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F-18 fluorodeoxyglucose positron emission tomography in the non-invasive staging of non-small cell lung cancer ☆

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Abstract

Objective: Positron emission tomography (PET) using F-18 fluorodeoxyglucose (FDG), a glucose analogue, as a metabolic tumour marker, has been proposed for the non-invasive staging of oncological disease. Tumours demonstrate increased glycolytic activity and thereby, FDG PET can differentiate benign from malignant lesions. To determine its role in the mediastinal staging of patients with suspected non-small cell lung cancer, a prospective study of FDG PET and computed tomography (CT) compared to surgery and pathology was performed. The analysis group consists of 50 patients, 37 men and 13 women, mean age 64 years (range, 41–78 years). **Methods**: A nuclear physician, blind to the clinical and CT data, graded the FDG PET studies qualitatively on a five-point scale, based on the intensity of glucose uptake, for the presence of mediastinal nodal tumour involvement. Scores of four or greater were considered positive for tumour. An experienced radiologist interpreted the patients' CT scans blind to the other data. The CT criterion for tumour involvement was a nodal long axis diameter of 10 mm or greater. All patients underwent either thoracotomy or mediastinoscopy to obtain surgical specimens. The PET, CT, surgery and pathology were mapped according to the American Thoracic Society nodal classification resulting in 201 nodal stations evaluated. The imaging studies were analysed for N2 or N3 tumour involvement compared to histology or dissection of nodal stations. **Results**: All patients had proven non-small cell lung carcinoma. PET excluded tumour in 175 of 181 nodal stations (specificity 97%) compared to 162 of 181 (specificity 90%) by CT. PET correctly identified 16 of 20 (sensitivity 80%) nodal stations with tumour compared to 13 of 20 by CT (sensitivity 65%). Overall, PET correctly staged 191 of 201 nodal stations (accuracy 95%) compared to 175 of 201 by CT (accuracy 87%). By the McNemar test, PET was significantly more specific than CT in excluding nodal tumour involvement ($\chi^2 = 5.5$, $P < 0.05$). **Conclusions**: FDG PET is more specific than computed tomography in the non-invasive mediastinal staging of non-small cell lung cancer and has an important clinical role in the pre-operative staging of lung cancer patients.

Keywords: Lung cancer staging; Fluorodeoxyglucose; Positron emission tomography

1. Introduction

Primary lung carcinoma is the leading cause of cancer death in men and women in Western countries. Surgery remains the only reliable method of curing lung cancer. At presentation, small cell lung cancer has almost invariably spread and patients are not candidates for resection. In non-small cell lung carcinoma, surgically curable disease is delineated by tumour involvement of mediastinal lymph nodes. Currently, accurate staging of the mediastinum requires invasive sampling of mediastinal lymph nodes. For patients with stage I and II disease (N0, N1) surgery is the treatment of choice. Patients with stage IIIB disease (N3) are considered unresectable. The surgical management of N2 disease (stage IIIA) remains controversial. N2 disease can be divided into 'minimal' disease (involvement of only one node with microscopic foci) or 'advanced' bulky disease. Only 20% of all cases of N2 disease are technically resectable, and most of these resectable cases are discovered to be N2 only at thoracotomy [1]. The structural imaging techniques of CT and MRI are not considered sufficiently sensitive

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or specific to substitute for invasive mediastinal staging [2]. The challenge for the non-invasive imaging modalities is accurate mediastinal nodal staging, thereby avoiding inappropriate surgery in patients with advanced N2 or N3 disease.

Positron emission tomography (PET) is a functional imaging modality that allows the non-invasive characterisation of tissue metabolism. Fluorine-18 decays with a half-life of 110 min by releasing a positron which combines with a nearby electron; their mass is converted to two high energy photons of 511 keV emitted at approximately 180° to each other. Fluorine-18 can substitute for hydrogen on many molecules producing a positron-emitting analogue, which can be detected by the PET scanner and quantitated using tracer kinetic modelling. F-18 fluorodeoxyglucose (FDG), a glucose analogue, is taken up into the cell, phosphorylated and trapped, neither entering the glycolytic or glyconeogenic pathways.

