Integrated PET/CT in Imaging of Non-Small Cell Lung Cancer

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ABSTRACT

Lung cancer is one of the most frequently occurring cancers in the world. Accurate staging of patients with non-small cell lung cancer (NSCLC) is of paramount importance. It will guide choices of treatment and determine prognosis and outcome. PET-CT, the integration of the functional data of PET with the anatomic data of CT, has emerged as a modality to potentially change the way patients are evaluated. Integrated PET/CT has several advantages. One of the advantages is the use of CT data for attenuation correction that is significantly faster compared to that in conventional PET systems. Due to the use of CT data for attenuation correction, artifacts can be generated on PET images related to the use of CT contrast agents, CT beam-hardening artifacts due to metallic implants and motion artifacts. PET/CT appears to offer superior staging of NSCLC compared with CT and PET individually. However, there are undoubtedly false-positives and false-negatives that need to be taken into account. The purpose of this review is to discuss some technical considerations concerning the use of PET/CT in lung cancer imaging and to give a short overview of the results of staging of NSCLC.

Key Words: PET/CT – Technical aspects – NSCLC.

INTRODUCTION

Lung cancer is a common disease with approximately 3 million new cases per year worldwide and is the leading cause of death in many countries. Non-small cell lung cancer (NSCLC) accounts for 75-80% of these cases [1]. The management of patients with NSCLC is directed by an optimal staging of the disease. Staging allows the distinction of patients who are candidates for surgical resection from those with inoperable disease who may be treated with chemotherapy and/or radiation therapy. Consequently, the accurate determination of tumor size, potential infiltration of adjacent structures, mediastinal lymph node involvement and the detection of distant metastases are of central importance.

Conventional imaging plays an essential role in the noninvasive and invasive methods of the evaluation and staging of patients with NSCLC. Traditionally computed tomography (CT) has been the mainstay on non-invasive staging. Although CT provides excellent anatomical description, it has several limitations [2]. Recently, positron emission tomography (PET) using the glucose analogue $^{18}$F-fluorodeoxy-glucose (FDG) has become the focus of attention. This technique possesses a greater sensitivity for detection of malignancy, though it is inhibited by relatively poor spatial resolution and anatomical localization of disease [3]. The combination of PET and CT in a single device (PET/CT) enables these limitations to be overcome and can be regarded as a considerable step forward. However, whilst acknowledging its diagnostic strengths, it is necessary to appreciate the shortcomings of PET/CT for accurate reporting and staging of lung cancer [4,5]. The purpose of this review is to discuss some technical aspects concerning the use of PET/CT in lung cancer imaging and to summarize its role in staging of NSCLC.

TECHNICAL ASPECTS

$^{18}$F-FDG PET/CT hardware and image fusion:

In general the CT component of PET/CT machines range from a single slice to a 16-section machine, although several manufacturers have now released multidetector models incorporating 64-sections. Before the advent of combined PET/CT, image registration - or fusion
of superimposed PET and CT images has been possible either by so-called software fusion or more simply by visual analysis. Both of these methods involve separate acquisitions of PET and CT data. Software fusion has been available for some time, whereby PET and CT images are projected over one another on a workstation. However, this process is relatively time-consuming and the accuracy of registration is limited outside the brain. Integrated PET/CT can obviate this problem, with some caveats, by virtue of so-called hardware fusion intrinsic to the technique [6]. In addition, PET/CT protocols are still being defined and evaluated and it will be a while before they become as well established as the protocols for CT. All PET/CT protocols, however, have certain common features [7] (Fig. 1).

Fig. (1): Typical imaging protocol for combined PET/CT: Topogram (A), or scout scan, is obtained for positioning. Spiral CT scan (B) is obtained, followed by a PET scan (C) over the same axial range as B. CT-based attenuation-correction factors are generated (D) and attenuation-corrected PET emission data are reconstructed (E). Finally, fused CT and PET images are displayed (F). (Quoted from Blodgett et al. [7]).

