

The Role of PET Scan in Diagnosis, Staging, and Management of Non-Small Cell Lung Cancer

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ABSTRACT

Positron emission tomography (PET) is now an important cancer imaging tool, both for diagnosis and staging, as well as offering prognostic information based on response. This report attempts to comprehensively review the value of PET in the locoregional and distant staging of non-small cell lung cancer (NSCLC), illustrate the potential effects on patient management, and give a short overview of newer applications. PET sets the gold standard in the evaluation of an indeterminate solitary pulmonary nodule or mass, where PET has proven to be significantly more accurate than computed tomography (CT) in the distinction between benign and malignant lesions. In the evaluation of metastatic spread to locoregional lymph nodes, PET is significantly more accurate

than CT, so that invasive surgical staging may be omitted in many patients with negative mediastinal PET images. In patients with positive mediastinal PET images, invasive surgical staging remains mandatory because of the possibility of false-positive findings due to inflammatory nodes or granulomatous disorders. In the search for metastatic spread, PET is a useful adjunct to conventional imaging. This may be due to the finding of unexpected metastatic lesions or due to exclusion of malignancy in lesions that are equivocal on standard imaging. However, at this time, PET does not replace conventional imaging. Large-scale randomized studies are currently examining whether PET staging will actually improve the appearance of lung cancer outcome. *The Oncologist* 2004;9:633-643

INTRODUCTION

Lung cancer is the most common cause of cancer-related death in the Western world, with approximately 3 million new cases per year estimated worldwide. Imaging techniques play an essential role in the diagnosis, staging, and follow-up of patients with lung cancer. Positron emission tomography (PET) has become an important innovation in lung cancer imaging. Standard imaging techniques are based on differences in the structure of tissues. PET with the glucose analogue 2-¹⁸F-fluoro-2-deoxy-D-glucose (FDG) is based on the enhanced glucose metabolism of lung cancer cells. FDG undergoes the same uptake as glucose but is metabolically trapped and accumulated in the cancer cell after phosphorylation by hexokinase. Reading of the FDG distribution in the

body by the PET camera allows differentiation between normal and malignant tissues.

DIFFERENTIAL DIAGNOSIS OF SOLITARY PULMONARY NODULES

A solitary pulmonary nodule (SPN), or "coin lesion," is defined as a single spherical or oval lesion completely surrounded by lung without associated atelectasis or adenopathy. Because lesions larger than 3 cm are almost always malignant, most authors currently agree that SPNs are 3 cm or less in diameter [1]. Larger lesions should be referred to as pulmonary masses and should be managed with the understanding that they are most likely to be malignant. Prompt diagnosis and resection is the preferred strategy.

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Central lung tumors can usually be approached by bronchoscopy, while peripheral SPNs often are a diagnostic challenge. The incidence of malignancy across studies ranges from 10%-68%, dependent on the definition of SPN (e.g., 1 cm to 6 cm) and the selection criteria of patients [2, 3]. Clinical risk factors for malignancy are age, smoking history, hemoptysis, and prior history of malignancy. Chest x-rays and computed tomography (CT) can provide useful information regarding nodule size, characteristics of the margins (irregular being suspect for malignancy), calcification, cavitation, and growth rate. SPNs that have been demonstrated to be stable on serial chest x-rays for 2 years or more can be considered to be benign [4]. Other findings, such as cavitation and satellite lesions, are less reliable in distinguishing benign from malignant nodules. Calcification within a nodule is usually an indicator of a benign lesion. However, not all patterns of calcification are associated with a benign diagnosis; stippled or eccentric nodules have been associated with malignancy [5]. After completing an initial history and radiological tests, clinicians will be able to classify the SPNs into one of three categories: benign, malignant, or indeterminate. Between 70%-75% of nodules that remain indeterminate will ultimately be malignant [5].

Bronchoscopy with brush cytology or transbronchial biopsy may be useful if the lesion is 2 cm or larger in size. The diagnostic yield of bronchoscopy for an SPN varies widely in the literature (20%-80%), depending on the size of the nodule, the incidence of malignancy in the study population, and the skill of the operator [6].

