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Review Article

The Role of PET in Lung Cancer from a Surgeon's Perspective

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Abstract

PET has been widely adopted and remains the most cost-effective investigation in clinical staging of non-small cell lung cancer. Minimal access thoracic surgeons pinned their hopes on this new non-invasive technique to stage the mediastinum. PET can be blinded to adenocarcinoma in the lung or in mediastinal nodes in 10-15% of cases. Faced with low sensitivity of PET, Multidisciplinary treating clinicians have to accept these limitations when constructing clinical pathways, and adjuvant therapy should be based on pathological staging by invasive techniques (mediastinoscopy, EBUS, operative Systematic Nodal Dissection). PET helps direct those biopsies and finds unsuspected extra-thoracic metastases in 7% of patients. Relying on PET staging alone can lead to significant over staging, denial of curative resection, stage migration and misleading survival statistics.

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INTRODUCTION

The advent of Positron Emission Tomography (PET) almost 30 years ago had a great impact on the management of lung cancer to the effect of making it a routine investigation. It has been widely adopted and considered a milestone in clinical preoperative staging of the disease. From a surgeon's perspective the idea of PET drawing a "physiologic map" to be superimposed on a detailed "anatomic map" drawn by CT (fused PET/CT) was a revolutionary one. Non-invasive evaluation of lung masses and mediastinal nodal stations is an attractive option, especially when minimal access surgery is planned for curative resection. Since staging the mediastinum is so vital in management of Non Small Cell Lung Cancer (NSCLC), clinicians pinned their hopes on PET to reveal the exact biological nature of lung masses and nodal tissue in the chest. Such added information could dictate inoperability or suggest improved survival if neo-adjuvant chemotherapy was contemplated before surgery [1,2].

UK and international guidelines

The British Thoracic Society (BTS) was formed in 1982 by the amalgamation of the British Thoracic & Tuberculosis Association and the Thoracic Society. In a joint initiative with the Society for Cardiothoracic Surgery in Great Britain and Ireland the BTS published guidelines on the radical management of patients with lung cancer in 2010 [3]. The guidelines establish the role of PET in the evaluation of patients for radical treatment. However; it also pointed out the limitations of PET-CT to be false negative scans resulting from disease with low metabolic activity or FDG uptake (carcinoid, former bronchioloalveolar cell carcinoma), misregistration due to breathing artifact, uncontrolled diabetes and small lesion size <8 mm. False positive uptake may be seen in inflammatory conditions, and therefore patients should not be denied radical treatment on the basis of occult metastatic disease on PET-CT alone (especially if it is isolated). Confirmation by biopsy or further imaging is required.

The Health Technology Assessment (HTA) programme is part of the National Institute for Health Research (NIHR) in the UK, set up in 1993. It produces high-quality research information on the cost-effectiveness and broader impact of health technologies for those who use, manage and provide care to patients seen within the National Health Service (NHS) in England. HTA published a report by Facey et al, in which the key research question was: What is the clinical effectiveness of FDG-PET for the management of lung and other cancers [4]. The research findings directly influence decision-making bodies such as the National Institute for Health and Clinical Excellence (NICE) and the National Screening Committee (NSC). An economic model for England showed that in non-small cell lung cancer ^{18}FDG-PET was cost-effective in CT node negative patients, but not in CT node-positive patients. For detection of Solitary Pulmonary Nodule (SPN) there was also impact on patient management, but the resulting effect on patient outcomes was unclear. FDG-PET was accurate in detecting distant metastases across several sites, but sensitivity was variable for detection of lymph-node metastases and poor in early stage disease where sentinel lymph node biopsy would be used and for small lesions. The use of PET for diagnosis of NSCLC to differentiate benign from malignant tumour (without biopsy) would not be seen as appropriate in the UK. Based on systematic reviews NICE undertook economic evaluations directly relevant to England and Wales, which showed convincing evidence of cost-effectiveness of the use of PET-CT in the management of lung cancer [5].

The other important systematic review was from the Health

Technology Board for Scotland (HTBS) that differentiated between CT node-positive and CT node-negative patients [6]. Seventeen diagnostic studies were identified and PET sensitivity and specificity were estimated to be 90% and 93% for CT node-negative patients and 94% and 71% for CT node-positive patients. The HTBS systematic review also showed that PET had sensitivity of 93% to detect any distant metastases, with specificity of 96%. The guideline indicated that from 1515 patients, a mean of 15% had unexpected distant metastases detected by PET, and PET led to change in management in 25% of patients.

