The role of positron emission tomography for evaluation of lung nodules and staging lung cancer

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Abstract Positron emission tomography with computed tomography (PET/CT) and the clinical use of this imaging technology has developed rapidly during the last decade, especially in the field of lung cancer. This review includes a brief introduction to the technology; including limitations and pitfalls as well as practical considerations with regard to patient preparation and scan acquisition. Through a presentation of recent meta-analyses as well as clinical studies, the role of PET/CT in diagnosing and staging patients with non-small cell lung cancer will be described and discussed.

Keywords Non-small cell lung cancer · PET/CT · Positron emission tomography · Solitary pulmonary nodule · Diagnosis · Staging · Diagnostic accuracy · Cost-effectiveness

Introduction

In order to improve survival of patients with lung cancer, focus has been on early diagnosis and accurate staging, as the cornerstone for a growing number of therapy options [1]. Treatment options for lung cancer patients are highly

dependent on the stage of the disease, making accurate and fast staging pivotal.

The process of diagnosing lung nodules and staging lung cancer has become increasingly complex, and is best done in multidisciplinary teams including pulmonologist, thoracic surgeons, pathologist, radiologists, and as the use of PET has become more widespread also a nuclear medicine physician. Imaging plays an increasingly important role in the management of cancer patients. Even though imaging technologies only account for a minor fraction of total cancer costs, they have been found to be increasing with at least double the rate of overall costs [2•]. Lung cancer is an illustrative example of this trend: From 1999 to 2006 the total Medicare costs per patient with lung cancer annually increased by 2.6%; in the same period imaging costs more than doubled, with an annual increase by 9.5%. This increase is mainly due to an increase in the use of positron emission tomography (PET); ie, the use of PET had an annual increase by 36%.

The purpose of this review is to describe and discuss the role of PET, more specifically PET/CT, in the discipline of lung cancer diagnosis and staging. The focus of this review will be non-small cell lung cancer (NSCLC). For a recent review on small cell lung cancer please refer to the work of Thomson et al. [3•].

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Positron emission tomography

Positron emission tomography with computed tomography (PET/CT) and the clinical use of this imaging technology has developed rapidly during the last decade. The increase in computer power and not least the development of a hybrid PET/CT scanner has changed the role of PET from a specialized research tool to a widely available clinical

workhorse. The first PET/CT scanner was introduced in 2000 in the United States, combining the functional information from the PET scanner with anatomical structures obtained by CT [4]. During the last decade approximately 2,000 PET/CT scanners have been installed in the United States (6.5 scanner per million people), 70 in Germany (1.2 scanner per million people), and 350 PET/CT scanners in Europe as a whole (0.4 scanner per million people) [5•].

[^{18}F]-Fluorodeoxyglucose (FDG) is by far the most commonly used PET tracer, exploiting the increased glucose uptake and metabolism in malignant cells [6]. The basis for the usability of FDG over a broad spectrum of different kinds of cancer is the increased expression and activity of glucose transporters as well as an overproduction of glycolytic enzymes in malignant cells [6]. The biodistribution of FDG allows sensitive detection in most organs, except brain and bladder. Isotopes for use in the PET technique decay by positron emission followed by annihilation under emission of two 511-KeV photons (Fig. 1). The PET technology is inherently extremely sensitive; in an experimental set-up we found the detection limit of PET to be in the magnitude of 10^5 to 10^6 malignant cells, less than or equal to a volume of 1 mm^3 [7]. However, movement of the positron before annihilation and slight variations in the angle between the two photons limit the spatial resolution of current clinical systems to 4–5 mm and in general the PET technique has been considered to be less accurate with regard to tumors smaller than 10 mm [8].