Initial oncological studies of F-18-fluorodeoxyglucose using positron emission tomography were performed in primary neurological malignancies. In cerebral glioma, the tumour metabolic activity correlated with grade of malignancy and prognosis [3]. On the basis of increased glucose metabolism, it was possible to distinguish benign from malignant tissue and thereby, differentiate radiation necrosis from recurrent or residual disease [4]. The metabolic characteristics of cerebral glioma were observed in other high grade solid tumours, including lung carcinoma. Early reports of FDG PET in lung cancer focused on the differential diagnosis of indeterminate solitary pulmonary nodules [5–7]. In the largest published series, Patz et al. [8] was able to differentiate benign from malignant pulmonary lesions in 51 patients with a sensitivity of 89% and 100% specificity. The study by Gupta et al. [5], although designed to evaluate pulmonary nodules, included six patients with hilar or mediastinal lymph node abnormalities. FDG PET correctly distinguished malignant from benign lymphadenopathy in all six cases leading Gupta to suggest a role for FDG PET in nodal staging of the mediastinum.

Mediastinal staging of lung cancer using FDG PET became feasible with improvements in PET instrumentation [9,10]. In a small series of 23 patients with newly diagnosed or suspected non-small cell lung cancer, Wahl et al. [11] compared computed tomography and FDG PET for mediastinal nodal staging. FDG PET was 82% sensitive, 81% specific, and 81% accurate, whereas, CT alone was 64% sensitive, 44% specific, and 52% accurate. Since this preliminary report, a number of other groups have confirmed their initial observations [12–16].

One advantage of PET is its ability to evaluate the primary lesion and the whole body for regional and distant metastatic disease. Some authors have advocated whole body PET imaging for staging of oncological disease [17]. Despite concerns that without correction for tissue attenuation this method is less sensitive in detecting small volume nodal disease within the mediastinum, it has been used in nodal staging of lung cancer [18,19]. Meikle et al. [20] has recently described a method that combines correction of whole body PET studies for tissue attenuation using low-count transmission data and iterative reconstruction to produce images of comparable quality to conventional PET methods without prolonging the acquisition time. Our study evaluates FDG PET and computed tomography in the mediastinal staging of non-small lung cancer patients using regional PET imaging over the thorax and upper abdomen with measured correction for tissue attenuation.

2. Materials and methods

Consecutive patients presenting with suspected non-small cell lung carcinoma that remained surgical candidates after conventional clinical staging procedures were enrolled into the study. The study protocol was approved by the Austin and Repatriation Medical Centre Human Ethics Committee and informed consent was provided by all patients enrolled. Exclusions included patients less than 18 years of age, patients with diabetes, pregnant women and those in whom informed consent was not obtained. Patients entered into the study subsequently found to have distant metastases by PET or CT confirmed on correlative studies did not proceed to thoracotomy, but were included in the analysis if mediastinoscopy had been performed. The analysis group consisted of 50 patients, 37 men and 13 women, mean age 64 years (range, 41–78 years).

Fluorine-18 was produced on site by the irradiation of an oxygen-18 enriched water target using an IBA 10/5 Cylcotron (Ion Bean Applications, Brussels, Belgium). F-18-fluorodeoxyglucose synthesis was performed in an automated synthesis unit (Ion Beam Applications, Brussels, Belgium) [21]. Following radiopharmaceutical quality control procedures, F-18-fluorodeoxyglucose was delivered to the scanner suite for patient administration. Approximately 400 MBq FDG was administered intravenously and following a 45 min uptake period, a 30 min emission scan was acquired encompassing the thorax and upper abdomen using a Siemens/CTI 951/31R body scanner (Hoffman Estates, IL) with a 6.5 mm FWHM resolution and 10 cm axial field-of-view. An 8-min per bed transmission scan was acquired, either before or after the emission scan, for attenuation correction of the emission data. The FDG PET scan was reconstructed into a 128×128-image matrix using filtered backprojection with a Hanning filter (0.35 cycles cut-off). The processed image data was reviewed on a Sun SparcStation computer (Sun Microsystems, Palo Alto, CA) using ECAT Tools software (Siemens/CTI, Hoffman Estates, IL), which allows interactive viewing of transaxial, coronal and sagittal slices and projection data.

