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REVIEW

Present and future roles of FDG-PET/CT imaging in the management of lung cancer

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Abstract Integrated positron emission tomography/computed tomography (PET/CT) using 2-[^{18}F]fluoro-2-deoxy-D-glucose (^{18}F-FDG) has emerged as a powerful tool for combined metabolic and anatomic evaluation in clinical oncologic imaging. This review discusses the utility of ^{18}F-FDG PET/CT as a tool for managing patients with lung cancer. We discuss different patient management stages, including diagnosis, initial staging, therapy planning, early treatment response assessment, re-staging, and prognosis.

Keywords Fluorodeoxyglucose (FDG) · Positron emission tomography/computed tomography (PET/CT) · Lung cancer · Staging · Treatment response assessment

Introduction

Lung cancer is the most common cancer; despite major advances in prevention and treatment, it remains the leading cause of cancer-related death worldwide [1]. Over 85 % of cases are of non-small cell lung cancer (NSCLC), while the remainder are small cell lung cancers (SCLCs) [2]. Accurate staging is essential for treatment planning and determining patient prognosis. NSCLC staging is performed according to the tumor, node, metastasis (TNM) classification, which was updated in 2009 by the International Union Against Cancer and American Joint Committee on Cancer to include proposals from the International Association for the Study of Lung Cancer [3].

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Integrated positron emission tomography/computed tomography (PET/CT) with 2-[^{18}F]fluoro-2-deoxy-D-glucose (^{18}F-FDG) is a powerful tool for combined metabolic and anatomic evaluation of cancer. In the clinical setting, ^{18}F-FDG PET/CT has improved diagnostic accuracy and influenced the initial staging, treatment optimization, therapy response monitoring, restaging, and prognostication of lung cancer. Here, we review the current and future roles of ^{18}F-FDG PET/CT in lung cancer management, and discuss its usefulness and limitations.

Diagnosis

A solitary pulmonary nodule (SPN) is defined as a single spherical or oval lesion (<3 cm in diameter) without accompanying atelectasis or adenopathy. ^{18}F-FDG PET/CT has 97 % sensitivity and 85 % specificity for diagnosing SPN malignancy [4]. In a meta-analysis of 8511 nodules including 70 ^{18}F-FDG PET and PET/CT studies [5], the pooled sensitivity for the detection of SPN malignancy was 0.89 [95 % confidence interval (CI), 0.86–0.91] and the pooled specificity was 0.75 (95 % CI, 0.71–0.79). Although the specificity of ^{18}F-FDG PET is superior to that of CT, it is far from ideal. Dual time-point ^{18}F-FDG PET by acquisition of delayed imaging has been proposed as a means to improve diagnostic specificity for SPNs [6], although its usefulness remains controversial [7]. A meta-analysis [8] demonstrated that the sensitivity and specificity of dual time-point ^{18}F-FDG PET/CT were 85 and 77 %, respectively, which are similar to those for single time-point ^{18}F-FDG PET/CT. Kawano et al. [9] has compared the maximum standardized uptake value (SUVmax) of primary lung cancer between free-breathing PET/CT and deep-inspiration breath-hold PET/CT, and demonstrated that the SUVmax of free-breathing PET/CT should not be considered to be accurate, especially in the lower lung area and for small pulmonary lesions, whereas breath-hold PET/CT presented a complete match between CT and PET, leading to the expectation that it provides precise SUVmax values.

There are several potential pitfalls for SPN assessment using ^{18}F-FDG PET. Inflammatory conditions such as pneumonia, aspergillosis, tuberculosis, active sarcoidosis, and granulomatosis with polyangiitis can result in high metabolic activity due to increased granulocyte and/or macrophage activity [10]. Current PET/CT cameras have limited spatial resolution (5–6 mm), leading to false-negative results and suggesting that a critical mass of metabolically active malignant cells must be present for accurate detection. Therefore, ^{18}F-FDG PET could result in a false-negative diagnosis for lesions <1 cm and those with low metabolic activity and low cell density (e.g., carcinoid tumors, adenocarcinoma in situ, and well-differentiated adenocarcinoma) [11, 12].

Staging

Initial disease staging in newly diagnosed NSCLC can correctly differentiate patients with potentially curable disease from those indicated for palliative therapy. ^{18}F-FDG PET/CT has greater staging accuracy than either of the modalities alone because of the improved detection of additional lymph node involvement or distant metastasis [13, 14].

T staging

Primary lung tumor extent is mostly evaluated using thoracic CT, which, in cases of superior sulcus extension, thoracic wall invasion, or heart or large vessel involvement, is supplemented by magnetic resonance imaging (MRI). The major contribution of ^{18}F-FDG PET/CT is accurate tumor delineation from surrounding post-obstructive atelectasis (Fig. 1), which is important for therapy planning; ^{18}F-FDG PET/CT can also be useful for detecting chest wall invasion [15].

Locoregional lymph node staging (N staging)

The most commonly used technique for N staging of patients with lung cancer is CT, due to its easy accessibility, relatively low cost, and noninvasiveness. Mediastinal and hilar lymph nodes with a short axis of >10 mm are classified as enlarged. However, lymph node size alone has poor specificity for detecting metastatic involvement because enlargement also occurs under benign inflammatory conditions. Moreover, small-sized nodes might contain tumoral deposits [16]. A critical advantage of ^{18}F-FDG PET/CT over CT is the detection of neoplastic mediastinal adenopathies <1 cm in size (Fig. 2); the superiority of ^{18}F-FDG PET [17] and PET/CT [18, 19] over CT for mediastinal staging is well established. A meta-analysis of 39 studies showed that the median sensitivity and specificity of CT were 61 and 79 %, respectively, whereas those for ^{18}F-FDG PET were 85 and 90 % [17]. Furthermore, in a meta-analysis including 20 studies involving 3028 patients with NSCLC, ^{18}F-FDG PET/CT had a pooled sensitivity of 0.72 (95 % CI, 0.68–0.75) and a specificity of 0.90 (95 % CI, 0.88–0.91) [18]. With respect to nodal size, the sensitivity of ^{18}F-FDG PET/CT in detecting malignant involvement was 32.4 % in nodes <10 mm and 85.3 % in nodes ≥10 mm [19].