The 3rd edition of the American College of Chest Physicians guidelines for lung cancer staging (2013) recommended that patients with abnormal lymph nodes on CT or PET, or centrally located tumors without mediastinal lymph nodes, should undergo invasive staging [7]. Minimally invasive needle techniques to stage the mediastinum, such as Endo Bronchial Ultra Sound guided biopsies (EBUS) have become increasingly accepted and are the tests of first choice to confirm mediastinal disease in accessible lymph node stations. If negative, these needle techniques should be followed by surgical biopsy.

PET versus CT in staging the mediastinum

The sensitivity and specificity of CT scanning for identifying mediastinal lymph node metastasis were approximately 55% and 81% respectively, confirming that CT scanning has limited ability either to rule in or exclude mediastinal metastasis [7]. Traditionally mediastinal nodes with a diameter ≥1.0 cm in its shortest diameter on the CT were suspicious of malignancy. A study by the American College of Surgeons Oncology Group undertook a trial to ascertain whether ^{18}FDG-PET could detect lesions that would preclude pulmonary resection in a group of patients with documented or suspected NSCLC found to be surgical candidates by routine staging procedures (Z0050 Trial) [8]. PET was significantly better than CT for the detection of N1 and N2/N3 disease (sensitivity 42% vs 13%, P = .0177, and specificity 58% vs 32%, P = .0041). The negative predictive value of PET for mediastinal nodal disease was 87% (i.e. PET says this is not cancer, final pathology agrees). Unsuspected metastatic disease or second primary malignancy was identified in 18 of 287 patients (6.3%). These results are impressive when comparing CT and PET, favouring the enhanced role of ^{18}FDG-PET. However; when PET is benchmarked against pathological staging obtained by Systematic Nodal Dissection (SND) during thoracotomy or Video Assisted Thoracoscopic Surgery (VATS), PET is disappointing [9]. False positives as well as false negatives have blighted PET, leading to stage migration and wrong survival statistics.

PET versus Pathological staging

The 'PLUS' meta-analysis reporting the value of fused PET-CT mediastinal staging in patients with NSCLC found the median sensitivity to be 85% (range 67% to 91%) and specificity of 90% (range 82% to 96%) [10]. Specificity could be reduced even further in geographical areas with endemic tuberculosis and fungal disease [11]. A meta-analysis by Gould et al suggested PET to have low sensitivity in picking up metastatic adenocarcinoma in mediastinal nodes [12]. Cerfolio et al studied the role of PET in NSCLC in 400 patients [13]. They concluded that there are many false positives lymph nodes and it may be more likely to miss N2 disease in the #5, #6, and #7 stations. They reported unnecessary mediastinoscopy in 38 patients. However; the same group reported in 2009 that despite its shortcomings PET is a worthwhile investigation to perform for early lung cancer [14]. In our series published 2011 we benchmarked ^{18}FDG-PET to operative VATS Systematic Nodal Dissection (SND) [9]. The unexpected N2 disease in clinical stage N0-1 was 9/86 (10.5%). SND resulted in 25/96 stage migrations over PET-CT; upstaged 16/96 (16.6%) all were adenocarcinoma, and down staged 9/96 (9.4%). Similar results were published by Augustin et al and Poncelet et al [15,16].

Comparative studies in breast cancer showed similar results with axillary nodes. The Blue Cross Blue Shield (BCBS) systematic review included eight diagnostic studies, with a total of 337 patients with breast cancer [17]. It concluded that PET scanning cannot be used to avoid axillary lymph node dissection in patients with clinically N0 axillae, because of unacceptably low sensitivity [ranged from 20 to 50%]. With this level of false negatives, if patients did not go on to have standard diagnostic tests, it was estimated that resulting suboptimal treatment would be associated with a reduction in 10-year survival of 8.2%.

WHY IS PET BLINDED TO ADENOCARCINOMA?

