Review Article

The Role of FDG-PET in the Management of Non-small Cell Lung Carcinoma

IA Ho Shon,[1] *MBBS, FRACP*, MN Maisey,[2] *MD, FRCP*

Abstract

Introduction: Positron emission tomography (PET) using ^{18}F-2-fluoro-2 deoxy-D-glucose (FDG) has been widely investigated and used in the non-invasive imaging of malignancy. Non-small cell lung carcinoma (NSCLC) is one of the most common and best validated indications for an FDG-PET scan. This review examines the roles of FDG-PET in the management of NSCLC and attempts to identify emerging uses and possible future developments. Materials and Methods: Literature review of English language literature indexed on Medline. Results: There is strong evidence to support the clinical efficacy and cost effectiveness of FDG-PET in the characterisation of solitary pulmonary nodules and in the staging of NSCLC. In addition, there are emerging uses in radiotherapy planning, monitoring of treatment response and prognostication. Conclusions: FDG-PET plays an integral role in the management of NSCLC and it is likely to expand as evidence supporting additional roles in the management of NSCLC becomes available.

Ann Acad Med Singapore 2004;33:166-74

Key words: ^{18}F fluorodeoxyglucose, Non-small cell lung carcinoma, Positron emission tomography, Solitary pulmonary nodule

Introduction

Carcinoma of the lung is the leading cause of cancer death in both men and women and is the second most common malignancy in both men and women. In 2003, it is estimated that there will be 171,900 new cases of lung carcinoma diagnosed in the United States and it will cause 157,200 deaths.[1] Similarly, in the United Kingdom, carcinoma of the lung is the leading cause of cancer death, accounting for 22% of all cancer deaths (33,386 patients) in 2001.[2] In addition, survival from carcinoma of the lung is poor at 14.9%.[1]

Non-small cell lung carcinoma (NSCLC) accounts for the majority of carcinomas of the lung. Although there are numerous investigative tools to diagnose and stage NSCLC, these remain suboptimal. Over the past 16 years, positron emission tomography (PET) has been shown to have roles in the management of NSCLC in terms of characterisation of solitary pulmonary nodules (SPNs) and staging, with emerging roles for radiotherapy planning and hypoxia imaging. This review examines the literature supporting the current roles of PET in the management of NSCLC and identifies emerging roles and future possibilities.

Principles of PET in NSCLC

In carcinoma of the lung, as in many other tumours, it is known that there are many molecular and metabolic derangements including increased glycolysis,[3] increased amino acid[4] and nucleic acid metabolism.[5] ^{18}F-2-fluoro-2 deoxy-D-glucose (FDG) is a glucose analogue that enters cells via the membrane glucose transporters (GLUT-1 to GLUT-7).[6] Once inside the cell it undergoes phosphorylation via hexokinase. FDG-6-phosphate is not a substrate for the next enzyme as it is conformationally selective and glucose-6-phosphatase is present in only low levels. Thus, FDG-6-phosphate is metabolically trapped intracellularly.[7] Specifically in NSCLC, GLUT-1 expression seems to be important for FDG uptake,[8] but other mechanisms such as upregulation of hexokinase and downregulation of glucose-6-phosphatase probably also play a role.[9] PET imaging of carcinoma of the lung, however, is not limited to imaging of glucose metabolism, and a number of other metabolic

[1] Department of Nuclear Medicine, PET and Ultrasound
Liverpool Hospital, NSW, Australia
[2] Radiological Sciences
Guys Hospital, London, United Kingdom
Address for Reprints: Dr IA Ho Shon, Department of Nuclear Medicine, PET and Ultrasound, Liverpool Hospital, 1 Elisabeth St, Liverpool, NSW, 2170 Australia.
Email: i.hoshon@unsw.edu.au

processes have also been imaged in lung carcinoma including nucleic acid metabolism[10] and hypoxia.[11]

FDG-PET and the SPN

SPNs, defined as circumscribed parenchymal lung lesions less than 3 to 4 cm in size and completely surrounded by normal lung, are a common problem affecting 1 to 2 per 1000.[12,13] These lesions pose a diagnostic dilemma as only 20% to 50% are malignant.[13-15] Differentiation of a benign from a malignant SPN is vital, but the existing diagnostic methods are suboptimal.

FDG-PET for the characterisation of SPN has been studied since 1990. In published literature of over 2000 patients with SPN all of whom subsequently had a histological diagnosis, the average sensitivity of FDG-PET for malignancy within a SPN was reported to be 95.9%, with a specificity of 78.1%.[16] Small size is one cause of the rare false negatives that may be seen when FDG-PET is used to characterise SPN,[17] particularly for lesions less than 5 mm in diameter, and lesions in the lung bases where respiratory motion may further degrade resolution.[17-19] However, although there is a trend towards lower sensitivity for smaller lesions, this is not statistically significant.[19] The second cause for false negative results with FDG-PET in the characterisation of SPN are low-grade well-differentiated malignancies such as carcinoids,[20] well-differentiated adenocarcinomas (especially "scar" adeno-carcinomas),[21] and occasionally bronchoiolo-alveolar carcinomas.[19,22] In view of these occasional false negatives, it is recommended that patients with a negative FDG-PET study undergo radiologic surveillance for 2 years to confirm benignity. However, even if a FDG-PET negative SPN is subsequently found to be malignant, the adverse impact on the patient may be small as it has been recently demonstrated that patients with FDG-PET negative T1 malignancies have significantly better survival than patients with FDG-PET positive T1 malignancies.[23]

False positive findings have also been reported with FDG-PET in the characterisation of SPNs and these are mainly due to benign inflammatory pathologies including necrotising granulomas,[17] histoplasmosis,[24] tuberculosis,[25] chronic pulmonary infections,[25] aspergillus infection,[26,27] pulmonary abscess formation,[28] sarcoidosis[29] and Wegener's granulomatosis.[25] Overall, despite the occasional false positives and false negatives, FDG-PET in the characterisation of SPNs has high positive and negative predictive values and accuracy at 92.6%, 87.0% and 91.3%, respectively.[16]

In the characterisation of SPN, FDG-PET has been compared to other modalities. In one study comparing FDG-PET with computed tomography (CT) in 50 patients with a total of 54 SPNs, FDG-PET was found to have a sensitivity of 90% and a specificity of 83%, compared to CT which was highly sensitive (100%), but poorly specific (52%).[30] Compared to transthoracic needle aspiration (TTNA) biopsy in 33 patients with 35 SPNs, FDG-PET had a sensitivity of 100% and a specificity of 78%. In contrast, TTNA had a sensitivity of 81% and a specificity of 100% due to a failure to diagnose 5 of 26 malignant lesions because of inadequate sampling of the lesion. Furthermore, 46% of patients developed a pneumothorax and 26% of all patients required a chest tube.[24] In another study of outcomes following fine needle aspiration biopsies that did not diagnose carcinoma, 29% of patients were subsequently found to have a malignant process and only 12% were diagnosed as benign by TTNA.[31] A recent review reported that bronchoscopy had a sensitivity of 88% overall and it was highest for central lesions while TTNA had a sensitivity of 90%.[32] FDG-PET thus compares favourably with both of these modalities.

