Enhancing Non-Small Cell Lung Cancer Management with Hybrid Imaging: A Review of FDG PET/CT Applications

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Abstract

Background: Positron emission tomography (PET) is a sensitive and specific method of molecular imaging that has become integral to oncologic studies. The use of F18-labeled glucose (FDG) in PET scans has revolutionized cancer diagnosis and management by providing valuable functional information based on increased glucose uptake and glycolysis of cancer cells. Integrated PET/CT scanners offer synergistic advantages by combining functional and anatomical data, enhancing image interpretation for more accurate staging and diagnosis while minimizing the limitations of standalone anatomical imaging .
Aim: This article reviews the role of FDG PET and FDG PET/CT in the diagnosis, staging, and treatment response assessment of lung cancer, emphasizing its clinical significance and the ongoing need for investment in PET services to meet increasing demand. The aim of our study was to search literature to understand the role of 18F-FDG PET and PET/CT in the management of lung cancer, to become familiar with recent advances and pitfalls in hybrid imaging of lung cancer.
Methods: We searched for articles in literature regarding the value of 18F-FDG PET/CT in lung cancer, describing different roles and applications of PET and PET/CT. We analyzed the data of articles published between 1994 and 2024 and summarized the information. .
Results:The application of FDG PET/CT is crucial for accurate diagnosis, staging, and restaging in lung cancer, enabling the detection of metabolic abnormalities before morphological changes occur. It also plays a significant role in monitoring response to therapy, allowing timely modifications to treatment regimens and ultimately improving patient outcomes. Despite its advantages, the technology faces challenges such as cost and infrastructure requirements.
Conclusions: F18-FDG PET/CT is a valuable imaging modality for diagnosis, staging, treatment response evaluation and management of lung cancer. FDG PET/CT is cost-effective compared to other imaging modalities alone in terms of accurate staging and resectability assessment. Recent advances in hybrid imaging, such as artificial intelligence (AI) have added value for the management of lung cancer. **(TCM-GMJ May 2026; 11 (1): P40-P51)**

Keywords: FDG PET, FDG PET/CT, Lung cancer, Hybrid imaging, NSCLC, SCLC

Introduction

Advances in PET Imaging—Technology, Radiopharmaceuticals, and Clinical Applications

The hybrid PET/CT imaging technique combines anatomical information from CT with functional data from PET, enhancing image interpretation and improving the accuracy of staging and diagnosis for oncological conditions. Modern PET/CT scanners, featuring 16-128 slice MDCT, produce high-quality diagnostic CT images. Many institutions utilize protocols that include contrast-enhanced CT, delivering comprehensive whole-body diagnostic images in a single scan ("one stop-shop" principle) [1].

The advantages of PET/CT over separate PET and CT scans are well-documented in numerous studies. A recent innovation in this area is the continuous bed motion acquisition (CBM), also known as mCT flow, which has replaced the traditional step-and-shoot (SS) approach. Patients have expressed a clear preference for CBM, finding it more relaxing (38% vs. 8%), quieter (34% vs. 8%), and smoother (64% vs. 8%) compared to SS ($P = 0.0001$). Although image quality, standardized uptake value (SUV), and CT misalignment were similar between techniques, CBM resulted in significantly better end-plane image quality ($P < 0.0001$). Regardless of the technique used, second examinations revealed higher tumor lesion SUVmax values ($P = 0.0002$) and increased CT misalignment scores ($P = 0.0017$) [2].

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The evolution of PET in oncology has established F18-labeled glucose as the most widely used radiopharmaceutical in cancer studies. This is due to its ability to target the high glucose uptake characteristic of most cancer types. Additionally, [F18] FDG, produced in a cyclotron, has a half-life of 110 minutes, allowing it to be transported from production sites to distant centers while maintaining sufficient radioactivity for effective imaging. Evidence suggests that malignant tumor cells predominantly use anaerobic glycolysis for energy, known as the Warburg effect. Hexokinases catalyze the first step of glucose metabolism by converting glucose to glucose-6-phosphate, trapping it inside the cell due to its impermeability to facilitated diffusion. This conversion creates a downhill gradient that increases glucose uptake via facilitative glucose transporters (GLUT1-13). Healthy cells metabolize glucose-6-phosphate through various pathways depending on their energy status and regulatory mechanisms. Fludeoxyglucose F18, an analog of glucose, replaces the hydroxyl group at the 2-C position with a radioactive tracer, 18-fluorine. When [F18] FDG enters cells using GLUT1 or GLUT3, it is phosphorylated but cannot be further metabolized, leading to its accumulation within the cell. Tumor cells, which typically lack sufficient glucose-6-phosphatase and express excessive glucose transporters, exhibit high glycolysis rates, resulting in increased FDG uptake compared to healthy tissues. PET scans detect this accumulation through the radioactive decay of fluorine-18 [3].

FDG uptake intensity can be assessed visually by comparing the uptake in a specific region to background activity (such as the mediastinal blood pool or liver) or through a semi-quantitative parameter, the standardized uptake value (SUV). SUV can vary significantly based on factors such as injected activity, patient weight, blood glucose level, time after injection, respiratory motion, and scanner settings. Data indicate that both visual assessment and SUV measurement offer comparable accuracy.

Methods

We searched for articles in literature regarding the value of 18F-FDG PET/CT in lung cancer, describing different roles and applications of PET and PET/CT. We analyzed the data of articles published between 1994 and 2024 and summarized the information.

Results and discussion

FDG PET/CT in the Diagnosis of Lung Cancer and evaluation of Solitary Pulmonary Nodules

A solitary pulmonary nodule (SPN) is a common, often incidental finding on radiological exams, defined as a round opacity in the lung parenchyma measuring less than or equal to 3 cm in diameter. Unlike pulmonary masses, which are larger than 3 cm and have a higher likelihood of malignancy, SPNs are usually discrete and not associated with atelectasis, lymph node enlargement, pneumonia, or pleural effusion. Differential diagnoses of SPNs on CT include a range of possibilities such as neoplastic lesions (both benign and malignant), inflammatory lesions (infectious and noninfectious), and vascular or congenital anomalies. SPNs may appear as completely solid or exhibit ground-glass attenuation, in which case they are termed subsolid nodules. MDCT is crucial for assessing the morphologic characteristics and growth patterns of SPNs through serial imaging. Despite most SPNs being benign, their incidental discovery in asymptomatic patients during routine CT scans poses significant diagnostic challenges [4]. Distinguishing between benign and malignant nodules can be difficult without biopsy, and repeated CT scans or biopsies carry their own risks. To address these challenges, the Fleischner Society guidelines—first published in 2005 and updated in 2017 [5]—are widely used to guide the evaluation of SPNs and other pulmonary nodules. This systematic approach aims to optimize management and reduce unnecessary interventions.

