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Review

PET/CT imaging in different types of lung cancer: An overview

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ABSTRACT

Lung cancer (LC) still represents one of the most common tumours in both women and men. PET/CT is a whole-body non-invasive imaging procedure that has been increasingly used for the assessment of LC patients. In particular, PET/CT added value to CT is mainly related to a more accurate staging of nodal and metastatic sites and to the evaluation of the response to therapy. Although the most common PET tracer for LC evaluation is 18F-FDG, new tracers have been proposed for the evaluation of lung neuroendocrine tumours (68Ga-DOTA-peptides, 18F-DOPA) and for the assessment of central nervous system metastasis (11C-methionine).

This review focuses on the main clinical applications and accuracy of PET/CT for the detection of non-small cells lung cancer (NSCLC), broncho-alveolar carcinoma (BAC), small cells lung cancer (SCLC), lung neuroendocrine tumours (NET) and solitary pulmonary nodules (SPN).

1. Introduction

Lung cancer (LC) incidence has rapidly increased since the beginning of the 20th century and LC currently represents the main cause of cancer mortality worldwide, in both men and women [1].

Lung cancer is the second most common cancer in both men and women in Europe and in the United States and represents a major economic issue for health care systems, accounting for about 12.7% of all new cancer cases per year and 18.2% of cancer deaths. In particular, each year there are approximately 1,095,000 new cancer cases and 951,000 cancer-related deaths in men and 514,000 new cases and 427,000 deaths in women [2].

Despite improvements in survival for many other tumours in recent years, the overall 5-year survival for LC remains relatively poor (around 10%) [2,3] mainly because LC is often well advanced at the time of diagnosis and treatment options are limited.

Smoking is the principal causal factor for LC and this association is one of the most carefully investigated associations in biomedical research [4].

The risk of LC is roughly ten-times higher among smokers than never smokers. This overall risk reflects the contribution of different aspects of tobacco smoking: average consumption, duration of smoking, time since quitting, age at start, type of tobacco product and inhalation pattern. Among all factors, the duration of tobacco abuse is the dominant factor. Compared with continuous smokers, the excess risk decreases in ex-smokers after quitting, although a small lifetime excess risk is likely to persist [5].

Moreover, exposure to involuntary smoking has been observed to be associated with an increased risk (around 20%) of LC as compared to non-smokers [6,7].

On the other hand, smoking is not the only causative factor for LC and it is likely that the incidence of LC could increase in never-smokers [8].

Several other environmental causes have been identified, including radiation exposure (radon decay products and X-rays), asbestos, occupational exposures to toxic agents, pollution and pulmonary diseases with associated increased risk of cancer (such as tuberculosis, chronic bronchitis and idiopathic pulmonary fibrosis) [9]. The main histological categories of lung cancer are non-small cells lung cancer (NSCLC), small-cell lung carcinoma (SCLC) and neuroendocrine tumours (NET) [5].

NSCLC accounts for 85–90% of all LC [10] and includes three main types: squamous-cell carcinoma, adenocarcinoma, and large-cell carcinoma. The first two types represent about 80% of all LCs worldwide. Squamous cell carcinomas are also predominantly associated with a smoking history and tend to form large tumours in the center of the lung [11].

On the contrary, adenocarcinomas usually occur at the lung periphery. They can be subdivided into acinar, papillary,

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bronchiolo-alveolar carcinoma (BAC) and solid adenocarcinoma with mucin production. Mixed hystologic patterns, however, are observed in the majority of cases. Adenocarcinoma is the most frequent type of lung cancer in non-smokers, however its incidence has been increasing in recent years also in smokers [12,13]. Large-cell carcinomas are relatively rare (approximately 5% of LC) and show no evidence of squamous or glandular differentiation [14].

SCLC is the most aggressive lung tumour as a consequence of its high metastatic potential as compared to other forms of LC. The association with active smoking is evident since nearly all patients (over 95%) with SCLC are current or ex-smokers [15].

The lung is the second most common site of NET primary localization, following the gastro-enteric tract. The prognosis of lung NET is relatively more favourable compared to the previously described tumour types since NET are characterized by a more indolent progression and lower proliferation rate [16,17].

The imaging diagnostic assessment of patients with LC includes morphological imaging modalities such as chest X-ray (CXR) and computed tomography (CT) as well as nuclear medicine procedures, including positron emission tomography (PET), bone scintigraphy and, in case of NET, somatostatin receptors scintigraphy (SRS).

In the past decade, PET has become a routinely used procedure for the assessment of solid tumours (breast, colon, lymphoma, lung) [18].

PET can detect functional abnormalities even before they become morphologically evident on conventional imaging. Moreover, PET may be useful for the detection of viable tumour cells after treatment, when the presence of fibrosis and/or oedema may limit conventional imaging assessment. Moreover, not relying on dimensional criteria, PET is more accurate than conventional imaging for the assessment of therapy response.

The development of integrated PET/CT tomographs, has greatly contributed to a more accurate delineation of areas of increased tracer uptake, overcoming the limits of patients repositioning when the two images were acquired independently and fused afterwards. The most commonly used tracer for lung cancer assessment is 18F-fluorodeoxyglucose (18F-FDG), an analogue of glucose labelled with 18Fluorine, that enters tumour cells due to their increased glucose metabolism [19]. Inflammation represents a potential false positive 18F-FDG PET finding, since inflammatory cells show an increased glucose metabolism. False negative findings are mainly represented by small lesions (<5 mm) although 18F-FDG PET sensitivity may be reduced in specific tumour types showing variable FDG uptake (such as BAC, NET, mucinous forms) and in the assessment of brain lesions (as a consequence of physiologically high glucose uptake by the surrounding normal brain).

18F-FDG PET has been reported to be useful in characterizing solitary pulmonary nodules [20], improving lung cancer staging [21], guiding therapy [22], monitoring treatment response [23] and predicting outcome [24]. The role of 18F-fluorothymidine (18F-FLT), an indirect marker of cells proliferation, has also been suggested for NSCLC patients evaluation [25]. Regarding lung NET, their typically low glucose metabolism limits the use of 18F-FDG in well differentiated NET and new PET tracers have been employed for the assessment of these patients (68Ga-DOTA-peptides and 18F-L-dihydroxyphenylalanine – 18F-DOPA).

This review focuses on the main applications of PET/CT in different forms of lung cancer.

2. Non-small cells lung cancer (NSCLC)

Initial staging of disease extent is important in patients with newly diagnosed NSCLC, in order to select the most appropriate therapeutic option and to derive prognostic information. In particular, it is extremely relevant to correctly differentiate patients with potentially curable disease (early stage), that may benefit from radical surgery, from those who are judged as unresectable for cure and are therefore addressed to chemotherapy, radiotherapy or both [26].

Patients with disease localized to a single pulmonary lobe, regardless of hilar lymphnode involvement, are usually treated with surgical resection. However, in cases clinically unfit for surgery, radiation therapy may be employed [27]. In patients with disease diffused to the mediastinum, a combination of chemotherapy and radiotherapy is usually performed before surgery, while cases presenting with distant metastatic spread are generally treated with chemotherapy only [28]. From a diagnostic point of view, various imaging modalities may be employed for NSCLC staging including CXR, ultrasound, CT, magnetic resonance imaging (MRI), bone scintigraphy and positron emission tomography (PET) [29].

