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FDG PET-CT for solitary pulmonary nodule and lung cancer: Literature review

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KEYWORDS

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Abstract The investigation of solitary pulmonary nodule (SPN) and non-small cell lung cancer (NSCLC) has rapidly become one of the main indications for \textsuperscript{18}F-fluorodeoxyglucose (FDG) positron emission tomography (PET), currently combined with computed tomography (PET-CT). In this literature review, we first attempt to clarify how PET imaging contributes to investigating SPN, in conjunction with conventional CT. We highlight the prospects of research underway to improve our understanding of SPN. In the second part of this review, we analyze the current role of PET-CT in the overall care process for lung cancer. We review the indications for which consensus has been reached, for example initial staging, as well as new indications such as radiation therapy planning or prognostic assessment.

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Positron emission tomography (PET) using 18F-fluorodeoxyglucose (FDG) and combined PET-computed tomography (PET-CT) using FDG are two widely used imaging techniques in oncology. The investigation of solitary pulmonary nodule (SPN) and non-small cell lung cancer (NSCLC) has rapidly become one of the main indications for such imaging. The advantages and limitations of FDG imaging are currently well established. In this review, we describe the current role of FDG PET-CT imaging compared with conventional CT for investigating SPN. We will then discuss emerging research, which should improve how pulmonary nodules are characterized. Finally, we will analyze the main indications for PET-CT in the overall care process for lung cancer.

FDG PET-CT and solitary pulmonary nodule

Role of PET in managing solitary pulmonary nodule

Characterizing a solitary pulmonary nodule detected incidentally or, as is the case more recently, on CT screening for lung cancer, is a major public health issue. The American College of Chest Physicians (ACCP) recommends the use of thoracic CT scans as one of the main modalities when screening for lung cancer in high-risk populations [1]. The ACCP also advises to perform PET in conjunction with chest CT in specific cases (Fig. 1) [2,3].

PET is not indicated for SPNs of less than 8 mm in diameter in the ACCP guidelines [2,3], or less than 10 mm in the French guidelines [4]. This threshold of 8–10 mm was set to take into account the spatial resolution of PET systems, due to the significant risk of false-negative findings for small lesions. However, over the last decade, the spatial resolution of PET has increased steadily between the first meta-analysis conducted by Gould et al. [5] and the more recent study by Cronin et al. [6] who reported a sensitivity of 95%, a specificity of 82%, a positive predictive value (PPV) of 91% and a negative predictive value (NPV) of 90%. The spatial resolution of the even more recent systems is still better.

The use of PET can be avoided for nonsolid nodules (ground glass opacity or mixed nodules) and replaced by thin-section CT of the lungs which performs well in these circumstances [2,4]. This eliminates one of the main sources of false-negative (carcinoma in situ and other forms previously called “bronchioalveolar carcinoma” [7]) and false-positive findings associated with PET (inflammatory episodes or infection). Such nodules are monitored using CT [8].

PET is therefore mainly used as a complementary modality to investigate solid nodules ≥ 8 mm. Nevertheless, PET should be included in a global strategy for characterizing SPNs that takes into account not only their size, doubling time, morphology, and density, but also the clinical likelihood of malignancy. When chest radiography or CT reveals a solid SPN, prior images of the same patient must be reviewed to determine whether the nodule was present at an earlier time and assess its progression and doubling time [9]. If the nodule is found on previous images and has not grown in size over a 2-year period, then it is most probably benign. Thin-section chest CT also provides specific information on the morphology of the SPN [2,3]. Various features are highly suggestive of benignity (rounded atelectasis, typical hamartoma-like fat content, various calcifications, etc.) (Fig. 2).

However, in the absence of such reassuring features, the nodule must be further investigated. The clinical likelihood of malignancy can be determined based on the CT features

