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Integrated PET/CT in the Staging of NSCLC

Walter De Wever
University Hospitals – Leuven
Belgium

1. Introduction

Lung cancer is a common disease with approximately 3-million new cases per year worldwide and is the leading cause of cancer-related death in many countries. Eighty percent of the lung cancers are non-small cell lung cancers (NSCLC) and 20% are small cell lung cancers (SCLC) [1]. The imaging diagnostic assessment of patients with lung cancer includes morphological imaging modalities such as chest X-ray, Computed Tomography (CT) and Magnetic Resonance (MR) as well as metabolic imaging modalities such as nuclear medicine procedures, including Positron Emission Tomography (PET) and PET/CT. Staging a patient with lung cancer implies an accurate determination of the size of the tumor, the potential infiltration of the tumor into the adjacent structures, the involvement of hilar and mediastinal lymph nodes and the detection of distant metastases. Till recently, CT was the routine imaging procedure for staging patients with NSCLC. The success of CT is related to the very detailed imaging information of the localization and extent of the tumor, the presence of enlarged lymph nodes and the presence of metastatic disease [2]. PET has more recently been introduced in tumor staging and it has been used successfully for detection of primary tumors, metastases, early tumor recurrence, and for the detection of metastatic lymph nodes [3, 4]. This imaging modality possesses a greater sensitivity for detection of malignancy though it is inhibited by relatively poor spatial resolution and anatomical localization of disease. Combining detailed anatomical information obtained by CT with metabolic information from PET seems logical, therefore. Integrated PET/CT is the most recent approach to post hoc image fusion. It combines these image modalities into one scanner that acquires accurately aligned anatomical and metabolic images in the same scanning session [1].

2. Evaluation of a solitary pulmonary nodule

Lung lesions detected in a chest radiograph, incidentally or by systematic investigation, need a definite confirmation of diagnosis. The key point is the evaluation of malignancy in peripheral lung nodules. A solitary pulmonary nodule (SPN) is defined as a focal round or oval lung lesion with a diameter smaller than 3 cm, completely surrounded by normal lung tissue, not associated with atelectasis or adenopathies. Lung lesions greater than 3 cm are classified as masses [5]. Non-invasive evaluation of SPN is usually performed by different imaging procedures including CT, MR, PET and PET/CT. CT is considered to be an excellent tool for the detection and localization of SPNs with a good sensitivity (96%, range 91–98%) but a poor specificity (50%, range 41–58%) [6]. CT provides data regarding the nodule shapes, borders and density [7]. Central or concentric calcifications, round shape or a morphologic stability

over 2 years are features of benignancy. On the contrary, non-demarcated borders, calcifications with eccentric appearance or spiculated pattern, a doubling time of <10 month and cavitation or pseudocavitation are features of malignancy [8, 9]. Contrast enhanced CT can be used to characterize SPN. Enhancement of the pulmonary nodule with 15 Hounsfield Units (HU) has a sensitivity and specificity of 98% and 58% in the detection of malignancy, respectively and the absence of lung nodule enhancement is strongly predictive of a benign diagnosis (negative predictive value of 96.5%) [10].

Several studies showed that PET had similar sensitivity (92–95%) but superior specificity (72–83%) as compared to CT for the characterization of SPN [11, 12]. In one of the largest published studies (450 patients) with lung nodules evaluated with PET, Gould et al. reported a high PET sensitivity (94.2%) and specificity (83.3%) [12]. Lower sensitivity (91.7%) but similar specificity (82.3%) was observed by Fletcher et al. in a population of 344 patients [13]. Malignant lesions with a size of more than 10 mm in diameter are detected with a sensitivity of 96% [14]. Gupta et al. showed that PET using Fluor-Deoxy-Glucose (FDG) as tracer, is highly accurate in differentiating malignant from benign solitary pulmonary nodules for sizes from 6 to 30 mm when radiographic findings are indeterminate [15]. An important contribution of two more recent meta-analyses [16, 17] is the assessment of the performance of FDG-PET in small lung nodules. Nomori et al. demonstrated that the sensitivity clearly decreases for malignant lung lesions of less than 10 mm in diameter [18]. For technical reasons, the lower limit has to be set in dependence from the spatial resolution and will be around 6–10 mm according to the most common PET scanners used. Thus, FDG-PET is not indicated for the evaluation of solitary pulmonary nodules of less than 6–10 mm. The meta-analysis of Ung et al. mentioned that the accuracy for the characterization of lung lesions by FDG-PET depends on the amount of tumoral FDG uptake given as Standardized Uptake Value (SUV) [16]. Grgic et al. reported that it is possible to estimate the individual risk for malignancy considering the SUVmax of a given nodule and clinically relevant information [19]. The authors reported that the mean SUVmax of malignant SPNs was higher than benign lesions (SUVmax 9.7 ± 5.5 vs. 2.6 ± 2.5 ; $P < 0.01$).

