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Review

Extended staging of oesophageal cancer using FDG-PET – A critical appraisal

Maria Cristina Marzola[a,*], Giovanni De Manzoni[b], Gaia Grassetto[a], Claudio Cordiano[b], Adil Al-Nahhas[c], Abass Alavi[d], Domenico Rubello[a,**]

[a] PET/CT Centre, Department of Nuclear Medicine, Radiology, Medical Physics, 'Santa Maria della Misericordia' Hospital, Via Tre Martiri 140, 45100 Rovigo, Italy
[b] 1st Clinical Surgery, University of Verona, Verona, Italy
[c] Department of Nuclear Medicine, Hammersmith Hospital, London, UK
[d] Division of Nuclear Medicine, Department of Radiology, University of Pennsylvania School of Medicine, Hospital of the University of Pennsylvania, Philadelphia, PA, USA

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ABSTRACT

Background and aim: Oesophageal cancer (OC) is a highly aggressive tumour with unfavorable prognosis due to early stages metastases. Treatment and survival rates are highly correlated with tumour wall invasion, lymphatic involvement and metastatic spread. Thus, an accurate staging at initial diagnosis is fundamental for optimal management. In the present review article the potential role of the FDG-PET in the staging of OC is discussed.
Methods: A systematic review of all papers published in PubMed until June 2010 was performed.
Results: Endoscopic ultrasound (EUS) is helpful for T and N staging but not for M staging. CT plays a complementary role to EUS in T staging, especially in excluding T4 disease. However, in N staging, CT relies on "size criteria" (<1cm = benign, >1cm = malignant) which reduces its sensitivity and specificity.

FDG-PET has been demonstrated to be a very helpful tool in staging and re-staging OC. Most OCs demonstrate high FDG accumulation and are usually well detected with PET. Unfortunately, PET cannot reveal very small lesions due to its limited spatial resolution, therefore limiting the usefulness of PET in T staging. In N staging, an FDG positive node is highly likely to contain disease. However, FDG-PET cannot reliably separate the primary site from closely adjacent nodes.

The real and unquestionable additional diagnostic value of FDG-PET in comparison to CT and EUS is in evaluating distant metastases.
Conclusions: It appears reasonable to include FDG PET/CT in the diagnostic algorithm of patients with OC in order to better define the optimal therapeutic approach.

1. Introduction

Oesophageal cancer is a highly aggressive disease, accounting for about 10% of all gastrointestinal malignancies (with an increased incidence in the past decade) and usually involving elderly patients, with a mean age of between 50 and 60 years [1,2].

Most oesophageal cancers are epithelial in origin and histologically are of two separate entities: adenocarcinoma and squamous cell carcinoma.

Squamous cell carcinoma arises from the squamous epithelium and is associated with smoking and alcohol consumption that are considered the most significant risk factors for its development. Other predisposing conditions include achalasya, lye strictures, celiac disease, Plummer-Vinson syndrome and tylosis [2].

Adenocarcinoma is typically localized in the distal portion of the oesophagus and gastro-oesophageal junction, generally developing in association with Barrett's columnar metaplasia, a known pre-malignant condition.

In the past, squamous cell carcinoma was the prevalent type of oesophageal cancer, accounting for about 95% of all oesophageal malignancies. However, the past two decades have witnessed a dramatic increase in the rate of adenocarcinoma, raising its percentage to 50% in many areas and replacing squamous cell variety in the United States and Western Europe.

Oesophageal cancer is considered unfavorable in terms of prognosis, firstly because it is often largely asymptomatic in early stages (thus most cases are diagnosed when the disease has become locally advanced) and also because it can develop lymph node or distant metastases from an early stage. Furthermore, the oesophagus is not surrounded by a real "serosa" and the lymphatic drainage is rich, making local infiltration into adjacent mediastinal structures more frequent at an earlier stage.

Oesophageal cancer is a typical "refractory cancer" with a 5-year survival rate still relatively low (6–11%) [3]. However, treatment

* Corresponding author. Tel.: +39 0425 39 4431; fax: +39 0425 39 4434.
** Corresponding author. Tel.: +39 0425 39 4428; fax: +39 0425 39 4434.
E-mail addresses: marzola.mariacristin@azisanrovigo.it (M.C. Marzola), domenico.rubello@libero.it, rubello.domenico@azisanrovigo.it (D. Rubello).

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outcomes have improved because of the advances in the screening procedures, the attention to pre-cancerous conditions and the development of surgical and non-surgical (chemo-radiation) therapy [4].

Treatment planning and survival rates are highly correlated with tumour wall invasion, lymphatic involvement and metastatic spread. In fact, patients with local or locally advanced disease at presentation are usually treated with surgery (oesophagectomy alone) with curative intent, while in other cases neo-adjuvant (chemo-radiation) therapy is offered, followed by oesophagectomy [2]. Figs. 1–5.

For these reasons, an accurate staging at initial diagnosis is fundamental to better define the therapeutic planning, provide optimal management and improve prognosis.

