of the metastatic deposit, is an independent prognostic factor for overall survival<sup>[25]</sup>.

A meta-analysis of the use of FDG-PET<sup>[26]</sup> found that a higher SUV indicated a worse prognosis and was associated with a higher risk of recurrence. A higher SUV was also associated with longer tumours, higher T-stage status, positive N-stage status and squamous cell histology<sup>[27]</sup>. Cheze-Le Rest et al.<sup>[28]</sup> using multivariate analysis, found only SUV<sub>max</sub> >9 and FDG-positive lymph nodes were independent predictors of poor outcome. However in a later publication, the same group<sup>[29]</sup> found no SUV measurement was a significant prognostic factor, and only functional tumour volume and length were independent prognostic factors.

FDG PET may also be helpful in indicating prognosis in patients with recurrent tumour. Jingu et al.<sup>[30]</sup> found cause-specific survival and local control rates were better in patients with an SUV<sub>max</sub> of <2.4 after therapy compared with those with an SUV >2.4. In this study, PET was performed less than 7 days after chemoradiotherapy and was better than CT in identifying a complete response early.

## Conclusions

FDG-PET/CT can identify the primary tumour but this is better assessed by EUS. A combination of PET/CT and EUS FNAC can be used for nodal disease. However, the presence of metastases dictates therapy and PET/CT is the best modality for identifying these. Whether it should be used as the initial staging investigation is more contentious and requires cost-effective studies to be undertaken.

PET/CT may provide information for response assessment especially with its high negative predictive value indicating non-responders. PET/CT can identify recurrent disease and may offer prognostic information.

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