**Attenuation correction:**

One of the advantages of an integrated PET/CT system is the use of CT data for attenuation correction, which is significantly faster compared to conventional PET systems. Attenuation correction in conventional PET systems can be performed by using the built-in germanium-68 sources of PET scanner, which rotate as an external radiation sources around the patient, to perform a transmission scan. This transmission scan adds at least 50% to the scanning time and results in data with a relatively high noise level [8]. To use the CT scan for attenuation correction, the attenuation values of low dose CT energies must be scaled to high dose (511 keV) PET energies using scaling algorithms. The use of the CT scan for attenuation correction reduces the whole-body scan times by at least 40% and so reduces the total imaging time to approximately 30 minutes and provides essentially noise-less attenuation correction factors compared to those from a standard PET transmission scan. Scaling algorithms typically use a bilinear function to transform the attenuation values above and below a given threshold with different factors [8]. The composition of biologic tissues other than bone exhibits little variation in effective atomic number and can be well represented by a mixture of air and water. Bone tissue does not follow the same trend as soft tissue because of the calcium and phosphorus content; thus, a different scaling factor is required that reflects instead a mixture of water and cortical bone. The break point between the two mixture types has been variously set at 300 and 0 HU [7]. However, some tissue types, such as muscle (~60 HU) and blood (~40 HU), have attenuation values greater than 0 HU and yet are clearly not a water-bone mix. A break point at around 100 HU would therefore appear to be optimal (Fig. 2). Hounsfield units define the linear attenuation coefficients normalized to water and are thus independent of the voltage setting of the X-ray tube. The scale
factor for the air-water mix below approximately 100 HU will be independent of the tube voltage. This does not apply to the water-bone mix; therefore, the scale factor for bone will be voltage dependent. The scaled CT images are then interpolated from the CT to the PET spatial resolution and the attenuation correction factors are generated by reprojecting the interpolated images. Furthermore, a number of practical aspects using CT-base attenuation correction such as patient respiration, the use of intravenous and oral CT contrast media and the presence of catheters and other metallic objects in the patients could potentially generate artifacts [4,9].

the examination, the FDG is injected. In the intervening period, patients are requested to lie still in order to minimize muscular activity, which may otherwise be a source of artifactual uptake [5].

**Misregistration:**

The PET/CT machine acquires a CT scout view initially. The patient subsequently undergoes the CT component of the examination and is then moved further into the gantry where the PET images are acquired. The two datasets are aligned to create a registered image. Typically, the patient’s arms are positioned above their head in specially designed arm rests, so as to avoid beam hardening artifacts [6].

Misregistration occurs as a result of differences in the position of the patient during the CT and PET examination. This may occur either as a result of voluntary motion of the patient during examination or more commonly because of discrepancies in the phases of the patient’s respiratory cycle during the CT and PET examinations. The CT is typically a snapshot of one phase of the respiratory cycle whereas the PET images represent an average of shallow tidal breathing. This has two consequences: First, incorrect anatomical registration of PET and CT images may occur, which can affect the accurate localization of uptake within pulmonary masses or lymph nodes. Furthermore, metastases within the dome of the liver can be misinterpreted as basal lung lesions [10]. Cohade et al. [11] attempted to qualify the degree of misregistration in the thorax in PET/CT. They found that the mean discrepancy between the location of pulmonary lesions on PET and CT was approximately 7mm, with better registration at the lung apices than bases. They commented that this degree of misregistration was minimal and did not lead to significant interpretive errors. This is in contrast to the finding from one study that showed significant misregistration occurred in one third of NSCLC patients where software fusion of PET and CT images was performed [12]. Second, the CT data which are used for attenuation correction may be incorrectly applied to the PET images. The implications of this include artificially low standardized uptake value (SUV) reading in pulmonary lesions adjacent to the diaphragm, as well as an apparent reduction of FDG activity in the sub-diaphragmatic tissues [7].

**Patient preparation:**

To minimize artifacts and reduce uptake in normal structures, careful patient preparation is critical. Patients are required to fast for 4-6 hours to minimize insulin secretion in order to reduce background uptake of FDG by muscle and adipose tissue. Diabetic patients require special attention and are usually rescheduled if the blood glucose level is greater than 8-11mmol/l [2]. Giving insulin immediately before the examination is to be avoided as this encourages uptake of FDG into background tissues rather than tumor. Approximately 1 hour before

Fig. (2): Graph shows bilinear scaling function used to convert CT numbers to linear attenuation values at 511 KeV. Linear attenuation coefficient at 511 keV is a function of corresponding CT value (in Hounsfield units) and is based on measurements from electron-density CT phantom with tissue-equivalent materials (Gammex 467; Gammex rmi, Middleton, Wis). Spiration between soft tissue (air-water mix) and bonelike tissue (water-bone mix) is around 100 HU. (Quoted from Blodgett et al. [7]).
Goerres et al. [13] found that optimal image fusion occurred when CT data sets were acquired during normal expiration. Similar studies also have shown a reduction in the severity and frequency of respiratory motion artifacts when a limited expiratory breath-hold protocol was used [14-16]. Gilman et al. [17] found that for combined PET/CT of the thorax, excellent image fusion was achieved during expiration, mid suspended breath-hold and quit breathing with no significant variation in scoring of anatomic alignment. A recent study demonstrated that breathing induced motion artifacts are significantly reduced using deep inspiration breath hold technique [18]. In the future it may be possible to use respiratory gating techniques to minimize misregistration due to respiration [19].