Since the introduction of F-fluorodeoxyglucose positron -emission tomography (18F-FDG PET), it has been extensively evaluated in patients with an indeterminate solitary pulmonary nodule. In 2001 in the meta-analysis of more than 40 studies Gould et al showed that PET had sensitivity and specificity of approximately 90% for detecting malignant nodules with a diameter of 10 mm or larger [6]. However, PET has a number of limitations. In a study by Nomori et al. the sensitivity (10%) and specificity (20%) of PET for evaluating ground-glass opacities were significantly lower than those for evaluating solid nodules (90% and 71%, respectively) [7]. In addition to the dimensions and morphologic characteristics (solid vs subsolid) of the solitary pulmonary nodule, false-negative results can be obtained in case of tumors with low metabolic activity (e.g., carcinoid tumors and adenocarcinoma in situ, formerly known as bronchoalveolar carcinoma) [8]. With the increasing use of AI and machine learning, interpretation can be significantly improved. A study compared the diagnostic efficiency of two nuclear medicine readers and a machine learning (ML) model in assessing solitary pulmonary nodules (SPNs). Human Reader 1 had an accuracy of 90.13%, while Human Reader 2 had 87.71%. The ML model, without human input, outperformed both with an accuracy of 92.95%. When incorporating human insights, the ML model's accuracy improved further to 95.39%. This study suggests that combining ML with human expertise enhances SPN classification accuracy, improving diagnostic precision [9].

Increased FDG uptake in a nodule can be evaluated visually or by measuring the standardized uptake value (SUV), the most common semi-quantitative method for assessing pulmonary lesions. In a retrospective study of 140 patients, Grgic et al. compared visual interpretation with various SUVmax cut-off points. Malignant nodules had higher SUVmax values than benign ones (9.7 ± 5.5 vs. 2.6 ± 2.5; $p < 0.01$). Over 90% of nodules with SUVmax < 2.0 were benign. The highest diagnostic accuracy was achieved with an SUVmax cut-off value of 4 [12].

One method assessed in pulmonary nodules is dual-time point FDG PET, where images are obtained and SUV measured at both 60- and 120-minutes post-injection. Matthies et al. evaluated this technique in 36 patients, finding a significant $20.5 \pm 8.1\%$ increase in SUV in malignant nodules ($p < 0.01$) [13]. However, these results were not replicated in studies from tuberculosis-endemic regions [14-

15]. A meta-analysis of 8 studies showed that the accuracy of 18F FDG PET/CT was similar between the standard and two-phase protocols, with the latter having slightly higher specificity [16].

The advent of integrated PET/CT scanners has allowed for the near-simultaneous acquisition of functional and anatomical data, significantly improving diagnostic accuracy. In a study comparing PET/CT with helical dynamic CT (HDCT) for evaluating SPNs, PET/CT demonstrated higher sensitivity (96% vs. 81%) and accuracy (93% vs. 85%) than HDCT [17]. Similarly, Kim et al. conducted a study in the United States comparing the accuracy of CT, PET, and PET/CT in characterizing SPNs, finding accuracies of 74%, 74%, and 93%, respectively. [18].

In a retrospective analysis of 754 patients, including 705 with pathologically confirmed lung cancer, Feng et al. reported a diagnostic accuracy of PET/CT scans of 93.5% and a false positive rate of 6.50%. The most common causes of false positives were inflammatory pseudotumor (42.86%) and tuberculoma (36.74%). In the group with confirmed lung cancer, adenocarcinoma (57.16%) and squamous carcinoma (33.19%) were the predominant histological types. In cases of false positives, detection of inflammatory markers such as IL-6 and the T-spot TB test may help improve the diagnostic accuracy of PET-CT [19].

In conclusion, integrating anatomical and metabolic data greatly enhances the diagnostic accuracy for characterizing pulmonary nodules. However, misregistration between CT and PET can introduce artifacts and quantitative errors, potentially resulting in underestimation of SUVs and false-negative results [20]. Recent strategies to address respiratory mismatches between CT and PET images include using respiratory-gated CT for PET attenuation correction [21] (Fig. 1-3). With the advancement of artificial intelligence, PET/CT systems have also benefited. OncoFreeze AI, which operates without a device, can compute SUVs and metabolic volumes comparable to those obtained with OncoFreeze, which requires a device to measure respiratory motion. Compared to static reconstruction, OncoFreeze AI delivers more precise lung lesion images with notably larger SUVs and smaller metabolic volumes [22].

FDG PET/CT in T Staging in Non-Small Cell Lung Cancer (NSCLC)

The International Association for the Study of Lung Cancer (IASLC) developed the lung cancer stage classification, which uses the TNM system to describe the tumor's anatomic extent. This classification helps select the most appropriate treatment for patients [26].

MDCT has been the cornerstone of lung cancer staging, while MRI is superior for local staging of Pancoast tumors. Due to its low spatial resolution, PET adds little value in assessing local spread and resectability, as it lacks detailed anatomical information. However, FDG PET/CT combines anatomical and functional data, providing more comprehensive information. Antoch et al. demonstrated the superiority of PET/CT over PET or CT alone in staging NSCLC, with PET/CT correctly identifying the primary tumor stage in more patients [27]. De Wever et al. confirmed these findings in a 2007 retrospective study of 50 patients [28] (Fig. 4). Additionally, PET/CT can differentiate metabolically active tumors from peritumoral inflammation or atelectasis [29-30], aiding in radiotherapy planning by distinguishing tumors from healthy tissues and preserving uninvolved lung (Fig. 5).

For preoperative T-stage assessment of NSCLC, 3T MRI was found to be slightly superior to MDCT for advanced tumors (T3, T4), particularly in determining pleural and mediastinal invasion. Despite these promising results, chest MRI use remains limited, especially after the widespread adoption of MDCT. Further technical improvements in spatial and contrast resolutions are needed to make chest MRI a viable replacement for MDCT in T-factor evaluation for lung cancer patients [31].

FDG PET/CT can guide biopsies by accurately localizing the hypermetabolic regions of tumors, which provide the most useful diagnostic information. Studies have shown that using FDG PET/CT to guide transthoracic biopsy helps identify the most viable part of the lesion, increasing the accuracy of diagnoses [33-35]. Additionally, Stefanidis et al. found that metabolic information from 18F-FDG PET/CT and targeting the PET-CT maximum activity region improve diagnostic biopsy rates, particularly in masses. This approach also results in fewer needle passes and complications when used pre-biopsy [36].

