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PET/CT Variants and Pitfalls in Lung Cancer and Mesothelioma

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2-deoxy-2-[^{18}F]fluoro-D-glucose [^{18}F]FDG-PET/CT represents the metabolic imaging of choice in various cancer types. Used either at diagnosis or during treatment response assessment, the modality allows for a more accurate definition of tumor extent compared to morphological imaging and is able to predict the therapeutic benefit earlier in time. Due to the aspecific uptake property of [^{18}F]FDG there is an overlap of its distribution in normal and pathological conditions, which can make the interpretation of the imaging challenging. Lung and pleural neoplasia are no exception to this, thus acknowledging of possible pitfalls and artifacts are mandatory for image interpretation. While most pitfalls and artifacts are common for all indications with metabolic imaging with [^{18}F]FDG-PET/CT, there are specific variants and pitfalls in lung cancer and malignant pleural mesothelioma. The aim of the present article is to shed light on the most frequent and relevant variants and pitfalls in [^{18}F]FDG-PET/CT imaging in lung cancer and malignant pleural mesothelioma.
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Lung Cancer Variants And Pitfalls on [^{18}F]FDG-PET/CT

Lung cancer is the leading cause of cancer deaths worldwide,[1] with less than one fifth of the patients still alive at 5 years after the diagnosis.[2] Up to 90% of lung tumors are caused by smoking habits, and the majority are represented by non-small cell lung carcinoma (NSCLC).[3] Clinical symptoms mostly referred at the time of diagnosis include cough, hemoptysis, dyspnea, and chest pain, while in 10-20% of the cases a paraneoplastic syndrome is associated.[4,5] Upfront surgery or neoadjuvant chemotherapy are considered the treatment of choice for early stage and locally advanced cancers, while platinum-based chemotherapy has been for long time the standard of care for first line therapy.[6] In recent years, the identification and targeting of programmed cell death-1 (PD-1) and its ligand, programmed cell death-ligand 1 (PD-L1), has dramatically changed the scenario in lung cancer, leading to the approval by the FDA and EMA of various checkpoint inhibitors for the first and subsequent lines of treatment.

The definition of tumor extent is essential for patient management; therefore, diagnostic imaging plays a crucial role in the assessment of lung cancer.[7] In this context, a proper place is kept by [^{18}F]FDG-PET/CT, whose use starts at a very early phase of lung cancer diagnosis, and continues with staging, tumor response assessment and tumor recurrence identification.

An overall accuracy of 91% has been reported for [^{18}F]FDG-PET/CT in lung cancer detection, with false-negative cases commonly referred to smaller lesions and tumors with a low metabolic activity, such as carcinoid, adenocarcinoma in situ (AIS) and minimally invasive adenocarcinoma (MIA).[8,9] This implementation of [^{18}F]FDG-PET/CT in the

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Table 1 The Most Common Artifacts on [^{18}F]FDG-PET/CT in Lung Cancer and MPM

Artifacts	Cause	Image	Solution
Motion artifacts	External patient motion Internal target motion	Spatial mismatch	Awareness Motion encompassing Controlled breathing Respiratory gating
Hot cloth artifacs	Microemboli with agglutinated [^{18}F]FDG due to blood aspiration into the injector, paravenous or high speed injection	Peripheral focal lung hotspot without CT substrate	Awareness Follow up
Partial volume effect	Limited spatial resolution	[^{18}F]FDG-uptake of small lesions are underestimated or missed	Awareness in small lesions
Attenuation artifacts	Dense material on CT is overestimated on PET	Non-existent lesions are mimicked or [^{18}F]FDG-uptake of existing lesions overestimated	Check non-attenuated images as well Remove all removable metal objects prior to scan Metal reduction algorithms on CT
Improper patient preparation	Hyperglycemia Hyperinsulinemia Cold exposure Muscle tension	Lower [^{18}F]FDG-uptake in tumor and higher [^{18}F]FDG-uptake in healthy tissue	Proper patient preparation Knowledge of preparation and scan circumstances taken into account when reporting