**Contrast media:**

The use of intravenous and oral contrast agents in CT protocols demonstrated a substantial benefit: Improve delineation of anatomic structures, increased sensitivity for detection of pathologic lesions and improved accuracy in lesion characterization [20,21]. Therefore, most CT protocols in daily radiological routine included contrast-enhanced images based on the application of oral and intravenous contrast agents. The role of intravenous contrast agents in PET/CT has been a cause for debate. Attenuation correction algorithms have been designed principally to apply to soft-tissue densities. When attenuation correction is applied in the presence of iodinated contrast media, overcorrection may occur. This can give to spuriously elevated standardized uptake values (SUVs) on the PET images and potentially cause "hot spots" over vessels [4]. Avoiding contrast agents altogether would clearly solve this problem, though this may potentially impact on the pre-surgery evaluation of mediastinal vascular structures. Consequently many centers do not routinely use intravenous contrast agents as part of PET/CT imaging and would instead advise an additional contrast-enhanced CT immediately after the PET/CT examination if this has not previously been performed a rare occurrence in practice. However, others have recently reported that using routine intravenous contrast media in PET/CT caused no significant impact on clinical diagnosis [14,22,23].

The use of oral contrast agents can produces also an overestimation of PET activity concentration. Dizendrof et al. [24] reported only a 4% overestimation of the related SUVs when evaluated in clinical routine. The effect of oral CT contrast agents on the SUV seems to be negligible when the contrast agent is distributed homogenously in the bowel. When there is an interpretation problem due to the use of oral or intravenous contrast agents, non-attenuation-corrected images can be used to solve these problems since artifacts will be found only on attenuation-corrected data. Hence, artifacts only found in areas of high contrast concentrations due to the use of intravenous or oral contrast agents rarely cause interpretation problems in the clinical setting [20]. Therefore, an artifact-free oral contrast agent would be highly desirable for PET/CT. Since all positive oral contrast agents are implicitly associated with an increase in attenuation, only a negative oral contrast agent has the potential to completely avoid high-attenuation artifacts [25].

A solution containing mannitol can be used as an oral contrast agent in PET/CT scanning because it provides excellent bowel distension while avoiding contrast material induced PET artifacts. Some centers use negative oral contrast medium. It has been suggested that in the clinical setting, use of low concentration barium may minimize artifacts [26].

**CT dose:**

An important question is which CT dose we must choose for our PET/CT protocol. The radiation burden using CT instead of a germanium scan is significantly higher. Kamel et al. [27] made a study to compare different CT doses (140 kV for all scan but different mAs: 10-40-120). Doses of 10-40 and 80 mAs were considered a low dose. The authors reported no significant differences in accuracy between these different CT doses concerning the lesion-by-lesion analysis. Concerning the patient-by-patient analysis there was a better result for the evaluation of the patient with a PET-80-mAs and PET-120-mAs CT. In conclusion, they found that PET-80-mAs reduced the number of undecided lesions, but that PET-120-mAs CT did not further improve lesion classification. Thus, it is feasible to incorporate a "low dose" 80mAs scan as a routine protocol in a diagnostic PET/CT.

The effective patient dose determined for a low-dose CT scan is less than 5mSv. This CT...
scan can be used for attenuation correction and for anatomic correction but not as a diagnostic CT scan. The effective patient dose of a high-dose, diagnostic CT scan varied between 14 and 18.6mSv. The first studies using PET/CT have shown that this technique improve diagnostic accuracy when compared to separately acquired CT and PET [21,28,29].

**STAGING OF NSCLC**

The management of lung cancer is directed by an optimal staging of the tumor. One of the advantages of integrated PET/CT is an improved image interpretation. This improvement can be the detection of lesions initially not seen on CT or PET, a more precise localization of lesions, a better characterization of the lesion as benign or malignant and a better differentiation between tumor and surrounding structures [30]. Staging of NSCLC is based on tumor size and location (T-status), nodal involvement (N-status) and the presence or absence of distant metastases (M-status) [31].