Transthoracic needle aspiration (TTNA) biopsy can also be considered for pulmonary lesions. This technique is most useful in lesions of at least 2 cm. In one study, the diagnostic yield was up to 60% for lesions smaller than 2 cm when peripherally located lesions only were considered and when several aspiration biopsies per patient were performed [7]. In general, false-negative results, occurring in up to 30% of the patients, remain a problem [8, 9]. While TTNA usually will not be indicated in operable patients with an SPN, it can be of use in patients who decline surgical intervention or who lack sufficient cardiopulmonary function to undergo surgical procedures [10]. TTNA is contraindicated in the patient with a single lung. Relative contraindications to this procedure are pulmonary hypertension, coagulopathy or bleeding diathesis, severe chronic obstructive pulmonary disease, or vascular malformations. Complications include hemoptysis and pneumothorax (up to 30% in some series). Consequently, a noninvasive imaging test, reliable in the differentiation between benign and malignant nodules, would be very useful in this setting to reduce the number of futile invasive procedures.

PET has been studied extensively in the evaluation of indeterminate lung lesions. This technique has been accurate

in differentiating benign from malignant lesions as small as 1 cm [11]. An overall sensitivity of 96% (range, 83%-100%), specificity of 79% (range, 52%-100%), and accuracy of 91% (range, 86%-100%) can be expected [12-14]. In the standard situation, semiquantitative image interpretation by measuring the standardized uptake value (SUV) does not improve accuracy compared with simple visual interpretation. In difficult cases, prolonged observation of the metabolic activity of the nodules, measured by SUV, has proven to assist in the differential diagnosis [15]. Early and delayed reading of FDG-PET (dual time-point FDG-PET imaging) shows higher SUV at 3 hours than at 1 hour post-injection for malignant lesions, and the opposite result for benign lesions [16].

False-negative results can occur in lesions smaller than 1 cm because a critical mass of metabolically active malignant cells is required for PET diagnosis. *Lowe et al.* found a sensitivity of 80% in lesions smaller than 1.5 cm compared with 92% in larger lesions [17]. In lesions smaller than 1 cm, only marked FDG uptake will be of diagnostic relevance. In a recent study, *Nomori et al.* examined 136 nodules smaller than 3 cm in diameter [18]. All of the 20 nodules smaller than 1 cm were negative on PET, eight of which were malignant. False negatives can also occur in tumors with a low metabolism, like carcinoid tumors and bronchioloalveolar cell carcinomas.

False-positive FDG uptake is seen in inflammatory conditions such as bacterial pneumonia; pyogenic abscesses; aspergillosis; and granulomatous diseases such as tuberculosis, sarcoidosis, histoplasmosis, Wegener's granulomatosis, and coal miner's lung. In these lesions the FDG uptake has been attributed to granulocyte and/or macrophage activity.

PET should be included as part of the work-up of an SPN if clinical decision-making will be changed by its findings [10]. In this respect, PET is not only useful in visualizing the SPN, but can also change patient management by detecting unsuspected nodal and metastatic disease. Because of its high negative predictive value, PET excludes malignancy correctly in the vast majority of cases. In these patients, thoracotomy can be avoided and follow-up with x-ray or CT scan at 3, 6, 12, and 24 months is advised [19].

Because of the specificity of 79%, the positive predictive value will be lower. In clinically suspicious cases, further investigations for detection of infection, Wegener's granulomatosis, or other granulomatous diseases are indicated. In cases of doubt, SPNs with high FDG uptake require resection.

LOCOREGIONAL STAGING: TUMOR AND LOCOREGIONAL LYMPH NODES

Staging directs the management of the case as well as the patient's prognosis. The most important decision is between those patients who are candidates for surgical resection and

those who are judged to be unresectable for cure but will benefit from chemotherapy, radiotherapy, or both.

T Factor

The extension of the primary tumor is usually assessed by thoracic CT, occasionally supplemented by magnetic resonance imaging (MRI), e.g., in situations where superior sulcus extension or relationship with the heart or large vessels is of importance [20]. Because of their anatomic detail, CT and MRI are excellent in evaluating the proximity of the tumor to local structures. PET offers little extra benefit in this respect because it has a limited ability for precise anatomic localization.