False-negative results due to micrometastasis occur because of the limited spatial resolution of PET, whereas false-positive results were reported in the setting of endemic granulomatous disease. Evidence suggests that

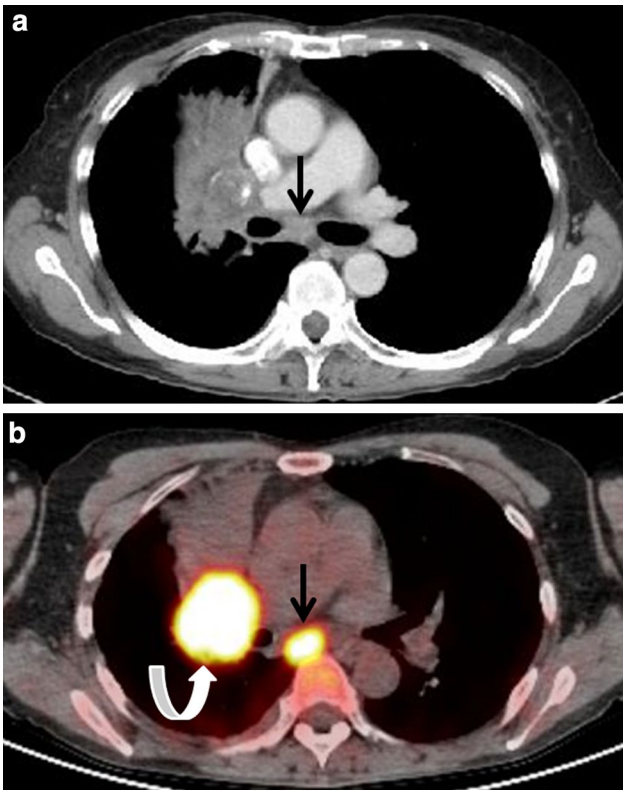

Fig. 1 A 68-year-old man with non-small-cell lung cancer with post-obstructive atelectasis and multiple lymph node metastases at initial staging. **a** Contrast-enhanced computed tomography (CT) shows a mass and atelectatic lung extending from the superior right hilum, without a clear distinction between the soft-tissue mass and the consolidated lung, as well as a 12 × 13 mm swollen subcarinal lymph node (#7) (*arrow*), suggesting the presence of spreading nodal cancer. **b** Positron emission tomography/CT using 2-[^{18}F]fluoro-2-deoxy-D-glucose (^{18}F-FDG) shows intense ^{18}F-FDG uptake in the primary tumor (*curved arrow*), with no uptake in obstructive atelectasis of the right upper lobe. The swollen subcarinal lymph node shows intense FDG uptake (*arrow*), confirming nodal metastasis

^{18}F-FDG PET findings should not replace histological confirmation. A recent multicenter study indicated that ^{18}F-FDG PET/CT had high NPV (91 %) and specificity (83 %) but a low positive predictive value (PPV) (29 %) [20]. Similar findings were confirmed in a prospective trial where the mediastinal staging of 149 patients by ^{18}F-FDG PET/CT was confirmed histopathologically; overall sensitivity, specificity, PPV, and NPV were 70, 94, 64, and 95 %, respectively [21]. The low PPV indicated that invasive mediastinal sampling should be conducted when lymph node involvement is suspected and when making curative surgical decisions because false positivity could be a confounding factor, especially in those with granulomatous diseases [22]. In contrast, the high NPV of ^{18}F-FDG PET/CT suggested that invasive sampling of mediastinal lymph nodes could be safely omitted. False-negative findings may be seen in cases of low tumoral burden in metastatic lymph nodes ("minimal N2"), where a reasonable prognosis after surgical resection is expected [23]. However, in the presence of a centrally located tumor or hilar lymphadenopathy, mediastinoscopy should be conducted because limitations in spatial resolution combined with highly active hilar lymph nodes or tumoral lesions might mask the metabolic activity of nearby lymph nodes.

In summary, ^{18}F-FDG PET/CT is more accurate for N staging than CT; however, the spatial resolution of PET is not sufficient to detect early lymph node involvement and micrometastases, and ^{18}F-FDG PET/CT cannot replace histological staging.

Extrathoracic staging (M staging)

Identification of distant metastases has major implications for management and prognosis. Approximately 18–36 % of patients with newly diagnosed NSCLC have distant metastases at presentation [24]. The adrenal glands, bones, liver, and brain are the most common metastatic sites.

Whole-body ^{18}F-FDG PET/CT is more accurate than conventional imaging for detection of metastatic foci (Fig. 3) [13, 14]. A meta-analysis involving 6 studies with 659 patients [25] revealed that the pooled sensitivity and specificity of ^{18}F-FDG PET/CT for detecting distant metastasis from NSCLC were 0.87 (95 % CI, 0.55–0.98) and 0.96 (95 % CI, 0.93–0.98), respectively.

^{18}F-FDG PET/CT has high sensitivity (97 %) and specificity (86 %) for metastatic adrenal disease in NSCLC [26], which eliminates the need for invasive sampling [27]. However, the partial volume effect must be considered when evaluating small lesions (<1 cm). False positives have been reported; therefore, histopathological confirmation is warranted when treatment decisions are based on an isolated adrenal gland finding.

In patients with lung cancer, whole-body ^{18}F-FDG PET/CT for detecting bone metastases showed sensitivity and specificity that were superior to bone scintigraphy [28, 29]. A systematic review that included 6 articles (1746 patients in total) demonstrated that the pooled sensitivity and specificity of ^{18}F-FDG PET/CT and PET were 0.93 (95 % CI, 0.88–0.96) and 0.95 (95 % CI, 0.91–0.98), respectively, whereas those for bone scintigraphy were 0.87 (95 % CI, 0.79–0.93) and 0.82 (95 % CI, 0.62–0.92), respectively [29].