False positive FDG-PET findings are represented by lung inflammatory conditions such as pneumonia, pyogenic abscesses, aspergillosis, granulomatous diseases (tuberculosis, sarcoidosis, histoplasmosis, Wegener's granulomatosis) [20]. False negative findings on PET images can be the result of small lesion size (<1 cm) or tumor types characterized by low glucose metabolism (such as Neuro Endocrine Tumors (NET), Broncho Alveolar Cell Carcinomas (BAC) or pulmonary carcinoids [21, 22].

The widespread introduction in clinical practice of FDG PET/CT has allowed a more accurate assessment of SNPs. With integrated PET/CT, additional certainty to the presence or absence of FDG uptake in the pulmonary nodule can be achieved because morphologic CT criteria and metabolic PET criteria are available simultaneously [23]. Kim et al. reported a sensitivity of 97% and a specificity of 85% for the detection of SPNs, concluding that the combination of the anatomical and metabolic images preserves the sensitivity of the CT and the specificity of the PET scan, but improves significantly the overall accuracy [24, 25].

3. Assessment of T stage

The most significant improvement in staging results with combined PET/CT compared with PET alone relates to T staging. This superiority is attributed entirely to the CT component of the examination [26]. The major benefit of PET/CT lies in the direct link between the information on metabolic changes of structures and the highly detailed anatomic CT

information of these structures. Recent published studies showed that PET/CT is the best noninvasive imaging technique for correct prediction of T-stage: PET/CT correctly predicts the T-stage in \pm 82% of cases, in comparison with 55, 68 and 76% for PET, CT and visual correlation of PET and CT, respectively [20]. Halpern et al.[27] demonstrated an accuracy rate of 97% with PET/CT compared with 67% with PET only. Another study by Cerfolio et al. [28] showed that PET/CT more accurately predicted T status (70% of cases) than did PET alone (47%). Lardinois et al. described accuracy rates for T staging with PET/CT and CT as 88% and 58%, respectively [29]. Pauls et al. found that the advantages of integrated PET/CT also depend on the histological T-stage of the primary tumor [30]. Changes of the therapeutic strategy due to PET/CT are especially seen in T3 and T4 tumors. It has been demonstrated that integrated PET/CT is a useful tool for the detection of tumor invasion into the chest wall [1, 29, 31]. Due to the exact anatomic correlation to the FDG uptake, the delineation of the primary tumor can be defined precisely. Integrated PET/CT provides important information on mediastinal infiltration as well. In addition, PET can be helpful in evaluating the cause of pleural effusions [29] (figure 1). One of the most important attributes of PET/CT is the ability to distinguish between tumor and distal atelectasis (figure 2). This is particularly important for the planning of radiotherapy in patients with lung cancer associated with atelectasis [23]. Table 1 summarizes the most important studies concerning T-staging with PET/CT.