CT has been employed in the past decades as the gold standard imaging modality for NSCLC staging [30]. In fact, CT can accurately determine tumour size, mediastinal and vascular invasion and suggest lymphnode involvement, when the nodal axial diameter is greater than 1 cm. The employment of contrast-enhanced chest CT including the upper abdomen is recommended [30] to evaluate the potential presence of liver and adrenal metastases.

The diagnostic and prognostic utility of 18F-FDG PET in LC has been extensively studied and a recent cost–effectiveness analyses showed that PET/CT can be recommended also from an economic point of view [31]. 18F-FDG is the most commonly employed tracer for the detection of NSCLC. The current system for staging lung cancer is based on the tumour–node–metastasis (TNM) classification that describes the primary tumour (T), the degree of lymhponode involvement (N) and the presence of metastasis (M). The current TNM classification (7th edition) introduces new dimension ranges for T and a different interpretation of additional tumour nodules, pericardial and pleural involvement, with consequent variations in the definition of tumour stages [32,33]. The 7th edition of the TNM staging system has also been reported to be able to prognostically differentiate distinct groups of patients operated for NSCLC [34].

2.1. PET/CT for T detection

For the assessment of T, the introduction of integrated PET/CT tomographs has increased the accuracy of tumour detection, chest wall and mediastinal infiltration as compared to PET alone [35–37]. However, the added value of PET/CT for T assessment remains limited as compared to CT [35], since CT can accurately detect both tumour size and infiltration of adjacent structures [36]. One potential advantage of PET over conventional imaging may be the evaluation of dissemination of the primary tumour to the pleura. In fact, pleural effusions are relatively common in patients with LC and their presence precludes curative surgery. On the contrary, surgery is not contraindicated in cases with benign reactive fluid collections. Conventional imaging modalities (CT, MRI) may detect pleural thickening or nodularity but these findings, although suspicious for malignant pleural involvement, may be encountered also in benign conditions [36]. Moreover, thoracocentesis may be falsely negative in 30–40% of patients with malignant pleural effusion [38]. On the contrary, PET was reported to have a high positive and negative predictive value for the evaluation of malignant pleural effusions [39,40]. In a population of 35 patients with LC and abnormal pleural findings on CT (pleural effusion in 34, nodularity in 1), PET correctly identified malignant pleural involvement in 14/35 cases, was falsely negative in 2 cases, true negative in 15 and falsely positive in one Overall, 18F-FDG PET was found to have a sensitivity of 88.8%, a specificity of 94.1%, a positive predictive value of 94.1%, a negative predictive value 88.8% and an accuracy of 91.4%

[39]. Similar data were obtained in a larger population of 92 patients with indeterminate pleural effusions on CT and either newly diagnosed NSCLC ($n = 41$) or NSCLC studied for restaging ($n = 51$) [41]. CT showed indeterminate pleural effusion in 65 (71%). All cases were also investigated by 18F-FDG PET and respective sensitivity, specificity, PPV, NPV, and accuracy were 100%, 71%, 63%, 100%, and 80%. Combined CT and 18F-FDG PET sensitivity, specificity, PPV, NPV, and accuracy were 100%, 76%, 67%, 100%, and 84%. These findings suggest that in case of an indeterminate pleural effusion on CT, the performance of 18F-FDG PET may be useful since its high negative predictive value may reduce the number of repeated thoracocenteses or thoracoscopic biopsies in patients with negative PET findings and benign effusions. On the contrary, a PET positive scan needs further diagnostic assessment to rule out the presence of viable tumour cells.

Several studies investigated the prognostic utility of the standardized uptake value (SUVmax) of the primary tumour on overall survival (OS) [42–47] with contradictory results. Although some authors reported that a high SUVmax was associated with a poorer prognosis [48], it was not found to be an independent predictor of OS [45,49,50]. In particular Hanin et al. [48] observed that in stage I NSCLC a high SUVmax was associated with significantly decreased OS. On the contrary, Agarwal et al. studied 363 patients with early-stage (I and II) NSCLC not receiving any neoadjuvant treatment. Overall, the pre-operative SUVmax (4.5 for stage IA, 8.4 for stage IB, and 10.9 for stage IIB) did not result as an independent prognostic factor for OS in both univariate and multivariate analysis. In particular, no statistical differences in OS were observed when SUVmax was stratified according to pathological stage [45]. Similar results were also obtained in NSCLC advanced stages: in a retrospective analyses of a population of 214 patients (stage IIIA, IIIB, and IV), SUVmax did not show any significant relationship with survival [51].

Recently, the prognostic potential of a new PET tracer (18F-α-methyl-tyrosine – 18F-FAMT) was evaluated [52,53]. 18F-FAMT is accumulated in tumour cells solely via an amino acid transport system. The authors reported that 18F-FAMT uptake in the primary tumour is associated with poor outcome of NSCLC.

2.2. PET/CT for N detection

Clinical staging of the nodal involvement in NSCLC is classified into four categories: N0, N1, N2, or N3. The identification of nodal involvement is extremely important to select candidate patients for curative surgery. In detail, patients with N0–N1 disease (no metastatic lymph nodes or only intrapulmonary/hilar nodes) are generally candidates for surgical resection. On the contrary, patients with N2 disease (ipsilateral mediastinal lymph nodes metastases) could gain benefit from a combination of local and systemic treatment. Patients with N3 disease (contra lateral mediastinal lymph nodes metastases) are considered non-resectable [29–54].

A large number of prospective studies compared the performance of CT and PET for mediastinal lymphnode staging [35,55–59].

Conventional imaging modalities (CT or MRI), using only dimensional criteria to detect nodal involvement, have poor discriminatory power in differentiating benign from malignant nodal disease (sensitivity ranging between 60% and 83% and specificity ranging between 77% and 82%) [60], 18F-FDG PET/CT was reported to have a higher diagnostic accuracy than either CT or PET alone [37], Ventura et al. analyzed 31 patients with lung cancer, 19 underwent 18F-FDG PET/CT and 12 had CT followed by 18F-FDG PET. Thoracic lymph nodes were sampled by mediastinoscopy or thoracotomy. Sensitivities, specificities, positive (PPV), and negative predictive values (NPV) were calculated based on histopathology. Ninety nodes (41 malignant) were identified. Sensitivity, specificity, PPV, and NPV were respectively 94%, 73%, 66% and 96% for 18F-FDG PET/CT. In 12 patients who underwent 18F-FDG PET and CT separately, corresponding values were 90%, 31%, 64% and 71% for PET and 81%, 50%, 69%, and 66% for CT [61].

Another recent study of 159 patients affected by NSCLC evaluated a total of 1001 nodal stations. Nodes were positive for malignancy in 48 patients and 71 nodal stations. At univariate analysis, lymphnode involvement was significantly associated ($p < 0.05$) with the following primary tumour characteristics: increasing diameter, SUVmax > 9, central location and presence of vascular invasion. The overall 18F-FDG PET/CT sensitivity, specificity, positive and negative predictive values for lymph nodes involvement were 54.2%, 91.9%, 74.3%, 82.3% and 80.5% on a per-patient basis, and 57.7%, 98.5%, 74.5%, 96.8% and 95.6% on per-nodal-station basis. With regards to N2/N3 disease, 18F-FDG PET/CT accuracy was 84.9% on a per-patient basis and 95.3% on nodal-station basis. Referring to nodal size, 18F-FDG PET/CT sensitivity to detect malignant involvement was 32.4% (12/37) in nodes <10 mm, and 85.3% (29/34) in nodes ≥10 mm [62].