PET may be more beneficial in evaluating pleural effusions. Pleural involvement is relatively common in patients with lung cancer. Differentiation between benign and malignant effusion is important in determining the resectability and use of radiotherapy. Pleural thickening or nodularity on CT may be suggestive for metastatic pleural disease. CT is not conclusive of the benign or malignant nature of the pleural disease. Similarly, MRI imaging has failed to show high accuracy in differentiating benign from malignant pleural effusions. Thoracentesis may not prove malignancy in 30%-40% of patients with truly malignant pleural effusion [21]. In one study, 35 patients with lung cancer and abnormal pleural findings on CT underwent PET [22]. Sensitivity, specificity, and accuracy of FDG-PET were 89%, 94%, and 91%, respectively. In another study, the sensitivity, specificity, and accuracy were 95%, 67%, and 92%, respectively [23]. The high negative predictive value of PET in pleural effusions may be of help in reducing the number of repeat thoracenteses or thoracoscopic biopsies in patients with negative PET findings and benign effusion.

N Factor

In the absence of distant metastasis, locoregional lymph node spread will determine therapy and prognosis. For patients without positive lymph nodes or with only intrapulmonary or hilar nodes, direct resection remains standard therapy. In case of positive ipsilateral mediastinal lymph nodes (N2), platinum-based chemotherapy combined preoperatively with surgery or concurrent or sequential radical radiotherapy are legitimate choices [24, 25]. Patients with contralateral metastatic mediastinal lymph nodes (N3 disease) generally are rejected for surgery but will receive nonsurgical combined modality treatment.

For years, CT has been the standard noninvasive staging method for the mediastinum. Enlarged lymph nodes (i.e., more than 1 cm in the short axis or 1.5 cm in the long axis) were considered to be metastatic. Size is, however, a

relative criterion, since lymph nodes can be enlarged due to infectious or inflammatory causes, and small-sized nodes can contain metastatic deposits. Different studies on CT have shown a marked heterogeneity in the results. Prospective comprehensive data from the Radiological Diagnostic Oncology Group pointed at a sensitivity and specificity of thoracic CT of only 52% and 69%, respectively [26]. In the Leuven Lung Cancer Group (LLCG) experience, the historical results of CT were a sensitivity of 69% and a specificity of 71% [27]. Because of the moderate performance of CT, invasive staging by mediastinoscopy or, more recently, esophageal ultrasound proved pathological means of assessing locoregional lymph node spread.

A large number of prospective studies have compared the performance of CT and PET in mediastinal lymph node staging. In nearly all, PET proved to be more accurate than CT [28-38] (Table 1). The reading of PET is improved when correlation with the CT images is available, as specifically illustrated in some studies [37, 38]. This gain is reached because the precise anatomic details on CT are complementary to the metabolic information on PET. The superiority of PET over CT in mediastinal lymph node staging has been confirmed in different meta-analyses [14, 39-41].

Of major clinical importance is the good negative predictive value of PET in lymph node staging, so mediastinal PET-negative patients may be adequately staged without invasive procedures and can proceed directly to thoracotomy [37, 42] (Fig. 1). False-negative results can occur when the cancer involvement of the mediastinal nodes is low. In these cases, the lymph node burden of disease can be determined pathologically at thoracotomy. Some refer to this as minimal N2 disease, which has a reasonable prognosis after surgery [43]. However, the number of nodes, number of levels of lymph node stations, and status of the nodal capsule require careful evaluation by the pathologist.

FDG-PET findings should not lead to omission of mediastinoscopy in patients with large central tumors or important hilar adenopathy. Because of limitations in spatial resolution, it is often not possible to distinguish the primary tumor or the hilar nodes from adjacent mediastinal lymph nodes in these instances. This was illustrated in a recent survey of 400 patients, where it proved to be more likely to miss N2 disease in the subaortic and subcarinal nodes [29].

A cost-effectiveness analysis utilizing PET for all patients who had node-negative CT results demonstrated that the cost of PET was nearly compensated for by the more refined selection of patients for surgery [44].

