Oncologic Imaging REVIEW

The role of PET/CT imaging in the management of patients with non-small cell lung cancer

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ABSTRACT

Lung cancer represents the main cause of cancer-related deaths, at a worldwide level. Lung cancer patients need imaging guide and PET/CT scan has proven to be an important imaging tool in the diagnosis and management of lung carcinoma. Hybrid imaging has the ability to combine anatomical and functional information posing it as a gold-standard non-invasive imaging not only in the detection and staging but also in guiding the therapy treatment and monitoring the treatment response.

KEY WORDS: PET/CT, 18F-FDG, lung cancer

Introduction

Lung cancer is considered to be the most commonly diagnosed cancer in the world with non-small cell lung cancer (NSCLC) accounting for the majority of cases. Approximately 2 million new cases being reported yearly, thus representing 11,6 % of all diagnosed malignancy types [1, 2]. It is also accompanied by a high mortality rate accounting for almost 2 million deaths (18,4%) as recorded in 2018. [1, 2].

The integration of [18F]-fluorodeoxyglucose-posi-

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tron emission tomography with computed tomography (18FDG-PET-CT) represents a combined medical imaging test, that provides specificity to anatomic findings and offers precise localization of metabolic activity [3]. Therefore, PET/CT is invaluable in terms of diagnosis and management of lung cancer patients and remains the gold-standard in monitoring treatment efficiency and response.

18F-FDG is the most common radiotracer in use today for the evaluation of pulmonary malignancies. From a chemical point of view, 18F-FDG is a glucose analogue that accumulates in tissues in proportion to the degree to which each tissue uses glucose. This means that, in the micro-environment of most malignancies, where the metabolism of glucose is fast, because of the increasing needs of the proliferating cells, FDG is highly expressed and thus it can serve as a major imaging tool.

The measurement of the relative FDG uptake in a region of interest is calculated with the use of SUV (Standard Uptake Value). It is expressed arithmetically as the ratio of tissue radioactivity concentration at a specific cellular point in time and the injected dose of radioactivity per kilogram of the patient.

Metabolic Tumor Volume (MTV) and Total Lesion Glycolysis (TLG) are two more imaging parameters whose use is limited mostly in the pre-treatment phase [4-6]. TLG is calculated as the product of MTV and the mean SUV of all voxels, while Metabolic Tumor Volume (MTV) is defined as the volume of the delineated tumor as it can be depicted with the use of PET.

The purpose of the current review is to present the current clinical applications of PET/CT, in the diagnosis and monitoring of lung cancer patients.

Diagnosis

One of the main indications for 18F-FDG PET/CT in lung cancer is the diagnosis, differentiation and characterization of pulmonary lesions [7-11]. The differential diagnosis includes the discrimination of neoplastic and benign lesions [12].

18F-FDG PET/CT has the ability to combine anatomy and metabolism which leads to an important increase of the total diagnostic rates [13,14] allowing a high sensitivity of 95% and a specificity of 83% for the diagnosis of pulmonary malignancies [9-11]. Additionally, PET/CT is an important tool in the differential diagnosis of malignant and non-malignant lesions, as pulmonary loci metabolically active are more likely to represent malignancy [14].

Characterization of PET positive solitary pulmonary nodule has been progressively modified. The previously described SUVmax "cut off" value of 2.5 is no recommended today [19], while currently a positive PET result (Fig.1) is when SUVmax is greater than the baseline mediastinal blood pool [15].

Grgic et al, showed that it is possible to evaluate the risk for cancer, via the measurement of the SUVmax of the suspected tissue area, in combination with the relevant clinical indications [16]. In the same study, the authors showed that the mean SUVmax of malignant solitary pulmonary nodules (SPNs) was more elevated, in comparison to the SUVmax of the benign nodules (SUVmax 9.7± 5.5 vs. 2.6 ± 2.5; $P < 0.01$). Interestingly, all SPNs with an SUVmax lower than 1.25 were accompanied by non-malignant histology.