![Figure 1. ACCP algorithm for assessing solid solitary pulmonary nodule.](image-url)
of the nodule such as its diameter, spiculated shape, location within the lung (risk assumed to be higher for superior lobe nodules), and the patient’s clinical particulars (age, smoker status, history of cancer). This likelihood can be assessed qualitatively or using algorithms [10]. ACCP classes patients into 3 groups: very low likelihood (<5%), low to moderate likelihood (5–60%), and high likelihood (> 60%) [11]. Patients with a very low likelihood are monitored adequately using CT, and if no increase in the size of the SPN is observed over a 2-year period, then it may be considered to be benign. If the likelihood of malignancy is high, PET-CT can be performed as part of staging. If the likelihood is intermediate (5–60%), FDG PET-CT is recommended to look for hypermetabolic activity suggestive of disease. Nevertheless, it should be borne in mind that the absence of significant FDG uptake does not officially exclude malignancy, and SPNs should be monitored 6 months later using CT. The standardized uptake value (SUV) threshold of 2.5 is generally used to designate a scan as positive. This threshold is arbitrary as the performances of new PET systems generally provide higher uptake values than those of older machines. In addition, the SUV is underestimated for small nodules owing to the partial-volume effect, and for nodules located in the lower lungs due to respiratory motion. Some authors recommend the use of relative analysis by comparing the SUV for the SPN to mediastinal background noise [12]. Fig. 3 shows two irregularly shaped nodules at the apex of the right lung in a smoker. These non-hypermetabolic nodules are in fact fibrous scars.

Optimizing PET performance for SPN investigation

Contribution of PET-CT compared with PET alone: joint analysis of functional and morphological images

Kim et al. compared the performances of PET alone, CT alone, and PET-CT [13]. They reported a sensitivity and specificity respectively of 93% and 31% for CT, 69% and 85% for PET, and 97% and 85% for PET-CT. Taking into account nodule morphology can explain the increased sensitivity of PET-CT compared with PET alone. Another study demonstrated that the CT data included in PET-CT analysis increased the specificity of the latter technique [14]. Several other studies underlined the value of joint morphological and functional analysis [15–17]. In these studies, the interpretation of the hypermetabolic foci seen on PET images also took into account the nodule’s morphological features (regular, lobulated or spiculated margins; presence of central, peripheral, or popcorn calcifications; etc.), its density (strong attenuation, ground glass opacity, fluid, necrosis), and lesion enhancement in the event of injection of iodinated contrast agent. For low-uptake solid nodules, it is important to look for features suggestive of carcinoid tumor (proximal endobronchial nodule, presence of calcifications, highly enhanced following injection of contrast agent, etc.) because typical carcinoid tumors can have a low glucose metabolic rate (low SUV). In contrast to carcinoid tumors, neuroendocrine large cell carcinomas generally show high-uptake levels [18]. Small cell lung cancer (SCLC) also shows a high level of FDG uptake [18]. The latter is most often visualized as a large hilar or perihilar mass with mediastinal

Figure 2. Investigation of a solitary pulmonary nodule in the lower lobe of the right lung. The final diagnosis is hamartoma: a: Fused PET-CT image: non-hypermetabolic nodule; b: CT image in the axial plane (parenchymal window): clearly delimited nodule; c: CT image in the axial plane (mediastinal window): fat density is not detected within the nodule.
lymph node involvement rather than as a solitary pulmonary nodule. Squamous cell carcinomas (SCC) and large cell carcinomas are generally high FDG uptake tumors [19]. SCC is most often observed as a central or perihilar mass that sometimes shows necrosis. In most cases of adenocarcinoma, imaging reveals a solid, generally peripheral nodule showing significant FDG uptake [20]. Adenocarcinoma sometimes shows ground glass or mixed opacity, with a solid component adjacent to the ground glass opacity, in which case the PET findings can be negative [20]. The following diseases are the most common causes of ground glass opacity: atypical adenomatous hyperplasia, adenocarcinoma in situ (previously called bronchioloalveolar carcinoma) and minimally invasive adenocarcinoma (lepidic predominant tumors) [20].

PET-CT scans are most often conducted without injection of iodinated contrast agent. Only a few studies have assessed the use of contrast agents in investigating lung cancer. Based on SUV data alone, Orlacchio et al. reported a sensitivity, specificity and diagnostic accuracy of 76.9%, 100% and 89.2% respectively; these values increased to 92.3%, 100% and 96.4% respectively when taking into account enhancement after injection of contrast agent [21].

However, in current routine clinical practice, nodule morphology cannot be analyzed in great detail using the CT data collected during PET-CT scans [9], due to respiratory blurring. In addition, in order to reduce patient exposure to radiation, the CT scan is usually performed using a low dose protocol. For this reason some authors suggest thin-section CT should be performed in complement to PET-CT.