Although 18F-FDG PET/CT resulted more useful than other imaging modalities for the assessment of nodal metastatic involvement, PET findings cannot replace histologic confirmation of FDG-positive lesions by mediastinoscopy [63]. In fact both false positive and false negative PET/CT findings may occur. False-negative rate for micrometastasis detection has been reported to be as high as 8% [64,65]. Conversely, false positive findings may be encountered in case of inflammatory lymphnodes in patients with coexisting pneumonia, post-obstructive pneumonitis, or chronic granulomatous infection (histoplasmosis or tuberculosis) [66]. On the contrary, 18F-FDG PET/CT may provide valuable information for the assessment of nodal stations that are inaccessible by mediastinoscopy and that may be missed by conventional imaging. Lymphnodes in the aorto-pulmonary window, anterior mediastinum and in the posterior sub-carinal region are difficult to reach without modifying the mediastinoscopic approach and are not routinely sampled. Up to 57% of false-negative cervical mediastinoscopy procedures (with an overall false-negative rate of 10%) are due to the presence of metastases in these inaccessible lymphnode stations [63].

18F-FDG PET detection of hypermetabolic lymphnodes at these stations, indicates the need of a different technique for invasive lymphnode sampling by anterior mediastinotomy, transbronchial or percutaneous biopsy, or by endoscopic-guided fine needle aspiration. In one prospective study of 61 patients with stage IIIA LC, who were candidates for neoadjuvant chemotherapy before planned surgical resection, 18F-FDG PET imaging resulted in tumour up-staging in 30%, and caused a switch to palliative treatment in 19% of these patients [67].

Finally, 18F-FDG PET was reported to have a higher accuracy than CT (83% vs. 50%) for mediastinal nodal staging in patients with idiopathic pulmonary fibrosis that are at increased risk of developing NSCLC (5- to 14-fold as compared to patients without IPF) and frequently show reactive mediastinal nodes [68].

2.3. PET/CT for M detection

The research of distant metastasis completes the staging of NSCLC. Approximately 18–36% of patients with a newly diagnosed NSCLC have distant metastases at presentation and their detection has major implications on management and prognosis [29]. Moreover, among the patients apparently radically treated for NSCLC, around 20% will relapse due to the presence of undetected micrometastasis at the time of initial staging. Metastatic spread typically involves the adrenal glands, bones, brain or liver [29].

Conventional staging for distant metastasis includes a CT scan of the chest including the upper abdomen for staging the adrenal glands and liver, while bone scintigraphy and brain imaging are performed only for stage IIIA or IIIB [69].

Being a whole-body minimally invasive technique, 18F-FDG PET/CT may provide valuable information regarding metastatic spread. 18F-FDG PET has been reported to detect clinically unsuspected distant metastases in up to 28% of patients with NSCLC [70] and 18F-FDG PET was reported to have a significant clinical impact in as many as 53% of cases [71].

In one randomized study using 18F-FDG PET imaging in addition to conventional preoperative evaluation of NSCLC patients, PET imaging reduced the number of futile thoracotomies respectively to 25% (from 46% with conventional work-up alone) in patients with clinical stages I–II tumours and to 11% (from 29% with conventional work-up alone) in patients with clinical stage III tumours [72].

Adrenal metastases occur in up to 20% of patients with NSCLC at initial presentation but approximately two-thirds of those actually represent adenomas, rather than metastases. Considerable work has recently been done using non-contrast CT, delayed enhanced CT, and MRI in evaluating adrenal masses, in order to overcome the limits represented by the significant overlap in appearance between benign and malignant adrenal lesions [73,74].

18F-FDG PET has shown promising results in differentiating benign from metastatic adrenal masses in patients with known or suspected malignancies [75]. However, only a few studies with limited patients populations, specifically addressed this issue in LC patients [76]. In particular, in the study with the largest patients population, Kumar et al. studied the usefulness of 18F-FDG PET in the evaluation of adrenal masses detected on CT or MRI of patients with LC. One hundred thirteen adrenal masses were evaluated in 94 patients and interpreted as positive if 18F-FDG uptake of the adrenal mass was greater or equal than that of the liver. The sensitivity, specificity, and accuracy for detecting metastatic disease were 93%, 90% and 92%, respectively [77].

For the detection of bone metastasis, 18F-FDG PET was found to have a higher specificity and sensitivity than bone scintigraphy and it has been suggested that FDG-PET was also more accurate than CT in detecting liver metastases, especially because of its better specificity [78–80].

On the contrary, brain metastasis are not easily visualized on 18F-FDG PET scans due to the high glucose consumption of the normal surrounding brain tissue resulting in an overall poor sensitivity. For the assessment of brain metastasis, apart from morphological imaging modalities, other PET tracers that do not show uptake in the normal brain may be employed (e.g. 11C-methionine).

Tracers other than FDG have also been proposed for NSLC assessment in a few recent studies. 18F- FLT (18-fluoro-L-thymidine), a tracer of cellular proliferation, has been recently used in NSCLC assessment in comparison with FDG in a population of 31 NSCLC cases: the overall sensitivity for primary tumour detection was 74% (vs. 94% for FDG) while for nodal involvement was 65% (vs. 85% for FDG) [25].

62Cu-ATSM (62Copper-diacetyl-bis-methylthiosemicarbazone), an hypoxia tracer, was also recently compared with 18F-FDG performance in patients with squamous cells lung cancer and lung adenocarcinoma. ATSM uptake was definitely lower than the one of FDG in all cases, however differences in tracer intra-tumour distribution were observed: squamous cells lung cancer showed high ATSM and low FDG uptake at the periphery and opposite tendency in the tumour central regions. In contrast, a matching increase of FDG and ATSM uptake was observed in adenocarcinoma, indicating homogeneous intratumoural distribution of the two tracers. These observations may suggest that glucose metabolism and hypoxic microenviroment may vary depending on tumour pathophysiology [81].

Further characterization of tumour biology has also been performed by the use of PET tracers that mark integrin expression (18F-GalactoRGD) in comparison with FDG. The authors reported that the highest perfusion is observed in areas that simultaneously presented high glucose metabolism and integrin expression [82].

Although these studies show that other PET tracers may be employed in LC assessment, considering the high sensitivity of FDG, the potential added value to FDG imaging is yet to be identified.

An example of NSCLC is showed in Fig. 1.

2.4. Radiation therapy planning

Radiation therapy (RT) is the attempted curative treatment for patients with early stages (I–II) NSLC who are not candidate for surgery. The use of 18F-FDG PET has important implications for the radiation oncologist, since PET may provide valuable information influencing radiotherapy techniques, target volumes definition and patients radiation exposure.

Of course the goal of the radiotherapy oncologist is to optimize the beneficial treatment effects of RT while limiting the dose administered to normal surrounding tissue. RT planning consists in the accurate definition of the regions to be irradiated. In particular, gross tumour volume (GTV) definition is a crucial step of RT planning and includes disease locations visualized on CT or simulator images. This volume is then expanded, to obtain a clinical target volume (CTV), derived by adding margins around the GTV to account for sub-clinical disease extension. The CTV is then further expanded to take into account both the patient and organs movements and setup errors (planning target volume, PTV). Although the definition of volumes on PET images alone might be more problematic due to the poorer resolution and higher noise levels; when combined with structural imaging, such as CT, 18F-FDG-PET provides the best available information on tumour extent. In fact PET/CT should be used for RT planning in NSCLC because it more accurately images tumour extent than CT alone [83].