diagnostic work-up has been reported to lead up to a 51% relative reduction in futile thoracotomy compared to conventional imaging alone.[10,11] The added value of [^{18}F]FDG-PET/CT remains the superiority in lung cancer staging. Of note the high negative predictive value for the detection of mediastinal metastases (up to 94%), as well as the high sensitivity and specificity (93% and 96%, respectively) for the identification of distant metastases.[11–13] Among them, brain metastases can be documented in 28.4% of the cases.[14] Given the physiologic intense uptake of [^{18}F]FDG in the normal brain, the sensitivity of PET/CT results suboptimal compared to other sites of metastases; pooled sensitivity of 21%, but specificity of 100%.[11,15] To partially overcome this limitation, delayed images can be acquired up to three hours post-injection.[16] Consequently, to maintain the high standards obtainable with PET imaging in lung cancer, it is important to be aware of the limitations and pitfalls affecting the interpretation of the imaging findings. A comprehensive summary of major variants and artifacts is presented in the following paragraphs for the benefit of the reader.

Artifacts

The interpretation of PET/CT in lung cancer patients can be hampered by several kinds of artifacts, which crucially need to be recognized by nuclear medicine physicians, in order to avoid incorrect diagnoses and treatment management decisions. Correct interpretation of PET/CT of the chest region in particular, can be disturbed by motion and respiration artifacts, hot-clot artifacts, attenuation artifacts, artifacts due to the partial volume effect and artifacts induced by improper patient preparation (Table 1).

Motion Artifacts

Motion artifacts can result from external patient motion (e.g. rotation of the head, arm movement) or internal target motion (e.g. diaphragm motion during breathing, bowel motion, bladder filling). For correct anatomical localisation, attenuation- and scatter correction, the (low dose) CT and the PET need to be spatially aligned. Respiratory motion artifacts can result in a spatial mismatch between PET and CT (Fig. 1) and in significant blurring of structures within the thorax and upper abdomen, reducing quantitative accuracy of radiotracer uptake and accurate volume definition in PET images, which could lead to inadequate target volume delineation for radiotherapy planning or incorrect treatment response measurement. Due to misregistration intrapulmonary nodules on CT can be falsely reported as FDG-negative or FDG-avid foci can be reported as foci "without visible substrate on CT". Respiratory motion artifacts will be largest in moving lesions at the interface of anatomic regions with different densities (e.g., the lower lung and liver dome). Attachment of lesions to other anatomical structures (chest wall or mediastinum), decreases displacement of the lesion during the patient's respiratory cycle.[17] Awareness of motion artifacts is mostly sufficient for the right interpretation of the images. Robust methods to control respiratory motion to reach a perfect PET and CT match can be divided into four broad categories:[18–20] motion-encompassing methods, controlled breathing, respiratory gating, data-driven gating.

Hot-Clot Artifacts

In 0.4% of PET/CT scans incidental focal uptake in a lung can be detected, without corresponding intrapulmonary nodule. When misregistration can be excluded, a hot-clot

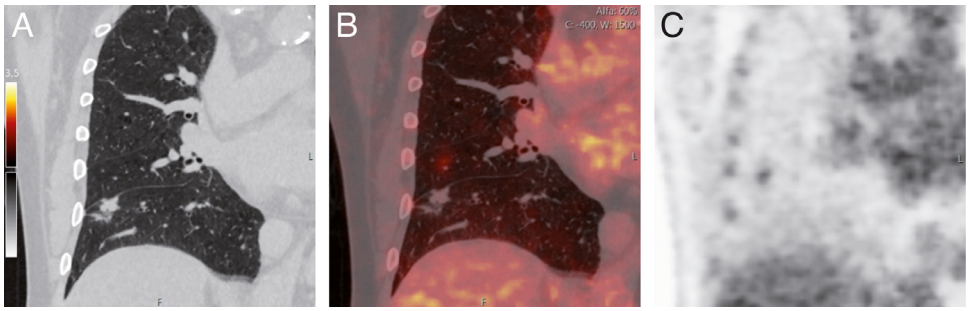

Figure 1 Example of a respiratory motion artifacts which resulted in a spatial mismatch of the lesion between PET and CT. Such mismatch cannot only lead to a positional mismatch (localization in incorrect lobe), but also to an inaccurate quantification of [^{18}F]FDG activity, which might be important in case of treatment response monitoring.