Taking into account nodule size

The sensitivity of PET is insufficient to properly characterize small nodules [22,23]. Only positive PET findings should be considered to be informative when dealing with subcentimeter nodules for which the uptake level is strongly affected by the partial-volume effect and respiratory blurring [24]. Thus, the standard diagnostic SUV threshold of 2.5 should not be applied to all nodules regardless, as it might lead to a loss in sensitivity for the detection of small lesions. In such cases, the clinician’s experience is particularly important since not only FDG uptake, but also nodule size and nodule location within the lung, need to be taken into account.

Analyzing non-attenuation-corrected images

PET images reconstructed following the estimation and correction of 511 keV photon attenuation in body tissues are called "attenuation-corrected images". Raw images that are not compensated for attenuation are called "non-attenuation-corrected images". Attenuation-corrected
images are used to visualize "truer" positron-emitting radiopharmaceutical distribution by "adding counts" to deeper body tissue and high-density regions (bones). In return, the attenuation correction technique used in hybrid PET-CT machines can result in the underestimation of the positron counts in peripheral tissue and low-density regions, especially the lungs, and prevent the proper visualization of small nodules. It may therefore be helpful to view both attenuation-corrected and non-attenuation-corrected images.

Delayed imaging
Several studies have reported the usefulness of dual time point imaging with an additional delayed scan performed at a late stage after FDG injection, a reduced SUV on the delayed image being in favor of a benign process [25,26]. Alkhawaldeh et al. reported that diagnostic accuracy increased from 85%, when the SUV of a single scan was used, to 92% when data from a delayed scan were included [26]. Still, consensus has not been reached on the discriminating power of this second delayed scan [27]. No standard acquisition protocol has been defined for such investigations, notably regarding the time between the two scans, and no consensus has been reached as to the criteria defining when PET findings should be considered positive or not. Finally, if delayed imaging could improve PET-CT specificity due to the decrease in FDG uptake of some inflammatory lesions over time, this is not the case for other inflammatory conditions (sarcoïdosis, various mycobacterial infections, aspergillosis, coccidioidomycosis, and histoplasmosis). Two recent meta-analyses conducted in 2012 [28] and 2013 [29] concluded that the overall diagnostic accuracy was similar for single and dual time point scans.

Respiratory gating
To minimize the "volume dilution" effect, various respiratory gating techniques have been developed to synchronize PET data acquisition and breathing cycles and have provided encouraging results [30,31], mainly for lower lung nodules. There are many different gating modalities. However, gating is associated with several disadvantages: besides its high cost, it also extends the scan time and therefore increases the likelihood of patient movement.

Using tracers other than FDG
As mentioned previously, the sensitivity of FDG is limited for certain histological types such as adeno- and small cell lung cancer. In addition, high tissue uptake of this tracer is not a specific feature of cancer. The use of other radiopharmaceuticals is therefore theoretically plausible.

18F-fluorothymidine (FLT) is a thymidine analog. The level of FLT uptake is an indicator of the tumor proliferation rate. In a small series of patients undergoing PET, the specificity of FLT was found to be greater than that of FDG, but its use led to a decrease in sensitivity and a higher false-negative rate [32].

Other substances of potential interest are 18F-fluorodihydroxyphenylalanine (FDOPA) and various somatostatin analogs such as 68Ga-DOTATOC and 68Ga-DOTANOC for neuroendocrine tumors [33].

PET-CT and lung cancer
Staging lung cancer
The guidelines for the first-line investigation of patients with suspected lung cancer recommend contrast-enhanced CT imaging. These guidelines apply both for NSCLC and SCLC [34].

For NSCLC patients who are potentially eligible for curative treatment, PET-CT is only indicated if CT staging findings suggest that the cancer is localized. In oligometastatic settings, for which surgery or multimodal therapy is considered in a curative approach, patients might benefit from PET-CT. In addition, as described previously, PET may be performed before histological diagnosis in order to investigate a pulmonary nodule. Pre-therapy PET-CT results in changes to staging in an important number of cases, as therefore has a significant impact on therapy planning. In a study by Gregory et al. that included 168 patients with NSCLC for whom curative treatment was considered, PET-CT and conventional staging findings were inconsistent for 50.6% of patients, with an impact on the therapeutic approach in 42.3% of cases [35].

PET-CT can also be indicated for patients with SCLC if the disease appears to be localized to the chest on conventional CT scan [36]. Thoracic SCLC without distant metastases can be treated by concomitant radiochemotherapy.