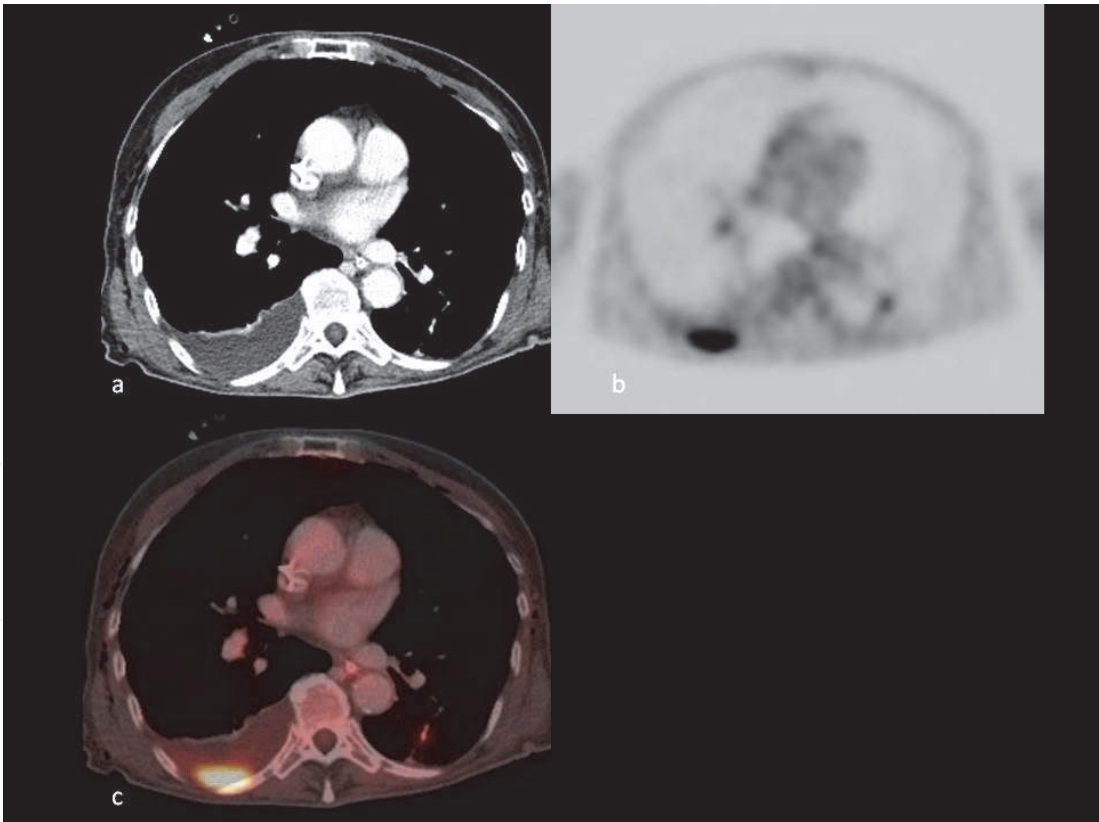


Fig. 1. A 74-year-old woman with an abdominal tumor. CT showed a pleural effusion in the right hemi-thorax (fig 1a). CT could not demonstrate contrast-captated pleural lesions suspect for pleural metastases. PET demonstrates FDG-uptake in the dorsal part of the right hemi-thorax (fig 1b). Integrated PET/CT localizes this FDG-uptake in the pleura, indicating pleural metastases. This was confirmed after pleuroscopy.

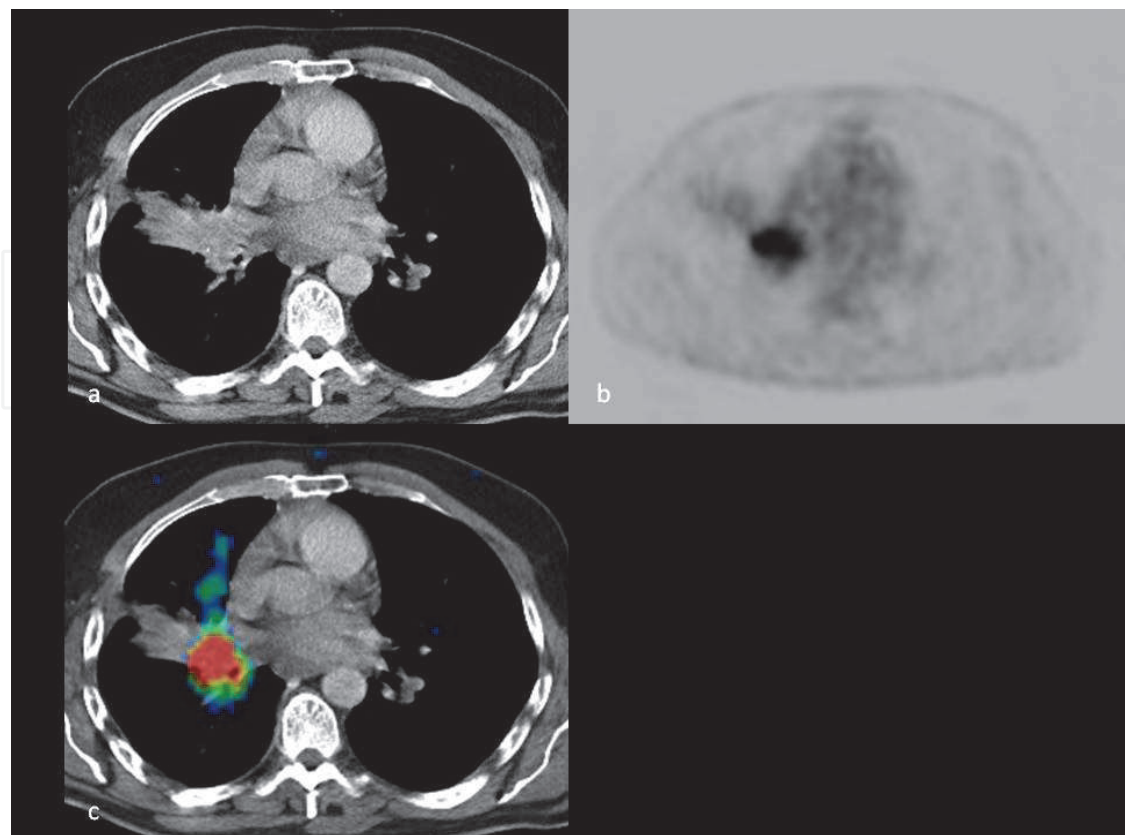


Fig. 2. A 57-year-old man with a central tumor in the right lung. CT demonstrates a central mass with a retro-obstructive consolidation in the right upper lobe (fig 2a). PET demonstrates FDG uptake in the right hilar region corresponding with the central tumor (fig 2b). Integrated PET/CT demonstrates the central tumor in the right lung and can delineate the tumor from the surrounding retro-obstructive consolidation in the right upper lobe (fig 2c).