False-negative results are usually related to size, generally with a diameter less than 8-10 mm, in low-grade malignancies, such as mucinous adenocarcinomas, tumors which have relatively large quantities of mucin, in contrast to a small population of cells [17], or in cases of a carcinoid tumor. Solid pulmonary nodules that have a diameter larger than 8-10 mm and demonstrate a low uptake of 18F-FDG have high chances to being benign in nature [18].

On the contrary, false positive results can be obtained in cases of infections and particularly in tuberculosis and granulomatous infections, as well as in non-infectious inflammatory conditions, such as in pulmonary sarcoidosis [19-20]. This can be attributed to the degree of hypermetabolism due to the inflammatory conditions which can be an equally typical characteristic of high-grade malignancies [17]. Last, motion degradation near the diaphragms may reduce the intensity of the perceived metabolic activity but may be addressed by new gated PET/CT protocols [11,21]

TNM Staging

In patients with newly diagnosed Non-Small Cell Lung Cancer (NSCLC), accurate disease staging plays a pivot role in prognosis and appropriate patient treatment. In the revised eighth edition of the TNM staging system, PET/CT is recommended by the NCCN and NICE guidelines to be performed for evaluation of patients with stage I to stage IV NSCLC [22, 23].

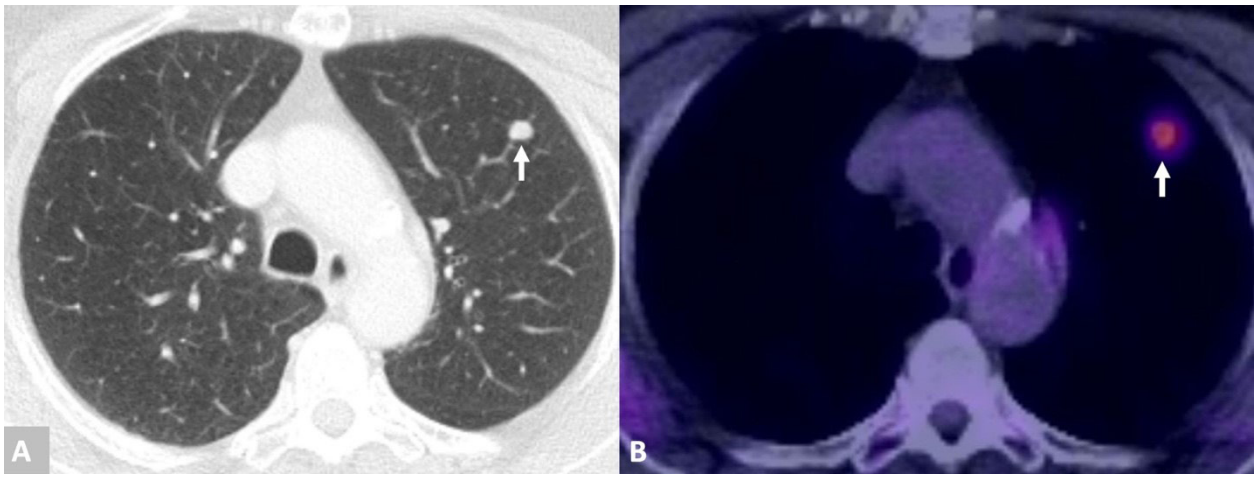

Fig. 1. A. *Axial CT image shows a 0.9 cm solitary pulmonary nodule in the left upper lobe (arrow).* ***B.*** *PET image demonstrates the left upper lobe nodule (arrow) with increased FDG uptake with SUVmax greater than the mediastinal blood pool. No lymphadenopathy or distant metastatic disease was shown. A biopsy was then performed. Pathological findings showed adenocarcinoma (T1aN0M0).*