Assessing the primary tumor
Chest CT is the standard imaging modality for assessing primary tumor size and identifying its margins. MRI can be performed on an exceptional basis to provide additional information on potential tumor resectability as regards to vascular and neuronal structures. PET-CT may nevertheless be helpful in assessing a nodule located in same lobe. It can also provide information on parietal or mediastinal involvement (Fig. 4). PET is useful for differentiating tumor tissue from atelectasis, which may be helpful if radiotherapy is planned to determine the target volume (see below "Role of PET-CT in radiation therapy planning").

Determining lymph node involvement
Precise determination of the status of mediastinal lymph nodes is essential when selecting patients eligible for curative surgery. Surgery is the first choice therapy for patients with localized disease without lymph node involvement or with N1 lymph node involvement (peribronchial or ipsilateral hilar region). In the event of N2 lymph node involvement (ipsilateral mediastinal and/or subcarinal), surgery is subject to controversy and should generally be preceded by neoadjuvant therapy.

In a meta-analysis published in 2014, the sensitivity and specificity of PET-CT for evaluating mediastinal involvement were of 77.4% and 90.1% when the level of lymph node uptake was compared to background mediastinal noise, and 81.3% and 79.4% when lymph node involvement was
evaluated based on a SUV threshold of 2.5 [37]. The authors of this study concluded that owing to the insufficient sensitivity of PET-CT (approx. 80%), invasive mediastinal investigation is required, even in the absence of hypermetabolic nodes in the mediastinum [37]. However, the results of the studies included in the meta-analysis were particularly heterogeneous. In another meta-analysis including 1,122 patients (10 studies) with T1-T2 N0 lung cancer based on PET-CT staging, the negative predictive value for N2 lymph node involvement was 93% [38]. In line with the data of this latter meta-analysis [38] and other reviews [39,40], the European Society for Medical Oncology (ESMO) [41] recently recommended not to perform complementary cytology or pathology investigations (mediastinoscopy, transtracheal, transbronchial or transesophageal needle aspiration) if no hypermetabolic lymph nodes are detected by PET, except in the following situations: long axis diameter of main tumor > 3 cm, central tumor (Fig. 5), cN1 disease and lymphadenopathy with a short axis diameter > 1 cm as determined by CT. The guidelines issued by the Institut National du Cancer (INCa) are slightly different and do not take into account the size of the tumor. INCa recommends invasive mediastinal investigation in the absence of hypermetabolic mediastinal nodes on PET images in the following situations: central tumor (Fig. 5), doubts about hilar node involvement, short axis diameter of a mediastinal node > 16 mm as determined by CT, low uptake by the primary tumor (Fig. 6).

The positive predictive value of PET is lower. Indeed, because of the potential substantial therapeutic consequences, histological assessment should always be discussed for patients with significant mediastinal uptake to exclude false-positives caused by inflammation or infection (Fig. 7).

Evaluating metastatic spread
FDG PET-CT performs well for detecting occult metastases in soft tissue, in distant lymph nodes, in the viscera (lungs, liver, adrenal glands, etc.) (Fig. 8) and in bone. It also proves very useful for investigating pleural effusion or a contralateral nodule (M1 involvement). However, specific morphological imaging must be performed in addition to FDG PET to detect brain metastases.

The important role of PET-CT in metastatic staging has been highlighted by recent meta-analyses. In a first study, the performance of PET-CT for diagnosing metastases was assessed, irrespective of the type of metastases [42]. This meta-analysis included 9 studies (780 patients) and reported an overall sensitivity and specificity for PET of 93% and 96%, respectively.

Two other studies focused more specifically on bone metastasis staging [43,44]. Both demonstrated that FDG PET performed well. The sensitivity of PET was found to be greater than 90%, which is similar to bone scintigraphy and well above MRI (approx. 80%). The specificity of the different imaging techniques was similar: 94.6% for PET, 96.3%
for MRI and 91% for bone scintigraphy. Bone scintigraphy is probably not necessary when FDG PET is performed. INCa recommends performing bone scintigraphy only when PET-CT is not indicated [34].

It is extremely important to note, in particular if a single metastatic site, or only a few metastases, are detected by PET, that the metastatic nature of the lesion be confirmed by biopsy. Indeed, remote FDG uptake could be non-tumor related (false-positive), or due to another primary tumor, and in both cases the consequences differ from those of NSCLC metastasis [45]. Histological confirmation is also necessary if an extrathoracic lesion is detected in a patient with SCLC [35].