Author	Year	Number of Subjects	Accuracy (%)
T staging			
Lardinois [29]	2003	40	88
Antoch [31]	2003	27	94
Cerfolio [28]	2004	129	70
Shim [41]	2005	106	86
Halpern [27]	2005	36	97
De Wever [1]	2007	50	86
Average		388	87

Table 1. Accuracy of PET/CT in T staging

4. Assessment of N stage

The accuracy of CT for the prediction of intrathoracic nodal spread of tumor remains limited and the more recently developed CT systems do not change this [7]. Lymph node size (diameter >10 mm in short axis) is used as the only criterion to determine metastatic disease. Different studies with CT have shown a marked heterogeneity in the results, going from 52% to 69% for sensitivity and from 69% to 82% for specificity [32].

Over the past years, several studies have found that FDG-PET has a significantly higher sensitivity and specificity than CT in the detection of tumoral involvement of mediastinal lymph nodes[33-35]. Meta-analyses have confirmed sensitivities ranging between 79-85% and specificities between 89-92% [36-38]. The clinical importance of FDG-PET lies in the high negative predictive value in lymph node staging, which has been estimated as >90% in several studies [39]. Some studies have demonstrated that the accuracy of PET imaging in the mediastinum is dependent on the size of lymph nodes. PET scanning is more sensitive but less specific when CT imaging identifies enlarged nodes. A median sensitivity and specificity of PET scans of 100 and 78%, respectively, in patients with enlarged lymph nodes has been reported [40]. It has been concluded that PET scanning is very accurate in identifying malignant lymph nodes when lymph nodes are enlarged. Conversely, PET scanning is less sensitive but more specific in patients with normal-sized mediastinal nodes on CT. It has been shown that CT of the mediastinum is falsely negative in about 20% of patients with normal-sized malignant lymph nodes. Gould et al. reported a median sensitivity and specificity in these patients of 82 and 93%, respectively [38]. There is an ongoing controversy whether a negative PET scan can be used to obviate further invasive mediastinal staging in patients with enlarged lymph nodes on CT. Microscopic foci of metastases cannot be detected with any imaging modality. In our institution, in patients with negative PET scan but with enlarged mediastinal lymph nodes on CT further evaluation by EBUS or mediastinoscopy will be performed.

PET/CT result in improvement of nodal staging compared with PET alone due to ability to reveal the exact location of metastatic lymph nodes [26]. Accurate anatomic correlation is of benefit for exact localization of a solitary lymph node metastasis and thus allows exact classification as N1 or N2 disease. PET/CT is also important when identifying supraclavicular N3 disease [26]. Initial studies demonstrated a pooled average sensitivity, specificity, positive predictive value, negative predictive value and accuracy of PET/CT of 73%, 80%, 78%, 91% and 87%, respectively. Shim and colleagues [41] demonstrated accuracy rate for PET/CT and CT in N disease of 84% and 69%, respectively. In a recent study by Kim et al.[42] the overall sensitivity, specificity and accuracy of PET/CT for mediastinal nodal staging were 61%, 96% and 86%, respectively. Another study by Yi et al. [43] reported that in T1 stage NSCLC, contrast-enhanced helical dynamic CT better predicts mediastinal nodal metastasis than PET/CT, whereas PET/CT shows perfect specificity and higher accuracy than helical dynamic CT [26]. Table 2 summarizes the most important studies concerning N stage with PET/CT. The benefit of PET/CT compared with PET for nodal staging appears to lie in an increase in specificity and positive predictive value, and the benefit in accuracy of PET/CT is due to the appropriate assignment of focally increased FDG uptake. This emphasizes the importance of anatomic information in conjunction with PET imaging for appropriate PET image interpretation.

False-negative results can occur when the cancer involvement of the mediastinal nodes is low (micro metastases). Because of limitations in spatial resolution of PET, it is often not possible to distinguish between a central tumor and hilar lymph nodes or adjacent mediastinal lymph nodes. Additionally, differentiation between malignant lymph node and residual brown fat or inflammatory lymph nodes can be challenging [44]. Therefore, mediastinal staging with mediastinoscopy or endo-bronchial ultrasonography or endo-esophageal ultrasonography remains the standard for mediastinal staging, even if not all mediastinal lymph nodes can be accessed with each technique alone [45] (figures 3-5). On the other hand, previous or concomitant inflammatory and infectious conditions even as granulomatous diseases are mainly responsible for false-positive results of PET/CT.