Cost-benefit analyses of FDG-PET in the characterisation of SPN have been performed. A study which compared 5 diagnostic strategies found that in SPN with an intermediate probability of malignancy (12% to 69%), CT with FDG-PET was the most cost-effective.[33] For SPNs with a low probability of malignancy, a watch and wait policy was the most cost-effective; while for SPNs with a high probability of malignancy a CT alone policy was the most cost-effective. In Europe, another cost effectiveness study reported that in patients who had undergone CT for SPN and whose SPNs were found to have a 10% to 70% likelihood of malignancy, FDG-PET resulted in a modest increase in life expectancy at a cost of €3218 per life year gained (a value generally regarded as acceptable).[34] Both of these studies reported that at high likelihood of malignancy FDG-PET was not cost effective. However, neither took into consideration the likely cost savings due to the fact that, in these patients FDG-PET is being performed not only to confirm the malignant nature of the SPN but also to simultaneously stage the disease, as up to 21% of T1 tumours may have regional lymph node metastases.[35] Gould et al[36] reported that in almost all circumstances CT is recommended initially and FDG-PET is cost effective when there is an intermediate post-CT probability of malignancy in the SPN (i.e. clinical and CT probabilities of malignancy are discordant). If the FDG-PET results are positive, surgery is recommended, but TTNA is recommended if FDG-PET results are negative (TTNA was slightly more costly but slightly more effective than watchful waiting).

These data suggest that when clinical and CT assessment results in an intermediate probability for malignancy in an SPN, FDG-PET should be routinely performed. However, it is likely that at some point along the diagnostic path, an

attempt will be made to obtain a histologic diagnosis. Firstly, if biopsy yields a specific benign diagnosis, then no further follow-up is necessary (in contrast to a negative FDG-PET where radiological follow-up is recommended due to the rare false negative). Secondly, if FDG-PET determines that the SPN is malignant, clinicians will still often require a histological diagnosis prior to definitive management as surgical resection may not be appropriate in all cases. Therefore, we believe that currently there are 2 approaches that may be adopted. First, an algorithm as outlined by Gould et al[36] using FDG-PET in all patients with SPNs with an intermediate post CT probability for malignancy to select the approach to histologic sampling (TTNA or surgery) may be adopted. Alternatively, all patients with SPNs of intermediate probability for malignancy following CT initially undergo an attempt at histological characterisation unless this is contraindicated. If this fails to yield a definite benign or malignant diagnosis, they then proceed to FDG-PET. If the FDG-PET is positive the SPN should be treated as if it is malignant, and if negative the SPN should be observed with serial radiology for 2 years. Patients with a SPN of low post-CT probability of malignancy should adopt a watch and wait policy; those with high probability of malignancy should be treated as malignant (an FDG-PET is indicated to stage the disease). With the increasing availability of FDG-PET however, it is likely that clinicians will have a lowered threshold for not submitting a patient to biopsy, for example in patients with reduced pulmonary reserve who may not tolerate pneumothorax well or those with lesions from which it may be difficult to obtain diagnostic material. They are also less likely to use histological sampling when the first attempt is non-diagnostic. The use of FDG-PET, when an attempt at histologic characterisation has failed or is contraindicated, termed the "metabolic biopsy" has been shown to be highly effective with a positive predictive value of 90% and a negative predictive value of 100%, sparing patients with a negative FDG-PET from the need for further invasive investigations.[37]

Preoperative Staging of NSCLC

NSCLC is most often staged using the International System for Staging Lung Cancer which uses the tumour-node-metastasis system.[38] A thorough knowledge of this staging system is necessary in order to report FDG-PET performed for the purposes of staging NSCLC. Accurate staging is required to determine appropriate management and for prognostication.[39] Surgical management offers the best chance of cure, but is generally limited to patients with disease limited to 1 hemithorax extending no further than adjacent resectable structures (T3) or hilar lymph nodes proximally (N1). N2 disease (ipsilateral mediastinal and/or subcarinal lymph nodes) is generally regarded as inoperable (although resection may occasionally be undertaken) as the prognosis is so much poorer regardless of the treatment offered.[40]

Current staging modalities remain suboptimal. CT is the most commonly used non-invasive staging procedure in NSCLC, but is suboptimal because it is based on size criteria (usually lymph nodes >1 cm in short axis in the transverse plane are regarded as abnormal).[41] It is, however, well known that lymph nodes <1 cm may still contain tumour and those >1 cm may be enlarged due to benign causes.[42] In a recent study of 256 patients, 180 of 405 lymph nodes (44%) involved by tumour were <1 cm in diameter. Conversely, 534 of 1953 (19%) lymph nodes that were tumour free were >1 cm in size. This gave CT a sensitivity of 57.1% and a specificity of 80.6%.[43] The British Thoracic Society reported the sensitivity of CT to be 60% to 65% and the specificity to be 60% to 70% with incorrect staging in up to 40% of patients.[44] CT is also used in the detection of distant metastases, as routine CT for NSCLC should include the upper abdominal organs, particularly the adrenal glands. However, enlarged adrenal glands in patients with potentially operable NSCLC are more likely to be benign rather than representing metastatic disease.[45]

Invasive staging of the mediastinum is most often done with mediastinoscopy. While a safe procedure, one series reported a complication rate of 2.3%.[46] When used routinely in patients with normal sized lymph nodes, there was a false negative rate of 10%, mostly due to lymph nodes out of reach of the mediastinoscope.[47]

FDG-PET has been extensively investigated as a staging tool in NSCLC (Fig. 1). In the role of staging the mediastinum, there are numerous reports of the efficacy of FDG-PET.[48-50] A recent review of studies including a total of over 1700 patients with histologic confirmation of thoracic lymph node status found a median sensitivity of 83.3% and a specificity of 92.2% with FDG-PET for thoracic lymph node staging. From a management viewpoint, the most important aspect of thoracic lymph node staging is the detection of metastases to mediastinal lymph nodes (N2/N3), and for this, FDG-PET is also highly effective with a median sensitivity of 84.5% and a specificity of 94.3%.[16]