All patients enrolled underwent computed tomography using a Picker PQ 2000 CT scanner (Picker International, Highland Heights, OH) in helical acquisition mode from thoracic inlet to the level of the adrenal glands. Scanning

parameters were 8-mm collimation, a helical pitch of 1:1, table feed 8 mm/s. Scans were obtained in a single breath-hold after hyperventilation. Dyspnoeic patients were scanned in quiet respiration. All scans were obtained after injection of 100 ml of iopromide (Schering AG, Germany) at a rate of 2 ml/s into an antecubital fossa vein. Scanning was commenced with a 50 s delay after commencement of injection. Contiguous 10 mm transverse sections were reconstructed. Lung and mediastinal windows were printed and the films reviewed.

Surgical specimens were obtained in all patients either by mediastinoscopy or thoracotomy.

An experienced nuclear medicine physician blind to the clinical data and CT results interpreted the FDG PET studies. On PET, nodal stations were graded qualitatively compared to normal tissues and blood pool, on a five-point scale, with grade 5 representing definite tumour, grade 4 probable tumour, grade 3 equivocal for tumour, grade 2 probably not tumour and grade 1 definitely not tumour. Scores 4 or greater were considered positive for tumour involvement for the purpose of calculating sensitivity and specificity. The CT films were interpreted by an experienced radiologist with the criterion for tumour involvement being a nodal long axis diameter of 10 mm or more [22]. The FDG PET, CT, surgical findings and pathology were all mapped according to the American Thoracic Society (ATS) nodal classification resulting in a total of 201 nodal stations evaluated. The PET and CT were analysed for N2 or N3 tumour involvement by nodal station and sensitivity, specificity and accuracy calculated compared to surgery and pathology as the 'gold standard'. The McNemar test was applied to assess the statistical significance of observed differences in the sensitivity and specificity between FDG PET and computed tomography [23].

3. Results

All patients had proven non-small cell lung carcinoma. The primary pathology consisted of 5 cases of undifferentiated carcinoma, 21 squamous cell carcinoma, 19 adenocarcinoma, four adenosquamous carcinoma and one large cell tumour. Mediastinoscopy and/or mediastinotomy only was performed in 13 patients, 10 patients underwent pneumonectomy, lobectomy was performed in 24 patients and three patients had wedge resections. Pathological TNM staging was possible in 43 of the 50 patients. T2 primary lesions occurred in 30 patients, T1 tumours in six, T3 in four and T4 in three patients. In 28 patients, there was no pathological evidence of nodal involvement (N0 disease), while five patients had N1, eight had N2 and three patients had N3 nodal disease. Distant metastases were encountered in only three cases. A total of 201 nodal stations were assessed with 20 positive and 181 negative for tumour involvement. The positive nodal stations comprised of 12 with intracapsular, six with extracapsular and two with microscopic tumour. Of the 181 negative nodal stations, 110 were defined as negative by tissue biopsy, and 71 defined as negative by dissection of the nodal station at surgery.