Author	Year	Number of Subjects	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)
N Staging							
Lardinois [29]	2003	40					81
Cerfolio [28]	2004	129	77-92				78
Shim [41]	2005	106	85				84
Halpern [27]	2005	36					78
Kim [59]	2006	150	47	100	100	87	88
De Wever [1]	2007	50					80
Yi [43]	2007	143	56	100	100	88	90
Lee	2007	126	86	81	56	95	82
Melek [60]	2008	170	74	73	55	87	74
Yang [61]	2008	122					85
Billé [62]	2009	159	45	94	67	88	85
Average		1231					82

PPV: Positive Predictive Value
NPV: Negative Predictive Value

Table 2. Accuracy of PET/CT in N staging

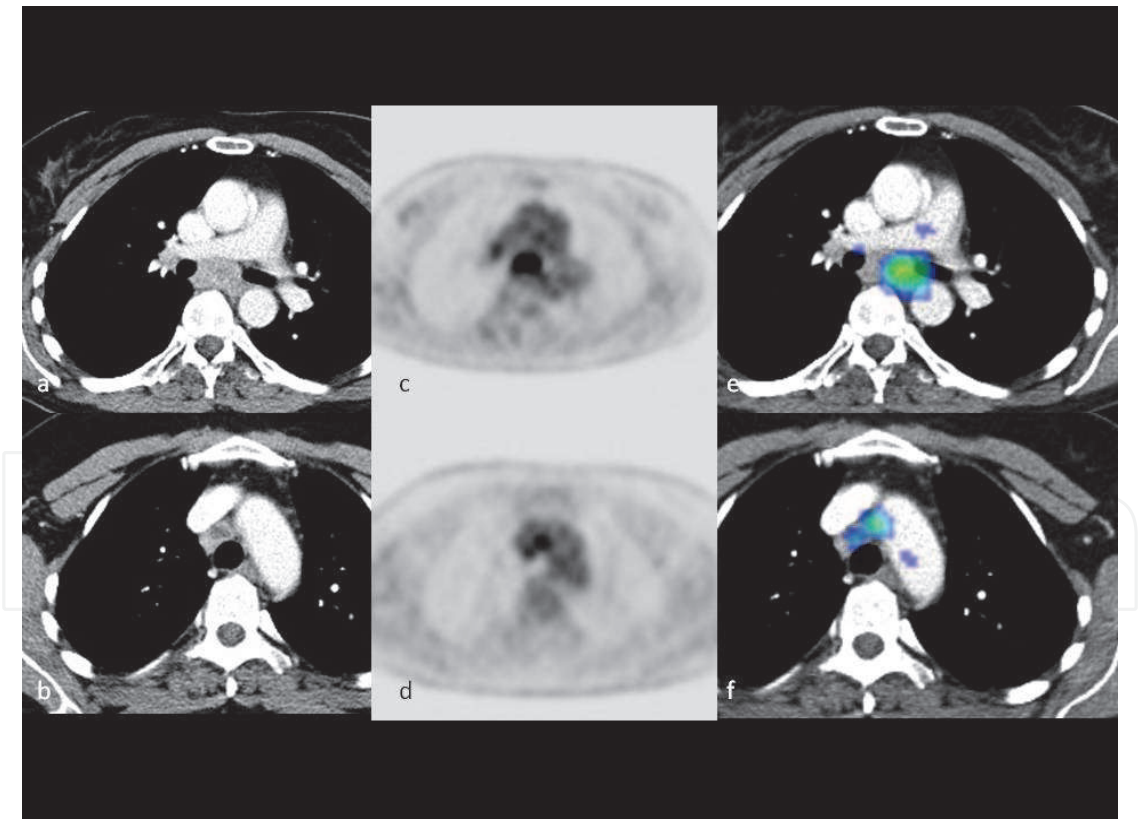


Fig. 3. A 55-year-old woman with an atypical carcinoid tumor in the right middle lobe. CT showed enlarged lymph nodes in the subcarinal (fig 3a) and right paratracheal (fig 3b) region. These lymph nodes are FDG positive on PET (fig 3 c,d). PET/CT (fig 3e,f) confirmed the correlation of these findings. On histopathology these nodes were metastatic lymph nodes.