The most significant improvement in results with combined PET/CT compared with PET alone relates to T staging. Halpern et al. [12] demonstrated an accuracy rate of 97% with PET/CT compared with 67% with PET only. Another study by Cerfolio et al. [32] showed that PET/CT more accurately predicted T status (70% of cases) than did PET alone (47%). This superiority was attributed entirely to the CT component of the examination. Indeed a further large study showed no significant difference in T staging between PET/CT and CT only, again suggesting that the PET images did not contribute to this assessment [33]. By comparison another report described accuracy rates for T staging with PET/CT and CT as 88% and 58%, respectively [34]. Recent trial by Pauls et al. [35] reported that integrated PET/CT was significantly more accurate for T-staging of NSCLC compared to CT or PET alone. The advantages of PET/CT are especially pronounced combining T1- and T2-stage as well as in advanced tumors. The reasons for this surprising finding were not fully explored, but it is worth reiterating that PET has a role in T staging by distinguishing between tumor and distant atelectasis.

Furthermore, PET/CT resulted in improvement of nodal staging compared with PET alone due to ability to reveal the exact location of metastatic lymph nodes: Accurate anatomic correlation is of benefit for exact localization of a solitary lymph node metastasis and thus allows exact classification as N1 or N2 disease. PET/CT is also important when identifying supraclavicular N3 disease [21,28,32,34]. Indeed, the benefit of PET/CT compared with PET in nodal staging appears to lie in a moderate increase in specificity. This observation was confirmed in study by Antoch et al. [21]. Meanwhile, Shim and colleagues [33] demonstrated accuracy rate for PET/CT and CT in N disease of 84% and 69%, respectively. In a recent study by Kim et al. [36] the overall sensitivity, specificity and accuracy of PET/CT for mediastinal nodal staging were 61%, 96% and 86%, respectively Another study by Yi et al. [37] reported that in stage T1 NSCLC, contrast-enhanced helical dynamic CT better predicts, but not significantly so, mediastinal nodal metastasis than PET/CT, whereas PET/CT shows perfect specificity and higher accuracy than helical dynamic CT (Fig. 3).

For M staging, an important role for PET is the detection of unsuspected metastases. Occasionally, however, the significance of isolated areas of avid FDG uptake, without anatomical reference, is uncertain. For example, one study cited two examples where solitary areas of uptake within the pelvis that could not be anatomically pinpointed with PET alone, were accurately attributed to pelvic bone metastases with the benefit of PET/CT fusion [34]. In a study of 27 patients, Antoch et al. [21] reported that PET/CT was marginally superior to CT alone for detection of metastases, but surprisingly they also found that CT revealed a greater number than PET (14 metastases detected on CT compared with 4 with PET; however, the statistical significance of this was not determined). The authors proposed that this was due to the fact that CT was performed from head to pelvis, whereas previous studies evaluating CT and metastatic disease have traditionally been performed incorporating the thorax and abdomen only. The results of some initial studies concerning the accuracy in TNM staging of NSCLC are summarized in Table (1).

In recent years, many of the radiation therapy planning systems have been upgraded to be able to incorporate both CT and PET data sets. Many
also have the ability to fuse the two data sets by using the planning software. Some preliminary studies have shown that radiation portals and tumor volumes change up to 50% of the time when both PET and CT data sets are considered compared with the traditional CT planning method [38]. This anatomic and functional plan has the biggest effect when there are portions of a tumor that may not be visible or are not included on CT images alone. With both the anatomic and metabolic data, radiation oncologists are able to define viable tumor volume more accurately, as well as minimize the amount of exposure to normal tissue.

Table (1): Sensitivity of FDG-PET versus FDG-PET/CT with respect to TNM and overall tumor staging.