The positive predictive value is reasonable, but false-positive results can be obtained in case of anthracosilicosis, infection, or granulomatous disorders. In these patients,

Table 1. Value of PET compared with CT in the detection of mediastinal lymph node metastases (N2-N3) in NSCLC (prospective comparative studies with at least 50 patients)

Study	n patients	Method of analysis*	Sensitivity (%)	Specificity (%)	Accuracy (%)	p value		
<i>Bury et al.</i> [28]	50	Independent	90	86	—	<0.05		
		CT	72	81	—			
<i>Cerfolio et al.</i> [29]	400	Complementary	N2	71	77	76	0.037	
			CT	43	75	68		
		N1	Complementary	67	78	78		NS
			CT	41	88	83		
<i>Fritscher-Ravens et al.</i> [30]	79	Independent	73	83	79	—		
		Complementary	81	94	88			
		CT	57	74	67			
<i>Kernstine et al.</i> [31]	64	Independent	70	86	84	<0.001		
		CT	65	79	76			
<i>Reed et al.</i> [32]	303	Complementary	61	84	—	—		
		CT	37	91	—			
<i>Saunders et al.</i> [33]	84	Independent	71	97	92	—		
		CT	20	90	77			
<i>Valk et al.</i> [34]	76	Complementary	83	94	91	<0.01		
		CT	63	73	70			
<i>Vansteenkiste et al.</i> [35]	68	Complementary	93	95	94	0.0004		
		CT	75	63	68			
<i>Vansteenkiste et al.</i> [36]	56	Complementary	89	82	86	0.04		
		CT	86	43	64			
<i>Vansteenkiste et al.</i> [37]	50	Independent	67	97	88	0.004		
		Complementary	93	97	96			
		CT	67	59	64			
<i>Weng et al.</i> [38]	50	Independent	73	94	87	0.03		
		Complementary	82	96	91			
		CT	73	77	76			

NS = not significant
p value is significance of the difference in accuracy between CT and PET, usually examined with a McNemar test.
*method of analysis: independent = interpretation of PET without CT; complementary = interpretation with aid of CT.

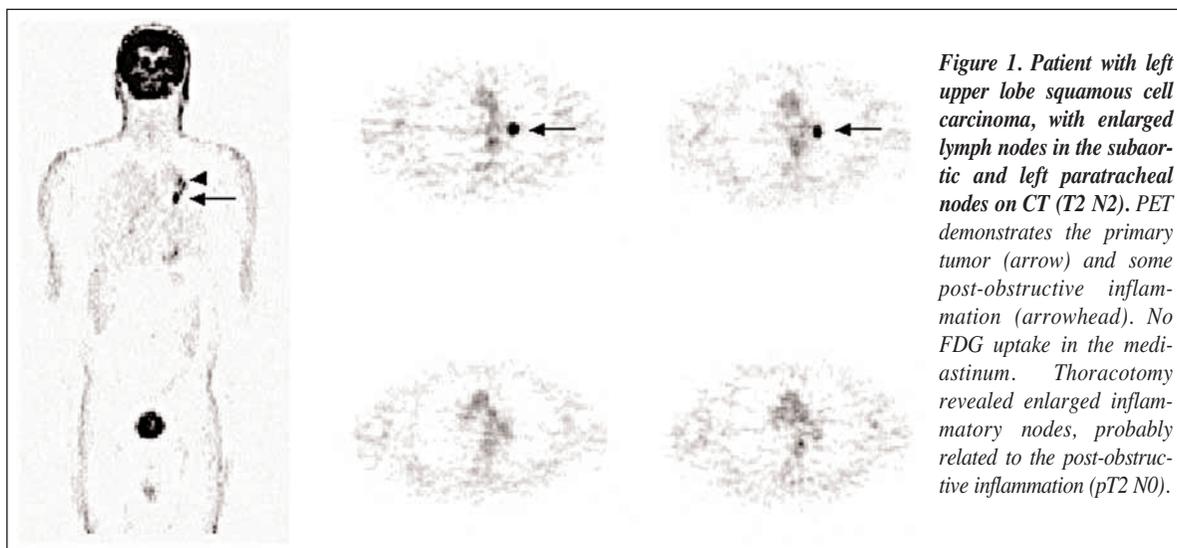


Figure 1. Patient with left upper lobe squamous cell carcinoma, with enlarged lymph nodes in the subaortic and left paratracheal nodes on CT (T2 N2). PET demonstrates the primary tumor (arrow) and some post-obstructive inflammation (arrowhead). No FDG uptake in the mediastinum. Thoracotomy revealed enlarged inflammatory nodes, probably related to the post-obstructive inflammation (pT2 N0).

confirmation of N2 or N3 disease by mediastinoscopy is mandatory to ensure that no patient with resectable N0 or N1 disease is denied the chance of curative surgery.