T Staging

CT is routinely used as the first staging test for the assessment of the T staging for primary pulmonary neoplasms. However, PET/CT imaging has shown to be more accurate with a much higher diagnostic accuracy in comparison to CT alone or PET alone (Fig. 1). In a meta-analysis, PET/CT was able to successfully determine T stage in 82% of the NSCLC patients, when, at the same time the respective rates were 55% for PET alone, and 68% for CT alone [24]. Another significant benefit of PET/CT is that offers the ability to distinguish the actual size of central tumors from post-obstructive atelectasis as the tumor will most often manifest an increased FDG uptake compared to post-obstructive atelectasis regions in an atelectatic lung (Fig 2), [25, 26]. PET/CT can also be helpful in detecting chest wall or mediastinum invasion [27] although often multimodality imaging approach is required and specifically MRI in cases with mediastinal or chest wall invasion (Fig.3).

N Staging

Lymph node staging is an essential diagnostic step in determining the surgical candidate and the type of surgical resection [28,29]. CT morphologic features and specifically the size of the lymph node is typically used to predict pathology. According to CT criteria, a lymph node with a diameter in short-axis larger than 1cm, is classified as pathologically enlarged, and therefore, it can be a strong predicting factor for metastasis. Nevertheless, CT has not demonstrated adequate diagnostic accuracy in the depiction of lymph node metastasis. Prenzel et al, showed that 44% of the patients with NSCLC had metastatic lymph nodes < 1cm, and 77% of patients without metastatic lymph nodes had a lymph node > 1 cm [30], which proves how lymph nodes dimensions alone cannot be diagnostically reliable. PET/CT is actually far more diagnostically reliable to determine lymph node metastasis in comparison to CT alone (Fig. 4), as it has been shown to demonstrate an outstanding accuracy in determining the degree of mediastinal lymph nodes involvement with a sensitivity: 66-100% and a specificity: 81-100%, while for CT the respective rates are 20-81% and 44 -100% [31].

M Staging

Precise depiction of distant metastasis is of great significance, guiding the therapeutic options. According to the most recent bibliographical data, 18-36% of the NSCLC newly-diagnosed cases have distal metastasis on the initial scan [29]. CT alone can diagnose metastasis at only 11-36% of the cases. At the same time, PET along reveal occult distant metastases in only 5–29% of the patients [32, 33]. Nonetheless, the lack of spatial localization can once again lead to errors. At the other hand, the two methods together, offer the most accu-

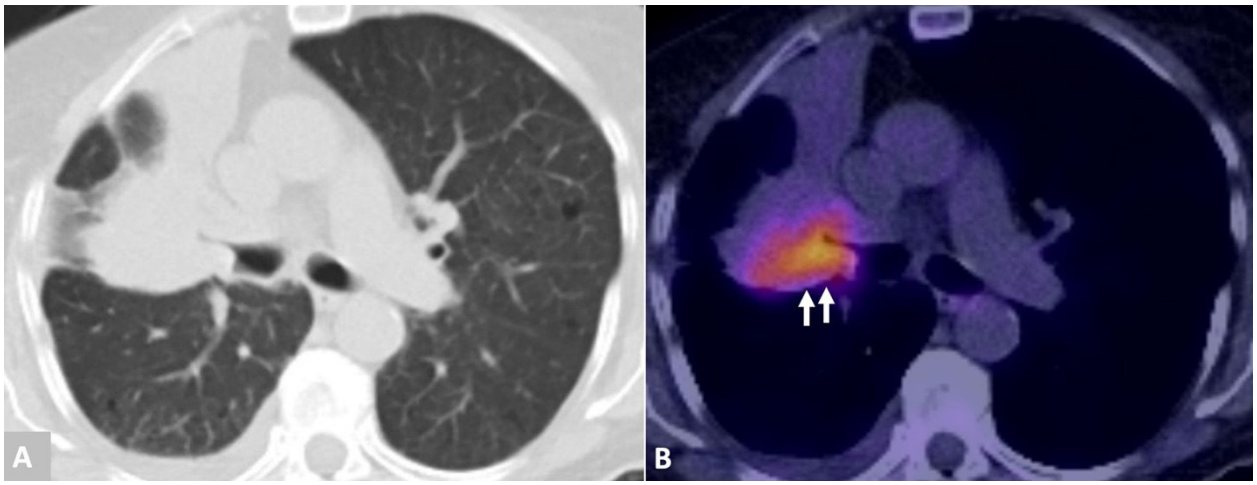

Fig. 2. A. *Axial CT image shows a lung mass extending from the right hilar region to the periphery.* ***B.*** *PET-CT delineates the avid central lesion (arrows) in the right hilar region with invasion of the right main bronchus causing obstructive atelectasis. As the viable tumor has a central location, transbronchial biopsy was performed.*