FDG PET/CT in N Staging in Non-Small Cell Lung Cancer (NSCLC)

Anatomic imaging, such as CT, uses size criteria for mediastinal and hilar staging, with 1 cm being the threshold for metastatic involvement. However, these criteria are limited by normal-sized lymph nodes infiltrated with tumor cells and enlarged lymph nodes due to benign causes. Numerous studies comparing FDG PET and CT for lymph node staging in NSCLC have demonstrated PET's superiority. Gould et al. conducted a meta-analysis comparing FDG PET and CT for mediastinal staging of NSCLC, finding PET to be more sensitive but less specific for enlarged lymph nodes (sensitivity: 100%, specificity: 78%), and less sensitive but more specific for normal-sized lymph nodes (sensitivity: 82%, specificity: 93%) [37]. These findings highlight PET's superiority in detecting malignant normal-sized and benign enlarged lymph nodes (Fig. 6). Preoperative PET/CT findings in 182 patients (pStage IB–III) were compared with pathological diagnoses after surgical resection. The standardized uptake value (SUV) ratio was determined using PET/CT images, with the I/C-SUV ratio calculated as ipsilateral hilar node SUV/contralateral hilar node SUV. ROC curve analysis established a cutoff I/C-SUV ratio of 1.34 for diagnosing lymph node metastasis. For tumor ipsilateral lymph node SUVmax ≥2.5, an I/C-SUV ratio ≥1.34 had the highest accuracy for predicting N1/N2 metastasis, with sensitivity, specificity, PPV, NPV, and accuracy of 60.66%, 85.11%, 84.09%, 62.5%, and 71.29%, respectively. This I/C-SUV ratio can be an effective criterion for determining surgical indications in advanced lung cancer. [38]

The anatomic-metabolic correlation and fusion of FDG PET and CT allows for better localization of involved lymph nodes, clearer delineation of the primary tumor from adjacent lymph nodes, and differentiation of mediastinal and hilar lymph nodes [39]. Studies comparing the accuracy of integrated FDG PET/CT with PET alone and CT alone for mediastinal staging of NSCLC show pooled average sensitivity, specificity, positive predictive value, negative predictive value, and accuracy of PET/CT to be 73%, 80%, 78%, 91%, and 87%, respectively [30]. Lardinois et al. and Cerfolio et al. documented the superior evaluation of N status with integrated PET/CT compared to PET alone [29-30, 32].

A meta-analysis by Birim et al. of 17 studies found FDG PET to be more accurate than CT in detecting mediastinal lymph node metastases [40]. Bille et al. reported an accuracy of 80.5% on a per-patient basis and 95.6% on a per-nodal-station basis for detecting metastatic lymph nodes with PET/CT. For N2/N3 disease, PET/CT accuracy was 84.9% per-patient and 95.3% per-nodal-station [41]. Wang et al. reported a 94% negative predictive value of FDG PET/CT for mediastinal metastases in T1 disease, suggesting a low yield from routine invasive staging procedures [42].

Zhou et al.'s retrospective study of 54 patients with T1-2N0M0 NSCLC found occult nodal metastasis in 25.9% of patients (14/54). The study indicated that combining tumor size with SUVmax provided predictive ability—tumors >2.5 cm with SUVmax >4.35 had an 88.9% chance of detecting occult lymph node metastases [43]. In a multicenter study, Li et al. reported a 91% negative predictive value of 18F-FDG PET/CT in mediastinal evaluation of early-stage T1-2N0 tumors, identifying patients suitable for stereotactic body radiotherapy (SBRT) [44].

A Japanese multicenter study also demonstrated a significant improvement in the diagnostic accuracy of mediastinal lymph node metastasis with integrated FDG PET/CT compared to standalone modalities [45].

Despite recent technological advances, FDG PET/CT is not a perfect method and can yield false negative results (due to low tumor load, micrometastasis, or small size) and false positive results (due to inflammation). Wang et al. conducted a meta-analysis and found the NPV of FDG PET for mediastinal lymph node involvement in T2 disease to be 89%. They recommended invasive staging procedures before any active treatment for patients with adenocarcinoma histology or high FDG uptake in primary lesions due to the high risk of nodal metastasis [42]. Divisi, Duilio et al. suggests that adopting standardized indexes can eliminate technical and protocol biases, enabling valid comparisons between patients and centers. Literature indicates that SUVmax alone is no longer sufficient as a predictive and prognostic parameter. It must be correlated with dimensional and tomographic attenuation characteristics for accurate preoperative evaluation [46].

Gao et al. evaluated 284 patients with T1-2N0 disease staged with FDG PET/CT between 2011 and 2015. They concluded that invasive mediastinal staging should be strongly encouraged for central tumors and solid T2 tumors because of the 10% risk of occult nodal metastasis. However, for patients with peripheral T1 tumors or peripheral T2 tumors with a ground glass component, invasive staging after a negative PET/CT is discouraged due to its low yield [47].

In a meta-analysis of 14 studies by Langen et al., a negative PET scan resulted in a post-PET probability for N2 disease of 5% for lymph nodes <15 mm, suggesting these patients should be planned for thoracotomy due to the low yield of mediastinoscopy. Conversely, the post-PET probability for N2 disease was 21% for lymph nodes ≥ 16 mm, suggesting these patients should be planned for mediastinoscopy [48].

A retrospective review by Lee et al. found the PPV of PET/CT to be only 56%, with false positive results often associated with inflammatory and infectious conditions [49]. Darling et al. reported a PPV of 64% for FDG PET/CT in mediastinal staging [50]. These data underscore the need for pathologic confirmation of mediastinal lymph node abnormalities (via Endobronchial Ultrasound (EBUS), Endoscopic ultrasound (EUS) with Fine needle aspiration (FNA) or invasive mediastinal staging) before planning thoracotomy and radical surgical treatment.

Efforts to increase the accuracy of FDG PET/CT include a meta-analysis of eight studies (654 patients), which showed better performance of dual time point PET/CT in mediastinal staging, though this has not yet been implemented in routine protocols [51] (Fig.7).

FDG PET/CT in M Staging in Non-Small Cell Lung Cancer (NSCLC)

One of the primary roles of whole-body FDG PET and PET/CT is to detect distant metastasis, accurately staging lung cancer by distinguishing patients with distant spread, who cannot be cured, from those who may benefit from radical treatment. Several studies have shown that FDG PET detects unsuspected distant metastasis in 5% to 29% of cases [56-61].

The most common sites for distant metastasis in lung cancer are the adrenal glands, liver, bones, and brain. Kumar et al., in a retrospective study of 94 patients, reported the sensitivity, specificity, and accuracy of FDG PET for detecting adrenal metastasis as 93%, 90%, and 92%, respectively [62]. Brady et al. (2009) proposed an algorithm combining density measurement on non-CE CT (HU > 10) and an SUV threshold (SUV > 3.1) to define malignancy. In a study of 147 patients, this algorithm proved to be more specific than PET or CT alone without losing sensitivity [63]. A recent meta-analysis of nine studies showed the pooled sensitivity and specificity of FDG PET/CT for detecting adrenal metastasis in lung cancer patients to be 89% and 90%, respectively [64].

FDG PET is superior to bone scintigraphy in detecting osseous metastasis, as the lesions are mostly osteolytic rather than osteoblastic. Liu et al., in a meta-analysis of 14 articles, reported 18F FDG PET to be the best modality for detecting bone metastasis in lung cancer patients, both on a per-patient and per-lesion basis, with MRI having the highest specificity on a per-lesion basis. PET/CT was shown to be better than PET alone [65]. PET/CT adds

value by demonstrating skeletal changes associated with malignancy, trauma, or degenerative changes, improving sensitivity and specificity. Another meta-analysis found that FDG PET/CT and FDG PET were more accurate for diagnosing bone metastases than MRI or bone scintigraphy [66].