2. Diagnosis

Imaging has a limited role in the detection of oesophageal cancer [2]. Double contrast barium studies were often used to evaluate patients with dysphagia, which is a typical symptom of oesophageal cancer in advanced stages, showing positive predictive value of about 42% [1]. Nevertheless, early oesophageal cancers often show very subtle findings on barium studies that are not enough to provide a rapid diagnosis. Therefore, all patients with abnormal barium examination should undergo upper GI endoscopy, and this is practically being offered to most patients presenting with dysphagia.

Endoscopy can better define the extent of the tumour, assess the patency of the oesophageal lumen and, above all, provide a definitive histologic diagnosis through fine-needle aspiration. It also provides important information regarding the feasibility of potential, and subsequent, endoscopic treatment such as dilatation of the stenotic lumen.

Once the diagnosis is made, defining the stage of the oesophageal cancer is the next essential step for further patient management [5].

3. Staging system for oesophageal cancer

Oesophageal cancer is most commonly staged according to the American Joint Committee on Cancer (AJCC) staging guidelines, which incorporate T, N, and M classification. Recently, the 7th edition of the AJCC Cancer Staging Manual has been published [6,7].

3.1. TNM classification

In "T" classification, Tis replaces the previous "in situ" stage and is defined as a "High grade dysplasia" and includes all non-invasive neoplastic conditions previously called "carcinoma in situ". "T1" is characterized by an infiltration of the lamina propria or tunica submucosa, "T2" by the infiltration of the tunica muscularis propria, "T3" by the infiltration of adventitia and "T4" by an invasion of local structures. In addition, T4 tumours have been classified as T4a (resectable cancers invading adjacent structures such as pleura, pericardium, or diaphragm) and T4b (unresectable cancers invading others adjacent structures, such as aorta, vertebral bodies and trachea) [6,7].

From the clinical point of view, T stage is strongly related to the treatment approach and T1 and T2 tumours, confined to the oesophageal wall, can be submitted to primary resection with curative intent. On the other hand, T3 cancers (extension to adventitia) are potentially still resectable, but require pre-treatment with neo-adjuvant chemo-radiation therapy. However, a higher T stage is associated with a higher likelihood of nodal spreading and a poor long-term prognosis and survival [8].

"N" classification expresses the regional lymph node involvement, which has been re-defined by recent classification to include para-oesophageal nodes extending from cervical region to celiac nodes."N0" designates no regional lymph node involvement, "N1" includes 1–2 positive lymph nodes, "N2" includes 3–6 positive regional nodes and "N3" is >=7 positive regional lymph nodes (similar to gastric cancer classification).

For tumours in the cervical oesophagus, loco-regional lymph nodes include scalene, internal jugular and supra-clavicular lymph nodes. For thoracic oesophagus they include peri-oesophageal and sub-carinal lymph nodes. For tumours arising from the gastro-oesophageal junction, loco-regional lymph nodes comprise the lower peri-oesophageal and pulmonary ligament lymph nodes as well as diaphragmatic, pericardial, left gastric and celiac lymph nodes [6,7].

The N stage is particularly important in clinical practice, since the 5-year survival rate for patients without nodal involvement is approximately 40%, diminishing to 3% for those with nodal metastases. In fact, the number of regional lymph node metastases is a strong and independent predictor for developing distant metastases, long-term prognosis and survival. It is also important in defining the treatment planning since the presence of local lymph nodes often requires pre-surgical neo-adjuvant therapy.

Furthermore, local peri-oesophageal nodes are usually excised "en bloc" with the primary tumour defined as a "two-field" dissection or, alternatively, a "three-field" dissection including the excision of cervical nodes in patients with upper-third tumours. Thus, an accurate evaluation of lymph node status is extremely important not only for prognostic implications but also in guiding the treatment options [9].

"M" classification is related to the absence (M0) or the presence (M1) of distant metastases, including both distant lymph-node and organ metastases (the sub-classification M1a and M1b, i.e. potentially resectable or unresectable metastases been eliminated).

Practically, distant metastases have been reported at initial presentation in 20–30% of patients with oesophageal cancer [10,11]. Organ metastases are usually located in the liver and, more rarely in the lungs and bones and are associated with a worse prognosis than distant (non-regional) lymph nodes metastases.

4. Morphologic imaging in staging: EUS, CT and MRI

4.1. EUS

Using an echo-endoscope (a modified upper endoscope directly passing into the oesophagus), endoscopic ultrasound (EUS) is considered the most accurate imaging modality to estimate the loco-regional disease in patients with oesophageal cancer [12].

EUS can precisely assess the depth of penetration of the primary tumour. The five layers of the oesophageal wall are depicted by EUS as five alternating layers of different echogenity, with oesophageal cancer appearing as a hypo-echoic mass disrupting this pattern [5,12].

The accuracy of EUS in determining the tumour depth has been estimated to be quite high. In a meta-analysis and systematic review of several studies, Puli et al. showed that the pooled sensitivity of EUS for tumour invasion is high (81–90%), and even higher for advanced T-disease than for earlier stages (81.6%, 81.4%, 91.4% and 92.4% for T1, T2, T3 and T4 respectively). The specificity to diagnose the depth of tumour invasion is also high at around 99% [13]. This is fundamental for defining the treatment approach which includes curative surgical, endoscopic mucosal or submucosal dissection. It also helps, in more advanced T-disease, to decide the feasibility of introducing neo-adjuvant treatment.