rate clinical evaluation of the total metastatic disease [34].

18F-FDG PET/CT scan has been proven to have a high sensitivity (97%) and specificity (86%) for the early detection of metastatic adrenal disease in NSCLC [35]. Subsequently, FDG PET-CT scan is a very useful diagnostic tool to distinguish benign adrenal lesions from metastatic [35].

In terms of liver metastasis, FDG PET/CT offers superior diagnostic results compared with other conventional imaging technique [36]. 18F-FDG PET/CT has also been proven to have a better sensitivity regarding the depiction of bone metastases (Fig. 5), (compared to CT and bone scintigraphy) [37]. An interesting meta-analysis suggested that the pooled PET/CT sensitivity for the detection of bone metastasis was 92%, and the respective specificity was 98%, when the respective results from bone scintigraphy gave as high as 86% and 88% [38].

On the contrary, 18F-FDG detection potential of brain metastases is typically characterized by very low sensitivity, due to the normally increased levels of glucose uptake from the healthy brain tissue as the brain used mainly glucose to work properly [39]. In those cases, conventional CT or MRI are the preferable choices that allow clearer results. To address this limitation, 11C-methionine has been proposed for the imaging of the central nervous system metastases.

Detection of a Second Primary Malignancy

Whole-body FDG PET/CT may detect lesions suspicious for secondary primary tumors in about 4% of the patients with NSCLC, where approximately 25% of these findings correspond to a second malignancy [35]. A study from Lin M. and Ambati C. showed that FDG PET/CT was found to identify secondary in 3% of patients with NSCLC, a result that would be able to change clinical management from a curative intent to palliation in 27% of the total cases studied [40].

Metabolic Guide For Tissue Diagnosis

Diagnostic percutaneous CT-guided fine-needle biopsy (FNB) is a relatively safe method for the diagnosis of lung tumors [41]. Its diagnostic accuracy ranges from 64% to 97% [42], and the parameters that seem to play a major role in the determination of the final accuracy include morphology, size and depth of the lesion, as well as the number of needle paths. CT is used as a guidance for FNB, however it does not include information of the metabolically active component within the tumor [43]. This means that when tissue biopsy is guided only by anatomic CT data, the needle might be placed into a non-viable area of the suspected lesion, which could possibly result to inadequate tissue sampling and higher risk for false-negative FNB results [43, 44].

On the contrary, 18F-FDG PET/CT is able to delineate the areas of high metabolic activity within a lung