The impact of PET on RT planning can be summarized in both a limitation of the dose delivered to normal surrounding tissue (when PET tumour area is smaller than the one defined on CT) and in the inclusion of areas with viable tumour cells outside the radiation fields (when PET detects a tumour area more extensive than CT).

FDG-PET was reported to significantly change lymph node staging in the thorax, usually by showing more positive nodes than CT [84], and PET/CT imaging can improve the accuracy of target volume delineation using anatomic biologic contour (ABC), determined directly on PET/CT images [85]. This is proven by a large surgical literature on the accuracy of FDG-PET in the lymph node staging of NSCLC [86,87].

A few recent studies have used RT simulation based on both CT and FDG-PET via image fusion. Mah et al. performed sequential CT and FDG imaging simulation and image fusion in 30 patients undergoing definitive radiation therapy for NSCLC before surgery. In 7 of the 30 (23%) cases, FDG-PET information changed management strategy from radical to palliative. In 5 of the remaining 23 (22%) cases, new FDG-avid nodes were found within 5 cm of the primary tumour and were included in the PTV. The PTV defined using coregistered CT and FDG-PET would have been poorly covered by the CT-based treatment plan in 17–29% of cases, depending on the physician, implying a geographic miss had only CT information been available. The effect of FDG-PET on target definition varied with the physician, leading to a reduction in PTV in 24–70% of cases and an increase in 30–76% of cases [89].

Twenty-six patients with stages I–III NSCLC were studied with sequential CT and FDG-PET simulation. PET clearly altered the radiation therapy volume in 14 (58%) and helped to distinguish tumour from atelectasis in all 3 patients with atelectasis. Diminishing the

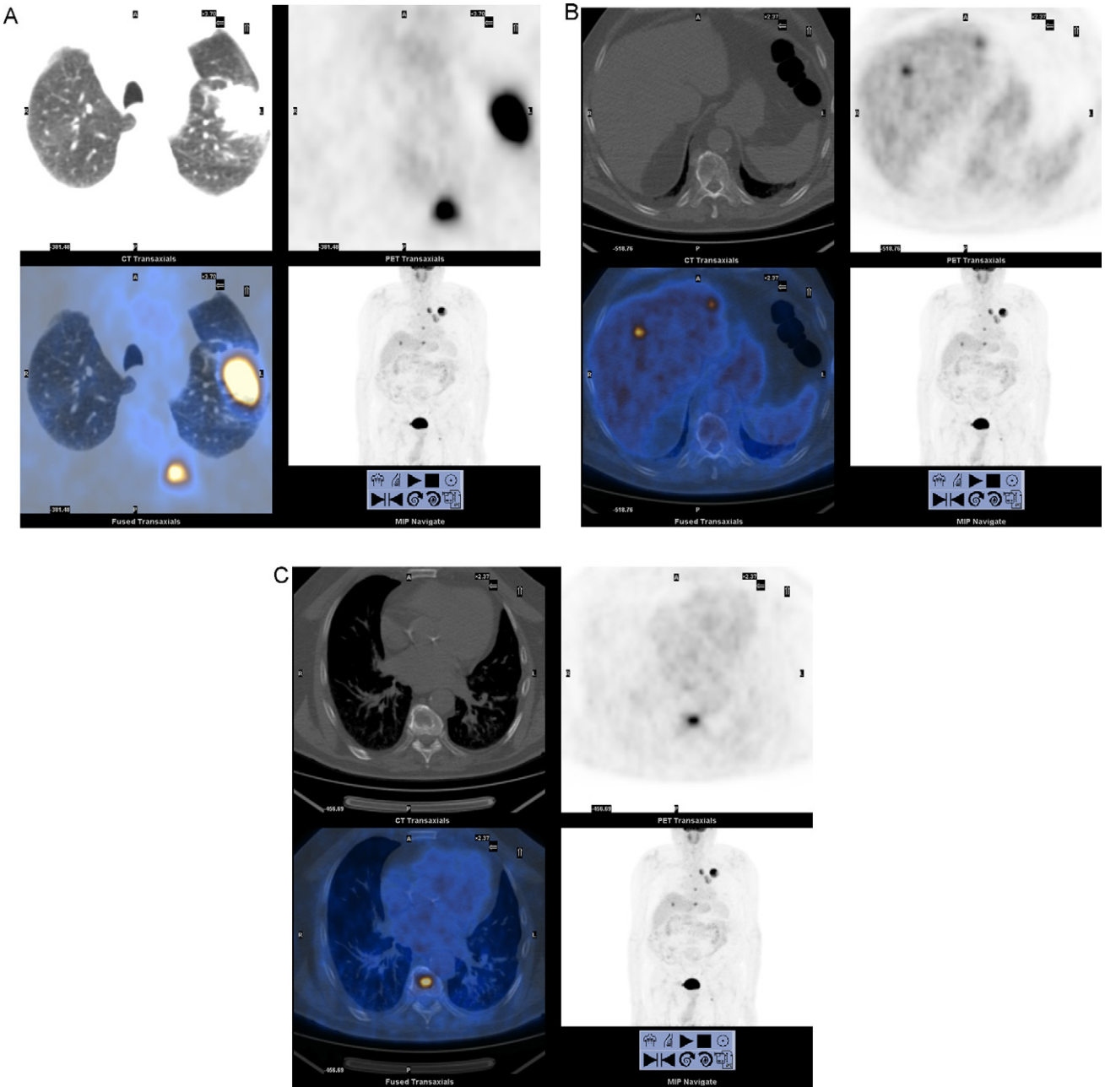

Fig. 1. 18F-FDG PET/CT images of a patient with NSCLC studied for staging. Hypermetabolic pathological lesions are detected in the left lung (SUVmax 22) (A) and to mediastinal lymphnodes (A), to the liver (B) and bone (SUVmax 9) (C).

target volumes in the patients with atelectasis led to decreases in these normal-tissue toxicity parameters [83].

In a modeling study, van Der Wel et al. reported that for 21 patients with N2 or N3 NSCLC, the use of PET/CT in radiotherapy planning resulted in a lower level of radiation exposure of the esophagus and the lungs, allowing a significant increase in the dose delivered to the tumour [90].

In fact De Ruysscher et al. [91] reported that selective mediastinal lymph node irradiation based on PET with 18F-FDG yielded a low rate of treatment failure for isolated nodes, suggesting that reducing the target volume does not result in poorer local control.

Finally, PET, especially PET/CT, imaging has another positive effect on tumour volume delineation. Many groups noted that the interobserver variability, as well as the intraobserver variability, was significantly reduced when the 18F-FDG PET image was available for tumour volume delineation [85–92].

3. Small cell lung cancer

Small cell lung carcinoma (SCLC) accounts for approximately 10–15% of all lung cancers [99]. Clinically, SCLC is more aggressive than non-small cell lung cancer (NSCLC), presenting with a rapid doubling time and higher propensity for widespread metastatic disease. Overall prognosis is severe: in fact, despite initial chemosensitivity, most patients with SCLC relapse and die from recurrent disease [100,101].

SCLC has been traditionally divided into two stages: limited disease (LD) or extensive disease (ED), according to the Veterans Administration Lung Group (VALSG) two-staged classification that was first introduced in the 1950s. Limited disease is defined as disease confined to one hemithorax, the mediastinum and the supraclavicular lymph nodes. All other patients are classified as having ED, including those with malignant pleural effusion [102].

At presentation about 60–70% of patients with SCLC have extensive disease while 30–40% have limited disease [103].