FDG PET is also valuable in detecting liver metastasis that is indeterminate on conventional imaging modalities [67]. However, FDG PET is limited in detecting brain metastasis due to high glucose uptake in brain tissue and high background activity, making it insufficient to exclude brain metastases. MRI (or CT) remains the preferred method for staging the brain, though occasionally brain hypermetabolic lesions detected by FDG PET are confirmed as metastases (Fig. 12).

With the introduction of hybrid PET/CT systems, the integrated information acquired simultaneously is more accurate than either PET or CT alone. Studies using integrated PET/CT, though limited in detecting brain metastases, found it significantly better than CT or PET alone for extrathoracic metastases [30, 32] (Fig. 8-9).

FDG PET is also effective in detecting pulmonary metastasis. While CT has higher anatomical and spatial resolution and is less affected by respiratory motion, integrated PET/CT is effective in identifying lung lesions with minimal FDG uptake. Modern PET systems can use deep inspiration breath-hold (DIBH) CT images. According to Cui et al., the SUVmax and SUVmean of the lung with 30-second DIBH (DIBH-30s) were significantly lower than with free-breathing (FB). The liver dome distances between PET and CT were smaller with DIBH-30s than with FB. Among 195 lesions in 106 patients, detection sensitivity was 97.9% for FB-300s and 99.0% for DIBH-30s. Lesion SUVs were significantly higher with DIBH-30s than with FB-300s for both small (n=86) and larger lesions ≥1 cm (n=91). Significant SUV differences were found in the lower thorax (n=97, $p<0.001$) but not in the upper thorax (n=80, $p>0.05$). The tumor-to-surrounding-background ratio (TsBR) was significantly increased in both regions. The TB DIBH PET/CT technique is feasible in clinical practice, reducing background lung uptake and improving registration and lesion quantification, especially in the lower thorax [68]. A 2013 meta-analysis of 56 studies by Wu et al. concluded that FDG PET/CT has significantly higher sensitivity and specificity than contrast-enhanced CT and higher sensitivity than FDG PET alone in staging NSCLC [69].

Evaluation of Treatment Response and Follow-Up of NSCLC with FDG PET and PET/CT

After lung cancer treatment, it is essential to evaluate the treatment response, detect residual tumors or recurrence, and plan further strategies. Structural changes post-surgery or radiotherapy are often inconclusive on conventional imaging. FDG PET differentiates between fibrosis/necrosis and residual or recurrent tumors, showing higher sensitivity than other imaging modalities [70]. It is crucial to perform PET scans at optimal intervals post-radiotherapy or surgery to minimize false positives due to inflammation. Erasmus and Patz reported high accuracy (78-98%) for recurrence detection when PET scans were delayed at least 2 months after surgery and 4-6 months after radiotherapy [71] (Fig. 10-11).

FDG PET can assess chemotherapy effectiveness. Weber et al. studied 57 patients with stage IIIB and IV NSCLC receiving platinum-based chemotherapy, finding a correlation between metabolic response after one chemotherapy cycle and overall therapy response [72]. MacManus et al. studied 73 patients who underwent radical radiotherapy or chemo-/radiotherapy followed by FDG PET after 10 weeks, showing FDG PET's superiority over CT in predicting survival duration [73]. In another study of 56 patients, SUV decrease post-adjuvant therapy was a more accurate predictor than size change on CT [74]. Several studies confirm FDG PET/CT's high diagnostic performance in metabolic response assessment of lung cancer with high NPV [75-77].

Positron Emission Tomography Response Criteria in Solid Tumors (PERCIST) can better predict histopathologic response than anatomic criteria like WHO and RECIST 1.1 [78]. Recently, new PET-based qualitative treatment response criteria (Hopkins's criteria) have shown high inter-reader agreement and accuracy [75]. In a study by Dang, Shreya et al., out of 44 patients, PERCIST classified 27 (61.3%) as responders and 17 (38.6%) as non-responders, while Hopkins classified 12 (27.3%) as responders and 32 (72.7%) as non-responders. The agreement between the criteria was low (kappa=0.19) with 45.5% discordance. Of the discordant cases, 88.8% predicted as non-responders by Hopkins were confirmed on follow-up. PERCIST responders had an OS of 96.4% at 9 months and 64.3% at 24 months, compared to 93.5% and 40.2% for non-responders ($P = 0.049$). Hopkins's responders had a 100% OS at 24 months, while non-responders had 93.5% at 9 months and 51.5% at 24 months ($P = 0.232$). Semi-quantitative PERCIST and visual Hopkins's criteria show low agreement, with visual criteria better predicting survival in NSCLC patients [79].

In a meta-analysis of 13 studies including 1035 lung cancer patients, He et al. reported PET/CT and PET as superior modalities for detecting lung cancer recurrence compared to conventional imaging, with PET/CT being superior to PET [80]. In a study of 90 patients, Dane et al. confirmed that PET/CT was more sensitive than CT alone for recurrence detection one year after lobectomy, due to PET/CT's superiority in identifying extrathoracic masses and new hypermetabolic pulmonary nodules [81]. In a prospective study of 358 patients, Choi et al. compared the effectiveness of postoperative follow-up FDG PET/CT with chest CT, finding that FDG PET/CT added value in 37% of cases (19 patients) where recurrence was confirmed only by FDG PET/CT [82] (Fig. 12).

The prognostic value of FDG PET/CT

The potential prognostic value of FDG PET and SUVmax for primary lung cancer has been widely reported across various studies involving different stages and treatment populations. A meta-analysis of 24 studies by Paes-

mans et al. concluded that patients with tumors exhibiting higher metabolic activity and higher SUV have shorter survival rates compared to those with tumors showing lower glucose metabolic rates [84]. Similarly, Na et al. reported in a meta-analysis that SUVmax in the primary tumor, both before and after RT, could predict patient outcomes and overall survival [85]. FDG PET also provides prognostic value and correlates with survival rates in treated lung cancer patients [86-87]. Induction chemotherapy, used as neoadjuvant therapy before consolidative radiotherapy, was shown in a study of 31 patients to be a more powerful prognostic marker for survival when a complete response on 18 FDG-PET was observed following induction chemotherapy for locally advanced, unresectable NSCLC, compared to a partial response on CT [88].