^{18}F-FDG PET/CT can be used as a reliable and noninvasive method for the detection of pleural dissemination (Fig. 4), but the tiny lesion could not even be detected by ^{18}F-FDG PET/CT (Fig. 5). Erasmus et al. [30] reported that the sensitivity, specificity, positive predictive value, negative predictive value, and accuracy of pretreatment ^{18}F-FDG PET/CT for detecting pleural metastases in

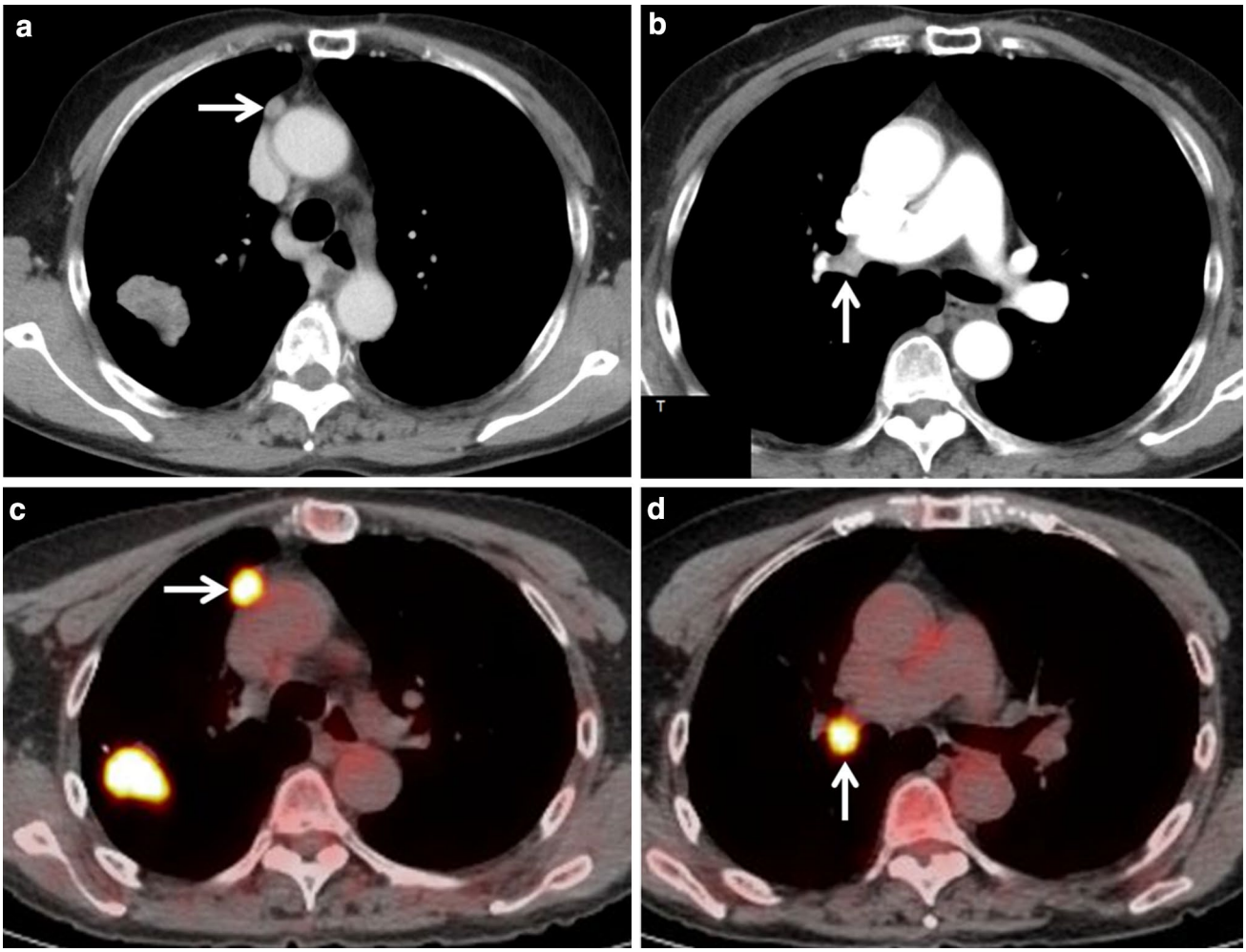

Fig. 2 A 65-year-old man with ipsilateral mediastinal and hilar nodal metastases arising from non-small cell lung cancer. **a** Contrast-enhanced computed tomography (CT) shows a 3.2 × 2.5 cm solid mass with enhancement in the right upper lobe, suggesting lung cancer. A small 7 × 8 mm lymph node is seen at the anterior mediastinum (#3a, *arrow*), suggesting the absence of spreading nodal cancer. **b** Contrast-enhanced CT shows one 10 × 12 mm swollen lymph node at the right hilar area (#12, *arrow*), suggesting the presence of spreading nodal cancer. **c** Positron emission tomography (PET)/CT using 2-[^{18}F]fluoro-2-deoxy-D-glucose (^{18}F-FDG) shows intense ^{18}F-FDG uptakes corresponding to the lung mass and the anterior mediastinal node (*arrow*), confirming lung cancer and ipsilateral mediastinal nodal metastasis. **d** ^{18}F-FDG PET/CT shows intense ^{18}F-FDG uptake corresponding to the right hilar node (*arrow*), confirming the ipsilateral hilar nodal metastasis. The patient underwent right upper lobe resection and lymph node dissection; examination of the histopathological specimen revealed extensive lymph node involvement in the two nodes (pT2N2)

25 patients with NSCLC were 95, 67, 95, 67, and 92 %, respectively.

High glucose uptake by gray matter and small lesion size limit the diagnostic power of ^{18}F-FDG PET, so MRI is the preferred modality for detecting brain metastases [31].

^{18}F-FDG PET/CT could unveil metastases that otherwise escape detection (e.g., soft-tissue lesions, small supraclavicular lymph nodes, and retroperitoneal lymph nodes). Previous studies found that ^{18}F-FDG PET and PET/CT resulted in a staging change in 27–62 % of patients with NSCLC and altered patient management in 19–52 % [13, 14, 32, 33]. Hicks et al. showed that ^{18}F-FDG PET staging had a major impact on the treatment plan in 54 of 153 (35 %) patients with newly diagnosed NSCLC [32]. Treatment was changed from curative to palliative in 34 patients and from palliative to curative in 6. In 14 patients, the treatment modality was altered without a change in treatment intent. In summary, ^{18}F-FDG PET/CT is a highly sensitive and specific modality for detecting distant metastases of lung cancer (excluding brain metastases).