Pitfalls and limitations

When using PET in the diagnosis of lung cancer a false-positive rate as high as 20–25% [9] is reported. This is mainly due to increased uptake of FDG in inflammatory

Fig. 1 Positron emission and detection. An isotope (eg, ^{18}F) decays under emission of a positron from the nucleus. In the tissue this positron will meet and annihilate with an electron under emission of two back-to-back photons each of 511 KeV. These photons will subsequently be detected by scintillator crystals in the detector ring of the PET scanner. If two photons are detected within a narrow time span (nanoseconds, the so-called coincidence window) they are assumed to be a result of the same annihilation and an event is recorded

cells. Major causes of false-positive results in the chest are granulomas, histoplasmosis, tuberculosis, chronic inflammation, sarcoidosis, and *Aspergillus* infection [10, 11]. Also pulmonary embolism or iatrogenic microembolism can cause FDG-uptake mimicking malignancy (but without correlate on CT, Fig. 2) [12]. Iatrogenic procedures might also induce false-positive results: of relevance in lung cancer is placement of chest tubes, percutaneous needle biopsy, mediastinoscopy, radiation pneumonitis, and esophagitis [13]. Finally, focal physiological FDG-uptake, especially in the gastrointestinal tract, can mimic malignancy; likewise can unilateral uptake in striated muscle, brown fat, and atherosclerotic plaques (Fig. 3). Detailed knowledge of patient history and the use of integrated PET/CT (with side-by-side reading by nuclear medicine physician and radiologist) can help to distinguish malignant FDG-uptake from uptake due to benign causes and improve specificity. False-negative results are less common and mainly due to small size or well-differentiated malignancies, such as bronchioloalveolar carcinomas and carcinoids [14–16]. Lesions smaller than 5 mm may be false negative due to the limited spatial resolution and partial volume effects; however, taking respiratory motion into consideration in practice the resolution is approximately 1 cm [17].

Achieving a high-quality PET/CT examination

In order to ensure a high diagnostic yield from the PET/CT scan, a number of factors need attention, also from the referring clinician. Most important are blood glucose level which, whenever possible, should be kept under 150 mg/dL, in order to minimize the effects of physiologic activity. Thus, patients should be fasting for at least 4 h, preferably 6 h. As noted above, detailed information on patient history improves the quality of the PET/CT report; especially knowledge about recent biopsy or surgery, chemotherapy, and/or radiotherapy is of importance. If possible a PET/CT scan should be scheduled 1–2 weeks after a biopsy and 2–6 weeks after surgery depending on the invasiveness and localization of the procedure as well as the clinical indication for performing the PET/CT scan. If the patient has received chemotherapy an interval between the last treatment and the PET/CT scan of approximately 2 weeks will be appropriate in most cases [18].

In the literature, the CT part of the PET/CT scan is often done as a whole-body low-dose scan without intravenous contrast (Table 1) [19]. By doing this it is possible to keep radiation dose from the CT scan at a minimum and avoid the use of IV contrast, which adds the risk of possible allergic reactions and nephrotoxicity. However, it is our experience and has also been demonstrated by recent studies, that the diagnostic accuracy and clinical value of the PET/CT is

Fig. 2 A 72-year-old woman with known endometrial cancer and two lung metastases, referred for PET/CT in order to exclude further lung metastases prior to stereotactic radiotherapy. **a**, FDG-PET reveals focal retention lateral in the right lung. **b** and **c**, There was no correlate on CT and the finding was characterized as a FDG embolus. (Courtesy of Dr. Johan Löfgren)

markedly improved by applying a standard dose contrast-enhanced CT, especially with regard to gastrointestinal cancer but also in the staging of lung cancer patients, especially

Fig. 3 A 79-year-old man with known asbestosis, but no known malignant diagnosis, referred for PET/CT in order to exclude malignant pleural mesothelioma. **a**, FDG-PET reveals increased uptake in the thoracic cage and between the spine and liver hilus. **b** and **c**, On the fused images the increased FDG uptake was found to be localized in the striated muscles between the ribs and in the diaphragmatic muscle (auxiliary respiratory muscles) and not in the pleura

with regard to assessment of lymph nodes and precise description of tumor extent [19, 20, 21•].