SUVmax is the most widely used parameter for diagnosis and response assessment due to its higher reproducibility and availability, despite only measuring a single volumetric pixel within the tumor. Recently, volumetric parameters such as metabolic tumor volume (MTV) and total lesion glycolysis (TLG) have been introduced and investigated. In a meta-analysis of 36 studies, Liu et al. examined the prognostic value of SUVmax, MTV, and TLG on disease-free survival (DFS) and overall survival (OS) in surgical NSCLC patients. The results indicated that high values of SUVmax, MTV, and TLG predicted a higher risk of recurrence or death in these patients, suggesting that FDG PET/CT can identify patients at high risk who may benefit from more aggressive treatments [89]. Lee et al. also evaluated the prognostic value of MTV in patients with NSCLC treated definitively and reported that tumor burden, as assessed by MTV, provides prognostic information on survival beyond that of established prognostic factors [90]. The study by Lee, H. et al. showed that MTV and TLG on preoperative FDG PET/CT were independent prognostic factors in operable lung adenocarcinoma patients, while SUVmax and SUVmean were not. A new staging system including MTV improved prognosis prediction compared to conventional pathological staging. Previous studies reported SUV as a good prognostic factor for NSCLC survival, but SUVmax alone cannot represent the entire tumor's metabolic activity. Volumetric parameters like MTV and TLG better reflect tumor burden and have shown prognostic significance [91].

The Impact of FDG PET and PET/CT on NSCLC Management and its Cost-Effectiveness

Numerous studies indicate that FDG PET significantly impacts the management of NSCLC by upstaging and detecting unsuspected metastasis or downstaging and excluding benign lesions, thereby preventing futile surgeries. A randomized study of 188 patients found a 51% reduction in futile surgeries with PET staging, with no extra cost [92]. A prospective multicenter trial by Kubota et al. reported a strategy modification rate of 72% for lung cancer patients before and after FDG PET/CT, higher than previously reported [93]. Both prospective and retrospective studies have shown a significant management impact with integrated FDG PET/CT in NSCLC patients intended for primary surgery or definitive RT, including a substantial percentage of avoided futile surgeries due to disease upstaging [94-96].

Several authors have addressed the cost-effectiveness of FDG PET and integrated PET/CT for lung cancer staging, finding it cost-effective compared to CT alone in terms of accurate TNM staging and resectability assessment [97-99]. They concluded that the costs for PET/CT were within the commonly accepted range for diagnostic tests or therapies. Differentiating benign from malignant pulmonary nodules was the first clinical indication where PET demonstrated cost-effectiveness. PET's higher specificity and diagnostic accuracy compared to standard imaging approaches make it a valuable, cost-effective tool in diagnostic work-ups. By reliably classifying suggestive lesions as benign, PET can prevent the need for fine-needle biopsies and thoracotomies [100].

FDG PET and PET/CT in Small Cell Lung Cancer (SCLC)

Small cell lung cancer is categorized into limited-stage and advanced-stage diseases. Limited-stage disease can be treated with curative chemo-radiotherapy or, in selected cases, with surgery, while advanced-stage disease requires systemic chemotherapy. Accurate staging is crucial for selecting the correct treatment options and serves as an important prognostic factor. The role of FDG and FDG PET CT in SCLC has not yet been fully established, but several studies have explored this topic. SCLC, an aggressive neuroendocrine tumor, is considered to be FDG-avid. Brink et al. evaluated the role of FDG PET in the staging of SCLC and reported that its sensitivity was significantly superior to that of CT in detecting extrathoracic lymph node involvement and distant metastases (except for the brain), leading to significant changes in treatment due to stage alteration [103]. Bradley et al. prospectively evaluated 24 patients with limited-stage SCLC and found that FDG PET upstaged the disease in 8% of cases and detected unsuspected nodal metastasis in 25% of cases, thus altering the radiation therapy plan [104]. In a more recent study, Azad et al. reported that FDG PET altered management in 12 of 46 (26%) patients [105].

Hybrid imaging using 18F-FDG PET/CT, which provides both functional and anatomical data, has been shown to be superior to 18F-FDG PET alone [106]. The most recent meta-analysis of 9 studies indicated that integrated FDG PET/CT can lead to significant changes in SCLC staging and thus can alter management in 5% to 21.9% of cases. This is largely due to the better diagnostic accuracy of 18F-FDG PET/CT compared to conventional imaging modalities in detecting distant metastases (except for the brain), as functional abnormalities detected by 18F-FDG PET usually precede anatomical abnormalities [107].

Kamel et al. attempted to evaluate the impact of FDG PET on the management of patients with SCLC. PET led to a change in management in 29% of patients, either by upstaging the disease or downstaging it by excluding mediastinal involvement or distant metastasis, and it also led to changes in the radiation treatment plan. In the setting of

restaging after therapy, PET correctly identified all patients with total remission and progressive disease, and 11 of 12 patients with residual disease [108]. Few studies have addressed the role of FDG in treatment response assessment in SCLC [109-110]. As in NSCLC, FDG PET can have prognostic value in SCLC [111-112].

Some studies suggest that FDG PET-CT is recommended for staging and target volume definition in limited-stage SCLC, though its impact on outcomes compared to CT staging and elective nodal irradiation (ENI) is unclear. Graabak G. et al. analyzed patients from the HAST and THORA trials receiving thoracic radiotherapy (TRT) to see if PET-CT staging reduces radiotoxicity and improves survival. 149 patients (PET-CT/SNI: n=76, CT/ENI: n=73) were included. There was no difference in median overall survival (24 vs. 25 months) or progression-free survival (11 months each). PET-CT staging reduces acute radiotoxicity but does not improve overall or progression-free survival in limited-stage SCLC [113].

Pitfalls, False Negative and False Positive results in FDG PET/CT

There are a number of limitations of FDG PET CT in lung cancer. False-positive results are not infrequent, with inflammatory disease being one of the known confounders in FDG PET CT studies. A retrospective study of patients with lung cancer revealed that false-positive results included inflammatory pseudotumor (43%), tuberculoma (37%), and organizing pneumonia (6%) (19). False-positive lymph nodes may also be related to the presence of interstitial pneumonitis, previous tuberculosis, silicosis, and emphysema [117-119]. These studies demonstrate an important limitation of FDG PET/CT and confirm that PET-positive lymph nodes still require pathological confirmation by mediastinoscopy [120]. In the post-treatment setting, false-positive results may be associated with post-radiotherapy inflammation, particularly after SBRT [121-122].

False-negative findings at PET can result from the small size of the nodule, low cellular density in lesions such as carcinoma in situ, or low metabolic activity and low tumor avidity for FDG. Positron-emission tomography has been shown to be less sensitive for the characterization of smaller lung lesions, potentially due to respiratory motion, which causes a significant underestimation of 18F-FDG uptake [123]. Tumors of certain histologic phenotypes, such as bronchoalveolar carcinoma and well-differentiated tumors, have been shown to be less 18F-FDG-avid [124]. According to Meirelles GS et al., understanding the normal FDG distribution, physiological FDG uptake, and their variants is crucial for interpreting oncologic PET/CT examinations of the chest. Awareness of these factors can help avoid false-positive and false-negative results, allowing for careful interpretation of both CT and PET findings. When these points are well understood by the interpreter, PET/CT becomes a powerful imaging technique for characterizing pulmonary lesions, providing accurate staging for lung neoplasms, and contributing to better evaluation of therapy effectiveness and prognostic assessment [125].