Although the specificity of FDG-PET is high, occasional false positives do occur. These are mostly due to inflammatory aetiologies such as respiratory tract infections with reactive lymph nodes,[51] rheumatoid disease,[51] tuberculosis,[52] aspergillus infection,[27,52] silicoanthracosis,[53] Wegener's granulomatosis[54] and sarcoidosis.[55] Tumours close to or invading the mediastinum may also occasionally result in false positives for mediastinal lymph node staging.[51] As a result, biopsy confirmation is recommended prior to denying a patient curative surgery on the basis of FDG-

PET findings in the mediastinum.[56]

False negative results are largely the result of the limits of resolution of FDG-PET. FDG-PET has been reported occasionally to be unable to resolve the primary tumour as separate from an adjacent lymph node when the primary is located close to the hilum or mediastinum.[57-59] Other false negative results with FDG-PET in the mediastinum have been reported where there are 2 closely adjacent nodes but at 2 different lymph node stations,[58] where lymph nodes may occasionally be misclassified to the wrong lymph node station (although usually within 1 level of the actual location)[60] and for microscopic tumour deposits in lymph nodes.[59,61,62] It is reported that FDG-PET has a slightly lower sensitivity for lymph nodes <1 cm than lymph nodes >1 cm.[63] Occasionally, if the primary lesion has low metabolic activity, FDG-PET may be falsely negative for lymph node metastases.[60] Therefore, it is imperative for staging of NSCLC with FDG-PET that instrumentation of the highest sensitivity and resolution possible be used, as lower specification instrumentation such as sodium iodide PET and gamma camera based PET may result in higher false negative rates.

In literature comparing FDG-PET to CT, CT had reported sensitivities of 57% to 65% and specificities of 77% to 82%.[16,49,64] In a review comparing FDG-PET to endoscopic ultrasound, which had a reported sensitivity of 78% and a specificity of 71%, FDG-PET was found to be superior.[64] The superior results with FDG-PET compared to CT in thoracic lymph node staging results in alterations in stage (both upstaging and downstaging) in up to 28.1% of patients (median 16.7%).[16]

FDG-PET has also been shown to be very effective in the detection of extra-cerebral metastatic disease. Even when compared with multiple conventional staging investigations (CT from lung apex to liver, cerebral CT or magnetic resonance imaging [MRI] and bone scintigraphy), FDG-PET detected unsuspected metastatic disease in 9% of all patients and correctly excluded metastatic disease at sites of abnormality on conventional imaging in 10% of patients.[65] Overall, FDG-PET is reported to detect metastatic disease in 94.2% of patients subsequently found to have metastases and in 48.4% of these patients this was only detected by FDG-PET.[16] FDG-PET is effective in the detection of metastatic disease in bone,[65] liver,[58,65-67] adrenal glands,[68] and various other extra-cerebral sites. For cerebral metastases however, FDG-PET is poorly sensitive, detecting only 60% to 68% of cerebral metastases, and there were no cerebral metastases detected by FDG-PET not detected by CT or MRI.[65,69] This is likely due to the high metabolic activity of normal cerebral tissue.

Not unexpectedly, the alterations in the overall staging of disease by FDG-PET (in 61% of patients in 1 study[59]) result in changes in management ranging from 24% to 40%.[66,70-72] A recent prospective multi-centre randomised trial reported that FDG-PET prevents futile thoracotomy in 1 out of 5 patients.[73]

FDG-PET in the staging of NSCLC has been shown to be cost-effective in pre-surgical patients. In patients with CT negative for nodal metastases, a strategy combining CT and FDG-PET, and biopsy of FDG-PET positive abnormalities has been shown to be the most cost-effective strategy without loss of life expectancy.[74,75] Similar findings were subsequently reported in a European setting.[63] Most recently, it has been reported that by preventing futile thoracotomy, FDG-PET results in a cost saving of €1289 per patient due to a reduction in the costs of postoperative hospitalisation.[76]

FDG-PET Staging of NSCLC Prior to Radiotherapy or Chemoradiotherapy with Curative Intent

Although surgery represents the best chance of cure in NSCLC, many patients are not surgical candidates because their disease is not surgically resectable, they are medically unsuitable for surgery or they refuse surgery. For these patients, an alternative is radical radiotherapy or chemoradiotherapy with curative intent. Although these therapies avoid the costs and morbidity of major surgery, they may be associated with significant morbidity. In a study of chemoradiotherapy, 51% of patients developed grade 3 or 4 neutropaenia and 52% developed grade 3 or 4 oesophagitis.[77] Therefore, it would seem logical to apply the superior staging information from FDG-PET in NSCLC to more appropriately select patients for these therapies (Figs. 2 and 3). These patients often have more locally advanced disease and it has been shown that the more locally advanced the disease, the higher the rate metastases detected by FDG-PET, such that in patients with stage III disease, 24% had FDG-PET detected distant metastases (P = 0.016).[78] In another study, FDG-PET upstaging, confirmed histologically or by follow-up, occurred in 30% of patients thought to have stage IIIA-N2 NSCLC prior to induction chemotherapy.[79] Staging with FDG-PET has been shown to better predict survival than CT in patients treated with radical radiotherapy.[80] Another study, which compared patients selected for radical radiotherapy with FDG-PET with a retrospective control group who underwent radical radiotherapy based on conventional imaging prior to the availability of FDG-PET, demonstrated significantly better survival in those patients selected with FDG-PET.[81] To our knowledge however, randomised trials comparing the clinical and cost effectiveness FDG-PET with conventional imaging in this setting are not yet available.