Tumour stage is very important since it is used to identify patients subgroups for different therapeutic options and is the most important prognostic factor of SCLC over performance status, weight loss, gender, lactate dehydrogenase (LDH), and albumin [104,105]. Therapeutic options for patients with LD include a combination of radiotherapy and chemotherapy [106] while chemotherapy is the only option for patients with ED [107]. The 5-year survival of patients with LD treated with combination therapy varies between 15% and 25% whereas patients with extensive stage disease have a 5-year survival of only 1–2%. Therefore, accurate staging of SCLC potentially has significant implications for management, toxicity, and prognosis.

The two stages classification in SD and ED is still the most widely used although the recent 7th edition of the TNM staging system was also proposed [108].

Diagnostic procedures commonly used to stage the disease include chest and abdomen CT, brain CT or MRI, radionuclide bone scans and bone marrow aspiration [109,110].

The impact of PET on stage classification of newly diagnosed SCLC has been investigated by several authors that reported how PET allowed a modification of stage and clinical management in 10–33% of cases.

Fischer et al. reported that PET/CT could improve accuracy of SCLC staging with a higher sensitivity than conventional imaging (93% vs. 79%, respectively) and equal specificity (100%). In their population PET/CT findings determined a change of stage in 5 of 29 patients (17%) [111]. In a population of 120 SCLC patients studied for staging by PET and conventional imaging, PET up-staged 10 patients and down-staged 3 patients [112]. Overall PET data resulted in a change of stage in 12% of patients.

In a recent study Azad et al. found that PET altered stage classification in 12 of 46 (26%) patients when compared with conventional imaging. In particular, among the 26 patients with LD on conventional imaging, 4/26 (15%) were accurately upstaged to ED after PET while among the 20 patients with ED on conventional imaging, 8/20 (40%) were downstaged to LD [113]. Only in one study PET did not alter stage classification in SCLC patients: infect Kut et al., in their population, found that PET scan findings agreed with conventional imaging in the majority of cases [114].

Because of the high physiologic accumulation of 18F-FDG in the brain, PET scans are not sensitive enough for the detection of brain metastases. For accurate screening of brain secondary lesions, PET with methionine or CT/MRI should be used. So in patients who are found to have LD with PET, if brain metastases need to be excluded, an MR scan of the brain is necessary [115].

The role of FDG PET for the assessment of the response to treatment has been widely investigated in many solid tumours, including NSLC. In these clinical settings, PET proved to be very useful since functional changes may often precede anatomical variations in tumour size and allow the differentiation of residual viable tumour interspersed in scar tissue. Fewer studies in the literature addressed this issue in patients with SCLC. Considering the unfavourable clinical course of SCLC cases, the early prediction of response may allow the distinction between responding and non-responding patients, avoiding unnecessary treatment of the latter cases.

In a small patients population (12 cases) Yamoto et al. found that PET was able to identify responding cases after the first cycle of chemotherapy [116].

FDG PET findings were also reported to be relevant for patients prognosis. In fact [117] high SUVmax was associated with significantly shorter OS (median OS for high mean SUVmax vs. low mean SUV max = 11.7 months, 95% CI = 7.5–15.9, vs. 24.3 months, 95% CI = 17.3–31.4; $P < 0.001$). Moreover, SUVmax was found to be a significant predictor for survival of SCLC together with well-defined prognostic factors (such as performance status, LDH, and tumour stage). The authors also observed significant differences in survival among patients presenting with both high SUVmax and ED as compared to cases with only one of these two risk factors or none of them.

An example of SCLC before and after neoadjuvant treatment is shown in Fig. 2.

4. Bronchioloalveolar carcinoma (BAC)

Bronchioloalveolar carcinoma (BAC) is a peripheral, well-differentiated neoplasm typically arising beyond a recognizable bronchus. The WHO defines BAC as a subtype of adenocarcinoma growing along the alveolar septa, without evidence of stromal, vascular, or pleural invasion.

Pure BAC represents only 4% of lung cancers [118] and the WHO classification describes three subtypes: non-mucinous (most frequent), mucinous (25%), and mixed forms (exceedingly rare) [119]. Among BAC histological subtypes, the mucinous form has been described to show poorer outcome as compared to most frequently encountered non-mucinous BAC [120]. However, up to 50% of lung adenocarcionomas comprise a heterogeneous group of tumours with associated BAC features [121]. In these cases, tumours show the concomitant presence of BAC and a varying population of invasive cells. Therefore a spectrum of disorders may be encountered, ranging from predominant BAC histology with a small focus of invasion, to invasive adenocarcinoma with an isolated peripheral BAC focus [118–122].

From a diagnostic and therapeutic point of view, it is important to differentiate between tumours with BAC features (pure or associated with adenocarcinoma) and adenocarcinoma. Pure BAC presents with lower rates of regional lymph node involvement and therefore less aggressive resections can be performed [123]. Moreover, both pure BAC and BAC associated with adenocarcinoma show a better outcome as compared to adenocarcinoma alone [120]. Imaging procedures usually employed for the diagnosis of BAC include CXR, CT, and 18F-FDG PET/CT.

BAC generally appears on CT as a peripheral nodule or area of localized ground-glass opacification (GGO) with or without consolidation. GGO derives from the combined effects of reduction of alveolar air spaces and increased cellular components, with alveolar cuboidal cell hyperplasia, thickening of alveolar septa, and partial filling of the alveolar air spaces by tumour cells [124] BAC is frequently associated with bubble-like areas of low attenuation and an open bronchus sign [125]. While non-mucinous BAC most commonly appears as a small peripheral nodule, mucinous BAC often mimicks pneumonia and its diagnosis may be delayed [120].

18F-FDG PET is widely used for the assessment of lung cancer but the accuracy for the detection of certain tumours histologic subtypes (e.g. mucinous forms) has been reported to be reduced. In particular, 18F-FDG PET accuracy for the detection of lung mucinous tumours is reduced, especially in hypocellular lesions with abundant mucin. Berger et al. found false-negative FDG PET results in 9 of 22 patients (41%) with mucinous carcinoma [126]. The uptake of FDG is significantly lower in pure BAC (often containing abundant mucin) than in adenocarcinoma. In fact Yap et al. reported that PET failed to identify 4 of the 6 pure BAC lesions resulting in a high percentage (66%) of false-negative results. Since pure BAC shows a low glucose metabolic rate, imaging with 18F-FDG PET might miss some pure BAC lesions [127].