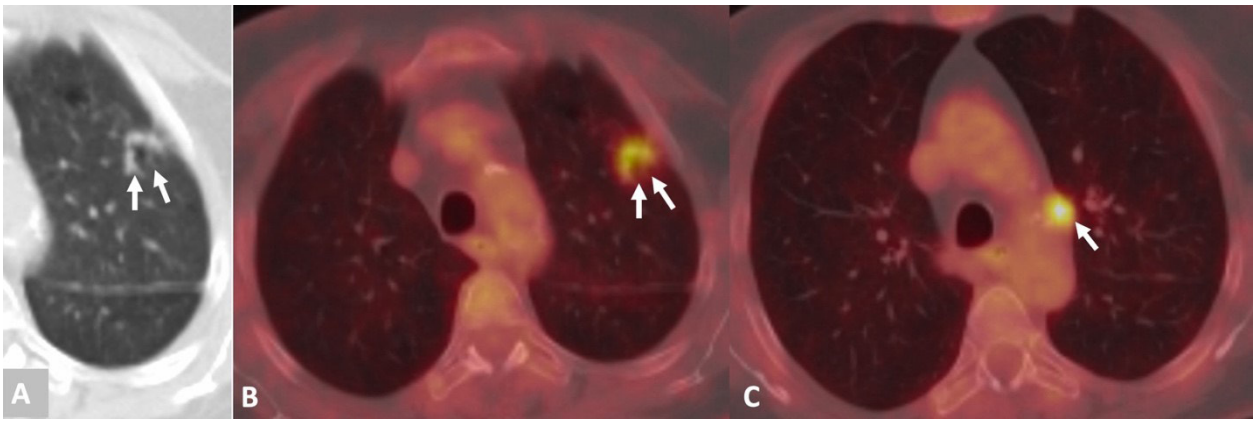

Fig. 3. A. *Axial CT image shows a pericystic lung nodule in the left upper lobe (arrows).* ***B.*** *PET axial image demonstrates the left upper lobe nodule (arrows) with increased FDG uptake.* ***C.*** *It also demonstrates a PET avid aortopulmonary window lymph node (arrow), upstaging to N2 disease.*

lesion and thus differentiate the viable, mainly malignant tissues from the non-malignant ones [45-47], lowering the sampling error, while rising the diagnostic accuracy of image-guided biopsy. At the same time, in patients with multiple lesions, PET/CT is proposed for targeting the metabolically active areas, with the highest 18F-FDG uptake, for needed biopsy [48].

18F- FDG PET-CT imaging offers also valuable data as a metabolic guide for potential malignant lung lesions and metastatic lymphadenopathy guiding the tissue sampling performed by bronchoscopic techniques (Fig. 2, 6) including endobronchial ultrasound (EBUS) guided biopsy alone or combined with transesophageal bronchoscopic ultrasound-guided fine-needle aspiration (EUS-B FNA).

Surgical Planning

Surgical anatomical and non-anatomical resection is considered the treatment of choice for patients who are surgical candidates and have disease classified as stage IIIA or lower [49].

Staging of NSCLC is considered to be the most critical part in the clinical assessment of the lung cancer surgical candidates. PET-CT contributes to the more precise and more timely staging of lung malignancy, via offering a clear anatomic view and an accurate lesion determination, which makes it superior to CT alone. In recent studies, PET-CT was able to successfully predict the T status, the N status, the M status and the TNM status in, 86%, 80%, 98%, 70% of the cases respectively, versus 68%, 66%,88%, 46% acquired with CT alone [43, 47]. 18F-FDG PET-CT may also be helpful in equivocal cases of chest wall invasion as frequently alters surgical management [49]. Moreover, PET-CT scan offers the ability to avoid a large number of non-therapeutic thoracotomies. Recent studies suggest that the clinical data coming from PET help surgical treatment in each and every step of it, and additionally lowers the total cost of hospital stay, because it is associated with a 51% decrease in the number of thoracotomies and their associated risks [50].

Radiation Therapy Planning

Radiotherapy planning is essential for the accurate and efficient radiotherapy treatment. Until recently, CT and MRI provided the necessary imaging anatomy information in the treatment planning process. The integration of PET-CT can help delineating the extent of the tumor with precision avoiding the unnecessary irradiation of healthy tissue [51, 52]. Specifically, in cases with mixed tumor and atelectasis, PET-CT helps to define the border between tumor and atelectasis, allowing a smaller volume of lung to be treated [53].

Treatment Response

PET/CT contribution is significant in the assessments of the patients' response to treatment, with either chemotherapy, radiotherapy and/or immunotherapy (Fig.7). It can be used as a baseline imaging test, while during therapy monitoring, PET/CT can assist clinical decision assessing the efficiency of the treatment.