We shall complete this section on staging by underlining the fact that several randomized studies have demonstrated the importance of PET (or PET-CT) in treatment planning for NSCLC, particularly in terms of reducing the number of unnecessary thoracotomies. In particular, Fischer et al. presented their findings for 189 patients who underwent pre-surgical staging and were randomized for assessment either by PET-CT (98 patients) or conventional staging (91 patients) [46]. Sixty patients in the “PET-CT” group and 73 patients in the “conventional imaging” group underwent thoracotomy ($P=0.004$). Among these, 21 (35%) of the thoracotomies in the PET-CT group and 38 (52%) in the conventional imaging group were finally deemed as unnecessary ($P=0.05$) [46].

**Figure 5.** Pre-therapy PET-CT in a 56-year-old man with a large isolated tumor in the right hilum, related to proximal squamous cell carcinoma. In this case, hypermetabolic lymph nodes are not observed within the mediastinum on PET-CT images whereas mediastinoscopy demonstrated mediastinal node involvement (N2 stage, false-negative PET findings): a: Fused PET-CT image in the axial plane, parenchymal window; b: Fused PET-CT image in the axial plane, mediastinal window.

**Figure 6.** Staging in a 45-year-old man with primary adenocarcinoma of the lower left lobe. PET-CT scans showed a primary tumor with low FDG uptake (SUV$\text{max} = 2.8$). Mediastinal lymph nodes did not appear to be hypermetabolic on PET-CT images whereas mediastinoscopy demonstrated node involvement (N2 stage, false-negative PET findings): a: Fused PET-CT image in the axial plane, parenchymal window, that shows the low-uptake tumor in the lower left lobe; b: Fused PET-CT image in the axial plane, mediastinal window, that shows the small non-hypermetabolic lymph nodes in the right paratracheal space and the aortopulmonary window.

**Role of PET-CT in radiation therapy planning**

PET-CT is frequently used by radiation oncologists to optimize radiation fields. In the case of atelectasis, it performs better than CT for delimiting the margins of the primary tumor. Bradley et al. [47] compared these two imaging modalities as regards to their ability to define the tumor volume in 54 patients with locally advanced-stage NSCLC treated with radiotherapy. The impact on the radiation fields used was significant. The contours of lymph node stations were changed in 51% of cases. The average dose to the lungs was lower using PET.

In the study by Gregory et al., on 49 patients with lung cancer initially considered for curative treatment by external beam radiation, PET-CT had an important impact on the care planned for 23 patients (46.9%) and resulted most often in a higher disease stage [36]. PET findings significantly changed the radiotherapy target volumes for 7 patients (14.6%) [36].
of more than 20 was associated with shorter survival (survival rate of approx. 17% at 12 months vs. 70% for patients with a SUV of less than 20).

In a small series of 39 patients, researchers from Rouen University Hospital demonstrated that areas within the tumor with higher SUV values were at a greater risk of relapse, and suggested that these regions be target volumes for radiotherapy dose escalation [50].

A meta-analysis of 13 studies [51] showed the tumor SUVmax values, both before and after radiotherapy, were independent prognostic indicators. Higher FDG uptake in the primary tumor was associated with less local control and shorter overall patient survival [51]. Nevertheless, depending on studies, the SUVmax threshold (for categorizing the disease as good or poor prognosis) ranged from 5 to 15 [51], which suggests that its use is site- or observer-dependent.

In addition to the usual SUV parameters reflecting the level of tracer uptake by the lesion, other parameters may be used such as the metabolically active tumor volume (MATV) that reflects the uptake volume of the tumor. Among such parameters, total lesion glycolysis (TLG) is defined as the product of the MATV by the SUVaverage (average SUV of each voxel within the tumor volume).

The multicenter prospective study of the American College of Radiology Imaging Network (ACRIN) 6668/Radiation Therapy Oncology Group (RTOG) 0235 that included 250 patients with NSCLC treated with concomitant radiochemotherapy, evaluated the predictive value of pre- and post-therapy PET imaging. The results of this study were reported in several articles [52—54]. In a group of 214 patients, the authors demonstrated that MATV is an independent factor for predicting overall survival [54]. In 2015, Im et al. published a meta-analysis (that did not take into account the results of the previous study) aimed at assessing the prognostic value of MATV and TLG [55]. Among the 13 studies included in the meta-analysis (1581 patients), the likelihood of worsening and death was greater for patients with higher MATV or TLG values. Nevertheless, the authors could not define precisely threshold values for MATV and TLG that could be used to predict prognosis [55].