Radiotherapy planning

Radiotherapy is the treatment of choice for curative intent in patients with early-stage (stage I–II) NSCLC who are

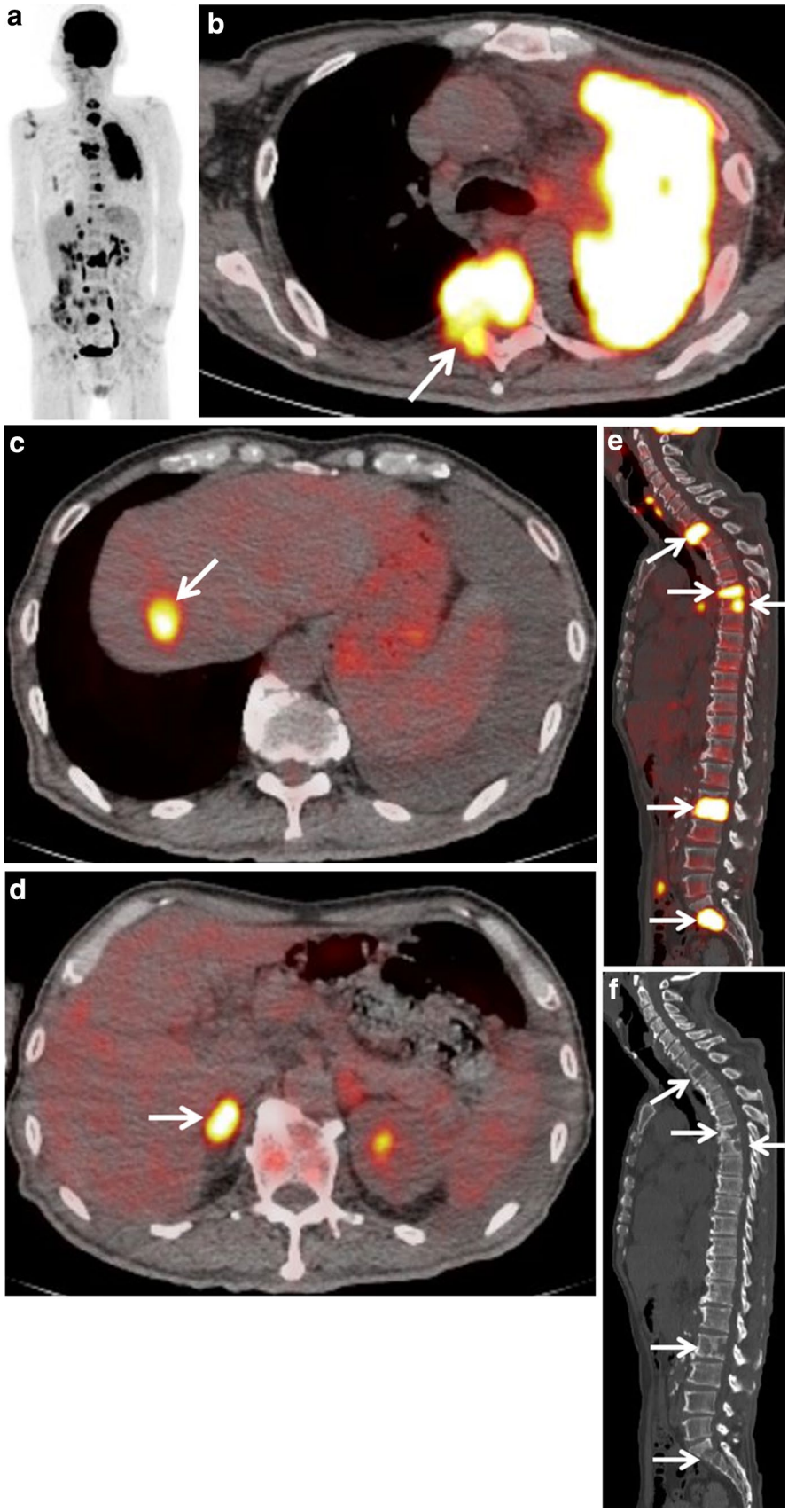

Fig. 3 A 64-year-old woman with non-small cell lung cancer with liver, adrenal gland, lung, and bone metastases at initial staging. **a** Maximum intensity projection of an image acquired by positron emission tomography (PET) using 2-[^{18}F] fluoro-2-deoxy-D-glucose (^{18}F-FDG) shows multiple abnormal intense uptakes in both lungs as well as the liver, right adrenal gland, and spine. **b** ^{18}F-FDG PET/computed tomography (CT) shows abnormal FDG uptakes corresponding to left lung cancer and metastasis to the vertebra (*arrow*). **c** ^{18}F-FDG PET/CT shows abnormal FDG uptake corresponding to liver metastasis (*arrow*). **d** ^{18}F-FDG PET/CT shows abnormal FDG uptake corresponding to adrenal gland metastasis (*arrow*). **e** ^{18}F-FDG PET/CT and **f** CT alone show abnormal FDG uptakes corresponding to multiple osteolytic changes in the spine (*arrows*), confirming multiple bone metastases