Lower 18F-FDG uptake in pure BAC could be the result of several different factors. It might be due to a low metabolic demand of slow-growing BAC or a small number of metabolically active malignant cells. Several studies have supported a relationship between

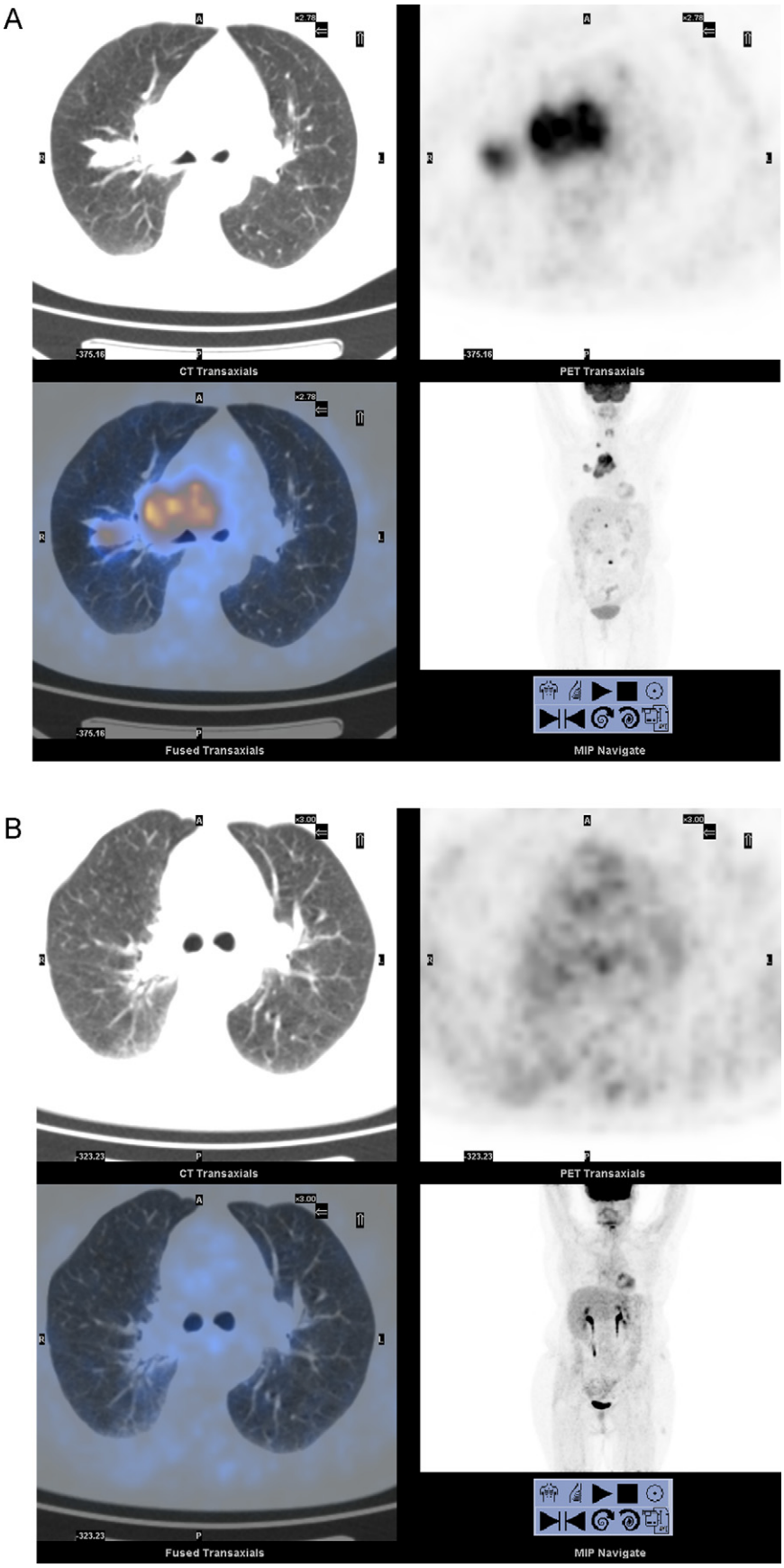

Fig. 2. 18F-FDG PET/CT images of a patient with SCLC studied before (A) and after (B) treatment. Pre-treatment evaluation (A) revealed a left hilar mass with multiple hypermetabolic lymphnodes and multiple bone lesions. PET/CT imaging after chemotherapy (B) shows a complete response.

glucose metabolism measured by 18F-FDG and the growth rate or malignancy grade in lung tumours [128]. Higashi et al. reported that in seven patients with pure BAC FDG uptake was significantly lower (SUVmax = 1.63 ± 0.82) than in nine patients with well-differentiated adenocarcinoma (SUVmax = 3.17 ± 1.28) ($P = 0.014$) [129].

It is interesting to notice, however, that FDG uptake is higher in adenocarcinoma with BAC features as compared to pure BAC. In their study, Goudarzi et al. reported that the mean SUVmax of the BAC group (1.77 ± 0.99) was lower than that of the adenocarcinoma with BAC components group (6.55 ± 4.33) ($P < 0.0001$) [123].

In particular, a recent study reported a significant inverse correlation between SUVmax and the percentage of BAC component [130].

An example of BAC positive at CT and negative at 18F-FDG PET is showed in Fig. 3.

5. Solitary pulmonary nodule (SPN)

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 adenopathy. Lung lesions greater than 3 cm are classified as masses [131].

Lung nodules can be benign or malignant and may reflect the presence of multitude causes, ranging from inflammatory and infectious processes to neoplasms: the differential diagnosis of an SPN includes neoplastic, inflammatory (infectious, collageno-vascular disorders, granulomatosis) vascular, traumatic, and congenital lesions [132].

The evaluation of a SPN often follows its incidental identification on chest CXR. Non-invasive evaluation of SPN is usually performed by different imaging procedures including CXR, CT, MRI, SPECT and PET [133]. Invasive procedures include fiber-optic bronchoscopy, transthoracic needle-aspiration biopsy, video-assisted thoracoscopy, video-assisted thorascopic surgery or thoracotomy. Although invasive procedures allow pathologic assessment of SPN, they are associated with considerable costs and morbidity (mortality associated with exploratory or curative surgery is respectively around 0.5% and 4%) [134].

The occasional finding of SPN on CXR should be followed by nodule characterization, in particular it is crucial to distinguish benign from malignant nodules. In fact the prevalence of malignant SPN has been reported to be up to 55% in Western countries [135]. Moreover, the vast majority of nodules of more than 2 cm in size are malignant, compared to a 50% rate of malignancy in all nodules smaller than 2 cm [136].

Although a uniformly and densely calcified rounded nodule on CXR is generally classified as benign, few nodules can be accurately assessed based on CXR characteristics only and most cases require referral for further diagnostic procedures.

In particular, CT still plays a relevant role in the evaluation of SPNs [137]. CT provides data regarding the nodule shapes, borders and density [138]. Lesions are usually considered benign if they show the following features: central, concentric calcifications, round shape or a morphologic stability over 2 years. On the contrary, malignant features typically include non-demarcated