A recent review of the evidence on mediastinal staging compared CT, PET, and endoscopic esophageal ultrasound (EUS) [41]. For CT, a sensitivity of 57% and a specificity of 82% were reported. For PET, this was 84% and 89%, while for EUS, a sensitivity of 78% and a specificity of 71% were mentioned. Accordingly, PET was superior, not only to CT but also to EUS. One recent series made the comparison between CT, PET, and EUS with fine-needle aspiration (FNA) [30]. PET and EUS each had similar sensitivities, but EUS with FNA had a superior specificity (100% versus 72% for PET, $p = 0.004$). This superior specificity of EUS with FNA allowed many patients to be classified as inoperable N3 disease without the need for invasive staging.

Extrathoracic Staging

The observation of metastases in patients with non-small cell lung cancer (NSCLC) has major implications on management and prognosis. Forty percent of patients with NSCLC have distant metastases at presentation, most commonly in the adrenal glands, bones, liver, or brain [45]. After radical treatment for seemingly localized disease, 20% of these patients develop an early distant relapse, probably due to systemic micrometastases that were present at the time of initial staging [46].

There are far fewer studies on the staging of distant organ sites than there are on locoregional lymph node staging. Organ-specific studies on the evaluation of distant metastases with PET often included only a small number of patients. In the evaluation of metastases by site, however, PET was almost uniformly superior to conventional imaging techniques. PET data, in comparison with conventional imaging, on the most frequent metastatic sites in NSCLC will be discussed briefly

In nearly 10% of the patients with NSCLC, enlarged adrenal glands are visualized on CT at initial presentation. Approximately two-thirds of these adrenal masses are benign or asymptomatic [47, 48]. Therefore, the presence of an isolated adrenal mass in a patient with otherwise operable NSCLC should not preclude radical treatment without pathologic proof of metastatic disease. PET can be a useful adjunct in this setting. The high sensitivity (100%) [49] and specificity (80%-100%) [49, 50] lead to a reduction of the number of unnecessary adrenal biopsies, which are not without risk and not always diagnostic. However, careful interpretation of PET is required for small lesions (less than 1 cm), since the experience with these is limited. False-positive findings on PET have also been reported. For this reason, pathologic proof is warranted in case a decision is to be

made on (curative) treatment intent based on an isolated adrenal gland finding.

At present, bone involvement is usually assessed by 99m Technetium methylene diphosphate (99m Tc MDP) bone scintigraphy, which has a good sensitivity (90%) but a low specificity ($\pm 60\%$), due to false-positive findings explained by the nonselective uptake of the radionuclide tracer in any area of increased bone turnover (i.e., degenerative or post-traumatic changes, inflammatory processes, etc.) [51]. Consequently, additional imaging by bone x-rays, bone CT, or MRI is often required. PET is reported to have a similar sensitivity ($\geq 90\%$), but a higher specificity ($\geq 98\%$) and accuracy ($\geq 96\%$), and is therefore considered superior to bone scintigraphy in the detection of bone involvement [50, 51]. Whether PET should replace bone scan in the detection of bone involvement remains unclear, as there are a few inconveniences of PET that need to be taken into account. Whereas bone scintigraphy images the entire skeleton, a standard PET images from the head to just below the pelvis, and thus could miss metastases in the lower extremities. A whole-body PET is possible, however, time consuming. On the other hand, false-negative findings have been reported in case of osteoblastic lesions, mainly in studies on breast cancer [52].

The standard method for the detection of liver metastases is ultrasound (US) or CT. There are no specific series on the use of PET in patients with liver metastases from NSCLC. Some general series on staging NSCLC suggest a superiority of PET by being more accurate than CT [34, 50]. Other series on different types of tumors have reported a nonsignificant difference in sensitivity, specificity, and accuracy, i.e., 93% versus 97%, 75% versus 88%, 85% versus 92%, respectively, for CT and PET in the detection of liver involvement [53, 54]. Thus, US and/or CT remain the standard imaging techniques for the liver. Additional diagnostic information is provided by PET combined with CT, namely in the differentiation of hepatic lesions that are indeterminate on conventional imaging [53].

FDG-PET is not suited for the detection of brain metastases. The sensitivity is low (60%) due to the high glucose uptake of normal surrounding brain tissue. CT and/or MRI remain the method of choice to stage the brain.