Conclusion

F18-FDG PET/CT is a valuable imaging modality for diagnosis, staging, treatment response evaluation and management of lung cancer. Applications of 18F-FDG PET/CT at initial staging include: characterization of solitary pulmonary nodules, delineation of regional lymph node metastasis and detection of distant metastasis. It is used for monitoring response to therapy and has prognostic value. Numerous studies have shown this imaging modality significantly impacts the management of NSCLC by downstaging or upstaging, and thereby preventing futile surgeries. Several authors have concluded FDG PET/CT is cost-effective compared to CT alone in terms of accurate TNM staging and resectability assessment. Recent advances in hybrid imaging, such as artificial intelligence (AI) have added value for the management of lung cancer.

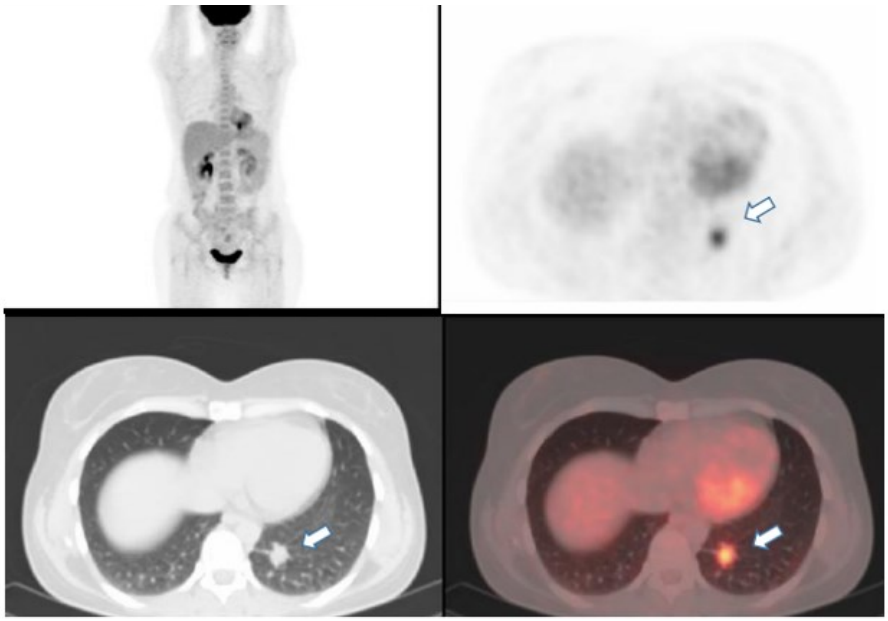

Fig. 1. y.o female with incidental finding on chest CT, hypermetabolic LLL SPN; MIP, PET, axial CT, axial fused images; postoperative morphology revealed adenocarcinoma.

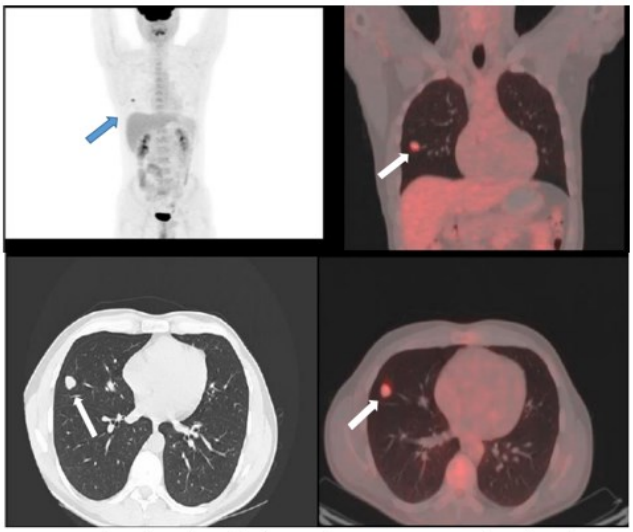

Fig. 2. y.o male, with incidental finding on chest CT, RML SPN, with moderately Increased metabolic activity, suspicious for malignancy; MIP, fused coronal, axial CT, axial fused images; morphology revealed atypic carcinoid

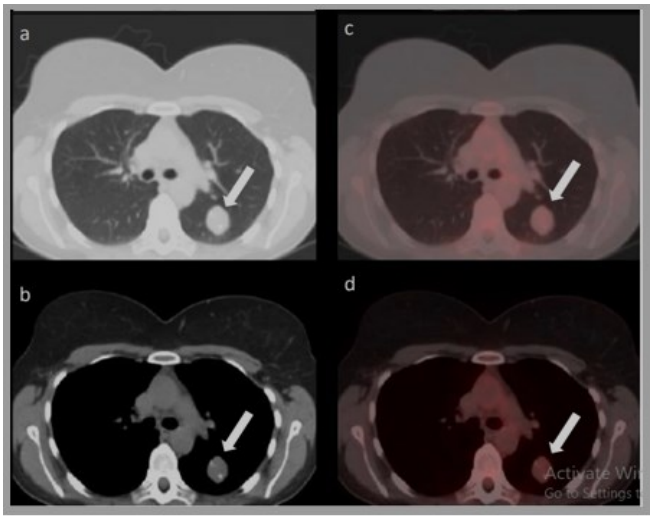

Fig. 3. y.o female with incidental finding on chest CT, LUL SPN without increased metabolic activity suggesting benign process, follow up recommended. CT (a,b) and fused PET/CT (c,d) images;

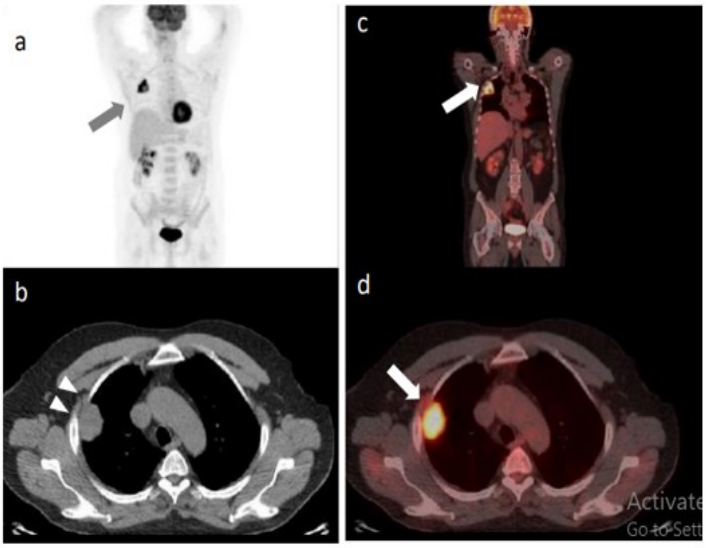

Fig. 4. y.o male, with morphologically proven NSCLC, hypermetabolic peripheral RUL lesion (arrow), with signs of visceral and parietal pleural invasion (arrowheads), metabolic stage T3 N0 M0

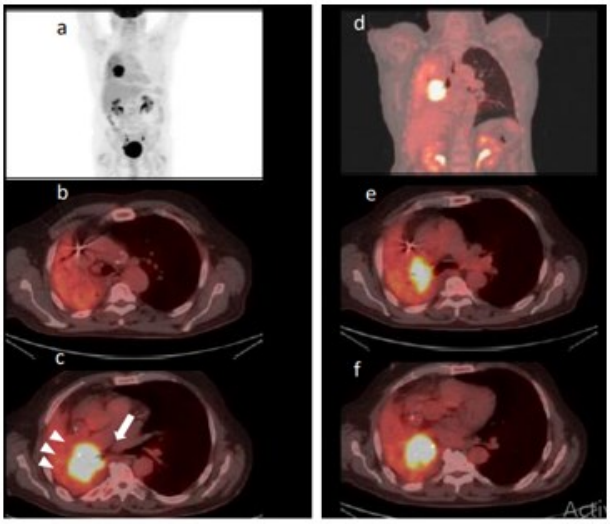

Fig. 5. y.o male with right central hypermetabolic tumor, invasion of main bronchus and right lung atelectasis, FDG PET CT can discriminate well between viable tumor (arrow) and atelectasis (arrowheads).