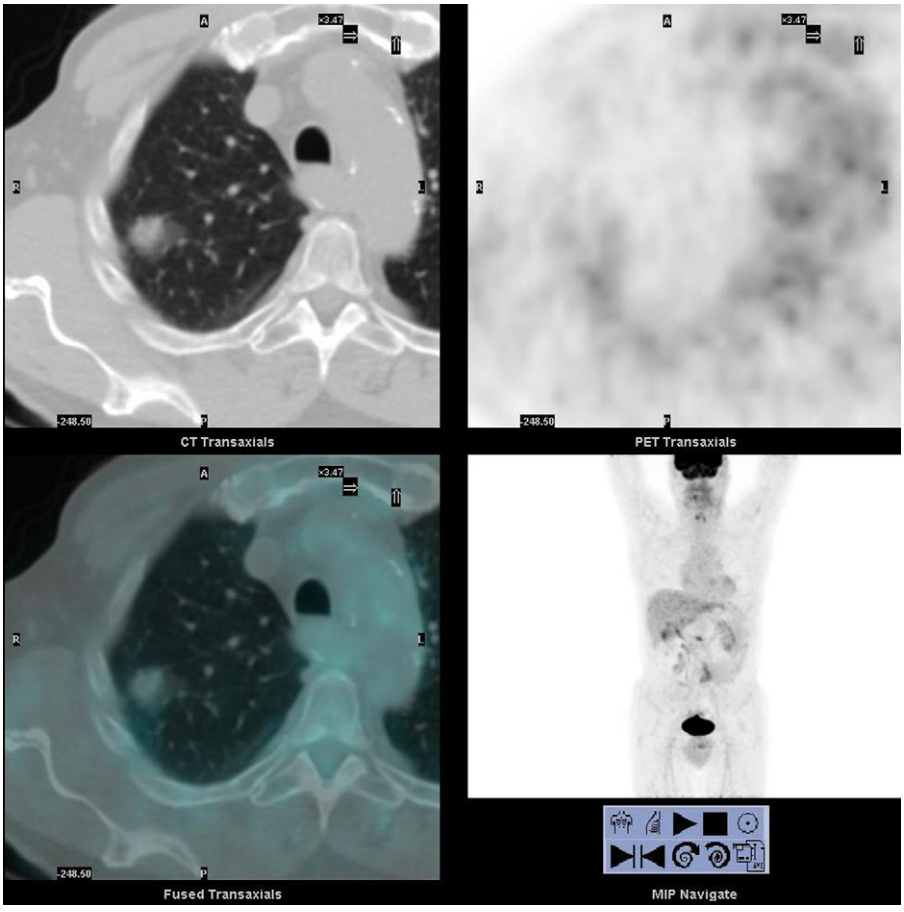

Fig. 3. 18F-FDG PET/CT images of a patient with a right BAC well showed at CT (upper right image) while FDG PET revealed faint uptake only (upper left PET and down right PET/CT fused images). MIP (multiple intense projection) on the down left position of the figure.

borders, eccentric appearance, speculated pattern, a doubling time of <10 month [139] and cavitation or pseudocavitation [140].

CT is considered 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%) [141]. In patients with normal renal function and an indeterminate SPN on CXR or chest CT, contrast enhanced CT should be performed. In a large multicenter trial (356 cases), using a threshold for enhancement of 15 HU, the sensitivity and specificity of contrast-enhanced CT were 98% and 58%, respectively and absence of lung nodule enhancement was strongly predictive of a benign diagnosis (the negative predictive value was 96.5%) [142]. However, malignant nodules are not always easily distinguished from benign lesions based on CXR or CT only: it has been reported that up to 25–39% of malignant nodules are inaccurately classified as benign after CXR or CT [143].

The widespread introduction in clinical practice of 18F-FDG PET/CT has allowed a more accurate assessment of SNPs, offering the advantage of providing both anatomical and metabolic characterization of a given lesion. 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, resulting in a significant improvement in overall accuracy [144,145].

Several studies showed that PET had similar sensitivity (92–95%) but superior specificity (72–83%) as compared to CT (sensitivity 95%; specificity 40%) for the characterization of SPN [20,146–149].

In one of the largest published patients population (450 cases) with lung nodules studied by 18F-FDG PET, Gould et al. reported a high PET sensitivity (94.2%) and specificity (83.3%) [148]. Lower sensitivity (91.7%) but similar specificity (82.3%) was observed by Fletcher et al. in a population of 344 patients [149].

As reported above, SPNs may result falsely negative on PET images in case of small lesions (<1 cm) or in tumour types characterized by low glucose metabolism (such as NET or BAC). False positive findings are mainly represented by lung inflammatory conditions such as pneumonia, pyogenic abscesses, aspergillosis, granulomatous diseases (tuberculosis, sarcoidosis, histoplasmosis, Wegener's granulomatosis). In all these conditions, FDG uptake has been attributed to granulocyte and/or macrophage increased glucose metabolism [150]. Although PET images are mostly interpreted visually, semi-quantitative analysis of glucose metabolism (SUVmax) can be performed in a given region of interest, it is observer independent [151] and well reproducible [152]. 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 informations [153]. The authors reported that the mean SUVmax of malignant SPNs was higher than the one of benign lesions (SUVmax 9.7 ± 5.5 vs. 2.6 ± 2.5; $P < 0.01$). Moreover, all SPN with an SUVmax < 1.25 were associated with benign histology. The authors concluded that in patients with an increased surgical risk and a lesion with a low SUVmax, omission of diagnostic thoracotomy may be warranted and the lesion monitored over time. On the contrary, SPNs with a high SUVmax have a high risk of malignancy and therefore require pathological evaluation.

6. Neuroendocrine tumours (NET) of the lung

Neuroendocrine tumours (NET) are heterogeneous slow-growing neoplasms, occurring in 1–4/100,000 people per year [154,155], and are characterized by peculiar biological features [156]. First of all, belonging to the APUD (amine precursor uptake and decarboxylation) cells system, NET can produce a wide variety of substances. Hormones or amines production is related to the presence of clinical syndromes in functional forms of NET (33–50% of cases). Finally NE cells express several receptors in high quantities [156].

Although the majority of NETs arise at gastro-entero-pancreatic level, the second most frequent location is the lungs, representing approximately 30% of all NET lesions [16,17] and accounting for 1–2% of all lung neoplasms [16–157].

Lung NET may be encountered in a wide age range, however the peak incidence is around the sixth decade. Lung NETs generally (80–90%) present as well-differentiated tumours that rarely metastasizes (5–20%); less frequently, they present as atypical forms with poorer prognosis (5-years survival of 44–78% vs. 87–89% of typical forms) [158]. The more severe prognosis of atypical forms is a consequence of a much higher metastatic potential even years after the resection of the primary lesion.

From a clinical point of view, lung NET may be present with symptoms related to luminal obstruction (cough, haemoptysis, pneumonia) [159], while in other cases the diagnosis is post-mortem.

Histologic grading is based on Ki67 levels and identifies three categories (G1: Ki67 < 2%, G2: Ki67 between 3 and 20%, G3: Ki67 > 20%) [160,161].

Although traditionally the TNM staging classification has not been applied to lung NET, the TNM has been demonstrated to be useful in these patients, therefore the International Association for the Study of Lung Cancer (IASLC) recently recommended that the TNM be applied to pulmonary NET [162].

An early and accurate diagnosis is of crucial importance for the outcome of these patients since radical surgery is associated with a very good prognosis [17].

From a diagnostic point of view, the evaluation of NET patients is challenging since these tumours show a slow glucose metabolism and may present as small lesions with variable anatomical localization.

The diagnostic work-up mainly relies on conventional morphological imaging procedures including CT, US and MRI combined with functional imaging, namely whole-body somatostatin receptor scintigraphy (SRS) [163,164].

However, although SRS showed a higher accuracy than CT [165] for NET diagnosis at both the primary and metastatic site, the development of novel PET tracers specific for NET has definitely changes the diagnostic approach. In fact the higher spatial resolution of PET as compared to the gamma-camera accounts for higher accuracy in lesions detection.

Currently, the PET tracers most commonly employed in the assessment of NET are 68Ga-DOTA-peptides and 18F-DOPA while 18F-FDG may provide valuable information in selected cases. Since well differentiated NET are characterized by a slow proliferation rate and therefore low glucose consumption, FDG is not suitable for the evaluation of well differentiated forms [166–168] while it still may be valuable in highly proliferating undifferentiated tumours or in cases of lesions presenting a low expression of somatostatin receptors (e.g. medullary thyroid carcinoma).

68Ga-DOTA-peptides specifically bind to somatostatin receptors (SST) over-expressed on NET cells. 68Ga-DOTA-peptides structure includes an active part binding to SST (TOC, NOC, TATE), a chelant (DOTA) and a beta-emitting isotope (68Ga).