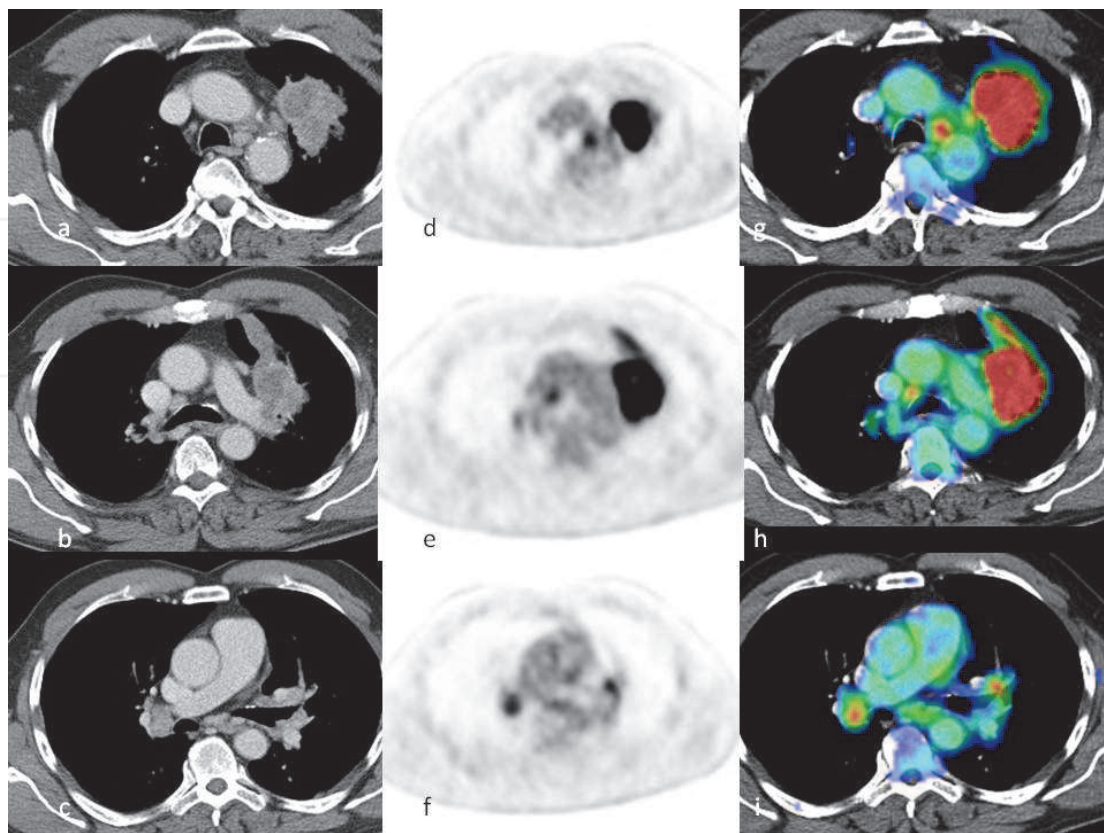


Fig. 4. A 60-year-old man with a spinocellular carcinoma in the left upper lobe. CT demonstrates the tumor in the left upper lobe (fig 4a), even as an enlarged lymph node in the right hilum (fig 4c) and not enlarged mediastinal lymph nodes (fig 4b) . PET and PET/CT (fig 4d-i) demonstrate FDG uptake on the tumor and the lymph nodes visible on CT. Histopathology examination of these lymph nodes could not demonstrate metastatic disease. These were false positive lymph nodes.

5. Assessment of M stage

The observation of distant metastases in patients with NSCLC has major implications for management and prognosis. In total, 40% of patients with NSCLC have distant metastases at presentation, most commonly in the adrenal glands, bones, liver or brain [46, 47]. After radical treatment for seemingly localized disease, 20% of these patients develop an early distant relapse, probably due to systemic micro-metastases that were present at the time of initial staging [48].

In general, a routine search for disease beyond the chest and the upper abdomen in asymptomatic patients is not undertaken with CT and so a staging CT for lung cancer is usually done caudally from the thoracic inlet to the inferior edge of the liver, including the adrenal glands. Many reports suggest that FDG-PET is more sensitive than CT in the diagnosis of extrathoracic metastases. Sensitivity rates of 88–100% have been reported in characterizing adrenal masses detected on CT in patients with lung and other primary cancers [49, 50]. Similarly, in a small series, figures of 100% sensitivity and specificity have been recorded in the detection of liver metastases from NSCLC with PET [51]. PET is also