Table 1
FDG PET and CT compared to surgery and pathology analysed by nodal station

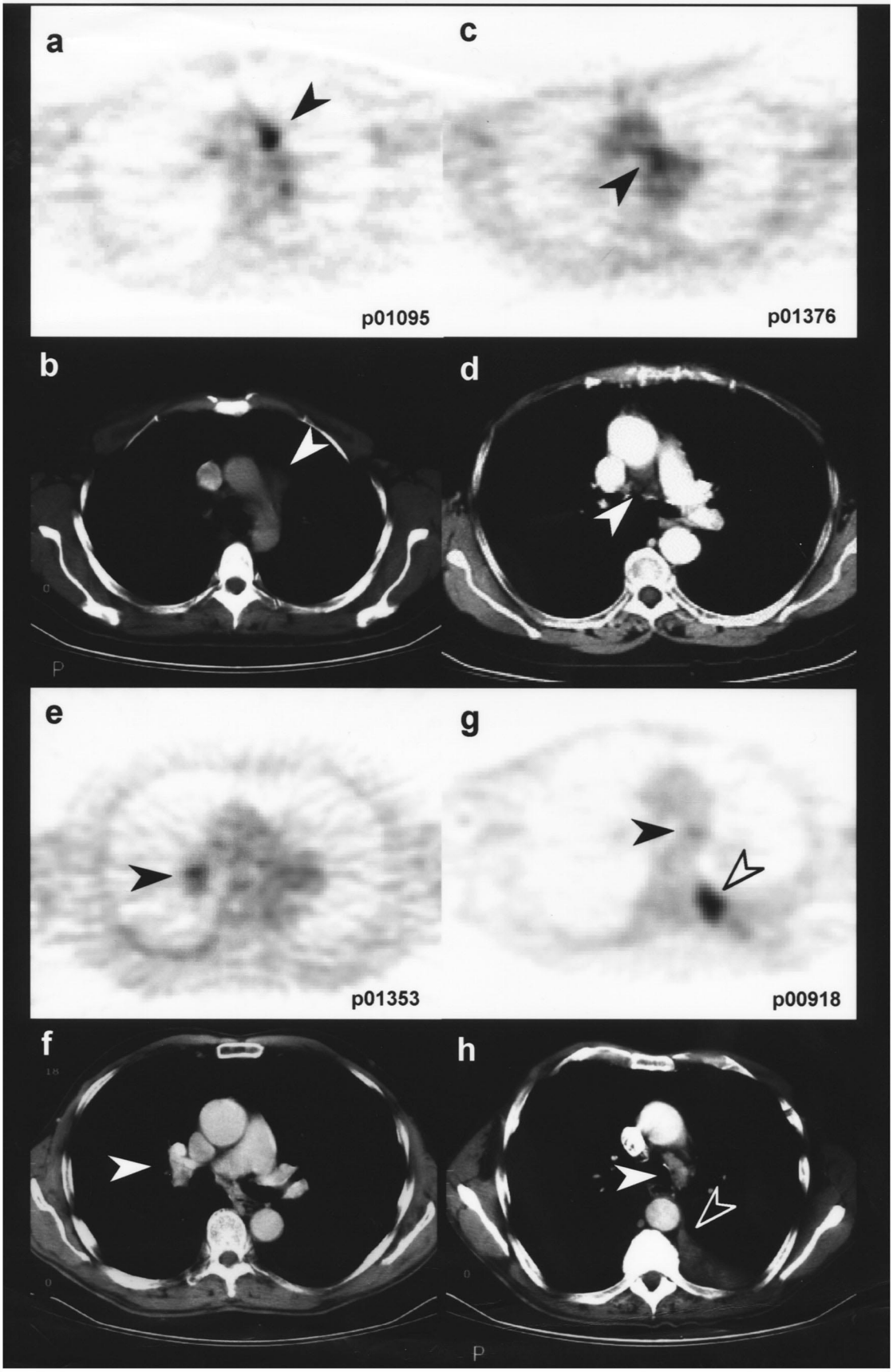
	Pathology	
	Positive	Negative
FDG PET		
Positive	16	6
Negative	4	175
CT scan		
Positive	13	19
Negative	7	162

Table 2
McNemar test of differences between CT and FDG PET interpretations

	PET positive	PET negative
Sensitivity[a]		
CT positive	11	2
CT negative	5	2
Specificity[b]		
CT positive	2	17
CT negative	5	157

[a] $\chi^2 = 2.3$, $P = \text{NS}$.
[b] $\chi^2 = 5.5$, $P < 0.05$.