One of the serious disappointments of PET scanning in lung cancer is the low uptake of adenocarcinoma and carcinoid tumours. Ground Glass Opacities (GGO) revealed on High Resolution CT (HRCT) due to lepidic growth pattern of adenocarcinoma (former Bronchiolo-Alveolar Carcinoma) particularly have low FDG uptake [18]. Gilles et al and Plathow et al have recently explained why tumours and nodes have erratic ^{18}FDG uptake on PET [19,20]. ^{18}FDG is an analog of glucose, taken up by the same cell membrane Glucose Transporters (GLUTs) that take up glucose and is phosphorylated by the same hexokinases, as is glucose. GLUTs are energy-independent glucose transporters across the cell membrane against a concentration gradient. There are 5 phenotypes Glut-1 (erythrocyte type), Glut-2 (liver type), Glut-3 (brain type), Glut-4 (muscle/fat type), and Glut-5 (small intestine type). Unlike glucose when FDG is phosphorylated to become FDG-6-phosphate in the cell, it is 'metabolically trapped'. The fluorine atom on the FDG molecule prevents its further metabolism and it can be neither metabolised further nor stored as glycogen. FDG trapping inside the cells will show up as foci of hypermetabolism, or "hot spots" on the subsequent PET scan images. The signal is quantified using the SUVmax (Maximum Standard Uptake Value).

Tumour cells adapt to hypoxia by upregulation of GLUTs and increased activity of Hexokinase. They cunningly increase their level of energy production through anaerobic glycolysis (2 ATP molecules), which is a relatively inefficient way to produce energy compared to oxidative phosphorylation (30 ATPs). However; the resultant ambient acidosis is lethal to normal cells while tumour cells evade apoptosis by maintaining normal intracellular pH. This process is thought to give the tumour cells a competitive advantage for local growth, ultimately leading to invasion of basement membrane, breaking barriers and sending distant metastases. Similar studies in breast cancer have shown that overexpression of glucose transporter Glut-1 may contribute

to the increased uptake of ^{18}FDG by these tumors observed by PET imaging [21]. On the other hand prostate cancer is the least FDG-avid tumour, further more accumulation of FDG in the urine compromises imaging of organs adjacent to the bladder [22]. It is concluded therefore, that different tumour cell types have different GLUT regulation. It is known that primary lung tumours, especially squamous cell and their nodal secondaries express high GLUT1 upregulation, and elevated levels of hexokinases (especially HK-II), adenocarcinoma does not consistently show this upregulation, and this is the basis for why PET is blinded to adenocarcinoma. For the same reason the importance of the SUVmax as a surrogate value for malignancy has been downplayed. Despite its name it is anything but standardised, as there is no universal agreement on a critical SUV value beyond which cancer diagnosis is guaranteed. Different PET scanners have different SUV for the same tumour. Add to that the fact that PET is not all or none, black or white, positive or negative, but a spectrum of avidity including the intermediate avidity, the interpretation of which is difficult and controversial.

Given the fact that the highest proportion of NSCLC in the UK is adenocarcinoma (40%) [1], and the fact that 10-15% of well differentiated lung adenocarcinomas, former bronchiolo-alveolar carcinoma and most neuroendocrine lung tumours show low avidity to FDG [23], treating clinicians should be aware of PET shortcomings, otherwise curative resection would be denied to a significant proportion of patients. a solitary pulmonary nodule with low FDG uptake should never be dismissed as benign without biopsy.

PET and inflammatory conditions

FDG-PET by design highlights hypermetabolic tissue, irrespective whether it is malignant or inflammatory. In fact interest is rising in using the radiotracer ^{18}FDG-PET in diagnosis and follow up of non-malignant disease such as large-vessel vasculitis, sarcoidosis, rheumatoid arthritis, inflammatory bowel disease, cardiac infections and the study of atheromatous plaques in coronary disease [24,25]. Chang et al in a most elegant publication showed 18 images of false positive and false negative PET scans in different thoracic conditions [26]. Insofar as lung cancer is concerned, this undesired crossover could lead to diagnostic dilemma. The specificity of PET imaging is slightly less than its sensitivity (i.e. its ability to tell us there is abnormal tissue, but not quite sure whether it is cancer or something else) because some inflammatory processes such as active granulomatous infections, sarcoid, pneumonia, tuberculosis, Weigner's granulomatosis and rheumatoid arthritis accumulate FDG avidly [26]. The role of PET will continue to evolve with further clinical studies using other new radiotracers such as the thymidine analogue 3'-deoxy-3'-[^{18}F] fluorothymidine and [^{18}F]-L:-FMAU, which more specifically target proliferative activity of malignant cells and can differentiate them from the false-positive inflammatory lesions [27,28].