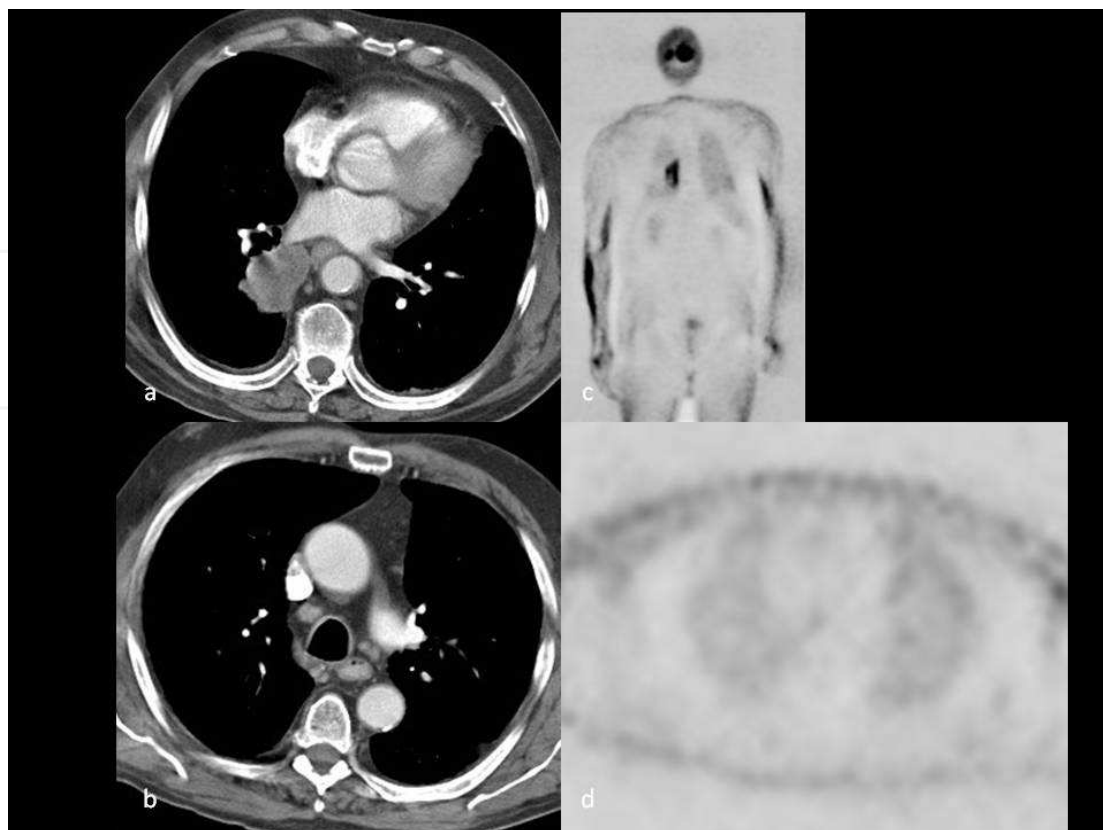


Fig. 5. A 88-year-old man with a spinocellular carcinoma of the right lower lobe. CT demonstrates a central tumor in the right lower lobe (fig 5a) and an enlarged lymph node in the right paratracheal region (fig 5b). PET (fig 5c-d) showed FDG-uptake on the tumor, but could not demonstrate FDG uptake on the CT-enlarged lymph node. Histopathological examination showed a metastatic lymph node in the right paratracheal region.

stated to be more specific than, and equally sensitive as, bone scintigraphy in the detection of bone metastases [52]. However, PET is less useful in recognizing brain metastases, owing to high levels of glucose uptake within normal brain tissue. The significance of isolated areas of avid FDG uptake, without anatomical reference, is uncertain and exclusion of malignancy by PET requires caution in the case of small lesions (<1 cm) [39].

The advantage of integrated PET/CT imaging is the ability to exactly locate a focal abnormality on PET images. PET/CT was found to be the best noninvasive imaging technique in evaluating distant metastases in several studies [20]. Cerfolio et al. [28] proved that PET/CT predicts the metastatic disease better than PET alone: 92% *versus* 87% correctly predicted. PET/CT and PET, respectively, correctly predicted 100% *versus* 86% of bone metastases, 80% *versus* 100% of the chest wall or pleural metastases, 100% *versus* 100% of the liver metastases, 66% *versus* 66% of the adrenal metastases and 100% *versus* 50% of the gastrointestinal metastases. PET/CT identified one brain metastasis while PET missed this metastasis.

6. Restaging and tumor recurrence

Patients with stage IIIA lung cancer and in whom neoadjuvant treatment results in “downstaging” may be candidates for potentially curative surgery. While PET is very good

in the initial nodal staging of lung cancer, PET alone has limited accuracy for mediastinal restaging after chemotherapy [53]. Furthermore, the results of remediastinoscopy are disappointing. De Leyn et al. used surgical findings as the gold standard for comparing the accuracy of PET/CT for N-staging with that of remediastinoscopy after neoadjuvant therapy. In this setting, PET/CT was more accurate than remediastinoscopy (83% versus 60%; $p < 0.05$) and significantly more accurate than PET or CT alone [54].