The most relevant difference among these compounds relies in a variable affinity to sst receptors subtypes [169]: all can bind to sst2 and sst5, only DOTA-NOC presents a good affinity also for sst3. However, the observed differences in receptors binding affinity, have not yet found a direct clinical correlate therefore there is no indication that such differences might be related to specific advantages in clinical employment.

In the past few years 68Ga-DOTA-peptides have been increasingly used for their high accuracy in NET lesions detection [170]

with overall accuracy higher than conventional imaging and SRS, especially for the detection of small lesions at node, liver and bone level [171–174]. However the employment of 68Ga-DOTA-peptides is still limited to specialized centres in the contest of clinical trials since these compounds still have not been registered for routine clinical use.

From a practical point of view, 68Ga-DOTA-peptides presents several advantages including that an easy labelling and synthesis process (not need of an onsite cyclotron) [175], they are not dependent on cells metabolism (as compared for example to 18F-DOPA or 18F-FDG) and non-invasively provide information on SST receptor expression with direct therapeutical implications. In fact are not only employed to assess disease extension (staging, re-staging, identification of the site of the unknown primary tumour in patients with proven NET secondary lesions) but also for the selection of cases that would benefit from therapy with either cold or hot (peptide receptor radionuclide therapy) somatostatin analogues [176] and derive patients prognosis [177].

To our knowledge, only few papers in the literature studied lung NET with 68Ga-DOTA-peptides.

Kayni et al. [178] performed both 68Ga-DOTATATE PET/CT and 18F-FDG PET/CT in 18 patients with lung NET (typical carcinoid, carcinoid tumourlets, large cells pulmonary neuroendocrine tumour, multiple carcinoid tumourlets and tumours, atypical carcinoid, adenocarcinoma with NE differentiation). The authors reported a good correlation between tumour differentiation grade and 68Ga-DOTATATE uptake: all typical carcinoids showed a preferential 68Ga-DOTATATE uptake. On the contrary, variable uptake was documented in the case of 18F-FDG: nearly half the cases showed no uptake while only a few patients presented a low uptake. Overall the superiority of 68Ga-DOTATATE over 18F-FDG for the assessment of well differentiated lung NET was evident. 68Ga-DOTANOC was also reported to provide valuable information in well differentiated bronchial carcinoids as compared to contrast-enhanced CT [179]. An example of metastatic lung carcinoid visualized by 68Ga-DOTANOC is shown in Fig. 4.

68Ga-DOTATATE was also assessed in comparison with 18F-DOPA, an amino acid labelled with 18F that avidly enters NET cells. Among the studied population, 6 cases had a primary lung NET studied for staging or re-staging: PET with 68Ga-DOTATATE was true positive in 5/6 cases while 18F-DOPA in 2/6 cases [180]. Literature reports specifically addressing the use of 18F-DOPA in lung NET are few and in most cases lung primary tumours are reported in the context of patients populations with NET of different primary origin studied with 18F-DOPA.

The use of 18F-DOPA in clinical practice is interesting since the uptake is dependent on cells metabolism and can therefore provide valuable information regarding the response to treatment. However, the difficulties in the synthesis process and the relatively high costs have limited its use in the assessment of well differentiated NET in favour of 68Ga-DOTA-peptides.

Resuming, there are several PET tracers for lung NET imaging: in well differentiated forms 68Ga-DOTA-peptides seems to be the most promising, providing data regarding both disease extent and pattern of SST expression (with direct therapeutical implications); in less differentiated forms or in cases with low expression of SST,

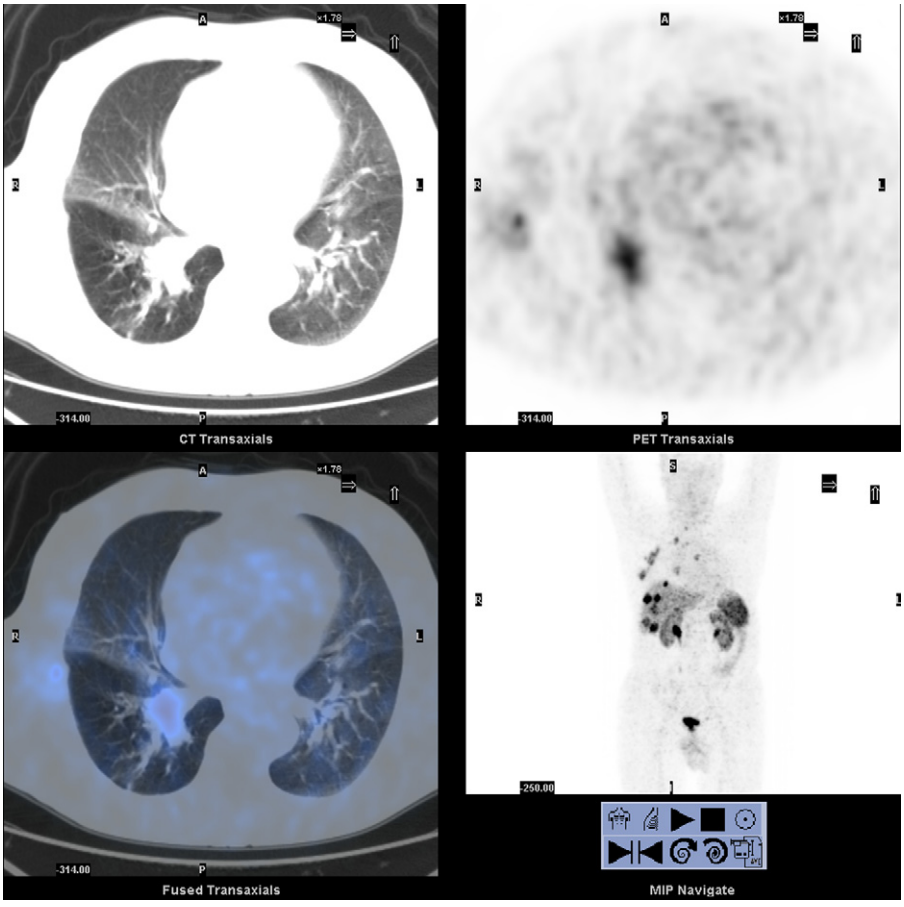

Fig. 4. 68Ga-DOTANOC PET/CT images of a patient with primary lung NET showing multiple lung, pleuric, lymphnodal, liver lesions with a high expression of somatostatin receptors.

18F-FDG is indicated and may provide valuable information on both disease extent and prognosis.

7. Conclusions

PET/CT has become a routinely performed imaging modality for the assessment of LC patients. The most commonly employed tracer for LC detection is 18F-FDG, that provides valuable information for patients management especially for the detection of nodal and metastatic sites involvement and for the assessment of the response to therapy. Pitfalls in 18F-FDG PET/CT may be encountered in cases of tumour hystotypes characterized by low glucose uptake (NET, mucinous forms, BAC), in the assessment of brain metastasis (due to the high physiologic 18F-FDG uptake in the brain) and in cases presenting with concomitant inflammation (due to the high FDG uptake of inflammatory cells). Recently, new PET tracers have been designed to overcome these limitations and have been successfully employed for the assessment of lung NET (68Ga-DOTA-peptides, 18F-DOPA) and in cases with suspected secondary brain lesions (11C-methionine). Overall, the information provided by PET/CT is very useful in the clinical management of LC patients.

Conflict of interest

The authors have no conflict of interest with the present paper.

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