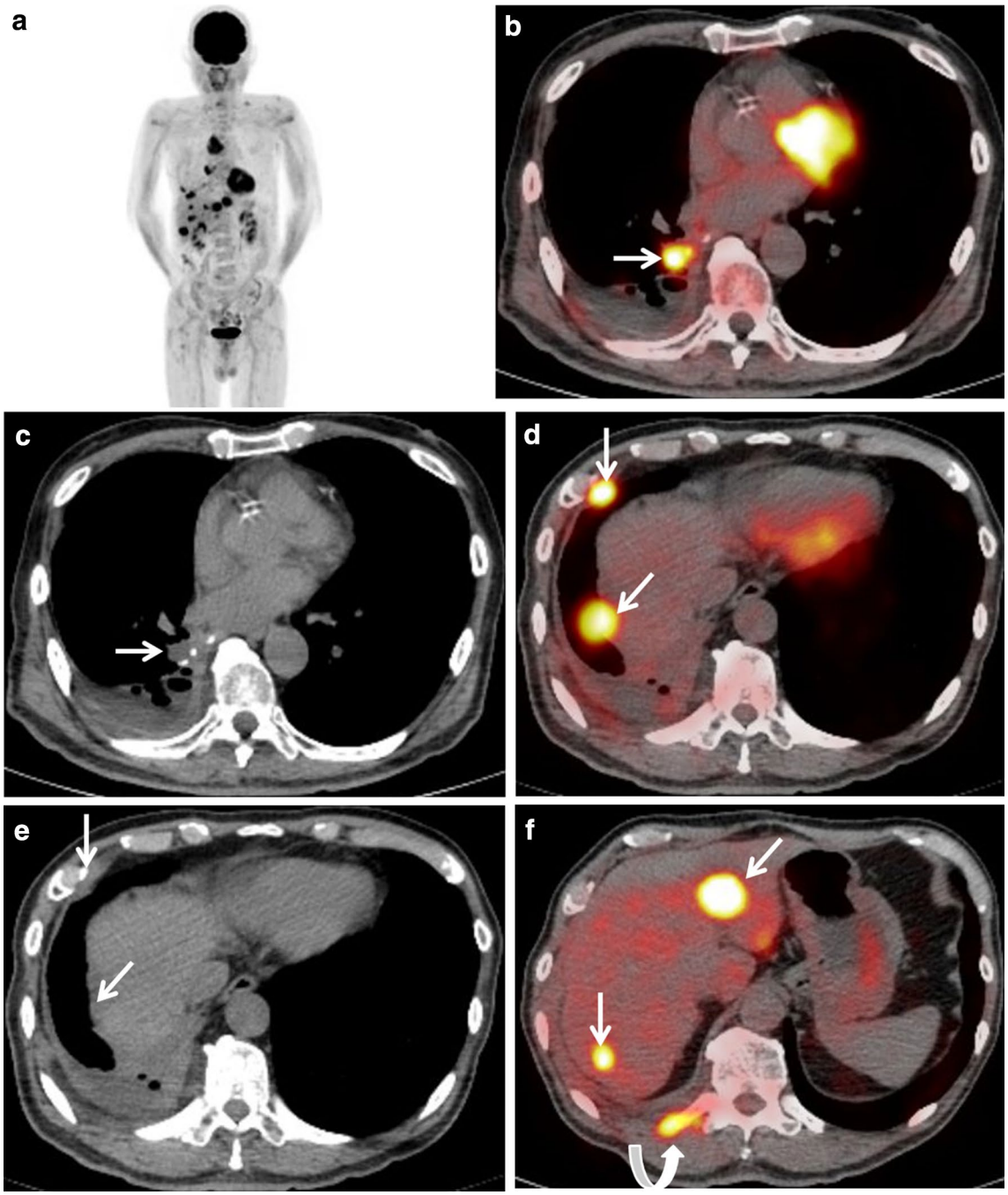

Fig. 4 A 76-year-old woman who underwent right lower lobe resection due to non-small cell lung cancer 6 months prior showing multiple recurrent lesions consisting of local recurrence, mediastinal nodal metastasis, pleural dissemination, liver metastases, and bone metastases at restaging. **a** Maximum intensity projection of an image acquired by positron emission tomography (PET) using 2-[^{18}F]fluoro-2-deoxy-D-glucose (^{18}F-FDG) shows multiple abnormal intense uptakes in the right lung, mediastinum, right pleura, liver, and spine. **b** ^{18}F-FDG PET/computed tomography (CT) and **c** CT alone show abnormal FDG uptake corresponding to local recurrence at the postoperative stump (*arrow*). It is difficult to diagnose this local recurrence by CT alone. **d** ^{18}F-FDG PET/CT and **e** CT show abnormal FDG uptakes corresponding to the right pleural dissemination (*arrows*). It is difficult to diagnose pleural dissemination by CT alone. **f** ^{18}F-FDG PET/CT shows abnormal FDG uptakes corresponding to liver metastases (*arrows*) and pedicle bony metastasis (*curved arrow*). It is difficult to diagnose this bone metastasis based on CT alone