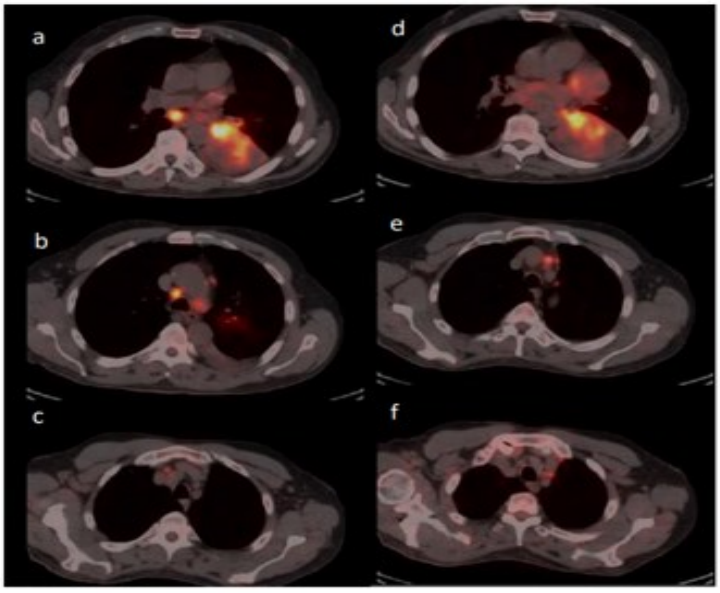

Fig. 6. y.o male, with NSCLC, left central hypermetabolic tumor, with peripheral LLL atelectasis, subcentimetric hypermetabolic ipsi- (a,e,f) and contralateral (b,c) mediastinal lymphadenopathy, suggesting N3 disease

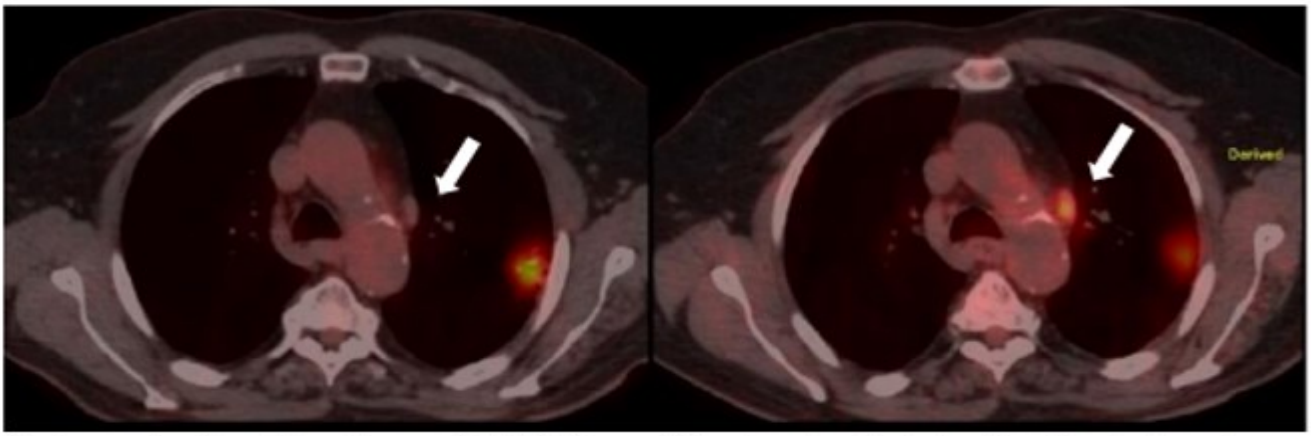

Fig. 7. y.o male with peripheral hypermetabolic LUL tumor (T3), subcentimetric station 5 lymph node shows increased metabolic activity (arrow) on dual-time-point imaging 60 min (a) and 120 min (b) post injection

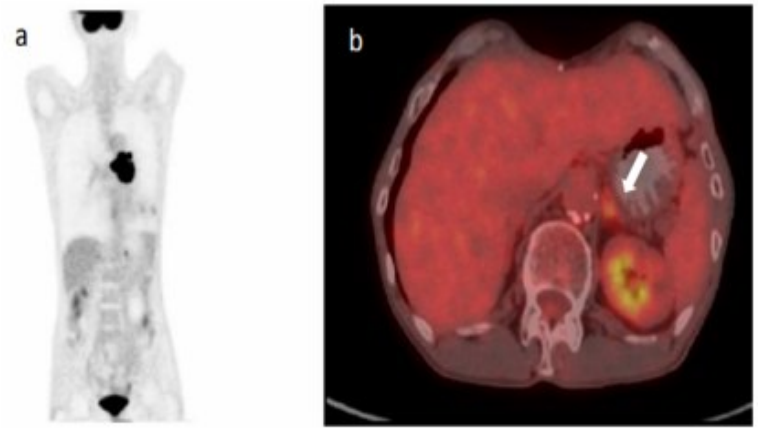

Fig. 8. y.o male, with left central NSCLC (a), unsuspected hypermetabolic lesion of the left adrenal gland (b), suggesting M1 disease

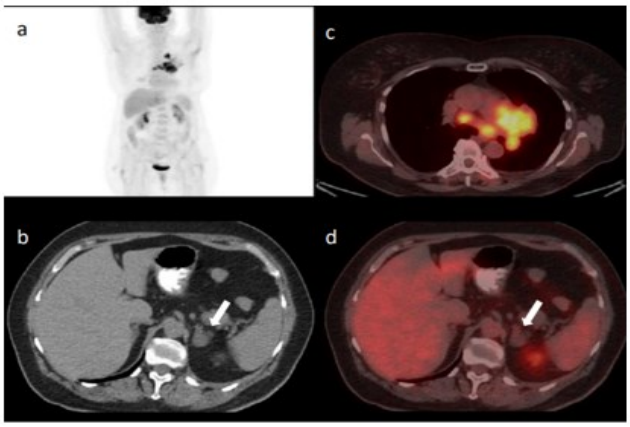

Fig. 9. y.o female with LUL central hypermetabolic tumor (a,c), hypermetabolic ipsi- and contralateral mediastinal lymphadenopathy, left adrenal lesion considered to be metastatic shows no increased metabolic activity (b,d arrow), the patient was downstaged