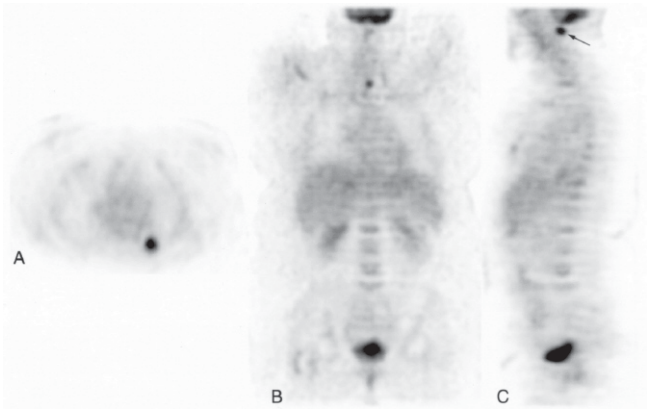
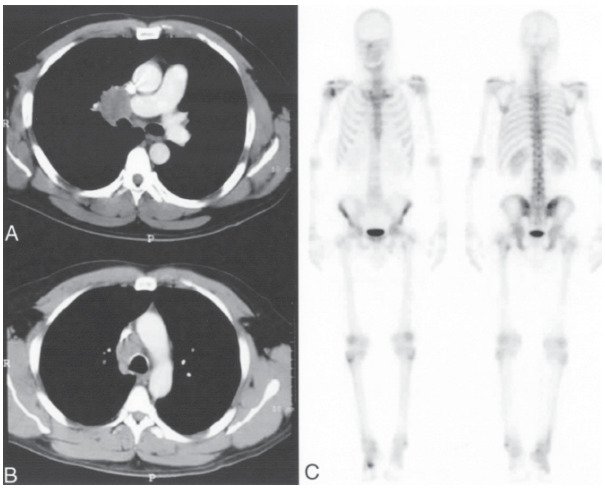
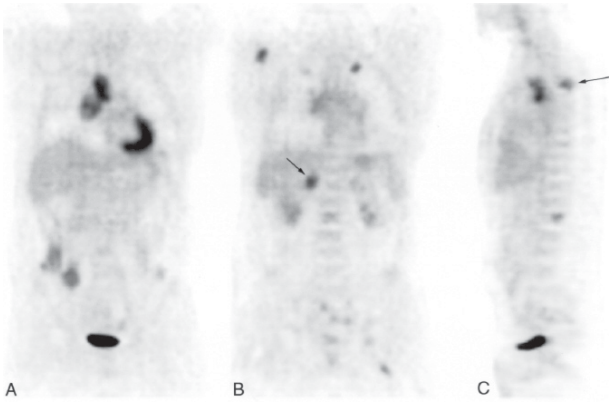


Fig. 1. Fifty-four-year-old female with newly diagnosed NSCLC in the lower lobe of the left lung thought to be T1,N0,M0 on conventional staging and being considered for curative surgery. FDG-PET demonstrated intense uptake in the known primary (A), but uptake in the upper para-tracheal region (B) and also in the upper cervical spine (C, arrowed). An MRI of the cervical spine confirmed a small metastatic deposit (the site was felt to be too dangerous to biopsy).





Figs. 2 and 3. Forty-six-year-old male with a new diagnosis of large cell carcinoma of the right lung adjacent to the hilum (2A). The CT demonstrated ipsilateral mediastinal lymph node metastases (2B). A bone scan was performed as the patient had thoracic back pain. This showed uptake in the right shoulder and minor uptake in the lower thoracic spine both felt to be arthritic in aetiology (2C). On conventional staging the patient was staged as T2, N2, M0. A FDG-PET was performed prior to chemoradiotherapy with curative intent. This demonstrates uptake within the known primary tumour, mediastinal lymph nodes (3A) but also in multiple sites indicative of metastatic disease. In particular, there are multiple osseous metastases (particularly in the upper thoracic spine (3C, arrowed) not seen on the bone scan) bilateral intra-pulmonary metastases and a right adrenal metastases (3B, arrowed) (CT at this site showed no enlargement of the adrenal gland). The patient subsequently developed cord compression in the upper thoracic spine that required surgical decompression. Histology of this confirmed metastatic large cell carcinoma.

Algorithm for FDG-PET in Staging NSCLC

A suggested algorithm for the use of FDG-PET in NSCLC should include patients who are considered curable by surgery on conventional staging, with possible extension to patients who are being considered for radical radiotherapy or chemoradiotherapy (although the evidence base for this group is not as strong). These patients should undergo FDG-PET and if this is negative for mediastinal and extra-thoracic metastases, these patients can proceed to curative therapy without further investigations, due to the high negative predictive value of FDG-PET. If the FDG-PET scan is positive either in the mediastinum or in an extra-thoracic location, confirmation preferably by biopsy (or if this is not possible by correlative imaging) is recommended to ensure that no patient is inappropriately denied curative therapy due to the small risk of a false positive finding on FDG-PET.[56] It is acknowledged, however, that certain pathognomonic appearances (such as widespread metastases) may not require biopsy. Occasionally, biopsy confirmation cannot be obtained, particularly in patients for non-surgical curative therapy who may be unable to tolerate invasive biopsy due to intercurrent medical illness. In this latter group, the risks of a potential false positive result must be weighed against that of a futile attempt at curative therapy.

Radiotherapy Planning and FDG-PET

Several studies have investigated the role of FDG-PET in radiotherapy planning. It has been reported that FDG-PET significantly improves tumour coverage compared to CT,[82] and may either increase treatment volumes (predominantly to incorporate unsuspected lymph node metastases)[83-85] or decrease treatment volume as FDG-PET is able to separate the tumour from adjacent atelectactic lung.[83,86] While these results are promising, no data are yet available to confirm that the FDG-PET induced changes in treatment volumes result in improved outcomes.

Treatment Response and Detection of Recurrent Disease

Limited data are available suggesting that FDG-PET may have a role in monitoring treatment response. Early

work in 15 patients, 9 of whom subsequently proceeded to surgery demonstrated that FDG-PET had an accuracy of 100% for predicting the presence or absence of disease following induction chemotherapy.[87] Another study following neo-adjuvant chemoradiotherapy demonstrated a sensitivity of 88% and a specificity of 67% for distinguishing residual malignancy from complete pathological response within the primary. In mediastinal lymph nodes, FDG-PET was able to differentiate residual malignancy from complete pathological response with a sensitivity of 58% and a specificity of 93%.[88] In a recent study of 27 patients who received chemotherapy and 7 who received chemo-radiotherapy, FDG-PET had significantly better positive and negative predictive values than CT for detecting residual tumour at the primary site and in paratracheal lymph nodes.[89] FDG-PET has also been used to assess survival following radiotherapy or chemoradiotherapy in 73 patients. While both CT and PET were found to be significantly associated with survival duration, on multivariate analysis, only FDG-PET was found to be significantly associated with survival duration.[90] While the results are promising, it should be noted that there is the potential for false positive results following radiotherapy due to radiotherapy induced inflammatory changes which may persist for up to 6 months.[91] Hence, it is best to delay post-radiotherapy FDG-PET for at least 3, and preferably 6 months.[92]

FDG-PET has been shown to have a high sensitivity of 97% to 100% for the detection of recurrent malignancy with a specificity ranging from 61.5% to 100%.[93,94] False positives have been attributed to post-radiotherapy inflammation. Occasionally, the uptake pattern may be helpful in identifying false positives (such as a curvilinear pattern). A repeat study 3 to 6 months after completion of radiotherapy may also be helpful.[93]

FDG-PET as a Prognostic Factor

Several studies have demonstrated that FDG uptake measure by the standardised uptake value (SUV) has prognostic significance. In a group of 77 patients considered for resection, a SUV >20 was found to confer a dismal median survival of 6 months.[95] Another study reported that in patients with a SUV >10 and a primary tumour size >3 cm had a median survival of 5.7 months.[96] Vansteenkiste et al[97] found on multivariate analysis that SUV >7 was significantly associated with survival. It is presently unclear how this data can be best incorporated into the management of NSCLC.