Positron emission tomography excluded tumour in 175 of 181 nodal stations (specificity 97%) compared to 162 of 181 (specificity 90%) by CT. Positron emission tomography correctly identified 16 of 20 (sensitivity 80%) nodal stations with tumour compared to 13 of 20 by CT (sensitivity 65%) (Table 1). Overall, PET correctly staged 191 of 201 nodal stations (accuracy 95%) compared to 175 of 201 by CT (accuracy 87%). By the McNemar test (Table 2), FDG PET was significantly more specific than CT in excluding nodal tumour involvement ($P < 0.05$). On 22 occasions, FDG PET and CT differed in their ability to exclude nodal tumour involvement. The small numbers of positive nodal stations in the cohort precluded analysis for statistically significant differences in the sensitivities of FDG PET and CT. The PET false interpretations consisted of four false negatives and six false positives (Table 1). Computed tomography, by comparison, resulted in seven false negative and 19 false positive interpretations. Three CT false negative lymph nodes measured less than 10 mm in diameter and 19 CT false positives were a result of benign nodes with long axis diameter of 10 mm or greater. The PET and CT positive predictive rates were 73 and 41%, and negative predictive rates 98 and 96%, respectively. The false positive rate for PET and CT nodal staging was 3 and 10%.



4. Discussion

The non-invasive staging of non-small lung cancer is hindered by the limited ability of the structural imaging modalities of CT and MRI to distinguish benign from malignant tissue on the basis of size criteria alone. The advantage of functional imaging methods is their ability to characterise tissue metabolism prior to structural changes becoming apparent. Similarly, in cases where structural changes are detected by conventional imaging, functional studies can improve specificity by providing data about the metabolic behaviour of tissue. The most accurate staging information should result from a combination of both structural and functional imaging data.

The sensitivity of FDG PET in identifying mediastinal nodal tumour involvement is determined by tumour volume, the tumour's inherent metabolic rate, the metabolic activity of associated reactive cells, the resolution of PET instrumentation and the contrast between lesion and surrounding normal structures. The qualitative interpretation of the FDG PET studies resulted in four false negatives. Two of the false negative PET interpretations were a result of misalignment of the PET findings to the ATS nodal map and the other two due to small volume disease subject to partial volume effects. In one case, there was tumour involvement of right tracheobronchial lymph nodes with multiple small deposits, the largest 0.5 mm in its maximal diameter. On CT, no lymphadenopathy was detected and on the FDG PET, no metabolic focus distinct from the right hilar primary was identified. The other PET false negative (Fig. 1c,d), involved subtotal tumour replacement of 10 and 15 mm diameter lymph nodes interpreted on the FDG study as grade 1 (definitely not tumour). On review, this lymph node does demonstrate increased glucose activity although its proximity to the aortic arch reduces the contrast between lesion and blood pool and therefore, its qualitative detection is more difficult. Combining the CT data with the PET in this case would have alerted the nuclear medicine physician to the presence of a small lymph node at the carina and allowances made for partial volume effects. Consequently, allowing for errors in nodal localisation and interpreting the PET with the CT scan, three of the four PET false negatives could be discounted, improving the overall PET sensitivity to 19 of 20 (90%).

The specificity of FDG PET is influenced by the prevalence of granulomatous disease in the patient cohort under investigation. Chronic granulomatous infectious disease is glucose-avid and indistinguishable from malignant lymphadenopathy [8]. Similarly, increased metabolic activity of sarcoid lymphadenopathy has been described [24]. Less well recognised is the increased glucose activity in reactive lymph nodes encountered in four of the six false positive PET interpretations in our study group (Fig. 1e,f). The pathology in the PET false positive nodes included non-specific reactive changes (two cases), non-necrotising granuloma and anthracotic change. In the remaining cases, there was a tendency for reactive nodes to be less metabolically active and less discrete than tumour-involved nodes (Fig. 1a,e). This was not a specific observation and the PET positives require confirmation by mediastinoscopy to ensure patients with N0 or N1 disease are not denied potentially curative surgery. On review of the PET, in one case, the false interpretation can be explained by artifactual activity between consecutive bed planes.