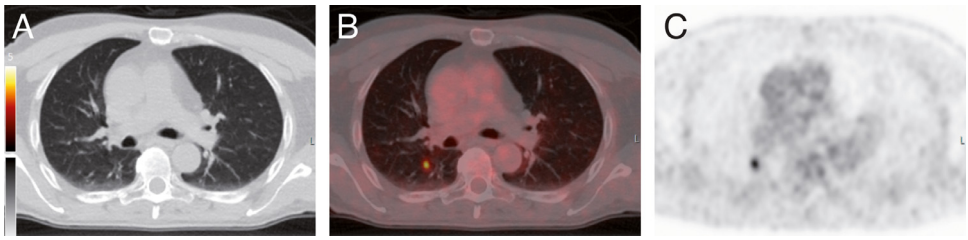

Figure 2 High intrapulmonary incidental focal uptake, without corresponding intrapulmonary nodule on low dose CT was detected in a patient who had no other pulmonary lesions. During 1 year of follow-up still no intrapulmonary abnormalities were detected, therefore it was assumed to be an FDG microembolus.

artifact should be considered (Fig. 2). These artifacts typically are localized in peripheral lung regions, show a relatively high [^{18}F]FDG uptake and disappear spontaneously without intervention by the next follow-up scan. They are caused by microemboli in the pulmonary arteries which can be a result of blood aspiration into the injector, paravenous or high speed injection.[21] There is agglutination of [^{18}F]FDG by erythrocytes within the cloth, which is responsible for visualisation.

Partial Volume Effect

Partial volume effects result from the limited spatial resolution of PET/CT of approximately 3-5 mm full-width-at-half-maximum. Due to this low spatial resolution the activity concentration of small lesions can be underestimated or might even be missed. The consequences of this effect should be considered in all small, low contrast lesions (typically < 2 cm) and depend, amongst others, on the resolution of the PET/CT-scanner, the applied reconstruction algorithm, the post-reconstruction filter and the shape, size, [^{18}F]FDG-uptake and motion of the lesion.[22]

Attenuation Artifacts

Attenuation artifacts are caused by dense material (such as metal) on the CT scan which are overcorrected on the PET images mimicking a nonexistent lesion. To prevent attenuation artifacts, it is required to remove all metal objects in the field of view, such as necklaces, metal underwired bras and piercings. Drains, stents and lines, shoulder prostheses, osteosynthesis material, pacemakers and implantable cardiac defibrillators, however, cannot be removed. For such cases interpretation of the non-attenuation corrected images are essential. Different metal artifact reduction algorithms have been developed as well, which can be helpful to reduce the CT induced quantification errors in the PET data.[23]

Improper Patient Preparation

High physiological uptake in healthy tissue or low uptake in tumour tissue can occur by improper patient preparation (hyperglycaemia, hyperinsulinemia, cold exposure, some drugs, muscle tension, vigorous exercise). Therefore, detailed knowledge of the patient preparation and scan circumstances are essential for optimal image interpretation.

Physiologic Uptake/Normal Variants

BAT Activity

In 3.7% of patients undergoing [^{18}F]FDG-PET/CT increased [^{18}F]FDG-uptake can be observed in brown adipose tissue and can be misinterpreted as primary malignancy or nodal metastasis (Table 2). Typically, it is more common in younger and cachectic patients and may occur after cold exposure. It is often multifocal, symmetric and bilateral and located in the adipose tissue of the neck, supraclavicular region, around large vessels of the mediastinum, the axillae, the perinephric region and in the intercostal spaces along the thoracic spine.[24]

Muscular Activity

The days before the scan, vigorous exercise should be omitted, since it can induce intense uptake in the associated

Table 2 The Most Common Non-Malignant Variants Causing Pitfalls on [^{18}F]FDG-PET/CT