SUVmax is the preferable semi-quantitative PET pa-

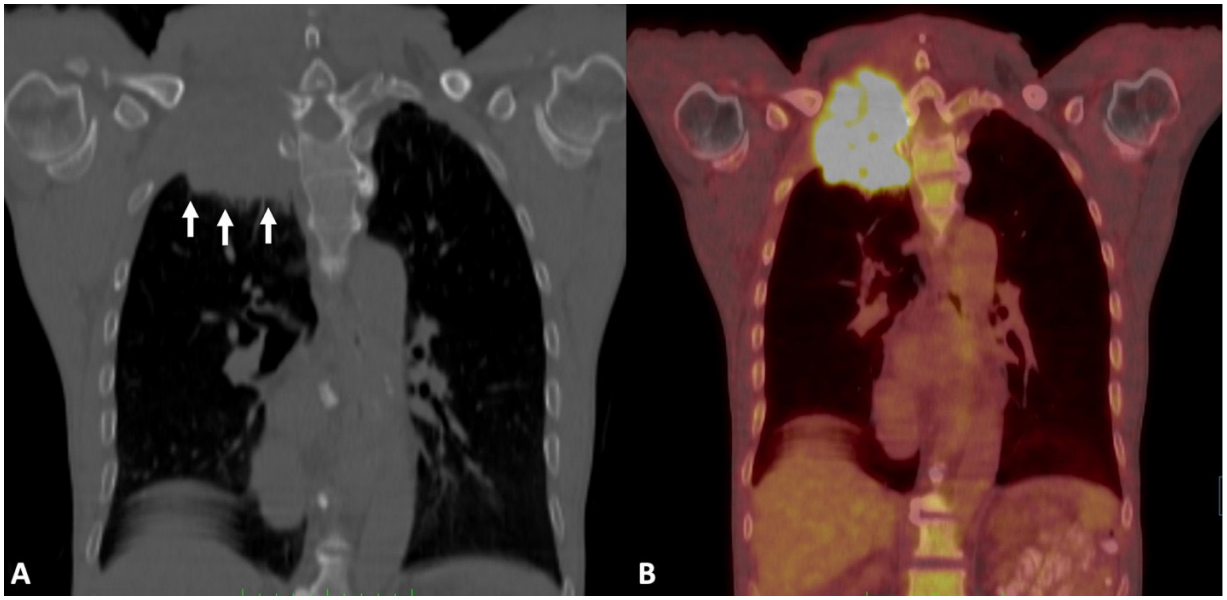

Fig. 4. ***A.*** *Coronal CT image shows a right apical mass (arrows), (Pancoast tumor) with chest wall invasion and destruction of the right 1st and 2nd rib.* ***B.*** *Coronal PET image demonstrates the extension of the viable tumor.*