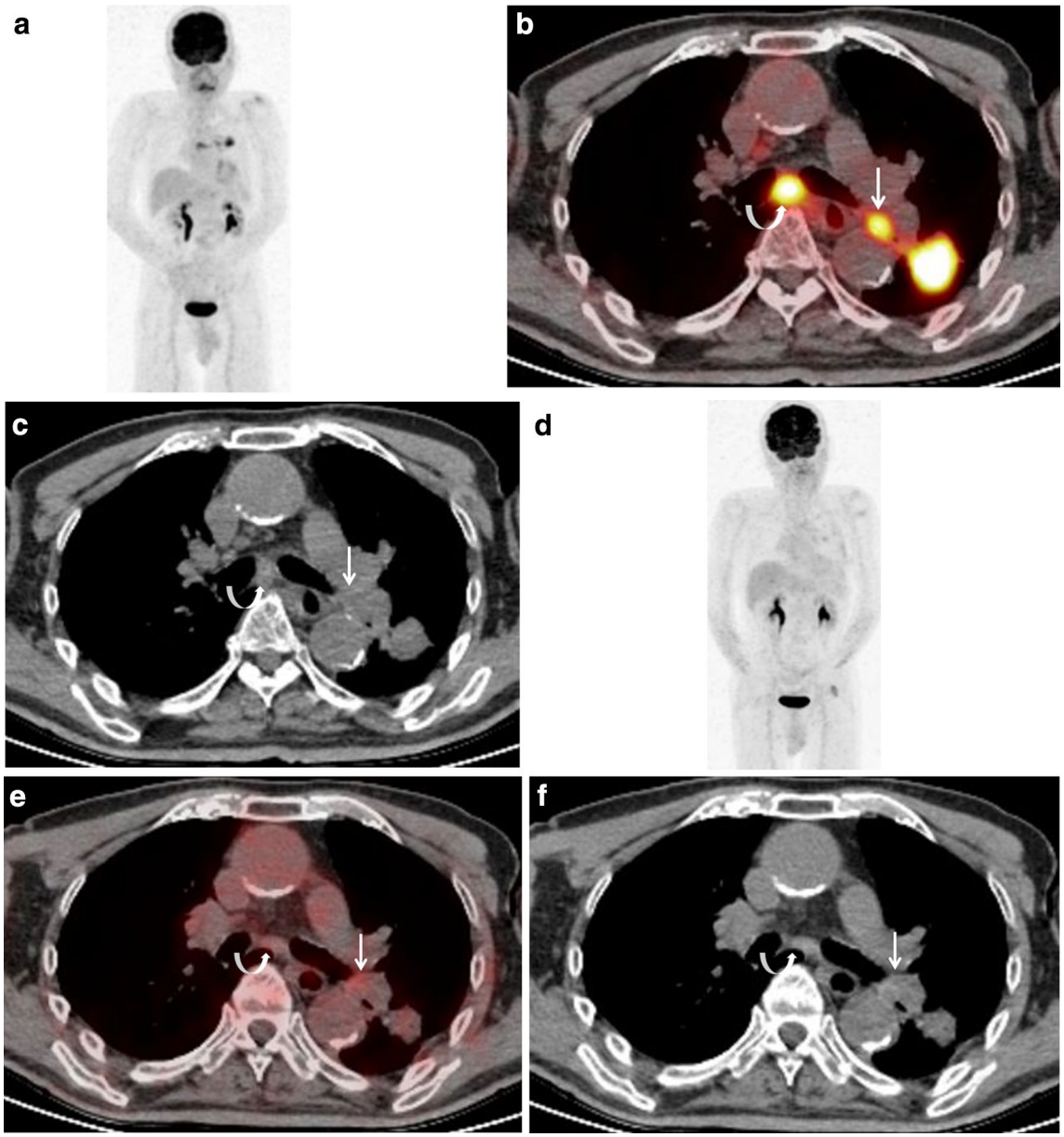

Fig. 5 A 79-year-old man with non-small cell lung cancer and mediastinal and hilar nodal metastases at therapy response evaluation. **a** Pretreatment maximum intensity projection of an image acquired by positron emission tomography (PET) using 2-[^{18}F]fluoro-2-deoxy-D-glucose (^{18}F-FDG) shows multiple abnormal intense uptakes in the left lung, hilum, and mediastinum. **b** Pretreatment ^{18}F-FDG PET/computed tomography (CT) and **c** CT show moderate FDG uptakes corresponding to one left 2.3 × 2.3 cm solid mass (SUVmax 8.38), one 9 × 9 mm swollen hilar lymph node (SUVmax 4.70, *arrow*), and one 14 × 16 mm swollen mediastinal lymph node (SUVmax 5.52, *curved arrow*), suggesting lung cancer with nodal metastases (cT1N2). Curative surgery was attempted in this patient but it was not accomplished because of tiny pleural dissemination which could not be detected by ^{18}F-FDG PET/CT. The patient underwent chemotherapy. **d** MIP by ^{18}F-FDG PET at 3 months after starting gefitinib treatment shows faint uptakes in the left lung, hilum, and mediastinum. **e** ^{18}F-FDG PET/CT and **f** CT at 3 months after starting gefitinib treatment show mildly decreased or a virtual absence of ^{18}F-FDG uptake corresponding to the primary tumor (18 × 21 mm, SUVmax 1.71), the metastatic hilar node (8 mm, SUVmax 2.15, *arrow*), and the metastatic mediastinal node (10 × 17 mm, SUVmax 1.70, *curved arrow*)

contraindicated for surgery. The majority of ^{18}F-FDG PET studies are performed for preoperative staging; however, the metabolic information provided by the procedure may facilitate radiotherapy planning. Accurate identification of locoregional tumor load could determine the type of therapeutic intervention, the tumor volume targeted by radiotherapy, and (consequently) the toxicity. For classical radiotherapy planning, CT is used to delineate the target tumor volume. Disadvantages associated with CT include poor delineation of some tumors because of accompanying

atelectasis and limited accuracy for detecting lymphatic involvement. With its improved accuracy, ^{18}F-FDG PET/CT-based radiotherapy planning could improve delineation and avoid unnecessary irradiation to adjacent nontumoral tissues. Furthermore, in patients with NSCLC, ^{18}F-FDG PET could lead to significant treatment strategy modifications and radiotherapy planning alterations [34]. Studies concerning the impact of ^{18}F-FDG PET/CT on radiotherapy planning have demonstrated that the tumoral and nodal contours could be altered in >50 % of patients with probable improved tumoral coverage [35]. Additionally, ^{18}F-FDG PET/CT-derived tumor volumes were smaller compared to those derived by CT alone; this facilitates radiation dose escalation while respecting normal tissue constraints [36]. In a study of 21 patients with clinical CT stage N2–3 tumors, the gross tumor volume significantly decreased from 13.7 ± 3.8 cm^3 on the CT scan to 9.8 ± 4.0 cm^3 on the ^{18}F-FDG PET/CT scan. In another study, the incorporation of ^{18}F-FDG PET/CT data for radiotherapy planning significantly reduced the estimated doses to the esophagus and lungs [37]. Moreover, interobserver variability in delineating tumor volumes was diminished when ^{18}F-FDG PET was used for planning [38]. In addition to its enhanced clinical value in radiotherapy planning, the use of ^{18}F-FDG PET/CT altered the therapeutic strategy in 40 % of patients with NSCLC, which resulted in an overall cost reduction for treatment in this group [39].

The use of respiratory gating in integrated ^{18}F-FDG PET/CT has been evaluated recently, especially its clinical impact on planning target volumes for radiation therapy. Preliminary results in patients with lung cancer showed that respiratory-gated ^{18}F-FDG PET/CT, which tailors the target volume to lesion motion, can affect the size and shape of target volumes, leading to improved delineation [40].