Non-malignant variants	Image	Problem	Solution
Brown adipose tissue	Focal [^{18}F]FDG-accumulation neck, supraclavicular, paravertebral, etc.	Misinterpretation for malignant lesion	Warm environment prior to scan Propanolol premedication
Muscular activity	[^{18}F]FDG-uptake in muscle	Lower sensitivity of tumor detection	No vigorous physical activity prior to scan Prevent muscle movement during administration of [^{18}F]FDG
Vocal cord paralysis	No [^{18}F]FDG-uptake in paralyzed vocal cord	Physiologic [^{18}F]FDG-uptake in non-paralyzed cord can be mistaken for tumor	Awareness Knowledge of patient history
Bone marrow	Increased uptake in bone marrow	Lower sensitivity for detecting bone marrow metastasis	Knowledge of therapy timing and medication (e.g. GCSF)
Adrenal lesions	[^{18}F]FDG-uptake in benign adrenal lesions	[^{18}F]FDG-uptake can be mistaken for tumor	Measure adrenal-liver SUVmax ratio on [^{18}F]FDG-PET/CT Measure HU of adrenal node on CT
Inflammatory conditions Radiotherapy or immunotherapy related, sarcoidosis	Moderate to high [^{18}F]FDG-uptake	[^{18}F]FDG-uptake can be mistaken for tumor	Compare to anatomical image on CT Knowledge of medical history Follow up
Infectious conditions Pneumonia, tuberculosis, pleurisy, abscess	Mostly high [^{18}F]FDG-uptake	[^{18}F]FDG-uptake can be mistaken for tumor	Compare to anatomical image on CT Knowledge of medical history Follow up
Medical devices Osteosynthesis material, Prostatic joint, cardiac pacemaker, lines, stents, tubes, sutures, surgical mat	Non-existent lesions are mimicked	[^{18}F]FDG-uptake can be mistaken for abnormality	Compare to anatomical image on CT Check non-attenuated images as well
After invasive intervention Biopsy, mediastinoscopy, RFA, (video assisted) surgery, tracheostomy, talk pleurodesis	Non-existent lesions are mimicked	[^{18}F]FDG-uptake can be mistaken for abnormality	Compare to anatomical image on CT Knowledge of medical history Follow up

skeletal muscles. Muscle movement or tension during administration of [^{18}F]FDG, can also result in muscle uptake, and crying, hyperventilation or severe dyspnea can result in uptake in the diaphragm and in accessory muscles of respiration.[25]

Contralateral Vocal Cord Paralysis

Asymmetric [^{18}F]FDG-uptake in one laryngeal muscles can be due to muscle overuse in case of contralateral vocal cord paralysis, due to recurrent laryngeal nerve palsy (Fig. 3). This should not be misinterpreted as a primary laryngeal malignancy.[26]

Thymus Uptake

Thymus uptake can appear as an upside down letter V in the anterior mediastinum in children and young adults and can also be observed in adults with thymic hyperplasia after chemotherapy.[27]

Adrenal Uptake

The adrenals are a common localisation of metastases and unfortunately also a common site for benign nodules (occurring in 1.5% of all CT studies). [^{18}F]FDG-PET sometimes can be helpful in the differentiation between malignant and benign adrenal disease with a 97% sensitivity and 91% specificity. In patients with known cancer the combination of [^{18}F]FDG-uptake $\leq$ liver or HU<10 or macroscopic fat on CT can exclude malignancy with an excellent diagnostic accuracy, but not a 100% sensitivity or PPV. A standardized uptake value (SUV)max adrenal-liver ratio of >2.5, however, in general excludes benign nodules. When a patient presents without known cancer or hormonal hypersecretion and when the adrenal-liver SUVmax ratio exceeds 1.8, further

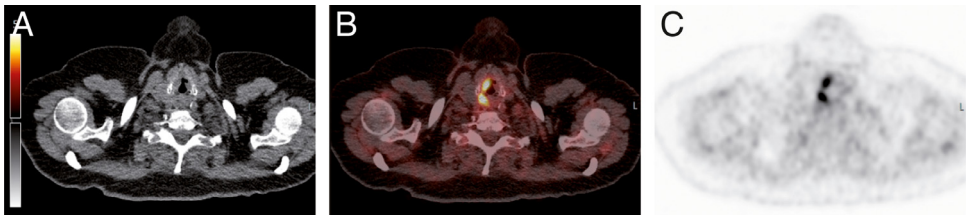

Figure 3 High [^{18}F]FDG-uptake in the right laryngeal muscles, caused by overuse due to left vocal cord paralysis in a patient with lung cancer in the left upper lung lobe and left recurrent laryngeal nerve palsy due to mediastinal invasion.