Two false negative PET and four false negative CT interpretations were attributable to difficulties in localisation to the ATS nodal map. Misregistration of the PET to the surgery and pathology occurred due to the paucity of anatomical information on the FDG PET study. Computed tomography had difficulty in translating boundaries between nodal stations on transaxial CT slices to the coronal plane on the nodal map. Our experience, like that Chin et al. [14], was that the misregistration occurred within adjacent nodal stations. Direct extension of the primary tumour from the hilum into the mediastinum was responsible for the final PET false positive interpretation. Nodal glucose uptake contiguous with the primary lesion cannot be distinguished from direct tumour extension into the nodal station. Several authors have proposed 'anatometabolic' fusion of PET and CT image data [11,25] to overcome the difficulties encountered both in nodal localisation and separation of nodal metastases from the primary lesion.

Correcting the CT interpretations for misalignment, the sensitivity of CT improved to 17 of 20 (85%) with three true false negatives in nodes less than 10 mm in diameter, each with microscopic, intracapsular and extracapsular tumour, respectively. FDG PET was positive in only one of the three nodal stations. The 19 CT false positives were a result of benign lymph nodes with long axis diameters between 10 and 15 mm in 17 nodal stations and greater than 15 mm in two (Fig. 1g,h). The optimal CT criterion for tumour nodal involvement for this patient cohort was a long axis diameter

Fig. 1. All case examples are paired transaxial FDG and CT sections. The FDG scans all include blood pool activity for reference and are windowed to best demonstrate the metabolic lesion. (a,b) A 41-year old woman with adenocarcinoma of the left lung and enlarged anterior mediastinal lymph node on CT (b, arrow), with focal increased glucose uptake (a, arrow) which was incorrectly localised to the 4L nodal station resulting in a PET false negative due to misregistration. (c,d) A 77-year old woman with left upper lobe adenocarcinoma and false negative 8 mm lymph node at the carina on CT (d, arrow), and negative FDG PET (c, arrow). The lymph node was partially replaced by tumour at pathology. (e,f) A 72-year old man with right lower lobe squamous cell carcinoma and hilar lymphadenopathy, false positive on both CT (f, arrow), and PET in the 10R nodal station. PET demonstrated moderate, grade 4, glucose metabolism (e, arrow) and in a node measuring11 mm in the long axis diameter on CT. Pathology of the 10R nodes showed anthracotic tissue without tumour. (g,h) A 71-year old man with squamous cell carcinoma of the left lung with a 20 mm diameter aortopulmonary lymph node on CT (h, filled arrow) and no corresponding increase in metabolic activity on FDG PET (g, filled arrow) proven to be benign on pathology. The apical extent of the primary lesion in the

of greater than 15 mm. At this threshold, the false positives were reduced to two (specificity 99%), at the cost of one true positive (sensitivity 60%). Although the negative predictive rates of PET and CT are comparable, the CT false positive rate is much greater than for PET. The clinical implication for patients with negative PET mediastinal staging is that they would proceed to thoracotomy without mediastinoscopy, thereby, avoiding an invasive procedure with its associated cost and morbidity. By comparison using CT as the only screening procedure prior to surgery, more patients would require pre-operative invasive mediastinal staging.

In summary, FDG PET is an accurate, non-invasive functional imaging modality which is significantly more specific than computed tomography. Positron emission tomography plays an important role in excluding mediastinal nodal tumour involvement, such that, patients negative for N2 or N3 disease by PET can proceed to surgery without invasive mediastinal staging. Mediastinal nodal glucose uptake is not specific for tumour and requires confirmation by mediastinoscopy to identify those patients with N0 or N1 disease who are optimally treated with curative resection.

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