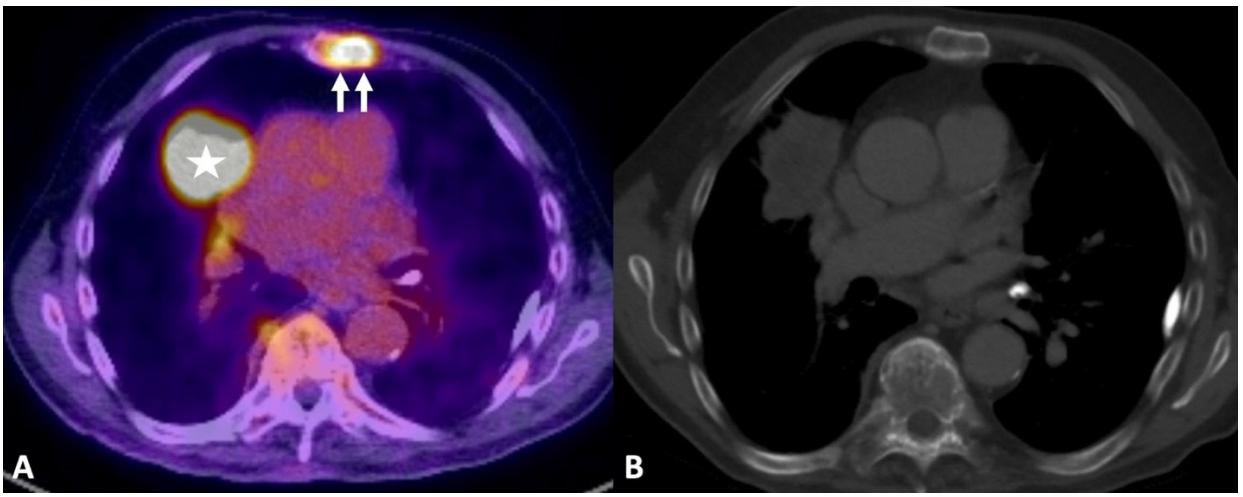

Fig. 5. ***A.*** *PET image shows an avid mass in the right upper lobe (asterisk). It also demonstrates a solitary avid bone metastasis (arrows) in the sternum (M1b disease).* ***B.*** *No bone lesion was demonstrated on the CT axial image with bone window.*

rameter for the evaluation of the treatment response. EORTC and PERCIST criteria propose the use of quantitative changes in SUV as an index of the treatment response [54]. On that basis, EORTC criteria suggest a reduction of a minimum 25% in the SUVmax, whereas PERCIST criteria recommend a 30% reduction of SUVpeak as corrected for lean body mass or by an absolute drop of 0.8 SUVpeak units [55].

Studies have shown that decreased FDG uptake has been linked to better prognosis of disease, and it is a marker of an effective responsiveness to the chemotherapy [62]. On the other hand, no change in the activity levels could pose an indication for a chemotherapy plan change. Previously presented evidence demonstrate that high FDG uptake after the first cycle of chemotherapy is associated with shorter overall survival compared with patients with a low FDG uptake and a median survival of 12 months instead 34 months [57, 58].

On the contrary, large tumors exhibiting central necrosis are typically accompanied with heterogene-

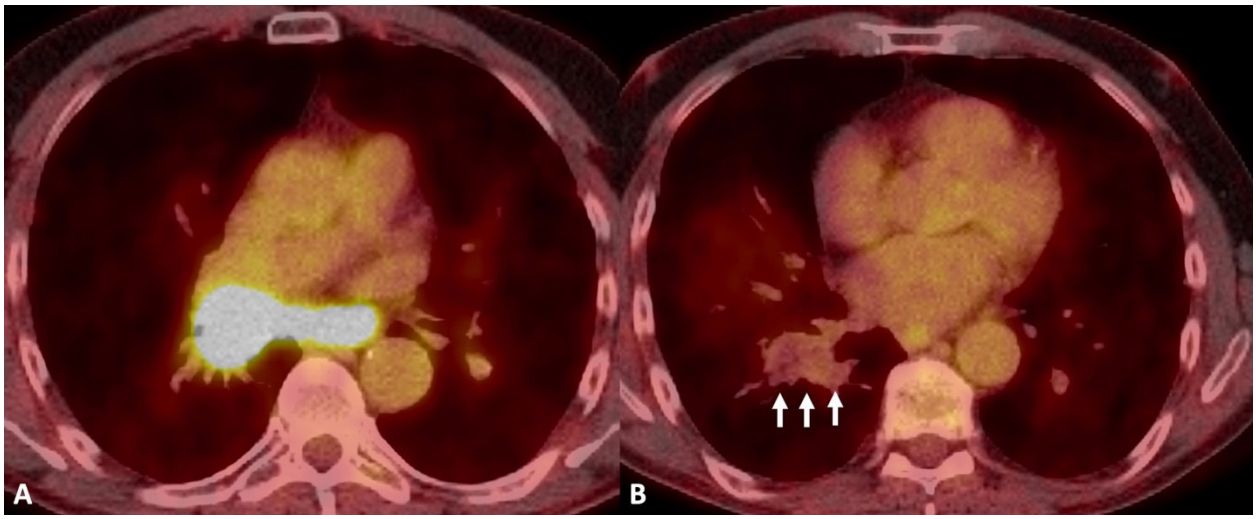

*Fig. 6. Large subcarinal PET-avid mass (**A**) with extension in the right lower lobe (**B**). EBUS was favored over CT-guided lung biopsy as the right lower lobe component is not metabolically avid (arrows).*