In the absence of a reproducible threshold that could be generalized to all sites, the prognostic value of quantitative parameters (SUV, MATV or TLG) remains questionable. In consequence, the only internationally recognized prognostic indication for PET-CT is accurate staging.

Evaluating the response to therapy

Evaluating the response to neoadjuvant chemotherapy and concomitant radiochemotherapy

An important meta-analysis mainly including patients with stage IB-IIIA NSCLC published in The Lancet, demonstrated that pre-operative chemotherapy improved survival [56]. Few studies have assessed the role of FDG PET in evaluating the response to neoadjuvant chemotherapy, either at an early stage (after 2–3 cycles) or at the end of treatment. An article published in 2008 in the Journal of Clinical Oncology showed, in a small group of 30 patients, that the selection of patients for curative surgery was improved by PET imaging at the end of induction chemotherapy [57]. In the

Figure 7. Staging in a 54-year-old woman with adenocarcinoma of the upper left lobe. FDG PET-CT shows a high-uptake primary tumor with moderately hypermetabolic mediastinal lymph nodes. Mediastinoscopy revealed that the moderate uptake within these lymph nodes actually reflected anthracycin (false-positive PET findings): a: Fused PET-CT image in the axial plane, parenchymal window, that shows a high-uptake tumor in the upper left lobe; b and c: Fused PET-CT image in the axial plane, mediastinal window, that shows moderately hypermetabolic bilateral mediastinal and hilar lymph nodes.

For specific indications, hypoxia or angiogenesis tracers could also be of interest.

Nevertheless, insufficient data is currently available to assert that using PET to define the target volume improves disease control and patient survival.

Prognostic value of pre-therapy PET-CT

The best prognostic tool is TNM staging. The diagnostic accuracy of PET-CT results in improved staging, and thus is of high prognostic value [48].

The level of FDG uptake could also be used to predict patient survival. The main parameter used in clinical practice to estimate FDG uptake is the maximum standardized uptake value, SUVmax (defined as the value of the voxel showing the highest uptake). In the study by Dhital et al. [49], the SUVmax of primary tumors emerged as an independent prognostic indicator in patients eligible for curative treatment. Indeed, the authors reported that an initial SUV
Figure 8. Staging in a 53-year-old man with a tumor of the left lung: a: Maximum intensity projection (MIP) PET image showing the tumor in the left lung as well as hypermetabolic subdiaphragmatic foci (multiple secondary foci in the adrenals and pancreas, and significant uptake by whole penis related to clinical priapism); b: Fused PET-CT image in the axial plane of the abdomen showing secondary FDG uptake foci in the adrenals (mostly the right adrenal) and the pancreas; c: Fused PET-CT image in the axial plane of the pelvic region showing hypermetabolic spread to the cavernous body causing priapism.

Prospective, phase 2, recently published NEOSCAN trial, PET was used to adapt neoadjuvant chemotherapy at an early stage [58]. In this trial, treatment was adapted for patients for whom the SUVpeak (average SUV of each voxel in a small region of interest centered on the voxel with the highest uptake) of the primary tumor decreased by less than 35% after two chemotherapy cycles. This study demonstrated that an approach based on the metabolic response measured by FDG PET could be useful for assessing the impact of novel drug strategies [58].

PET could also be useful for evaluating the early response to targeted therapy, particularly tyrosine kinase inhibitors [59,60]. In a group of 60 patients with NSCLC treated with neoadjuvant erlotinib, an EGF receptor inhibitor, FDG PET imaging three weeks into treatment was shown for to be relevant for assessing the histopathological response, a significantly greater decrease of the SUVmax, being associated with a favorable histopathological response. At this same time point, the relative change in tumor size on diagnostic CT was not a significant predictor [60].

FDG PET has also been used to evaluate the early response to concomitant radiochemotherapy [61]. In a series of 28 patients with NSCLC, all treated with concomitant radiochemotherapy, the relative change of TLG after two weeks of treatment (20 Gy) was found to be a predictor of progression free survival (PFS) [61]. It should be noted that pretreatment TLG was also prognostic for PFS [61].