evaluation with CT or MRI is recommended. Also, in other patients with a SUVmax ratio close to 1.8 and when CT features cannot diagnose an adenoma or myelolipoma, close follow-up should take place. The interpretation of [^{18}F]FDG-PET in characterizing adrenal lesions smaller than 10 mm should be performed with caution, due to a high false negative rate due to the partial volume effect. Other reasons for a false negative [^{18}F]FDG-PET can be haemorrhage, necrosis and micro metastases. Therefore, histological confirmation is generally recommended when the presence or absence of adrenal metastases will change patient management decisions.[21]

Bone marrow uptake

Diffuse increased bone marrow accumulation can be due to bone marrow recovery after chemotherapy, which in general resolves 1 month after treatment. Furthermore, it can be present in patients with anemia or who are treated with erythropoietin, hematopoietic growth factors or granulocyte (-macrophage) colony-stimulating factor. In this category of patients, the identification of bone marrow metastases on [^{18}F]FDG-PET might be challenging. It could be helpful to wait 2-4 weeks to perform the [^{18}F]FDG-PET/CT, although in some cases [^{18}F]FDG -uptake remains increased, also after 4 weeks of treatment.[25]

Difficulties in the Detection of Recurrent Disease

False Negatives

The success of lesion detection depends on the metabolic profile of the tumour histology as some subtypes are notoriously false-negative (eg, low grade tumours such as most neuroendocrine tumours, adenocarcinoma in situ (AIS) or those with much extracellular matrix, such as tumours with mucinous components). Knowledge of the various appearances of AIS on CT is important to prevent misinterpretation (ground glass opacities with or without a solid component, solitary or multiple pulmonary nodules).[28]

False Positives

False-positive lesions can be found on PET/CT-images due to influx of inflammatory cells (lymphocytes, macrophages), due to infection (eg, pneumonia), inflammatory conditions (eg, radiotherapy related, immunotherapy related, sarcoidosis, post-tuberculosis) or after invasive intervention (eg, biopsy, mediastinoscopy, radiofrequency ablation (RFA), surgery, sternotomy, tracheostomy, pleurodesis, insertion of central lines, chest tubes, gastrotomy tubes, cardiac pacemaker implantation). In the verification of such lesions the CT component may be helpful and also correlation with the patients' medical history is important.[29]

Local Recurrence

Posttreatment, after certain interventions and after pulmonary infection and inflammation it is difficult to identify recurrent disease. Therefore, it is important that the radiologist and nuclear medicine physician take into account the recurrence risk of the individual patient and that they recognize the distinct patterns of posttreatment changes associated with the different therapeutic modalities.

Increased [^{18}F]FDG-uptake can be visualized adjacent to surgical clips, which may last for up to 3 months after surgery and in general will decrease thereafter. Local recurrence will present as a growing mass at the anastomosis, the bronchial- or pulmonary artery stump.[30]

Due to radiation pneumonitis well-defined intense FDG-uptake can last for up to 6 months and low-level less well-defined uptake can last for up to 2 years after radiotherapy or stereotactic body radiation therapy (SBRT), which might hamper early detection of tumor recurrence. Only growth of consolidation on CT after 12 months was a significant predictor of recurrence. Other signs of recurrence are: filling of ectatic bronchi, development of bulging at margins of radiation-induced consolidation and new pleural effusion. It has been reported that an [^{18}F]FDG-PET/CT within 3 months has a low specificity and a high false positive rate for recurrence detection. [^{18}F]FDG-PET/CT after 6 months shows better correlation with treatment outcome. [^{18}F]FDG-PET/CT, however, has a high negative predictive value, since the absence of intense focal uptake indicates good treatment response. Therefore, the mainstay for detection of recurrence after SBRT is the combination of [^{18}F]FDG-PET and CT. In case of high focal uptake, [^{18}F]FDG-PET based targeted biopsy is recommended for histopathological confirmation.[31]