Table 1 Papers comparing the diagnostic accuracy of PET/CT and CT with regard to solitary pulmonary nodules, published within the last 5 years

	<i>N</i>	PET/CT		CT		Note
		Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)	
Kagna et al. [26], 2009	93	0.94 (0.81–0.98)	0.71 (0.58–0.80)	0.97 (0.85–0.99)	0.48 (0.36–0.61)	Retrospective, LD-CT no contrast
Jeong et al. [27], 2008	100	0.88 (0.74–0.95)	0.77 (0.65–0.86)	0.80 (0.65–0.90)	0.67 (0.54–0.77)	Retrospective, LD-CT no contrast
Kim et al. [28], 2007	42	0.97 (0.83–0.99)	0.85 (0.58–0.96)	0.93 (0.78–0.98)	0.31 (0.13–0.58)	Retrospective, LD-CT no contrast
Yi et al. [25], 2006	119	0.96 (0.89–0.99)	0.88 (0.74–0.95)	0.81 (0.71–0.88)	0.93 (0.80–0.97)	Prospective, HD- CT with contrast

HD-CT high-dose CT; *LD-CT* low-dose CT

Diagnosing lung cancer: the solitary pulmonary nodule

A solitary pulmonary nodule (SPN) is defined as a lesion smaller than 3 cm in diameter completely surrounded by lung tissue [22]. In early systematic reviews comparing the diagnostic value of PET to CT in discriminating malignant from benign pulmonary nodules, PET was found to be highly sensitive (approximately 95%) but less specific (75–80%) [23]. A comprehensive meta-analysis has compared the diagnostic accuracy of CT, MRI, FDG-PET, and ^{99m}Tc-depreotide single photon emission computed tomography (SPECT) for evaluation of solitary pulmonary nodules [24]. Surprisingly, they did not find any significant difference with regard to sensitivity, specificity, and predictive values between any of the four modalities. However, only the meta-analysis on FDG-PET and CT included more than 1000 patients, all CT studies were with dynamic and contrast-enhanced CT acquisition, and the majority of the PET studies were performed on a single modality PET scanner—not PET/CT. This meta-analysis suggests that the diagnosis of SPN should, to some extent, be guided by local practice and experience.

More recent studies comparing CT and PET/CT (Table 1) have, however, found a significant difference between CT and PET/CT, in favor of the latter. This difference is seen both with regard to sensitivity and specificity, but especially the difference in specificity decreases when comparing the PET/CT with a high-dose CT with contrast enhancement [25].

The rational choice of diagnostic tests and the consequence of a positive respectively negative outcome depend on the probability of malignancy. In short, patients with a SPN later diagnosed with lung cancer originate from three groups, each representing different pre-test probabilities for cancer: a) patients referred for further examination after presenting with symptoms suspicious for lung cancer (eg, cough, dyspnea, pain, or hemoptysis, or in patients known with another malignancy); b) patients with an incidental finding of a solitary pulmonary nodule (eg, after performing a cardiac CT due to angina or chest X-ray during a health

examination); and c) participants in a lung cancer screening trial.

The probability of malignancy in a SPN in each group will also vary significantly dependent on, eg, smoking history, age, and radiological characteristics [29]. The prevalence of malignancy in group a) will typically be 30–70%. In group b) and c) the incidence of SPN will vary dependent on the quality of the CT, field of view, and screening population, but has been reported at approximately 20–30%, whereas the prevalence of malignancy in these groups will be less than 3% [30, 31]. The prevalence or pretest probability of malignancy will significantly influence the predictive value of any diagnostic test. Thus, assessing the pre-test probability of malignancy in a given SPN facilitates interpreting the results of diagnostic imaging (eg, PET) [32] and clinical decision-making.

As prevalence falls, positive predictive value falls with it, whereas negative predictive value rises. In most studies PET/CT has a higher negative predictive value compared to CT. The ability of PET to rule out a malignant diagnosis can potentially reduce the number of invasive procedures resulting from, eg, screening trials and auxiliary findings on cardiac CT [33, 34]. However, in a screening population an increased frequency of small and relatively low-metabolic tumors can be expected, hampering the diagnostic accuracy of the PET technique [35]. This problem can be minimized by combining the information of tumor growth rate (eg, after 3 months) with FDG uptake [31, 36], making PET/CT a valuable second step test in the diagnosis and follow-up of indeterminate pulmonary nodules, and also in screening studies (Table 2).