<table>
<thead>
<tr>
<th>Study</th>
<th>Patients</th>
<th>TNM</th>
<th>FDG-PET</th>
<th>FDG-PET/CT</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cerfolio et al.</td>
<td>129</td>
<td>T</td>
<td>38%-70%</td>
<td>50%-100%</td>
<td>0.001</td>
</tr>
<tr>
<td></td>
<td></td>
<td>N</td>
<td>60%-80%</td>
<td>77%-92%</td>
<td>0.008</td>
</tr>
<tr>
<td></td>
<td></td>
<td>M</td>
<td>81%-82%</td>
<td>90%-92%</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Overall</td>
<td>17%-83%</td>
<td>50%-94%</td>
<td>NR</td>
</tr>
<tr>
<td>Halpern et al.</td>
<td>36</td>
<td>T</td>
<td>67%</td>
<td>97%</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Overall</td>
<td>57%</td>
<td>83%</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Lardinosis et al.</td>
<td>50</td>
<td>N</td>
<td>49%</td>
<td>93%</td>
<td>0.013</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Overall</td>
<td>40%</td>
<td>88%</td>
<td>0.001</td>
</tr>
<tr>
<td>Aquino et al.</td>
<td>45</td>
<td>N</td>
<td>59%-76%</td>
<td>71%-76%</td>
<td>0.01</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Overall</td>
<td>53%-62%</td>
<td>73%-66%</td>
<td>0.001</td>
</tr>
<tr>
<td>Antoch et al.</td>
<td>27</td>
<td>Overall</td>
<td>74%</td>
<td>96%</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Shim et al.</td>
<td>106</td>
<td>N</td>
<td>–</td>
<td>85%</td>
<td>–</td>
</tr>
<tr>
<td>Keider et al.</td>
<td>42</td>
<td>Restaging</td>
<td>96%</td>
<td>96%</td>
<td>NS</td>
</tr>
</tbody>
</table>

Abbreviations: NR: Not reported, NS: Not significant.

Concerning restaging following extensive surgery or radiation, it is fairly common to have some degree of scarring within the remaining lung parenchyma. Serial CT to identify areas of growth or change is typically used to follow these patients up. With PET and PET/CT, most of these patients can be evaluated more accurately and earlier than with other imaging modalities. Much of the FDG uptake due to inflammation from surgery resolves relatively quickly.

Fig. (3): 46-year-old man with adenocarcinoma in right lower lobe and metastasis in right paratracheal lymph node, which was predicted by integrate PET/CT but not by helical dynamic CT. Transverse conventional (5.0-mm section thickness) enhanced CT scan (A) shows lymph nodes in right paratracheal area (arrow) with short-axis diameter of 7mm, representing benignity with CT size criteria for malignant nodes. Integrated PET/CT image (B) shows high 18F-DFG uptake with maximum standardized uptake value of 8.0 in right paratracheal lymph node (arrow). (Quoted from Yi et al. [37]).
(typically within 6 weeks) and these patients can be reevaluated at this time for residual or recurrent tumor, particularly patients in whom the margins may not have been clear. In the restaging evaluation of patients with lung cancer, one of the most challenging aspects is differentiating recurrent or residual tumor from post-therapy changes. Both processes can appear identical on CT images, which present a challenge to the use of this modality in the posttreatment patient with lung cancer. Conversely scar and fibrosis are, by definition, dead tissue and should not result in any FDG uptake, which makes PET or PET/CT ideal for this indication. PET has been shown to have a sensitivity of 98%-100% for the differentiation of tumor from posttreatment changes in the lung [39]. Furthermore, De Leyn et al. [40] found that PET/CT was more accurate than mediastinoscopy (83% Vs 60%, p<0.05) and significantly more accurate than PET or CT alone for nodal restaging after neoadjuvant chemotherapy.

**The limitations of PET/CT:**

Recognizing the strengths and weaknesses of PET is important for the accurate interpretation of PET/CT images. The assessment of FDG uptake in PET may be performed either qualitatively or semi-quantitatively. In other word, FDG uptake can be either visually compared with background or mediastinal blood pool activity or measured by the SUV calculation. As a general rule a SUV greater than 2.5 is considered to reflect malignancy. However, rigid adherence to this somewhat arbitrary figure can produce both false-positive and negative results [6,29].