To date, in most of the series, PET is used as a complementary tool to conventional imaging. PET offers an additional value in the detection of distant metastases in potentially operable NSCLC by two means. First, there is the detection of unexpected metastatic spread. After a negative conventional staging, unknown metastases were found on PET in 5%-29% of the patients [33, 34, 50, 55-60] (Table 2). The incidence of occult metastatic lesions increases with increasing pre-PET stage from 8% in stage I, to 18% in stage II, to 24% in stage III [57]. In some series, the detection rate

Table 2. Value of PET in the detection of unexpected distant metastases

Study	n of patients	Detection of extra lesions (%)
<i>Bury et al.</i> [55]	109	6
<i>Lewis et al.</i> [56]	34	29
<i>MacManus et al.</i> [57]	167	19
<i>Marom et al.</i> [50]	100	9
<i>Pieterman et al.</i> [58]	102	11
<i>Saunders et al.</i> [33]	97	17
<i>Stroobants et al.</i> [59]	144	5
<i>Valk et al.</i> [34]	99	11
<i>Weder et al.</i> [60]	100	15

of occult metastases might be overestimated depending on the definition of conventional staging (consisting of CT of the chest and upper abdomen alone, or also with systematic brain CT and/or bone scintigraphy) as well as on the definition of unexpected lesions (taking into account a negative conventional staging or a combination of negative and equivocal readings at conventional imaging) [59]. If PET detects a single metastatic lesion in a potentially curable case, confirmation by additional imaging studies or pathological proof is prudent, given the possibility of false-positive results on PET. Second, PET is able to determine the nature of equivocal lesions on conventional imaging, present in 7%-19% of the patients [34, 50, 55, 59]. Exclusion of malignancy by PET requires caution in case of a small lesion (<1 cm).

Despite the overall better sensitivity, specificity, and accuracy of PET in detection of metastatic spread, to date PET is not yet ready to replace conventional staging procedures because most of the studies were performed in an additional setting. Furthermore, the number of organ-specific studies is small and the experience with small lesions is too limited.

Impact on Staging and Management

PET is an attractive staging tool because of its ability to define the primary tumor as well as local and distant metastases in a single noninvasive examination, and because of its overall greater accuracy than conventional imaging procedures, hence, the potential impact of PET on stage designation and therapeutic management. The use of PET imaging for clinical staging resulted in a different stage from the one determined by conventional methods in 27%-62% of the patients with NSCLC [33, 55, 56, 58, 61-63] (Table 3). Upstaging was more frequent than downstaging and is related mainly to the detection of unexpected distant lesions by PET. Across series, a change in patient management was reported in 25%-52%

of patients [33, 55, 56, 61-63] (Table 3). Mainly, treatment intent (curative versus palliative) was altered. In one study, an intramodality change was reported in 26% of patients [61]; in a survey by means of questionnaires sent to referring physicians, this was 39% [64]. Alteration of modality (chemo versus radiotherapy, radical radiotherapy versus surgery) was present in these series in 9% and 15% of the cases, respectively [61, 64].

FDG-PET can also influence the target volume for radiation therapy [63, 65]. Metabolic radiation treatment planning by PET led to smaller planning target volumes (between 3%-21% in 25 of 27 patients), resulting in a reduction of dose exposure to healthy tissue. Two other patients needed a larger target volume due to positive lymph nodes on PET [63].

Whether the use of PET improves the management of NSCLC remains unsettled. There is evidence that PET reduces the need for invasive procedures by more accurate staging. Whether it seemingly improves survival due to stage migration, or whether it truly may improve survival because of better therapeutic strategies, remains to be determined.

A PRELIMINARY VIEW ON NEWER APPLICATIONS AND FUTURE DEVELOPMENTS

Response assessment on conventional imaging is mainly based on changes in tumor volume. Changes in tumor size, however, do not necessarily correlate with changes in tumor viability and outcome. Therefore, it might be more appropriate to assess tumor response by tumor activity, which can be measured by FDG uptake on PET. The experience with PET in this setting is still limited.