Therapy response evaluation

In oncological settings, early assessment of therapeutic response enables treatment alteration in cases of nonresponse. Response assessment using conventional imaging depends mostly on changes in tumor volume. Therapy-induced tumor size reduction is measured by radiologic techniques, such as CT, according to the World Health Organization and the response evaluation criteria in solid tumors (RECIST). However, compared to conventional structural imaging modalities, evaluation of metabolic activity using ^{18}F-FDG PET provides valuable response information at an earlier time point [41]. In 73 NSCLC patients evaluated using ^{18}F-FDG PET and enhanced CT before and at a median interval of 70 days after radiotherapy and chemoradiotherapy, ^{18}F-FDG PET metabolic and CT morphologic response categories were identical in 40 % of patients, with significantly more patients ($n = 34$) showing a complete metabolic response (CMR) than showing a complete response on CT ($n = 10$) [42]. Furthermore, response assessment with morphologic imaging techniques has limitations in distinguishing necrotic tumors or fibrotic scars from residual tumor tissue. From this point of view, PET can be used to characterize tissues based on their biochemical and biological features (Fig. 5) [41].

Response evaluation using ^{18}F-FDG PET in patients who underwent chemotherapy or chemoradiotherapy has been evaluated extensively [43–46]. Studies comparing ^{18}F-FDG PET and non-enhanced CT suggested that ^{18}F-FDG PET was a better predictor of response [47]. Changes in tumor metabolic activity on ^{18}F-FDG PET scans were significantly greater in histologically confirmed chemotherapy responders compared to nonresponders [43]. Furthermore, the change in SUVmax after chemotherapy/chemoradiotherapy showed a near-linear relationship with the percentage of nonviable tumor cells in the resected tumors [44]. The outcomes of patients who demonstrated a CMR were superior to those of the patients who did not [41–46].

The utility of ^{18}F-FDG PET for therapy response assessment and outcome prediction after neoadjuvant radiochemotherapy was evaluated in 70 patients with stage III NSCLC [45]. That study demonstrated that the sensitivity, specificity, and accuracy of FDG-PET to detect residual viable primary tumor were 95, 80, and 91 %, respectively. Additionally, patients with a CMR (as determined by qualitative criteria) or an 80 % reduction in the SUVmax had significantly longer survival compared to those with a partial metabolic response (PMR). Progressive disease on ^{18}F-FDG PET was significantly associated with an unfavorable outcome. Similarly, Mac Manus et al. [42] demonstrated that patients showing a CMR survived longer than those showing a PMR; in turn, survival in the latter group was superior to that of nonresponders (stable or progressive metabolic disease). By contrast, a recent study involving 89 patients from two consecutive phase II clinical trials of chemotherapy for NSCLC found that the response on ^{18}F-FDG PET did not predict outcome, whereas RECIST responses were associated with overall survival (OS) [47].

Total lesion glycolysis (TLG) is calculated as the product of metabolic tumor volume (MTV) and the mean SUV of all voxels. MTV is defined as the volume of the delineated tumor on PET. In patients with locally advanced NSCLC treated with concomitant chemoradiotherapy, TLG has emerged as a predictor of progression-free survival (PFS) [48] and OS [49]. Yossi et al. [49] showed that a TLG decrease of >15 % after 30 Gy (up to a total dose of 66–70 Gy in 2-Gy fractions) was associated with improved OS and PFS.

One advantage of ^{18}F-FDG PET is the early detection of biological changes caused by decreased glucose metabolism in nonvital tissue, which facilitates earlier detection of responders and nonresponders as measured by ^{18}F-FDG retention [41, 50]. A significant reduction of ^{18}F-FDG uptake after one chemotherapy cycle was noted with various therapeutic regimens, and changes in uptake correlated with both response according to RECIST1.1 and survival [51–53]. Treatment can be adjusted on an individual basis according to tumor chemosensitivity as assessed by ^{18}F-FDG PET. Measurement methods of ^{18}F-FDG uptake are diverse, and timing with respect to anticancer therapy and thresholds used to define responses are variable. Therefore, further studies are required before definite conclusions can be drawn on using ^{18}F-FDG PET as a tool for therapy response monitoring.

In addition to its role in response evaluation of neoadjuvant chemotherapy in NSCLC, ^{18}F-FDG PET/CT has shown promise in monitoring response to biological agents such as epidermal growth factor receptor tyrosine kinase inhibitors (Fig. 5) [54–57]. A review of ^{18}F-FDG PET/CT use in targeted treatment for NSCLC suggested that response monitoring could be performed 1–2 weeks after treatment initiation, and that tumors showing a substantial decrease in metabolic activity would probably benefit from continued treatment. Refining FDG-PET response criteria might assist in clinical decision-making on the continuation or discontinuation of targeted treatment [57].

In summary, ^{18}F-FDG PET/CT is emerging as a promising tool for early monitoring of the effectiveness of chemotherapy or chemoradiotherapy in lung cancer. However, there are substantial disparities with respect to response assessment, so standardization remains a requirement.

Monitoring of recurrence (restaging)

NSCLC has a high recurrence rate, even in patients treated with curative intent. Therefore, a method of selecting patients who have an increased risk of recurrence for further adjuvant therapy would be highly beneficial. Imaging plays a central role in recurrence detection, but chest radiograph and CT scan interpretation can be challenging because of posttreatment anatomical changes such as bronchi distortion, lung parenchyma infiltration, and fibrosis. In these settings, ^{18}F-FDG PET/CT is a powerful adjunct for patient follow-up after therapy (Fig. 4). After radiotherapy, local tumor recurrence usually occurs within 2 years, but may create a diagnostic challenge because of the presence of mass-like radiation-induced fibrosis [58]. ^{18}F-FDG PET can distinguish recurrent tumors from fibrosis, providing that sufficient time (i.e., 3 months) has elapsed since treatment to eliminate the risk of false positivity associated with inflammatory changes [59]. In 62 NSCLC patients with suspected postsurgical recurrence, ^{18}F-FDG PET had a sensitivity and specificity of 93 and 89 %, respectively, for relapse detection [60].

Distant metastases are the most prevalent form of NSCLC recurrence. Several groups have demonstrated the usefulness of NSCLC restaging using ^{18}F-FDG PET/CT (Fig. 4) [61, 62]. ^{18}F-FDG PET/CT showed high diagnostic performance for recurrence detection in 241 consecutive patients who underwent potentially curative surgery for NSCLC [61]. Because of the high NPV for recurrence detection, it was proposed that further conventional imaging (except for brain MRI) could be omitted in cases where ^{18}F-FDG PET/CT did not detect recurrence. In a recent meta-analysis that included 13 studies (1035 patients in total) on lung cancer recurrence, the pooled sensitivity and specificity were 0.90 (95 % CI, 0.84–0.95) and 0.90 (0.87–0.93), respectively, for ^{18}F-FDG PET/CT; and 0.78 (0.71–0.84) and 0.80 (0.75–0.84), respectively, for conventional imaging techniques [62]. Despite extensive studies showing excellent results for NSCLC restaging using ^{18}F-FDG PET/CT, the most recent American College of Chest Physicians evidence-based guidelines do not recommend ^{18}F-FDG PET/CT for routine surveillance after curative-intent treatment [63].