Up to three months after RFA an inflammatory rim like increase of [^{18}F]FDG-uptake can be observed. Focal uptake at the periphery of the ablation site, however, is suspicious for residual or recurrent disease. Recurrences occur usually with 2 years after RFA.[32]

During or after treatment with a molecular targeted therapy, sometimes the overall size of the neoplasm may paradoxically increase, due to intratumoral necrosis, hemorrhage

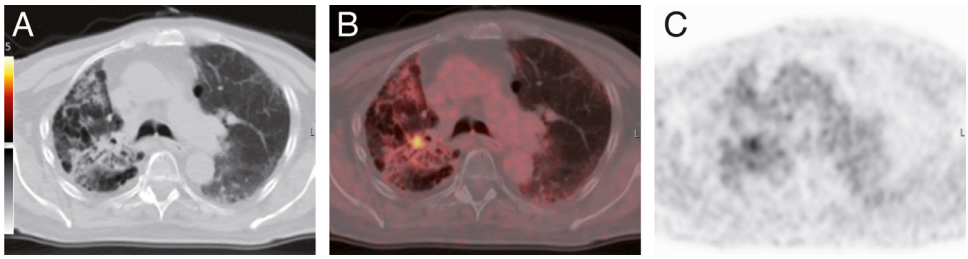

Figure 4 [^{18}F]FDG-PET/CT of a patient with a T4N2M0 squamous cell carcinoma located centrally around the right hilum, which was treated with radiochemotherapy with curative intent six months earlier. Bone metastases were detected three months ago in his left ischium and the patient started with immunotherapy. The patient, however, developed a colitis and immunotherapy related pneumonitis. The [^{18}F]FDG-PET/CT after cessation of immunotherapy shows ground-glass opacities, traction bronchiectasis, a reticular interstitial pattern and active inflammation in the right upper lobe. In this patient, it is difficult to differentiate tumor recurrence from radiotherapy and immunotherapy related inflammation.

or myxoid degeneration, as a result of response to therapy. To prevent incorrect interpretation, hybrid imaging with PET might be helpful.

Detection of recurrent disease in patients who were treated with immunotherapy (Fig. 4) in adjuvant setting can be cumbersome in case of immunotherapy induced pneumonitis, caused by infiltration of autoreactive T-cells, causing such immune related adverse event (irAE). Also in the palliative setting interpretation of [^{18}F]FDG-PET/CT needs special knowledge to recognize the challenging pitfalls. Immunotherapy may induce unconventional response patterns, including a paradoxically increase in size or metabolic activity due to immune cell infiltration and/or the appearance of new lesions followed by tumor regression. Progressive disease should therefore be confirmed after 4 weeks according to the immune-specific response criteria (iRECIST and iPERCIST). Adding [^{18}F]FDG-PET after 4 weeks has the advantage of being predictive of treatment outcome.[33]

During or after all kinds of pneumonic infections it is difficult to differentiate malignant tissue from pneumonia related increased [^{18}F]FDG-uptake. Especially after a COVID-19 or a tuberculosis infection, intrapulmonary changes can last very long. In such cases, it is difficult to detect recurrent disease on CT. Hybrid imaging combining [^{18}F]FDG-PET and CT might sometimes be helpful (Fig. 5). It is, however, important to keep in mind, that PPV always depend on population characteristics. In case of occupational-related lung disorders, endemic granulomatous disease, or in the middle of a pandemic (such as the COVID-19 pandemic), the PPV of [^{18}F]FDG-PET/CT can be decreased.