Prognosis and the use of standardized uptake values

PET can be evaluated visually and/or semiquantitatively by means of the Standardized Uptake Value (SUV). SUV is the activity concentration in the lesion normalized for the

Table 2 Positive and negative predictive value (PPV and NPV) of PET/CT and CT with regard to solitary pulmonary nodules

	Prevalence of lung cancer	PET/CT		CT	
		PPV (95% CI)	NPV (95% CI)	PPV (95% CI)	NPV (95% CI)
Kagna et al. [26], 2009	0.38	0.66 (0.52–0.78)	0.95 (0.85–0.99)	0.53 (0.41–0.65)	0.97 (0.83–0.99)
Jeong et al. [27], 2008	0.40	0.71 (0.79–0.96)	0.90 (0.70–0.91)	0.62 (0.48–0.74)	0.83 (0.58–0.82)
Kim et al. [28], 2007	0.69	0.93 (0.79–0.98)	0.92 (0.65–0.99)	0.75 (0.59–0.86)	0.67 (0.30–0.90)
Yi et al. [25], 2006	0.66	0.94 (0.86–0.97)	0.92 (0.79–0.97)	0.96 (0.88–0.98)	0.71 (0.58–0.82)

injected dose and the weight or body surface area of the patient [37]. Due to high reproducibility of SUV and possible correlation with prognosis [38–40], SUV is often reported in clinical studies and is considered mandatory when using PET for therapy evaluation [41]. A recent retrospective study on 363 patients in stage I–II, performing preoperative FDG-PET/CT, found that SUV was a predictor of overall survival, but that this correlation was not independent of stage [42]. SUV has also been suggested as a useful tool for separating malignant and benign SPN [43, 44]. The use of SUV is intriguing—captivating the nature of the tumor (malignant or benign) as well as the prognosis of the patient in a single number. However, SUV is highly dependent on a number of factors related to the patient (eg, length of fast, period between injection of FDG and scan time), the type of scanner, and reconstruction algorithm, making it unsuitable for uncritical comparison between different scanners, centers, and time periods. Further, most studies exploring the prognostic value of SUV try to establish an optimal SUV cutoff, based on ROC analysis of own data without performing a validation study in another dataset. This has made comparison between studies difficult and numerous different cutoff values have been suggested [42]. Thus outside clinical trials, SUV should be used with caution, if at all [45].

Staging non-small cell lung cancer

Non-small cell lung cancer is staged according to the TNM system as initially suggested by Mountain [46], and recently revised by the International Association of Lung Cancer [47, 48]. Only patients with localized disease (TNM stage I–IIB, possibly IIIA) will be candidates for primary curative surgery [49]. For most patients with advanced disease (stage IV) palliative treatment with chemotherapy will be the only option. Thus, in order to allocate the patient to the correct treatment, accurate description of possible 1) distant metastases and 2) mediastinal spread (N) is mandatory, whereas

the T stage at this point will substantially influence the treatment choice only in the case of tumor invasion making resection impossible (Fig. 4).

Primary tumor (T stage)

Single-modality PET is insufficient for an accurate description of T stage, whereas combined PET/CT is significantly more accurate than both PET [50–52] and standard CT (diagnostic quality with intravenous contrast) [53, 54]. A recent study compared the measurement of primary T1 and T2 NSCLC at PET/CT to determine the correlation with histological findings: A high concordance was found between both PET and CT measurements and histological measurements, but PET was better for delineating the tumor in the presence of surrounding atelectasis or consolidation [55].

Mediastinal lymph nodes (N stage)

Mediastinal staging is, in patients without distant metastases, the most significant factor for treatment planning as mediastinal spread (N2–N3 disease) excludes the patient from primary surgery. Initial studies on PET reported very high accuracy with regard to N-staging, significantly higher than the accuracy of CT [56]. In more recent studies this difference seems to narrow down, probably due to the improved quality of CT, but still a staging strategy including PET/CT appears more sensitive with regard to mediastinal disease [54, 57]. The European Society of Thoracic Surgery (ESTS) as well as the American College of Chest Physicians (ACCP) has published guidelines for proper preoperative mediastinal staging [58, 59], both including a PET/CT examination. However, it remains more uncertain what consequences should be drawn from the PET/CT result. For example, it has been suggested that mediastinoscopy or other invasive staging can be omitted in cases where the mediastinum is PET-negative [58, 59]. But by doing this, 16% of the patients will have occult N2 disease [57, 60]. In