Future Possibilities

From the above discussion, it can be seen that FDG-PET is a significant improvement on current non-invasive imaging, particularly in terms of diagnosis and staging of NSCLC. In the very near future, combined or fused anatomic-metabolic imaging will be widely used for lung carcinoma. Recently, it was reported that fused PET-CT acquired on a combined PET-CT scanner is superior to PET visually correlated with CT.[98] However, even with combined PET-CT scanners there is significant risk of mis-registration particularly due to respiration with reported mis-registrations of lung lesions of 7.55+/-4.73 mm.[99] However, current state-of-the-art software fusion of PET and CT images acquired on separate stand-alone devices can achieve similar results, with a reported mean mis-registration error of 6.2 mm.[100] Undoubtedly, however, combined PET-CT provides a high level of convenience but at a significant capital cost. While fused anatomic-metabolic imaging is of importance, the optimum method remains controversial.

In the longer term, new tracers will provide significant additional information that will allow greater metabolic characterisation of individual patient's NSCLC and lead to more individualised therapies. While many possibilities exist, of particular interest in NSCLC is the non-invasive imaging of tissue hypoxia. A recent study found that tissue hypoxia measured with PET using copper-60 diacetyl-bis(N(4)-methylthiosemicarbazone) (60Cu-ATSM) (a tracer that is taken up in proportion to tissue hypoxia) accurately predicted the response to therapy.[11]

Conclusions

FDG-PET has established roles in the characterisation of SPNs and should be a routine part of staging of NSCLC prior to surgery with strong evidence of its clinical efficacy and cost effectiveness. It should also be routinely used for staging prior to radiotherapy or chemoradiotherapy with curative intent as there is emerging evidence to support this indication. There is now promising data to support additional roles for FDG-PET in radiotherapy planning, assessment of treatment response and prognostication. However, additional work is needed and how this additional information can be best incorporated into management remains to be determined. In the longer term, new tracers may allow greater metabolic characterisation (such as that of hypoxia) of individual tumours to allow greater individualisation of therapy.

REFERENCES

1. Ries L, Eisner M, Kosary C, Hankey B, Miller B, Clegg L, et al. SEER Cancer Statistics Review, 1975-2000, National Cancer Institute, 2003. Available at http://seer.cancer.gov/csr/1975_2000. Accessed 22 July 2003.
2. Mortality: Cancer Research UK 2003. Mortality UK, CancerStats, 2003. Available at http://www.cancerresearchuk.org/aboutcancer/statistics/cancerstatsreport/. Accessed 22 July 2003.