**False positives:**

FDG uptake and resulting increased PET signal is not limited to neoplastic tissue. Causes of false-positive cases can be broadly categorized into physiological uptake, inflammatory, iatrogenic and miscellaneous benign processes (Table 2) [6]. It is thought that increased FDG uptake in inflammation is the result of elevated levels of metabolic activity within accumulated macrophages and lymphocytes [41]. Within the lungs a spectrum of pneumonias may give rise to false-positive PET results, including tuberculosis, bacterial and fungal pneumonia, as well as organizing pneumonia [42] (Fig. 4). There is some evidence to suggest that "dual-time-point" imaging may be helpful in differentiating malignant versus inflammatory and infectious processes [15]. This involves performing the first PET or PET/CT examination at the usual time after FDG injection (approximately 1 hour) and then performing another examination at a later time (average of 2-4 hours after FDG injection). The reasoning behind this delayed second examination is that malignant nodules generally tend to continue to accumulate FDG over time, whereas inflammatory and infectious processes tend to show less FDG uptake over time. By obtaining images at more than one time point, it is possible to determine the trend of FDG uptake. In addition, non-infectious inflammatory conditions including sarcoidosis, Wegner’s granulomatosis and amyloidosis, have been reported to generate increased FDG activity [43,44]. False-positive lung FDG uptake has also been attributed to pulmonary infarction secondary to pulmonary embolus [27].

<table>
<thead>
<tr>
<th>Category</th>
<th>Causes</th>
</tr>
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<tbody>
<tr>
<td>Physiological uptake</td>
<td>Normal uptake in brain, heart, kidneys, spleen, gastrointestinal tract, thyroid gland, thymus, mediastinal vasculature</td>
</tr>
<tr>
<td></td>
<td>Movement of neck and back muscles</td>
</tr>
<tr>
<td></td>
<td>Brown fat-related thermoregulation</td>
</tr>
<tr>
<td>Infection</td>
<td>Pneumonia (bacterial, fungal, viral and tuberculosis), empyema, organizing pneumonia</td>
</tr>
<tr>
<td>Inflammation</td>
<td>Sarcoïdosis, wagener’s granulomatosis, pulmonary fibrosis, amyloidosis</td>
</tr>
<tr>
<td>Infarction</td>
<td>Pulmonary embolus</td>
</tr>
<tr>
<td>Iatrogenic</td>
<td>Talc pleurodesis, biopsy</td>
</tr>
<tr>
<td>Other</td>
<td>Hamartoma, oesophagitis, aortic atheroma</td>
</tr>
</tbody>
</table>
In the context of staging lung cancer, the issue of false-positive disease is even more relevant in the mediastinum. The positive value of PET for nodal disease is lower than the negative predictive value at approximately 78% due to the significant number of false-positive results [45]. These are due to either to nodal granulomatous disease or nodal inflammation associated with co-existent pulmonary disease. Hara and colleagues [46] reviewed 20 cases of NSCLC that had been diagnosed as N3 on PET by visual criteria. They found an astonishingly high number of false-positives (18/20). However, specificity improved when a SUV threshold of 2.5 instead of subjective visual assessment was used. As a consequence, Hara et al. [46] recommended that all cases with FDG positive mediastinal disease should undergo mediastinoscopy, so as not to deny patients with potentially treatable disease the option of surgical resection. Other causes of false-positive FDG uptake in the thorax include: Pulmonary

Fig. (4): PET/CT evaluation of upper lobe pulmonary nodule in 54-year-old man. (A) Transverse CT image shows single upper lobe cavitary nodule (arrow). (B) Transverse fused PET/CT image shows intense focal FDG uptake (arrow). Malignancy, fungal infection and tuberculosis were appropriately included in differential diagnosis. Although all can have a similar appearance, this was tuberculosis, an important cause of positive PET images that can be misinterpreted as malignancy. (Quoted from Bakheet et al. [42]).

Fig. (5): Images in 53-year-old man who underwent reevaluation just 5 weeks after receiving high-dose radiation to medial portion right lung because of adenocarcinoma. (A) Transverse CT image shows geographic areas of parenchymal changes (arrow) corresponding to radiation portal; finding are compatible with radiation pneumonitis. (B) Transverse fused PET/CT image shows diffuse intense FDG uptake (arrow) in corresponding abnormality, making any assessment of underlying tumor impossible. Typically, patients should not be referred for FDG PET for 2-3 months after radiation treatment. (Quoted from Nestle et al. [50]).
hamartomas and empyema as well as iatrogenic causes; for instance, needle biopsy, mediastinoscopy, or talc pleurodesis [47].