Fig. 4 A 69-year-old man with a tumor (NSCLC) in the right lung, hilar region, referred for staging by PET/CT. **a** and **b**, FDG-PET shows increased uptake in the primary tumor in the right lung. **c**, On CT there is an enlarged lymph node anterior to the left main bronchus, but without increased FDG uptake. PET/CT suggested stage T2aN0M0, which was confirmed by EBUS. (Courtesy of Dr. Charlotte B. Christensen)

order to avoid under-staging the mediastinum, it is thus recommended that in patients with central tumors, enlarged lymph nodes on CT, and/or N1 disease on PET/CT a confirmatory invasive examination should be performed (Fig. 4). Recent findings also emphasize the use of information provided by both PET and CT (eg, PET/CT cannot exclude nodal disease where nodes are enlarged on CT [> 10 mm]), whereas in nodes not significantly enlarged on CT, the false-negative rate of PET/CT is below 5% [57, 61].

Distant metastases

NSCLC most frequently metastasizes to bones, brain, adrenals, and liver and M1 disease is reported in 5–15% of otherwise operable patients performing PET or PET/CT [52, 56], [62•].

With regard to the bones several studies indicate that PET is as sensitive and more specific than bone scan and CT for detection of bone metastases [63–66]. FDG-PET images tumor cells and not changes in the bone structure respectively metabolism, as is the case with CT and bone scan [67]. Thus PET often can diagnose bone metastasis before they become visible on CT or bone scan. A bone-seeking tracer for PET (^{18}F -fluoride, NaF) has become widely available as an alternative to the traditional bone scans. The experience in staging of lung cancer is scarce, but a recent study compared FDG-PET/CT with bone scan or ^{18}F -fluoride-PET, finding that FDG-PET/CT was superior to both [68]. Thus having performed a FDG-PET/CT for staging neither bone scan nor ^{18}F -fluoride PET will be indicated.

PET performs poorly in the detection of brain metastases, mainly due to the high background signal caused by physiologic cerebral FDG uptake. This was confirmed in a recent study comparing cerebral MRI and FDG-PET/CT for diagnosing brain metastasis at initial staging in 104 neurological asymptomatic patients: the sensitivity of PET/CT was 27% (95% CI, 13–48%), whereas due to the relatively

low prevalence in this study (20%) the negative predictive value reached an acceptable 83% (95% CI, 75–89%) [69]. Thus, in case of neurological symptoms a negative PET/CT scan does not exclude brain metastases.

Indeterminate adrenal masses on CT are seen in approximately 5–15% of patients with NSCLC; approximately 60% represent metastases [70, 71]. Several studies have shown that PET, and recently PET/CT, is effective in discriminating between malignant and benign adrenal masses [72–75]. PET-negative adrenal lesions will usually not be metastatic; however, isolated PET-positive lesions should be confirmed in order to avoid deeming a patient inoperable on a false-positive basis [76].

No studies specifically address the value of PET in diagnosing hepatic metastases, but successful detection has been reported [9, 14]; however, especially in smaller metastases the sensitivity is hampered by physiologic FDG uptake of the liver.

Pleural effusion and metastases are often found when staging patients with lung cancer. With the new TNM staging system malignant pleural effusion is classified as M1 disease (instead of T4), making correct assessment even more important. It is broadly accepted that PET is inferior to CT in detecting pleural effusion. Some studies have shown that PET might be useful in discriminating between malignant and benign pleural effusion diagnosed by CT [77], but this is still controversial and thoracentesis should be attempted.