3. Warburg O. The Metabolism of Tumors. London: Constable, 1930: 129-69.
4. Isselbacher KJ. Increased uptake of amino acids and 2-deoxy-D-glucose by virus-transformed cells in culture. Proc Natl Acad Sci USA 1972;69:585-9.
5. Bello LJ. Regulation of thymidine kinase synthesis in human cells. Exp Cell Res 1974;89:263-74.
6. Mueckler M. Facilitative glucose transporters. Eur J Biochem 1994;219:713-25.
7. Gallagher BM, Fowler JS, Gutterson NI, MacGregor RR, Wan CN, Wolf AP. Metabolic trapping as a principle of radiopharmaceutical design: some factors responsible for the biodistribution of [18F] 2-deoxy-2-fluoro-D-glucose. J Nucl Med 1978;19:1154-61.
8. Brown RS, Leung JY, Kison PV, Zasadny KR, Flint A, Wahl RL. Glucose transporters and FDG uptake in untreated primary human non-small cell lung cancer. J Nucl Med 1999;40:556-65.
9. Smith TA. FDG uptake, tumour characteristics and response to therapy: a review. Nucl Med Commun 1998;19:97-105.
10. Buck AK, Schirrmeister H, Hetzel M, Von Der Heide M, Halter G, Glatting G, et al. 3-deoxy-3-[(18)F]fluorothymidine-positron emission tomography for noninvasive assessment of proliferation in pulmonary nodules. Cancer Res 2002;62:3331-4.
11. Dehdashti F, Mintun MA, Lewis JS, Bradley J, Govindan R, Laforest R, et al. In vivo assessment of tumor hypoxia in lung cancer with (60)Cu-ATSM. Eur J Nucl Med Mol Imaging 2003;30:844-50.
12. Midthun DE, Swensen SJ, Jett JR. Approach to the solitary pulmonary nodule. Mayo Clin Proc 1993;68:378-85.
13. Shulkin AN. Management of the indeterminate solitary pulmonary nodule: a pulmonologist's view. Ann Thorac Surg 1993;56:743-4.
14. Swensen SJ, Viggiano RW, Midthun DE, Muller NL, Sherrick A, Yamashita K, et al. Lung nodule enhancement at CT: multicenter study. Radiology 2000;214:73-80.
15. Viggiano RW, Swensen SJ, Rosenow EC, III. Evaluation and management of solitary and multiple pulmonary nodules. Clin Chest Med 1992;13:83-95.
16. Ho Shon I, O'Doherty MJ, Maisey MN. Positron emission tomography in lung cancer. Semin Nucl Med 2002;32:240-71.
17. Kubota K, Matsuzawa T, Fujiwara T, Ito M, Hatazawa J, Ishiwata K, et al. Differential diagnosis of lung tumor with positron emission tomography: a prospective study. J Nucl Med 1990;31:1927-32.
18. Hoffman EJ, Huang SC, Phelps ME. Quantitation in positron emission computed tomography: 1. Effect of object size. J Comput Assist Tomogr 1979;3:299-308.
19. Lowe VJ, Fletcher JW, Gobar L, Lawson M, Kirchner P, Valk P, et al. Prospective investigation of positron emission tomography in lung nodules. J Clin Oncol 1998;16:1075-84.
20. Rege SD, Hoh CK, Glaspy JA, Aberle DR, Dahlbom M, Razavi MK, et al. Imaging of pulmonary mass lesions with whole-body positron emission tomography and fluorodeoxyglucose. Cancer 1993;72:82-90.
21. Dewan NA, Gupta NC, Redepenning LS, Phalen JJ, Frick MP. Diagnostic efficacy of PET-FDG imaging in solitary pulmonary nodules. Potential role in evaluation and management. Chest 1993;104:997-1002.
22. Yap CS, Schiepers C, Fishbein MC, Phelps ME, Czernin J. FDG-PET imaging in lung cancer: how sensitive is it for bronchioloalveolar carcinoma? Eur J Nucl Med Mol Imaging 2002;29:1166-73.
23. Marom EM, Sarvis S, Herndon JE, II, Patz EF, Jr. T1 lung cancers: sensitivity of diagnosis with fluorodeoxyglucose PET. Radiology 2002;223:453-9.
24. Dewan NA, Reeb SD, Gupta NC, Gobar LS, Scott WJ. PET-FDG imaging and transthoracic needle lung aspiration biopsy in evaluation of pulmonary lesions. A comparative risk-benefit analysis. Chest 1995;108:441-6.
25. Knight SB, Delbeke D, Stewart JR, Sandler MP. Evaluation of pulmonary lesions with FDG-PET. Comparison of findings in patients with and without a history of prior malignancy. Chest 1996;109:982-8.
26. Lowe VJ, Duhaylongsod FG, Patz EF, Delong DM, Hoffman JM, Wolfe WG, et al. Pulmonary abnormalities and PET data analysis: a retrospective study. Radiology 1997;202:435-9.
27. Wilkinson MD, Fulham MJ, McCaughan BC, Constable CJ. Invasive aspergillosis mimicking stage IIIA non-small cell lung cancer on FDG positron emission tomography. Clin Nucl Med 2003;28: 234-5.
28. Hubner KF, Buonocore E, Singh SK, Gould HR, Cotten DW. Characterization of chest masses by FDG positron emission tomography. Clin Nucl Med 1995;20:293-8.
29. Hubner KF, Buonocore E, Gould HR, Thie J, Smith GT, Stephens S, et al. Differentiating benign from malignant lung lesions using "quantitative" parameters of FDG PET images. Clin Nucl Med 1996;21:941-9.
30. Prauer HW, Weber WA, Romer W, Treumann T, Ziegler SI, Schwaiger M. Controlled prospective study of positron emission tomography using the glucose analogue [18F]fluorodeoxyglucose in the evaluation of pulmonary nodules. Br J Surg 1998;85:1506-11.
31. Calhoun P, Feldman PS, Armstrong P, Black WC, Pope TL, Minor GR, et al. The clinical outcome of needle aspirations of the lung when cancer is not diagnosed. Ann Thorac Surg 1986;41:592-6.
32. Schreiber G, McCrory DC. Performance characteristics of different modalities for diagnosis of suspected lung cancer: summary of published evidence. Chest 2003;123:S115-S128.
33. Gambhir SS, Shepherd JE, Shah BD, Hart E, Hoh CK, Valk PE, et al. Analytical decision model for the cost-effective management of solitary pulmonary nodules. J Clin Oncol 1998;16:2113-25.
34. Dietlein M, Weber K, Gandjour A, Moka D, Theissen P, Lauterbach KW, et al. Cost-effectiveness of FDG-PET for the management of solitary pulmonary nodules: a decision analysis based on cost reimbursement in Germany. Eur J Nucl Med 2000;27:1441-56.
35. Seely JM, Mayo JR, Miller RR, Muller NL. T1 lung cancer: prevalence of mediastinal nodal metastases and diagnostic accuracy of CT. Radiology 1993;186:129-32.
36. Gould MK, Sanders GD, Barnett PG, Rydzak CE, Maclean CC, McClellan MB, et al. Cost-effectiveness of alternative management strategies for patients with solitary pulmonary nodules. Ann Intern Med 2003;138:724-35.
37. Hain SF, Curran KM, Beggs AD, Fogelman I, O'Doherty MJ, Maisey MN. FDG-PET as a "metabolic biopsy" tool in thoracic lesions with indeterminate biopsy. Eur J Nucl Med 2001;28:1336-40.
38. Mountain CF, Dresler CM. Regional lymph node classification for lung cancer staging. Chest 1997;111:1718-23.
39. Feld R, Abratt R, Graziano S, Jassem J, Lacquet L, Ninane V, et al. Pretreatment minimal staging and prognostic factors for non-small cell lung cancer. Lung Cancer 1997;17:S3-10.
40. Ginsberg R, Evertt E, Rosenzweig K. Non-small cell lung cancer. In: DeVita V, Hellman S, Rosenberg S, editors. Cancer Principles and Practice of Oncology. Vol. 1. Philadelphia: Lippincott Williams and Wilkins, 2001:925-83.
41. Glazer GM, Gross BH, Quint LE, Francis IR, Bookstein FL, Orringer MB. Normal mediastinal lymph nodes: number and size according to American Thoracic Society mapping. AJR Am J Roentgenol 1985;144:261-5.
42. Dales RE, Stark RM, Raman S. Computed tomography to stage lung cancer. Approaching a controversy using meta-analysis. Am Rev Respir Dis 1990;141:1096-101.
43. Prenzel KL, Monig SP, Sinning JM, Baldus SE, Brochhagen HG, Schneider PM, et al. Lymph node size and metastatic infiltration in non-small cell lung cancer. Chest 2003;123:463-7.
44. British Thoracic Society and Society of Cardiothoracic Surgeons of Great Britain and Ireland Working Party. BTS guidelines: guidelines on

the selection of patients with lung cancer for surgery. Thorax 2001;56: 89-108.