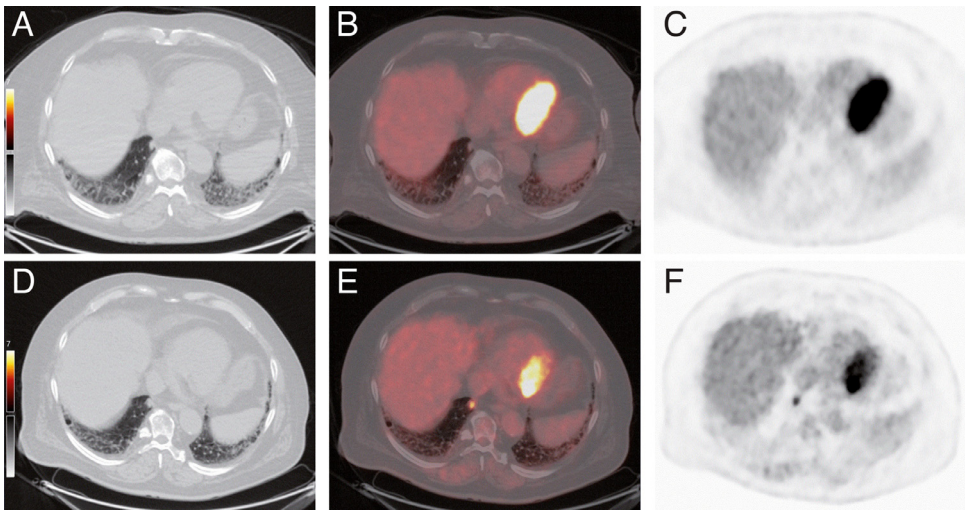

Figure 5 **A-B-C**: [^{18}F]FDG-PET/CT of a patient with a history of lung cancer who suffered from COVID-19 infection four months earlier. Residual COVID-19 related ground-glass opacities / crazy paving involving peripheral bilateral lung bases are still visible. The [^{18}F]FDG-PET/CT was performed to evaluate the persistent solid subpleural lesion in the right lower lobe, closely related to the mediastinal fat. The lesion did not show very clear [^{18}F]FDG uptake. It is difficult to differentiate malignant lesions from (post)-pneumonia related lesions. **D-E-F**: Follow-up scanning, however, was helpful. The [^{18}F]FDG-PET/CT 3 months later showed resorption of the COVID-19 related pulmonary lesions, however, the solid subpleural lesion in the right lower lobe persisted and started to accumulate [^{18}F]FDG. It turned out to be a pulmonary metastasis.

Nodal Recurrence

Regional nodal recurrence after resection of early stage NSCLC occurs in approximately 10% of cases, most often in station 4, 7 and 10. In particular left-sided tumors more frequently show contralateral mediastinal nodal recurrence than right-sided tumors. After chemoradiation of locally advanced disease local recurrence occurs in up to 85% of cases. [^{18}F]FDG-uptake higher than the liver in new, growing or enlarged lymph nodes, or in a previously silent node is suspicious of nodal recurrence. Sensitivity increased when [^{18}F]FDG-PET was added to CT alone from 50-70% to 75-85% and specificity increased from 65-85% to 85-90%.[29]

Pleural Recurrence

Pleural effusion not disappearing during follow-up, pleural thickening, new pleural nodules and contrast enhancement on CT and high [^{18}F]FDG-uptake of the pleura and/or the soft tissue within the pleural space, is suspected of recurrence. It occurs in 6-17% after surgery and in 12% of cases after SBRT and RFA. Patients have an increased risk after percutaneous biopsy (OR 10.8). Pleural recurrence occurs more often in patients with adenocarcinoma than in squamous cell carcinoma and is related to higher nodal stage at initial diagnosis. Certain pitfalls in the differentiation of benign and malignant causes include post-surgical inflammation within 3 months after surgery or a status after talc pleurodesis, which can result in multiple highly intense pleural foci which can persist for years. Talc pleurodesis typically is performed in patients with recurrent and/or malignant pleural effusion. It often results in intensely [^{18}F]FDG-avid pleural foci of high attenuation on CT.[34–36]

Distant Recurrence

Of all recurrences, metastatic recurrence occurs most often (39-66% of all recurrences) and is more prevalent in higher nodal stages, probably due to the fact that existing N2 drainage routes into the superior vena cava can lead to pulmonary metastases. [^{18}F]FDG-PET/CT has a high negative predictive value, especially in the detection of extra thoracic metastases. Distant recurrences occur most commonly in the lungs (44%), bones (21%), brain (18%), liver (15%), adrenals (6%) and distant nodes (6%). A new solitary pulmonary nodule in a previously curative treated patient can either be a metastasis or a secondary primary.[29]