Clinical impact of staging by PET/CT

The clinical impact of PET/CT can be assessed as the frequency of change in patient management due to information provided by PET/CT. Assigning the overall TNM stage (stage I–IV), PET/CT appears to be the most accurate imaging method and is superior to most invasive methods being a “whole-body” examination [53, 54]. Behind the chase for initial correct T, N, and M classification resides the wish to avoid futile surgery—ie, performing a thoracotomy in a patient who

eventually has an early local or distant relapse or in whom surgery results in incomplete resection or resection of a benign nodule [78, 79]. Two randomized studies have recently demonstrated that preoperative staging with PET/CT significantly reduces the frequency of futile thoracotomies without affecting overall survival [62•, 80•]. The improvement in preoperative staging is mainly due to increased sensitivity of the PET/CT strategy and applies to all patients independent of the initial stage at presentation. Specificity of PET/CT is hampered by false-positive findings and hence (solitary) positive foci on PET/CT with potential influence on the choice of treatment need confirmatory biopsy. Even so, the number of work-up procedures in a PET/CT strategy seems to be fewer than or equal to a strategy without PET/CT [80•, 81].

Considerations on health economy

The cost effectiveness of stand-alone PET as an adjunct to mediastinoscopy and CT has been examined in several studies during the past 15 years with general findings pointing in a positive direction [82–85]. Only one economic evaluation has been conducted alongside a randomized clinical trial: Verboom et al. [86] reported that the addition of PET to conventional staging was associated with a cost saving of €1,289 (1999 price level) due to the cost of the scan being more than outweighed by the more precise selection of candidates for thoracotomy. We performed a similar analysis alongside a randomized study on PET/CT [87], reporting an incremental cost of the PET/CT-based regimen at €3,927. As five PET/CT scans should be performed in order to avoid one futile thoracotomy, the resulting incremental cost effectiveness ratio (ICER) was €19,314 per avoided futile thoracotomy.

These two analyses differ in several ways. The Dutch study [86] adapts a restricted hospital perspective (ie, from the provider's perspective, including only costs associated with hospital days, thoracotomies, invasive and noninvasive diagnostic tests, and excluding costs associated with comorbidity, chemotherapy, and radiotherapy). In the Danish study [87], a full health care sector perspective was sought and costs were calculated from the payer's perspective using DRG (diagnosis-related group) tariffs. When costs of comorbidity-related hospital services were excluded from the Danish study, the PET/CT regimen appeared superior to the conventional staging regimen, saving €899 per patient.

An attempt to estimate the cost-utility (cost per quality-adjusted life-year, QALY) of staging with PET/CT has recently been performed by a German group [88]. A direct measurement of the quality of life was not attempted; instead a modeling approach was adapted, defining quality of life as 1 for patients alive, 0 in the case of death, and a loss in quality of life due to surgical morbidity of 0.15 QALYs. The group report an ICER pr. QALY of €59,272 for staging

by PET/CT versus CT alone [88, 89], thus substantially higher than the willingness to pay (€34,000) suggested by NICE (National Institute for Clinical Excellence, the British Institute for Assessment of Health Technologies) [90].

Conclusions and perspectives

The role and potential impact of PET/CT in diagnosing and staging patients with non-small cell lung cancer is well established and incorporated in several clinical guidelines and recommendations.

PET/CT can differentiate between malignant and benign SPN. This is particularly useful in order to minimize the number of invasive examinations necessary to exclude malignancy in pulmonary nodules found in patients without symptoms. A PET/CT scan, performed with a fully diagnostic, contrast-enhanced CT, can accurately stage patients with NSCLC according to the TNM system. It is now documented by two randomized clinical trials that PET/CT improves preoperative staging and reduces the number of futile thoracotomies.

PET/CT is potentially hampered by a relatively high frequency of false-positive findings; however, both specificity and sensitivity can be increased by detailed knowledge of patient history and side-by-side reading by an experienced radiologist and nuclear medicine physician. However, in the case of solitary PET-positive findings excluding the patient from potentially curative treatment, verification by biopsy should be sought.

Finally, it should be emphasized that PET/CT is not only for diagnosis and staging. It is beyond doubt that the majority of future research on PET/CT and lung cancer will focus on the increasingly important role of PET/CT in especially radiotherapy planning [91, 92•] but also evaluation of treatment with chemotherapy and in the diagnosis of relapse [41•, 93]. A carefully performed PET/CT scan can not only assist in diagnosing and staging lung cancer, but also serve as a baseline scan for evaluation during and after chemotherapy as well as in the detection of relapse.

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