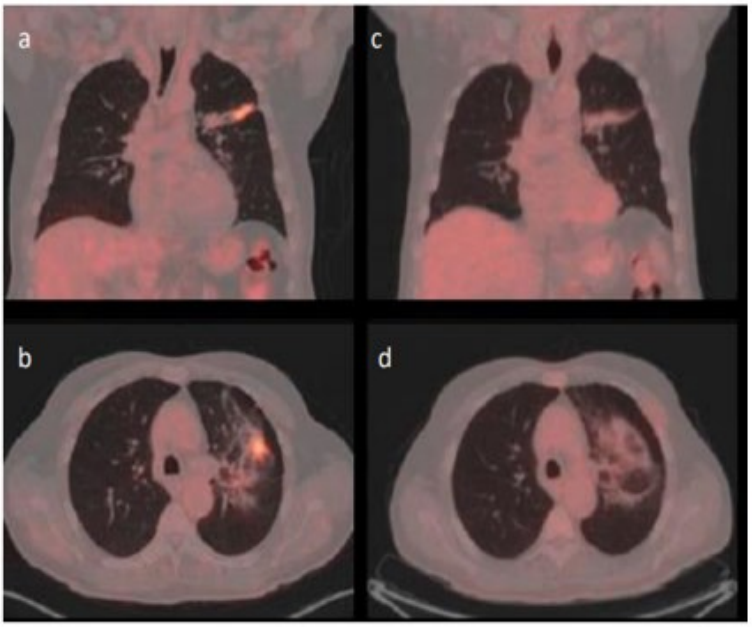

Fig. 10. y.o male treated for the left NSCLC, follow up FDG PET images show complete metabolic response and only fibrosis/necrosis in irradiated area; Pre-treatment (a,b) and posttreatmet fused PET/CT images (c,d).

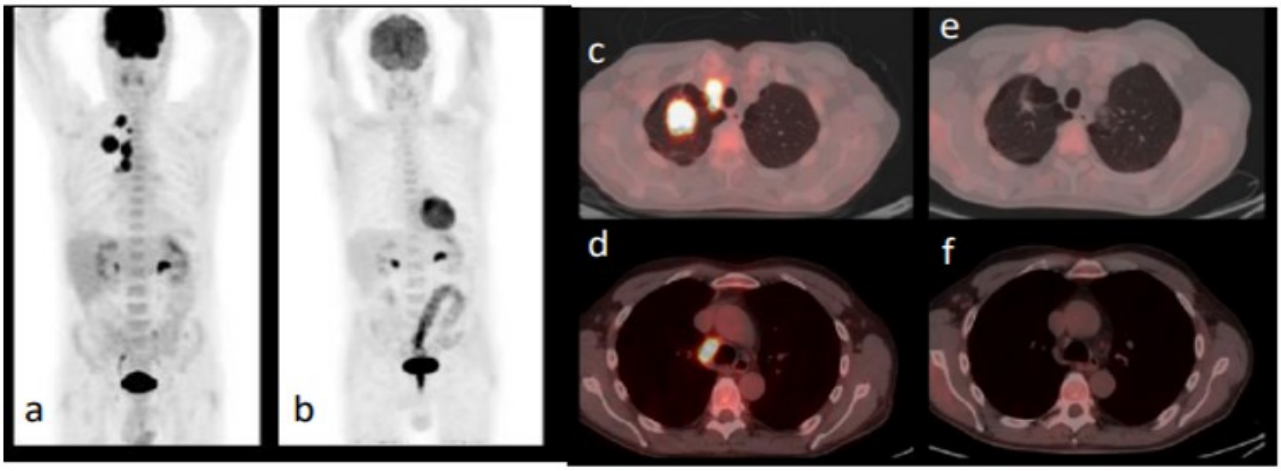

Fig.11. y.o male with NSCLC, treated with chemotherapy and immunotherapy, shows complete metabolic response and disappearance of metabolically active lesions; pre-treatment (a,c,d) and post-treatment MIP and fused (b,e,f) images;

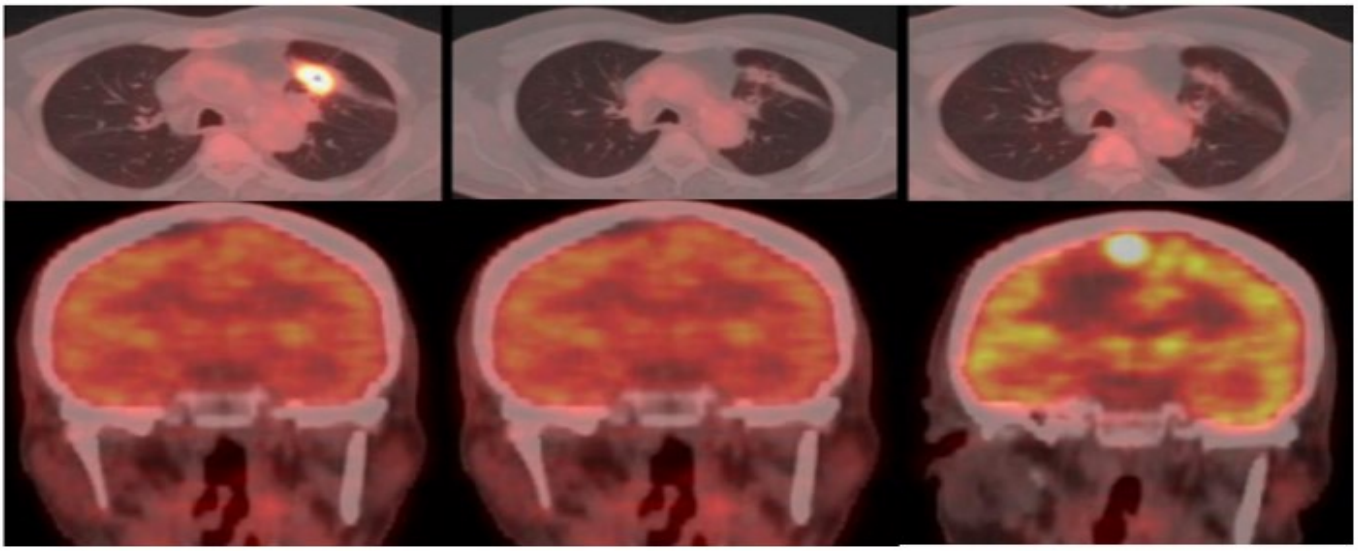

Fig. 12. y.o male treated with immunotherapy for T4N2M1 left NSCLC, axial fused PET CT images (a,c,e) show complete metabolic response in lungs, coronal fused PET CT images (b,d,f) show incidental hypermetabolic brain lesion; oligoprogression was proved by brain MR

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