Prognostication

Primary lesion metabolic activity is associated with indicators of aggressive biologic behavior such as the tumor doubling time and degree of differentiation [64]. Therefore, ^{18}F-FDG PET metabolic information might provide additional prognostic information based on the biological behavior of the tumor. Although most studies have reported that a high SUVmax was associated with a poorer prognosis [65–69], others found that it was not an independent predictor for OS [70, 71]. In a study of 162 consecutive patients with stage I–IIIb NSCLC, the presence of low tumoral SUVmax was associated with increased 2-year disease-free survival rates for both early (I–II) and late (IIIa–IIIb) stage patients [65]. In a study that included 487 patients, SUVmax was an independent prognostic determinant along with the TNM stage, but it did not contribute to the prognostic value of pathologic staging [67]. A recent meta-analysis (1805 patients in total) including 18 studies demonstrated that both pre-radiotherapy and post-radiotherapy primary tumor SUVmax could predict the outcomes of patients with NSCLC who underwent radiotherapy [68].

In contrast, Agarwal et al. studied 363 patients with stage I and II NSCLC and demonstrated that the preoperative SUVmax was not an independent prognosticator for OS [70]. Similar results were noted in a retrospective analysis of 214 patients with stage IIIA, IIIB, and IV NSCLC

[71]. SUVmax is not recommended for risk stratification in the 7th edition of the American Joint Committee on Cancer staging manual [3], and is not considered a prognostic biomarker in the National Comprehensive Cancer Network guidelines (version 3, 2014) [72].

Recent studies suggest that, compared to SUVmax, metabolic indices such as MTV and TLG might have better prognostic implications related to whole-body and primary tumor burdens [73–78]. A recent meta-analysis (1581 patients in total) including 13 studies demonstrated that patients with a high MTV had worse prognosis for adverse events [hazard ratio (HR), 2.71; 95 % CI, 1.82–4.02] and death (HR, 2.31; 95 % CI, 1.54–3.47) compared to those with a low MTV [78]. Additionally, patients with a high TLG had worse prognosis with respect to adverse events (HR, 2.35; 95 % CI, 1.91–2.89) and death (HR, 2.43; 95 % CI, 1.89–3.11) [78].

In addition to its prognostic value in pre-treatment evaluation, a recent prospective trial in patients with stage III NSCLC indicated that high tumor SUV after treatment was associated with poor prognosis [79]. A retrospective study of surveillance ^{18}F-FDG PET/CT during follow-up >6 months after treatment showed that ^{18}F-FDG PET was a prognosticator of OS [80]. Patients without recurrence according to ^{18}F-FDG PET/CT had a median survival time (MST) of 81.6 months compared with an MST of 32.9 months in those with suspected recurrence. Zhang et al. demonstrated that postsurgical whole-body metabolic tumor burden and tumor SUVmax were related to OS in patients with NSCLC, independent of age, sex, TNM restaging, and postsurgical therapy [81].

In summary, ^{18}F-FDG PET/CT, including SUVmax, MTV, and TLG, might have prognostic value in patients with lung cancer, but further clarification studies are warranted.

SCLC

SCLC accounts for 15 % of lung cancers and is characterized by a rapid doubling time and aggressive clinical behavior, with a high prevalence of disseminated disease at diagnosis [2]. Although TNM staging is applied occasionally, the simplified dichotomous classification method of limited stage (LS) and extensive stage (ES) is used for SCLC staging. The standard therapies are concurrent chemoradiotherapy for patients with good performance status and LS disease, and palliative chemotherapy for those with ES disease. Despite initial chemosensitivity, overall prognosis is poor due to relapses. Given the difference in treatment strategies, accurate staging of SCLC is crucial. However, data concerning the use of ^{18}F-FDG PET/CT for SCLC staging [25, 28, 29, 82–87], radiotherapy planning [82, 83], therapy response evaluation [88–90], and prognosis [89–94] are limited.

In a recent meta-analysis encompassing 12 papers and 369 patients, the pooled sensitivity and specificity of ^{18}F-FDG PET or PET/CT for the detection of extensive disease in SCLC were 0.98 (95 % CI 0.94–0.99) and 0.98 (95 % CI 0.95–0.99) [86]. The impact of ^{18}F-FDG PET on stage classification of newly diagnosed SCLC has been investigated in several studies which suggested that ^{18}F-FDG PET facilitated modifications of stage and clinical management in 12–26 % of cases [82–86]. Studies indicated that the incorporation of ^{18}F-FDG PET/CT data during initial staging led to changes in radiation fields in 37 % of patients [82]. High mean SUVmax values in pre-treatment ^{18}F-FDG PET/CT scans were associated with poorer OS and PFS in both LS and ES SCLC patients [91]. Whole-body MTV of ^{18}F-FDG was of prognostic value in SCLC, and incorporation of metabolic data during TNM staging has been proposed to improve prognostic information [92]. Moreover, changes in MTV after radiotherapy correlated with survival in patients with LS SCLC [93].

Conclusion

^{18}F-FDG PET/CT permits the combined metabolic and morphological assessment of tumors, with significant improvements in diagnostic accuracy and considerable impact on patient management, initial staging, therapy planning, early treatment response assessment, re-staging, and prognostication of lung cancer.

Further analyses to refine ^{18}F-FDG PET/CT response criteria, the standardization of ^{18}F-FDG PET/CT timing for chemotherapy or chemoradiotherapy response evaluation, the development of new PET cameras with higher spatial resolution, and the design of new radiotracers other than ^{18}F-FDG are required.

Compliance with ethical standards

Conflict of interest We declare no financial support or relationship that may pose a conflict of interest.

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