One of the main findings of the prospective, multicenter ACRIN 6668/RTOG 0235 study including 250 patients treated with concomitant radiochemotherapy was that high SUVmax (and SUVpeak) values, measured approximately 14 weeks after the end of treatment, are associated with shorter survival, although a prognosis threshold could not be defined precisely. In that study, pretreatment SUVmax values were not associated with survival [52]. A more recent study showed that persistent high nodal SUVs after the end of radiochemotherapy were associated with poorer local control (P < 0.001) [53].

In short, several studies have shown the relevance of FDG imaging in evaluating the response to induction chemotherapy and concomitant radiochemotherapy, both during and after the end of treatment. PET performs well for assessing the response to targeted therapy such as tyrosine kinase inhibitors. However, most of the studies were conducted in a single center setting and on small series of patients and different evaluation criteria were used. Prospective, multicenter trials are therefore needed to confirm the role of FDG PET in evaluating the response to therapy.

Evaluating the response to therapy in patients with metastatic cancer

CT-based evaluation of therapy generally follows the RECIST criteria (Response Evaluation Criteria in Solid Tumors). However, limitations for RECIST criteria have been reported in certain situations. Indeed, certain metastatic lesions such as bone metastases are difficult to evaluate using CT. A
metabolic response is usually observed earlier than the decrease in size of the tumor. As could be expected, FDG PET imaging has been included in the revised RECIST 1.1 criteria [62], and the detection of new lesions by FDG PET is now used to categorize a patient as having progressive disease.

Several studies have demonstrated that PET imaging proves useful for assessing the response to chemotherapy [63,64] or targeted therapy [65] in patients with metastatic NSCLC (Fig. 9). Still, the best time for evaluating the response to therapy using PET has not been determined, and unlike CT-based evaluation, no consensus has been reached or interpretation criteria validated for PET findings. Qualitative analysis is subjective; quantitative analysis depends on the many parameters used, for the most part technical (PET-CT system specifications, acquisition and reconstruction parameters). Several workgroups have developed SUV-based criteria. This was the case for the criteria published by the European Organization for Research and Treatment of Cancer (EORTC) in 1999 [66], and more recently the PERCIST criteria published by an American team [67].

PET imaging is therefore considered to be a relevant tool for assessing the treatment of metastatic disease and is routinely used for this indication. Nevertheless, PET interpretation criteria are not as well defined as for CT imaging and, more often than not, the analysis is qualitative, and therefore partly subjective.

Detection and staging of recurrent disease

A significant portion of patients monitored for NSCLC are at risk of recurrence, even after curative surgery. It has not been evidenced that follow-up imaging improves the survival of such patients. As of yet, only CT is recommended for asymptomatic patients, and clinicians are advised not to use PET on a routine basis to monitor these patients. However, PET imaging may be useful for the differential diagnosis of recurrence or residual disease and post-radiotherapy fibrosis (if performed at least 3 months after radiotherapy). It has also been shown to perform well for detecting mediastinal recurrence or remote metastatic sites. The performances of PET alone, PET-CT and conventional imaging techniques (radiography, CT, bone scintigraphy, and MRI) for detecting recent lung cancer were compared in a meta-analysis of 13 studies (1035 patients) [68]. The sensitivity and specificity of PET-CT were significantly higher than those of conventional imaging. The sensitivity of PET, PET-CT and conventional imaging were estimated at 94%, 90%, and 78% respectively. The specificities reported were 84%, 90% and 80%, respectively.

PET-CT seems therefore to be a promising tool for monitoring patients treated for lung cancer. Nonetheless, these findings need to be confirmed at a larger scale in multicenter, randomized, prospective studies.

Conclusion

PET-CT may be a useful tool for investigating SPNs of >8 mm in diameter. However, due to the risk of false-negative findings, PET is not indicated for characterizing small nodules. The main cancers for which false-negative findings are observed are typical carcinoid tumors and certain early forms of adenocarcinoma, such as adenocarcinoma in situ.

FDG PET imaging is indicated both for loco-regional and remote staging of lung cancer (except for brain metastases) when the first-line modality, CT of the thorax/abdomen/pelvis and brain with injection of contrast medium, does not reveal the presence of remote sites. Negative PET-CT findings for N2 stage disease avoid the need for invasive investigation, except in the following cases: central tumor, doubts about hilar lymph node involvement, large mediastinal lymph node on CT scan, or low level of uptake by the primary tumor [34]. If areas of increased uptake are observed within the mediastinum, histological assessment should be performed to exclude false-positive findings owing to the potential impact of such findings on treatment.
The level of FDG uptake, which can be quantified using various PET imaging parameters (SUV, MATV, TLG), is of prognostic value for NSCLC, but a prognosis threshold for categorizing patients still needs to be defined.