A few series assessed the role of PET in response evaluation after radiotherapy [66-68]. There was a tendency of more prominent decrease in FDG uptake in responding patients than in nonresponders, suggesting a relation between tumor size after radiation and metabolic activity [66]. In a study of 73 patients undergoing both CT and

Table 3. Impact of PET on patient management in NSCLC

Study	n of patients	Change of stage (%)	Impact on management (%)
<i>Bury et al.</i> [55]	109	34	25
<i>Hicks et al.</i> [61]	153	43	35
<i>Hoekstra et al.</i> [62]	57	30	19
<i>Lewis et al.</i> [56]	34	—	41
<i>Pieterman et al.</i> [58]	102	62	—
<i>Saunders et al.</i> [33]	97	27	37
<i>Schmucking et al.</i> [63]	63	—	52

FDG-PET before and after radical radiotherapy or chemoradiotherapy, there was poor agreement between CT and PET responses [68]. Significantly more patients were judged as complete responders by PET ($n = 34$) than by CT ($n = 10$). Both CT and PET responses were significantly associated with survival, but PET was a much better predictor of survival in multivariate survival analysis ($p < 0.0001$).

Also interesting is the recent prospective study in which metabolic response was measured after one cycle of platinum-based chemotherapy in 57 patients [69]. A metabolic response was defined as a decrease of FDG uptake that is larger than two times the standard deviation of spontaneous changes of tumor glucose use as measured by FDG-PET. The metabolic response correlated well with subsequent decrease of tumor size as assessed by standard response criteria. For patients with metabolic response, the 1-year survival was also significantly better than those patients without metabolic response after one cycle of chemotherapy, so FDG-PET could lead to more efficient use of chemotherapy in patients with advanced NSCLC. In patients without a metabolic response, the drug regimen may be changed to second-line therapy after the first therapy cycle, thereby significantly reducing the morbidity and costs resulting from ineffective therapy.

Some series focused on restaging after induction chemotherapy for locally advanced NSCLC. In a small prospective pilot study at the LLCG, PET was performed pre- and post-induction chemotherapy. Response on PET was defined as a more than 50% decrease of the SUV of the primary tumor and the absence of increased FDG uptake in the mediastinal nodes. The accuracy of PET in restaging the mediastinal nodes was 100% (compared with 67% for CT) [70]. Two other studies, however, reported more moderate results when using PET to assess mediastinal downstaging: a sensitivity of 67% in one series [71] and 58% in the other [72] was noted. The interim results of our experience in a multicenter prospective experience confirmed these latter findings (sensitivity for PET of 71%, specificity of 88%) [73]. Perhaps more important, both the primary tumor response and mediastinal downstaging on post-induction PET were of high prognostic significance ($p = 0.008$), whereas CT only had limited value in predicting outcome ($p = 0.10$) [73]. Further prospective study of FDG-PET is warranted.

In the follow-up of patients after initial treatment and the detection of relapse, it can be difficult to differentiate therapy-induced fibrosis from tumor on conventional imaging. Nevertheless, early detection of a relapse has become important in the light of new salvage therapies that are available. Some studies have focused on the use of PET in this situation. PET was able to correctly confirm or exclude

disease relapse in an indeterminate lesion on CT scan with a sensitivity of 97%-100%, a specificity of 62%-100%, and an accuracy of 78%-98% [74, 75]. False-positive studies may occur if PET is performed shortly after radiotherapy or surgery. To reduce the post-radiotherapy changes interfering with correct staging to a minimum, an interval of 3-6 months is recommended between initial treatment and restaging by PET.

The best tool for prognosis and prediction of survival of newly diagnosed patients with NSCLC is tumor-node-metastasis staging. However, it does not always give a satisfactory explanation for the differences in survival. Molecular biological factors of the tumor may account for this. Metabolic changes, such as derangements in the glucose metabolism of NSCLC tumors as measured by PET, may be one of these factors. FDG uptake, a measurement of the glucose metabolism, has been correlated with growth rate and proliferation capacity [76]. Consequently, the SUV, a semiquantitative measurement of FDG uptake on PET, was found to have a prognostic value in different series [77-81]. In multivariate analysis, the SUV was independently predictive of disease-free and overall survival [77, 78, 80, 81].

Based on the more accurate staging by additional PET in comparison with conventional imaging techniques, in several series the prognostic value of PET after treatment was examined as well [33, 61, 68, 82]. PET stage was highly predictive of survival, even after adjustment for the therapy given, whereas conventional staging offered only modest prognostic stratification.