45. Oliver TW, Jr, Bernardino ME, Miller JI, Mansour K, Greene D, Davis WA. Isolated adrenal masses in non-small cell bronchogenic carcinoma. Radiology 1984;153:217-8.
46. Luke WP, Pearson FG, Todd TR, Patterson GA, Cooper JD. Prospective evaluation of mediastinoscopy for assessment of carcinoma of the lung. J Thorac Cardiovasc Surg 1986;91:53-6.
47. De Leyn P, Vansteenkiste J, Cuypers P, Deneffe G, Van Raemdonck D, Coosemans W, et al. Role of cervical mediastinoscopy in staging of non-small cell lung cancer without enlarged mediastinal lymph nodes on CT scan. Eur J Cardiothorac Surg 1997;12:706-12.
48. Fischer B, Mortensen J, Hojgaard L. Positron emission tomography in the diagnosis and staging of lung cancer: a systematic quantitiative review. Lancet Oncol 2001;2:659-66.
49. Dwamena BA, Sonnad SS, Angobaldo JO, Wahl RL. Metastases from non-small cell lung cancer: mediastinal staging in the 1990s—meta-analytic comparison of PET and CT. Radiology 1999;213:530-6.
50. Reske SN, Kotzerke J. FDG-PET for clinical use Results of the 3rd German Interdisciplinary Consensus Conference, "Onko-PET III", 21 July and 19 September 2000. Eur J Nucl Med 2001;28:1707-23.
51. Roberts PF, Follette DM, von Haag D, Park JA, Valk PE, Pounds TR, et al. Factors associated with false-positive staging of lung cancer by positron emission tomography. Ann Thorac Surg 2000; 70:1154-60.
52. Guhlmann A, Storck M, Kotzerke J, Moog F, Sunder-Plassmann L, Reske SN. Lymph node staging in non-small cell lung cancer: evaluation by [18F]FDG positron emission tomography (PET). Thorax 1997;52:438-41.
53. Gupta NC, Tamim WJ, Graeber GG, Bishop HA, Hobbs GR. Mediastinal lymph node sampling following positron emission tomography with fluorodeoxyglucose imaging in lung cancer staging. Chest 2001;120: 521-7.
54. Albes JM, Lietzenmayer R, Schott U, Schulen E, Wehrmann M, Ziemer G. Improvement of non-small cell lung cancer staging by means of positron emission tomography. Thorac Cardiovasc Surg 1999;47:42-7.
55. Brudin LH, Valind SO, Rhodes CG, Pantin CF, Sweatman M, Jones T, et al. Fluorine-18 deoxyglucose uptake in sarcoidosis measured with positron emission tomography. Eur J Nucl Med 1994;21:297-305.
56. Silvestri GA, Tanoue LT, Margolis ML, Barker J, Detterbeck F. The noninvasive staging of non-small cell lung cancer: the guidelines. Chest 2003;123:S147-56.
57. Wahl RL, Quint LE, Greenough RL, Meyer CR, White RI, Orringer MB. Staging of mediastinal non-small cell lung cancer with FDG PET, CT, and fusion images: preliminary prospective evaluation. Radiology 1994;191:371-7.
58. Valk PE, Pounds TR, Hopkins DM, Haseman MK, Hofer GA, Greiss HB, et al. Staging non-small cell lung cancer by whole-body positron emission tomographic imaging. Ann Thorac Surg 1995;60:1573-82.
59. Pieterman RM, van Putten JW, Meuzelaar JJ, Mooyaart EL, Vaalburg W, Koeter GH, et al. Preoperative staging of non-small cell lung cancer with positron emission tomography. N Engl J Med 2000;343:254-61.
60. Poncelet AJ, Lonneux M, Coche E, Weynand B, Noirhomme P. PET-FDG scan enhances but does not replace preoperative surgical staging in non-small cell lung carcinoma. Eur J Cardiothorac Surg 2001;20: 468-75.
61. Scott WJ, Schwabe JL, Gupta NC, Dewan NA, Reeb SD, Sugimoto JT. Positron emission tomography of lung tumors and mediastinal lymph nodes using [18F]fluorodeoxyglucose. The Members of the PET-Lung Tumor Study Group. Ann Thorac Surg 1994;58:698-703.
62. Vansteenkiste JF, Stroobants SG, De Leyn PR, Dupont PJ, Bogaert J, Maes A, et al. Lymph node staging in non-small cell lung cancer with FDG-PET scan: a prospective study on 690 lymph node stations from 68 patients. J Clin Oncol 1998;16:2142-9.
63. Dietlein M, Weber K, Gandjour A, Moka D, Theissen P, Lauterbach KW, et al. Cost-effectiveness of FDG-PET for the management of potentially operable non-small cell lung cancer: priority for a PET-based strategy after nodal-negative CT results. Eur J Nucl Med 2000;27: 1598-609.
64. Toloza EM, Harpole L, McCrory DC. Noninvasive staging of non-small cell lung cancer: a review of the current evidence. Chest 2003;123: S137-S146.
65. Marom EM, McAdams HP, Erasmus JJ, Goodman PC, Culhane DK, Coleman RE, et al. Staging non-small cell lung cancer with whole-body PET. Radiology 1999;212:803-9.
66. Bury T, Dowlati A, Paulus P, Corhay JL, Hustinx R, Ghaye B, et al. Whole-body 18FDG positron emission tomography in the staging of non-small cell lung cancer. Eur Respir J 1997;10:2529-34.
67. Kinkel K, Lu Y, Both M, Warren RS, Thoeni RF. Detection of hepatic metastases from cancers of the gastrointestinal tract by using noninvasive imaging methods (US, CT, MR imaging, PET): a meta-analysis. Radiology 2002;224:748-56.
68. Boland GW, Goldberg MA, Lee MJ, Mayo-Smith WW, Dixon J, McNicholas MM, et al. Indeterminate adrenal mass in patients with cancer: evaluation at PET with 2-[F-18]-fluoro-2-deoxy-D-glucose. Radiology 1995;194:131-4.
69. Griffeth LK, Rich KM, Dehdashti F, Simpson JR, Fusselman MJ, McGuire AH, et al. Brain metastases from non-central nervous system tumors: evaluation with PET. Radiology 1993;186:37-44.
70. Saunders CA, Dussek JE, O'Doherty MJ, Maisey MN. Evaluation of fluorine-18-fluorodeoxyglucose whole body positron emission tomography imaging in the staging of lung cancer. Ann Thorac Surg 1999;67:790-7.
71. Lewis P, Griffin S, Marsden P, Gee T, Nunan T, Malsey M, et al. Whole-body 18F-fluorodeoxyglucose positron emission tomography in preoperative evaluation of lung cancer. Lancet 1994;344:1265-6.
72. Weng E, Tran L, Rege S, Safa A, Sadeghi A, Juillard G, et al. Accuracy and clinical impact of mediastinal lymph node staging with FDG-PET imaging in potentially resectable lung cancer. Am J Clin Oncol 2000;23:47-52.
73. van Tinteren H, Hoekstra O, Smit E, van den Bergh J, Schreurs A, Stallaert R, et al. Effectiveness of positron emission tomography in the preoperative assessment of patients with suspected non-small cell lung cancer: the PLUS multicentre randomised trial. Lancet 2002;359: 1388-92.
74. Gambhir SS, Hoh CK, Phelps ME, Madar I, Maddahi J. Decision tree sensitivity analysis for cost-effectiveness of FDG-PET in the staging and management of non-small cell lung carcinoma. J Nucl Med 1996;37:1428-36.
75. Scott WJ, Shepherd J, Gambhir SS. Cost-effectiveness of FDG-PET for staging non-small cell lung cancer: a decision analysis. Ann Thorac Surg 1998;66:1876-85.
76. Verboom P, Van Tinteren H, Hoekstra OS, Smit EF, Van Den Bergh JH, Schreurs AJ, et al. Cost-effectiveness of FDG-PET in staging non-small cell lung cancer: the PLUS study. Eur J Nucl Med Mol Imaging 2003;30:144-9.
77. Vokes EE, Herndon JE, II, Crawford J, Leopold KA, Perry MC, Miller AA, et al. Randomized phase II study of cisplatin with gemcitabine or paclitaxel or vinorelbine as induction chemotherapy followed by concomitant chemoradiotherapy for stage IIIB non-small cell lung cancer: cancer and leukemia group B study 9431. J Clin Oncol 2002;20:4191-8.
78. MacManus MP, Hicks RJ, Matthews JP, Hogg A, McKenzie AF, Wirth A, et al. High rate of detection of unsuspected distant metastases by PET in apparent stage III non-small cell lung cancer: implications for radical radiation therapy. Int J Radiat Oncol Biol Phys 2001;50:287-93.
79. Hoekstra CJ, Stroobants SG, Hoekstra OS, Vansteenkiste J, Biesma B,

Schramel FJ, et al. The value of [18F]fluoro-2-deoxy-D-glucose positron emission tomography in the selection of patients with stage IIIA-N2 non-small cell lung cancer for combined modality treatment. Lung Cancer 2003;39:151-7.