PET-CT imaging performs better than CT for defining the target volume when planning radiotherapy, however its potential positive impact on the overall care and notably the survival of patients with lung cancer remains to be confirmed.

PET-CT is potentially an interesting modality for evaluating the response to neoadjuvant treatment, concomitant radiochemotherapy and chemotherapy in patients with metastatic disease. PET-CT also seems promising for monitoring patients treated for lung cancer. Nevertheless, its role for these indications and its potential advantages over CT need to be confirmed via a greater number of prospective, multicenter studies.

### Clinical case

Fifty-nine-year-old man with a history of smoking, showing syndrome of inappropriate ADH secretion.

### Questions

1. In this patient suspected of having a paraneoplastic syndrome, which of the following imaging examinations should be performed?
   a) Chest X-ray
   b) Thoracic CT
   c) Pituitary MRI
   d) FDG PET-CT

2. PET-CT shows infiltration of the right hilum, mediastinal lymph node involvement and a lesion within the liver (Fig. 10). What is the next step for this patient?
   a) Brain MRI
   b) Immediate chemotherapy
   c) Bronchial fibroscopy with bronchoalveolar lavage and sampling
   d) Liver biopsy

Following 3 cycles of chemotherapy with etoposide and cisplatin, a complete metabolic response is reached. Chemotherapy is discontinued due to acute renal failure. Thoracic radiotherapy, during which the patient received 55 Gy over 20 sessions, was started on June 25, 2015. It was followed by prophylactic cranial radiotherapy, then liver radiofrequency ablation. The patient’s response to therapy is reassessed by PET in December 2015, at some interval after the end of treatment (Fig. 11). What are the findings of this PET scan?
   a) Has the liver lesion disappeared?
   b) Is the metabolic response complete in the mediastinum?
   c) Are post-radiotherapy lung lesions observed?

### Answers

1.
   a) Chest X-ray
   b) Thoracic and abdominal CT. CT revealed multiple enlarged mediastinal and hilar lymph nodes and suspicious features within the liver.
   c) MRI is not a first-line modality.
   d) FDG PET-CT (Fig. 10)

2.
   a) Brain MRI is indicated in lung cancer staging. MRI is normal for this patient.
   b) Chemotherapy should never be implemented without prior histological confirmation of malignancy.
   c) Bronchial fibroscopy is performed to collect histological samples, which here resulted in the diagnosis of clear cell carcinoma. The disease is classified as T0 N3 M1.
   d) Liver biopsy is not performed at first because it is an invasive procedure; MRI of the liver is performed to confirm the metastatic disease.
Figure 10. Initial PET-CT assessment of a 59-year-old man with syndrome of inappropriate ADH secretion (February 2015): a: MIP PET image shows hypermetabolic foci in the right hilum and mediastinum, as well as a small hypermetabolic nodule in the dome of the liver; b: Fused PET-CT image in the axial plane through the mediastinum revealing hypermetabolic lymph nodes anterior to the superior vena cava, within the paratracheal space and aortopulmonary window; c: Fused PET-CT image in the axial plane through the dome of the liver showing a small hypermetabolic nodule in the liver.

Figure 11. Same patient as in Fig. 10. PET-CT assessment of therapy after the end of treatment in December 2015: a: MIP PET image that shows residual hypermetabolic foci in the right hilum and mediastinum. The hypermetabolic nodule in the dome of the liver has disappeared; b: Fused PET-CT image in the axial plane through the thorax, parenchymal window, showing hypermetabolic foci in the subcarinal region, in the right hilum, and in the paramediastinal region of the lower right lobe, in a context of limited radiation-induced pneumopathy; c: Fused PET-CT image in the axial plane through the thorax (same level as previous section), tissue window, showing hypermetabolic lymph nodes in the subcarinal region and in the right hilum.
3.
   a) The hypermetabolic nodule in the liver has disappeared.
   b) The mediastinal response is not complete, as is confirmed by PET-CT imaging in April 2016 (images not shown).
   c) Post-radiotherapy lesions are observed but are limited.

Disclosure of interest

The authors declare that they have no competing interest.

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