Progression of disease may occur as intrathoracic recurrence or metastases. The differentiation of recurrent lung cancer and post-therapeutic changes remains a problem for radiological imaging. Both processes can appear identical on CT images, which present a challenge to the use of this modality in the post-treatment patient with lung cancer. Conversely scar and fibrosis are, by definition, dead tissue and should not result in any FDG uptake, which makes PET or PET/CT ideal for this indication. A high accuracy of F-18 FDG-PET or PET/CT in distinguishing recurrent disease from benign treatment effects has been reported [55-57]. PET has been shown to have a sensitivity of 98%-100% for the differentiation of tumor from post-treatment changes in the lung [26].

Concerning restaging following extensive surgery or radiation, it is common to have some degree of scarring within the remaining lung parenchyma. Serial CT is typically used to follow these patients up. With PET and PET/CT, most of these patients can be evaluated more accurately and earlier than with other imaging modalities. Much of the FDG uptake due to inflammation from surgery resolves relatively quickly. Therapy changes after radiation therapy resolves typically within 6 weeks, and these patients can be reevaluated at this time for residual or recurrent tumor. Patients should be evaluated a minimum of 2 months after completion of therapy. Otherwise, post-therapeutic healing processes or radiation pneumonitis may result in false positive findings [23].

7. Radiation treatment and PET/CT

In recent years, many of the radiation therapy planning systems have been upgraded to be able to incorporate both CT and PET data sets. Many also have the ability to fuse the two data sets by using the planning software. Some preliminary studies have shown that radiation portals and tumor volumes change up to 50% of the time when both PET and CT data sets are considered compared with the traditional CT planning method [58]. This anatomic and functional plan has the biggest effect when there are portions of a tumor that may not be visible or are not included on CT images alone. With both the anatomic and metabolic data, radiation oncologists are able to define viable tumor volume more accurately, as well as minimize the amount of exposure to normal tissue.[26]

8. Conclusion

Integrated PET/CT is the best imaging technique for T-staging; it is better than CT alone, PET alone and visual correlation of PET and CT. With integrated PET/CT, tumors can be better delineated from surrounding structures, such as chest wall, mediastinum or surrounding atelectasis, which is important in the exclusion of T3 or T4 stage. For N-(re)staging, integrated PET/CT increases the specificity and positive predictive value, owing to the combination of metabolic and anatomic information. For M-staging, the additional value of integrated PET/CT is related to the availability of a whole-body CT and the better localization of FDG-hotspots. The CT part of the integrated PET/CT is often able to detect

and diagnose metastatic disease, obviating specific diagnostic CT examinations while the additional FDG hotspots detected with PET are better characterized when the CT information is used. However, there are still many indeterminate lesions that need histopathological proof, and integrated PET/CT can be helpful in guiding these interventional procedures.

9. References

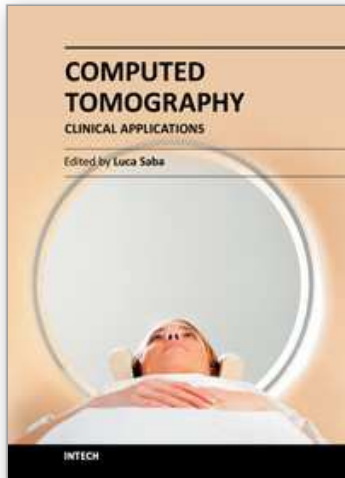
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Computed Tomography (CT), and in particular multi-detector-row computed tomography (MDCT), is a powerful non-invasive imaging tool with a number of advantages over the others non-invasive imaging techniques. CT has evolved into an indispensable imaging method in clinical routine. It was the first method to non-invasively acquire images of the inside of the human body that were not biased by superimposition of distinct anatomical structures. The first generation of CT scanners developed in the 1970s and numerous innovations have improved the utility and application field of the CT, such as the introduction of helical systems that allowed the development of the "volumetric CT" concept. In this book we want to explore the applications of CT from medical imaging to other fields like physics, archeology and computer aided diagnosis. Recently interesting technical, anthropomorphic, forensic and archeological as well as paleontological applications of computed tomography have been developed. These applications further strengthen the method as a generic diagnostic tool for non-destructive material testing and three-dimensional visualization beyond its medical use.

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University Campus STeP Ri
Slavka Krautzeka 83/A
51000 Rijeka, Croatia
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中国上海市延安西路65号上海国际贵都大饭店办公楼405单元
Phone: +86-21-62489820
Fax: +86-21-62489821

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