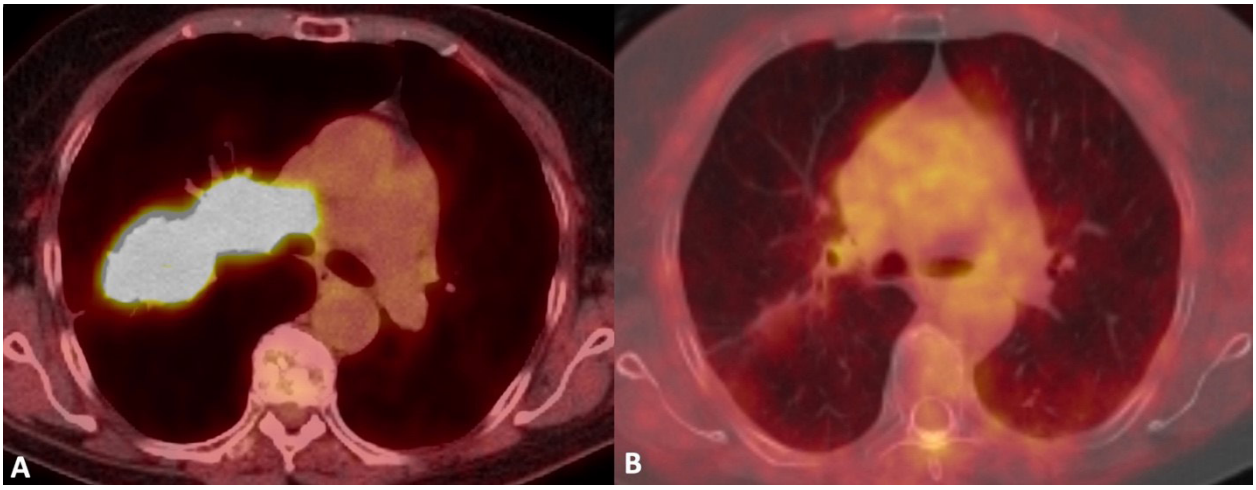

*Fig. 7. **A.** PET-CT shows a large lung mass extending from the right hilar region to the right upper lobe. The patient was treated with durvalumab. **B.** PET-CT performed after 3 months shows almost complete response to immunotherapy.*

ous 18F- FDG uptake, and subsequently, SUVmax will not provide detailed information about each tissue's metabolic activity. In those clinical cases, it might be preferable to use metabolic parameters that incorporate both tumor volume and the intensity of uptake [59]. Metabolic Tumor Volume (MTV) and Total Lesion Glycolysis (TLG) are two such quantities proposed for clinical use [60-62]. Furthermore, it has been scientifically proven that Background Activity-Based PET Metrics (BSL) and Background Subtracted Volume (BSV) are some of the most promising new prognostics markers for future research [63, 64]. More specifically, Burger et al. have recently demonstrated that BSL and BSV show a in much clearer way the patients' tumor response compared to MTV and TLG [64].

Similarly, Hopkins criteria have recently been suggested as the new PET-based criteria that evaluate lung cancer patients' treatment response [65]. These criteria, are essentially qualitative in estimating mediastinal blood pool and liver 18F-FDG uptakes as the reference's standard.

Conclusions

PET/CT represents a medical hybrid imaging diagnostic tool that combines metabolic and anatomic data and is proven essential in the management of lung cancer patients. 18F-FDG PET/CT provides significant data regarding the biological aggressiveness of lung tumor and patients prognosis. PET/CT imaging is an important imaging modality not only for the staging of lung cancer patients but also is recommended as a metabolic guide for tissue diagnosis and for the appropriate treatment planning and adequate monitoring assessment of therapy response. **R**

Disclosures:

The authors have no relevant disclosures.

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