Dual-phase, or dual time point FDG-PET studies (DTP FDG-PET) are conducted with imaging 1,2 and 3 hours after the FDG injection. Hope was pinned on this technique to differentiate between malignant and inflammatory processes. The assumption was that malignant tissue goes on to concentrate FDG in the cells up to 5 hours after the injection. A recent meta-analysis concluded that DTP FDG-PET had similar sensitivity and specificity to single time point STP FDG-PET in the diagnosis of Solitary Pulmonary Nodules (SPN) [29]. This technique may provide additional information in selected cases with equivocal results from initial scanning [30]. Further prospective research is required to better define the potential benefits of DTP 18F-FDG PET imaging [31]. Dynamic Nuclear Polarization (DNP) is a new technique that enhances the signal tens of thousands-fold. Recent in vivo animal studies of metabolic imaging that used hyperpolarized ^{13}C demonstrated its potential in diagnosis and treatment monitoring [32]. Whether hyperpolarized ^{13}C magnetic resonance spectroscopy will replace PET in future remains to be seen [33].

Tumour Critical mass for PET

Another important snag about the uptake of the FDG radiotracer is the mass of the active tissue. PET is poor at detecting micrometastases. A node under 1cm in diameter is unlikely to be detected as a hot spot on PET even if it was completely replaced by metastatic malignant tissue. Al-Sarraf et al found that integrated PET-CT images had reduced sensitivity (40%) for non-enlarged subcentimeter nodes [34].

PET and distant metastases

FDG-PET is highly sensitive and specific for determining the presence or absence of malignancy in the adrenal gland, bone and liver. In fact it is more specific than bone scintigraphy in detecting skeletal secondaries [35]. Discordant findings of skeletal metastasis between Tc-99m bone scans and ^{18}FDG PET-CT imaging may be seen in 20% of patients with NSCLC [36]. Normal brain tissue concentrates FDG because it metabolises glucose exclusively; therefore PET is not the best investigation for brain metastases, and MRI remains the test of choice [37]. Other confusing issues are tissues in which glucose metabolism is normally high; these include the heart muscle, skeletal muscle, bladder and brown fat (a specialised kind of heat-generating fat located mainly between the shoulder blades). FDG uptake is also reduced when the blood sugar level is high, as in poorly controlled diabetes.

Restaging following chemo/ Radiotherapy

Recently there has been heavy reliance on PET in guiding radiotherapy and chemotherapy treatments. Reduction in metabolic activity on PET after initiating chemotherapy (1-3 cycles) or standard treatment dose radiotherapy denotes good clinical response to treatment. In the absence of change in PET after treatment initiation, second-line chemotherapy or timely supplementary therapy could be offered. Management changes based on PET are as high as two thirds of cases [38]. Hyperactivity of the bone marrow and thymus in the recovery phase after chemotherapy treatment could be confused with bone and thymic metastases (Flare Phenomenon) [39].

PET and screening

At the moment there is no national screening programme for lung cancer in the UK. The usefulness of Chest X-Ray study (CXR) and sputum cytology in lung cancer screening was examined in five randomized control trials in the 1970s and 1980s [40-42]. Dual screening did not improve survival. Low Dose Non-Contrast

CT (LDCT) scan has been used for screening lung cancer in high-risk population (over 40, smokers and chronic obstructive pulmonary disease). The International Early Lung Cancer Action Program (I-ELCAP) study was a multicenter international trial that screened 31,567 patients with LDCT between 1993 and 2005 [43]. LDCT showed a four-fold increased ability to detect lung cancer compared with CXR, and a six-fold increased ability to detect Stage I Early Lung Cancer [44]. A similar trial is ongoing in the Netherlands and Belgium (NELSON trial) where 16,000 smokers have been randomly assigned to LDCT screening or usual care, targeting to close recruitment in 2016. A recent meta-analysis about the role of ^{18}FDG PET in screening for lung cancer was published by Chien et al [45]. The detection rates of lung cancer was low, however; PET has high sensitivity and specificity (83% and 91%, respectively) as a selective screening modality. There are recent campaigns in the UK to raise awareness about lung cancer, and target 'patient delay' in high-risk categories. This approach might prove more cost effective than general population screening programmes.