The potential of FDG-PET is also explored in the field of lung cancer screening. Nonrandomized screening studies have demonstrated that low-dose spiral CT of the chest effectively detects early-stage lung cancer in high-risk individuals [83]. One of the problems associated with screening is the potential need for invasive procedures in patients with benign nodules. Indeed, the differential diagnosis of nodules (benignant versus malignant) is not always possible based on radiological signs or short-term follow-up. A recent study of *Pastorino et al.* examined the selective use of FDG-PET in a screening trial with low-dose spiral CT once a year for 5 years in heavy smokers [84]. In the protocol, a biopsy was mandated for each noncalcified nodule ≥ 2 cm, while the additional value of FDG-PET was sought for in nodules ≥ 7 mm. FDG-PET, available in nine prevalence cancers, was correct positive in eight of nine (one 8-mm adenocarcinoma was missed). It was also correct positive in 10 of the 11 incidence cancers (with one 11-mm predominantly bronchioloalveolar tumor missed). This stands for a sensitivity of FDG-PET of 90% in this screening cohort, a more than promising finding.

New tracers other than FDG hold promise for the future, but the current clinical experience is still limited. ^{11}C -thymidine was the first radiotracer for noninvasive imaging of tumor proliferation. The short half-life of ^{11}C and the rapid metabolism of ^{11}C -thymidine in vivo made the radiotracer less suitable for routine use. The thymidine analogue 3'-deoxy-3'- ^{18}F fluorothymidine (FLT) is a more stable proliferation marker. FLT is phosphorylated by thymidine kinase 1, which is present in large quantity in proliferating lung cancer cells. The resulting FLT uptake in cancer cells is therefore correlated with DNA synthesis and tumor growth. A prospective study by *Buck et al.* demonstrated that FLT uptake correlates better with proliferation of lung tumors than does uptake of FDG and might be more useful as a selective biomarker for tumor proliferation [85]. No FLT uptake was visible in nonproliferating tumors. Therefore, FLT may be used to improve the specificity of PET in the differentiation of benign from malignant lung lesions.

PET/CT fusion machines are another area of development. The anatomical detail on CT and the functional imaging with PET give a different type of information on the tumor status. As CT images are available in every patient with treatable lung cancer, correlative reading of PET and CT images is always indicated.

More recently, studies have evaluated if digital fusion of the images (either by software or by hardware in an integrated PET-CT scanner) is superior to simple correlative reading [36, 86-88]. With regard to staging of the primary tumor, the spatial resolution of CT (1 mm for modern scanners) is far superior to that of current PET cameras (6-8 mm), so that the extra gain with fusion is not expected to be large. Recent reports pointed at the potential benefit of fusion images in the setting of radiotherapy planning, e.g., in patients with a centrally located tumor complicated with atelectasis [89-91]. Regarding lymph node staging, the question whether digital fusion is superior to simple correlative reading needs further study because the available data are conflicting [36, 86-88]. *Vansteenkiste et al.* [36]

and *Magnani et al.* [86] reported no significant difference in accuracy with digital software fusion PET-CT, in an analysis either by N stage or by individual lymph node stations. In contrast, *Aquino et al.* retrospectively found an equal sensitivity but a statistically improved specificity and accuracy for digital software fusion in identifying the absence of disease per lymph node station [87]. *Lardinois et al.* reported that nodal staging was significantly more accurate with digital hardware fusion PET-CT than with visual correlation ($p = 0.021$) [88]. The latter study has been criticized because the accuracy of PET in lymph node staging was only 49%, far below what has been consistently reported in the literature [14, 35, 39-41]. The PET-CT question is one of "panacea, redundancy, or something in between" [92]. Future prospective studies should further evaluate the role of digital fusion in lung cancer imaging.

CONCLUSION: RECOMMENDATIONS FOR PET IN THE STAGING OF NSCLC

PET is useful in the assessment of SPNs and in the staging of NSCLC patients who are considered to be candidates for radical treatment. As a complimentary tool to CT, PET has become more widespread and reimbursed in many countries. The technique should not be used in patients with, for example, metastatic lymph nodes at clinical examination or when a simple US study already points at diffuse hepatic metastases.

The main additional interest of PET is its ability to assess locoregional lymph node spread more precisely than CT, to detect metastatic lesions that would have been missed on conventional imaging or are located in clinically hidden or difficult areas, and to help in the differentiation of lesions that are equivocal after conventional imaging.

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