The role of FDG PET in detecting unsuspected metastatic disease has already been discussed. However, even in this context there are instances where false-positives may occur. In a large series by Kumar et al. [48], which reported a specificity of 90% for characterizing adrenal masses in patients with NSCLC, there were four false-positives. These comprised three benign adrenal adenomas and one phaeochromocytoma. In a recent study, Lardinois et al. [49] showed out of 69 patients with NSCLC and solitary extrapulmonary FDG uptake, 32 were not due to metastatic disease. The aetiologies described included fractures, degenerative changes, benign adenomas of the colon and thyroid, as well as in some instance a second primary tumor. In addition, radiation pneumonitis is a cause of false-positive FDG PET images. Evaluation of the primary tumor is generally not possible in the setting of radiation pneumonitis. Because of the radiosensitivity of the lung, patients who have undergone irradiation to the lungs are not typically reevaluated for 2-4 months after their last treatment (Fig. 5). However, the inflammatory effects of radiation can last more than a year [50].

False negatives:

False-negative FDG uptake can be divided into those cases related to technological limitations of PET and others related to inherent properties of neoplasms. Although PET sensitivity depends primarily on activity concentration, structures that measure less than two to three times the spatial resolution of the scanner (i.e., ~2cm) will appear less active and return a lower SUV than is real due to the partial volume effect. This restricted its ability to reflect true neoplastic activity within small pulmonary nodules. A recent study showed sensitivity for detecting pulmonary metastases of 78% in nodules measuring 8-10mm and only 40% in those measuring 5-7mm [51]. Furthermore, PET may not recognize small-volume mediastinal nodal disease. In a study of a highly selected group of patients, Takamochi and co-workers [52] reported the sensitivity of PET for nodal involvement as only 39%. They reported that PET was unable to identify several small volume tumor foci, the largest of which was 7.5mm. However, others have also described false-negatives with neoplastic lymph nodes of up to 2cm, indicating that other factors, including PET spatial resolution and tumor “indolence”, may be important [53]. It is also recognized that lower SUV readings may be a feature of predominantly necrotic tumors with only a narrow perimeter of viable tumor tissue [54].

Bronchioloavleolar cell carcinoma (BAC) is well known as a cause of false-negative results on PET. Kim et al. [55] and other investigators [56] have reported significantly reduced SUVs in patients with BAC compared with other lung neoplasms. It has been hypothesized that the reduced cellularity and nuclear atypia of BAC results in a lower metabolic activity reflected in the relatively low SUV. Another primary tumor with reportedly low relative FDG uptake is carcinoid tumor, which like BAC, can be a cause of false-negative PET images [57].

Although many studies have described very high sensitivities for PET in accurately detecting adrenal metastases in lung cancer, there are reports of false-negatives. Kumar et al. [48] described five such cases, which were attributed to either the small size of the adrenal lesions or a necrotic metastasis in one patient. At present there are little or no data on the role of PET/CT in the detection of brain metastases, compared with PET or CT alone. However, the current literature indicates that FDG-PET is not a sensitive technique for detecting brain metastases for lung cancer or other primary tumors [58].

The cost-effectiveness of PET/CT in NSCLC staging:

Several cost-effectiveness analyses have been published evaluating PET in lung cancer staging, though data specifically on PET/CT is lacking. Although some authors have found no significant reduction in the number of avoidable thoracotomies performed when employing additional PET imaging in NSCLC [59], the general consensus is that PET can reduce needless thoracotomy rates [60]. In addition, some practitioners suggest by-passing mediastinoscopy in PET-negative patients. These benefits can be quantified by calculating the incremental cost-effectiveness ratio (ICER), which may be measured in monetary terms per life years saved (LYS) or per quality adjusted life year (QALY) [61]. A recent study used a decision tree analysis model to compare various strategies including
CT only, PET for patients with negative CT and PET plus CT. They concluded that employing a combination of both PET and CT was the most cost-effective [62].

CONCLUSION

PET/CT is a major development in imaging technology. One of the advantages is the use of CT data for attenuation correction that is significantly faster compared to that in conventional PET systems. Available data on lung cancer suggests that its superiority to lone PET lies principally in better T staging, but it also provides tangible benefits for N and M staging. PET/CT also appears to have a role in selecting patients for mediastinoscopy because of its high negative predictive value for nodal disease. It is important, nevertheless, that the false-positives and false-negatives associated with PET/CT are appreciated, as well as some of the other pitfalls, such as misregistration. At present, the majority of patients who undergo a PET/CT have already undergone an initial diagnostic CT examination inevitably resulting in some duplication. With these considerations in mind, the potential diagnostic benefits of this new technology can be explored fully.

REFERENCES

4- Townsend DW, Carney JP, Yap JT, Hall NC. PET/CT today and tomorrow. J Nucl Med. 2004, 45S: 4S-14S.