For a screening test to prove effectiveness, it must ultimately improve mortality, and not just detect cancer and improve 5-year survival. Screening tests might give false sense of improved survival. The lead-time bias theory seem to suggest that overall survival is a function of a finite biological behavior from the time a single cell behaves in a malignant way till the time of demise due to the cancer. As a corollary to this early intervention as a result of early screening programme might give false impression of improved survival due to earlier diagnosis in the natural history of the disease, without affecting survival. Whereas later intervention at say size 30 mm might suggest shorter overall survival, the later diagnosis and intervention does not take into account the fact that the patient had already lived 2 years for the nodule to grow from 0 to 30 mm, the latter is a function of tumour doubling time. More research is needed to understand the influence of timing of intervention on overall survival, and the role of PET in this timeline.

PET and the flieschner Society pathway

Solitary Pulmonary Nodules (SPN) can pose a challenge to treating clinicians, especially if they are <8mm in diameter. This is the crucial cut-off size under which PET is not reliable in excluding malignancy. The role of PET in characterising subcentimeter SPN has been elucidated by Gould et al [46]. The Flieschner society guidelines for surveillance of SPN suggests that nodules <8mm in diameter on contrast-CT should be followed up 3,6 and 12 monthly by CT whereas lesions between 8-30 mm necessitate further investigation (such as PET or histological confirmation). If there is no change in size, configuration or intensity of contrast uptake, benignity is presumed and patient taken off the surveillance programme [47]. However; A sizable chunk of these nodules progress to become invasive primary lung cancers. Whether waiting for a subcentimeter lesion to declare itself biologically at a larger size has a detrimental effect on survival is unknown. The lead-time bias theory seams to suggest not. However; the general rule is to be able to detect the cancer when it is amenable to curative treatment. Following in the footsteps of breast cancer, curative resections for lung cancer are evolving. In 1995 Sublobectomy resections were considered to be suboptimal and a compromise to the 5-year survival [48]. On the other hand there are recent publications to suggest that T1a N0 lesions could be cured by segmentectomy alone [49]. Further development is awaited to elucidate the nature of the subcentimeter lung lesion and how to investigate and treat it.

Practical use of PET for the thoracic surgeon and multidisciplinary clinicians

Based on risk stratification and clinical presentation PET is asked to make a presumptive diagnosis of lung cancer. An FDG avid spiculate lesion in the lung of a male over the age of 40 years, who is a smoker and presenting with haemoptysis in an area where tuberculosis is not endemic, is likely to be lung cancer. However; in the same scenario PET could never rule out TB or other benign lesions. A negative PET in the same high-risk patient could not rule out primary adenocarcinoma. The picture is even more complex when known benign tumours change their biological behavior and become FDG-avid. Sclerosing haemangioma and Chondroid Hamartomats could behave in such way [50,51]. Histology is mandatory to establish diagnosis. How and when to obtain histology is an art. Nevertheless; this uncertainty about specificity will not deny PET its leading role in lung cancer investigation. The reason for that is twofold; firstly, its value in detecting extrathoracic asymptomatic metastases that preclude curative resection (bone, liver, adrenals etc.). Secondly, its role in staging the mediastinum. Its role here is debatable; an FDG avid node should be biopsied to obtain histological confirmation, and an FDG low avidity node that is significant by CT criteria should also be biopsied [52]. No further investigation is required for subcentimeter nodes that are not hypermetabolic on PET.

CONCLUSION

Bar the limitation of sensitivity, PET-CT is the best currently available non-invasive tool to tell us whether a lung lesion is likely to be malignant. Multidisciplinary management of NSCLC has to accept the limitations of PET when constructing clinical pathways, and adjuvant therapy should be based on pathological staging by invasive techniques (mediastinoscopy, EBUS, operative SND). PET helps direct those biopsies and finds unsuspected extra-thoracic disease in 7% of patients. PET can be blinded to adenocarcinoma within lung parenchyma or mediastinal nodes in 10-15% of cases. Relying on PET staging alone can lead to significant over staging and denial of curative resection. Stage migration in the absence of histological confirmation of mediastinal nodes can result in misleading survival statistics. And finally from a surgeon's perspective "When PET is positive you need to do something about it (i.e. obtain histological confirmation), but if it is negative it does not rule out malignancy".

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