80. MacManus MP, Hicks RJ, Ball DL, Kalff V, Matthews JP, Salminen E, et al. F-18 fluorodeoxyglucose positron emission tomography staging in radical radiotherapy candidates with non-small cell lung carcinoma: powerful correlation with survival and high impact on treatment. Cancer 2001;92:886-95.
81. MacManus MP, Wong K, Hicks RJ, Matthews JP, Wirth A, Ball DL. Early mortality after radical radiotherapy for non-small cell lung cancer: comparison of PET-staged and conventionally-staged cohorts treated at a large tertiary referral center. Int J Radiat Oncol Biol Phys 2002;52: 351-61.
82. Vanuytsel LJ, Vansteenkiste JF, Stroobants SG, De Leyn PR, De Wever W, Verbeken EK, et al. The impact of (18)F-fluoro-2-deoxy-D-glucose positron emission tomography (FDG-PET) lymph node staging on the radiation treatment volumes in patients with non-small cell lung cancer. Radiother Oncol 2000;55:317-24.
83. Erdi YE, Rosenzweig K, Erdi AK, Macapinlac HA, Hu YC, Braban LE, et al. Radiotherapy treatment planning for patients with non-small cell lung cancer using positron emission tomography (PET). Radiother Oncol 2002;62:51-60.
84. Kiffer JD, Berlangieri SU, Scott AM, Quong G, Feigen M, Schumer W, et al. The contribution of 18F-fluoro-2-deoxy-glucose positron emission tomographic imaging to radiotherapy planning in lung cancer. Lung Cancer 1998;19:167-77.
85. Featherstone C, Holloway L, Vinod S, Ho Shon I, Kaplan A. The Influence of 18FDG-PET on conformal radiotherapy planning for patients with non-small cell lung carcinoma (NSCLC), International Congress of Radiation Research, Brisbane, 2003.
86. Nestle U, Walter K, Schmidt S, Licht N, Nieder C, Motaref B, et al. 18F-deoxyglucose positron emission tomography (FDG-PET) for the planning of radiotherapy in lung cancer: high impact in patients with atelectasis. Int J Radiat Oncol Biol Phys 1999;44:593-7.
87. Vansteenkiste JF, Stroobants SG, De Leyn PR, Dupont PJ, Verbeken EK. Potential use of FDG-PET scan after induction chemotherapy in surgically staged IIIa-N2 non-small cell lung cancer: a prospective pilot study. The Leuven Lung Cancer Group. Ann Oncol 1998;9:1193-8.
88. Ryu JS, Choi NC, Fischman AJ, Lynch TJ, Mathisen DJ. FDG-PET in staging and restaging non-small cell lung cancer after neoadjuvant chemoradiotherapy: correlation with histopathology. Lung Cancer 2002;35:179-87.
89. Cerfolio RJ, Ojha B, Mukherjee S, Pask AH, Bass CS, Katholi CR. Positron emission tomography scanning with 2-fluoro-2-deoxy-d-glucose as a predictor of response of neoadjuvant treatment for non-small cell carcinoma. J Thorac Cardiovasc Surg 2003;125:938-44.
90. MacManus MP, Hicks RJ, Matthews JP, McKenzie A, Rischin D, Salminen EK, et al. Positron emission tomography is superior to computed tomography scanning for response-assessment after radical radiotherapy or chemoradiotherapy in patients with non-small cell lung cancer. J Clin Oncol 2003;21:1285-92.
91. Frank A, Lefkowitz D, Jaeger S, Gobar L, Sunderland J, Gupta N, et al. Decision logic for retreatment of asymptomatic lung cancer recurrence based on positron emission tomography findings. Int J Radiat Oncol Biol Phys 1995;32:1495-512.
92. O'Doherty MJ. PET in oncology I – lung, breast, soft tissue sarcoma. Nucl Med Commun 2000;21:224-9.
93. Inoue T, Kim EE, Komaki R, Wong FC, Bassa P, Wong WH, et al. Detecting recurrent or residual lung cancer with FDG-PET. J Nucl Med 1995;36:788-93.
94. Patz EF Jr, Lowe VJ, Hoffman JM, Paine SS, Harris LK, Goodman PC. Persistent or recurrent bronchogenic carcinoma: detection with PET and 2-[F-18]-2-deoxy-D-glucose. Radiology 1994;191:379-82.
95. Dhital K, Saunders CA, Seed PT, O'Doherty MJ, Dussek J. [(18)F] fluorodeoxyglucose positron emission tomography and its prognostic value in lung cancer. Eur J Cardiothorac Surg 2000;18:425-8.
96. Ahuja V, Coleman RE, Herndon J, Patz EF, Jr. The prognostic significance of fluorodeoxyglucose positron emission tomography imaging for patients with non-small cell lung carcinoma. Cancer 1998;83:918-24.
97. Vansteenkiste JF, Stroobants SG, Dupont PJ, De Leyn PR, Verbeken EK, Deneffe GJ, et al. Prognostic importance of the standardized uptake value on (18)F-fluoro-2-deoxy-glucose-positron emission tomography scan in non-small-cell lung cancer: an analysis of 125 cases. Leuven Lung Cancer Group. J Clin Oncol 1999;17:3201-6.
98. Lardinois D, Weder W, Hany TF, Kamel EM, Korom S, Seifert B, et al. Staging of non-small cell lung cancer with integrated positron emission tomography and computed tomography. N Engl J Med 2003;348: 2500-7.
99. Cohade C, Osman M, Marshall LN, Wahl RN. PET-CT: accuracy of PET and CT spatial registration of lung lesions. Eur J Nucl Med Mol Imaging 2003;30:721-6.
100. Skalski J, Wahl RL, Meyer CR. Comparison of mutual information-based warping accuracy for fusing body CT and PET by 2 methods: CT mapped onto PET emission scan versus CT mapped onto PET transmission scan. J Nucl Med 2002;43:1184-7.