New Primary

No simple method exists to differentiate recurrent disease and a second new primary. Most commonly it occurs in patients who continue smoking. Some papers state that a new primary is most likely in case of another histology, or after a disease free period of at least 4 years, or when the new tumor is located in a different lobe or originates from a carcinoma in situ and no pulmonary metastases were present at the time of diagnosis. Pulmonary metastases often appear as smooth nodules at the periphery of the lungs, while primary tumors often have ill-defined margins and are located more centrally. One should, however, be aware of the fact that AIS may be [^{18}F]FDG-negative, and active CT follow-up should be performed in suspicious cases.[37]

Mesothelioma Variants And Pitfalls on PET

Malignant pleural mesothelioma (MPM) is the most common primary malignant tumor affecting the pleura, associated in a vast proportion of cases (40%-80%) to asbestos exposure.[38] From a histopathological point of view, MPM is classified into three different subtypes, that is, epithelial (55%-65%), sarcomatoid (10%-15%), and mixed or biphasic forms (20%-35%),[38,39] each owing a different prognosis. Typically, MPM involves the parietal and visceral pleural layers, and is associated to pleural effusion in up to 95% of cases. While it affects conventionally one side of the thorax, spreading also to interlobar fissures, diaphragm, mediastinum and pericardium, it is also possible for more advanced staged disease to involve contralateral pleura or the peritoneum. Metastases to locoregional lymphnodes include mostly mediastinal lymphatic stations (approximately 50% of the cases), followed by internal mammary lymph nodes and intercostal lymph nodes, respectively for anterior and posterior parietal pleura involvement. Extrathoracic spread can affect 50-80% of the patients and this includes distant metastases.[38,40]

The clinical onset of MPM can be rather subtle, starting with slowly progressing chest pain up to breathing difficulties, dysphagia, phrenic nerve paralysis, superior vena cava syndrome, etc. The early appearance of pleural effusion is to be considered an alert for clinicians. Although affecting the majority of MPM, unilateral pleural effusion is not always attributable to malignancy. In fact, it can be documented also in pleural infection, congestive heart failure, pulmonary thromboembolism, collagen vascular diseases, etc. Consequently, a proper differential diagnosis frequently requires core needle biopsy during video-assisted thoracoscopy (VATS), which reaches up to 98% of diagnostic rate.[38,41]

Conventional treatment for early stage MPM relies mostly on surgery followed by chemotherapy and/or radiotherapy, while advanced disease demands an upfront chemotherapy with cisplatin and pemetrexed.[42,43,44] In recent years, implementation of immunotherapy with checkpoint inhibitors has promoted clinical research also in MPM, with checkpoint blockade based on anti-PD1/PD-L1 and anti-CTLA4 used either alone or in combination, yielding 25% to 29% objectives responses in pretreated patients.[43–46]

[^{18}F]FDG-PET/CT retains a complementary role to morphological imaging in the diagnostic pathway of MPM, particularly in the first steps of tumor diagnosis, in the preoperative staging and at disease recurrence. Superior to CT in MPM assessment,[47] [^{18}F]FDG-PET can determine a treatment change in over one third of the cases[38,48] and appears to be more suitable for response assessment, thanks to the earlier metabolic changes occurring on PET compared to dimensional response on CT.[49–51] However, the modality is not without drawbacks and errors. Every investigator must

be aware of the potential pitfalls and artifacts commonly affecting [^{18}F]FDG-PET/CT interpretation in MPM patients. Next to the earlier mentioned pitfalls and artifacts in lung cancer which could also apply to MPM, it is important to know that MPM may present some very specific traits especially when it comes to normal variants and pitfalls.

Normal Variants

The imaging presentation of MPM is generally rather peculiar, since it derives as a consequence of the ring-like growth of the tumor along the pleura. Based on the extent of the disease, it can be characterized by single or multiple, limited or diffused pleural thickening, variably associated to pleural effusion, mostly unilateral. The major differences in MPM variants herein are documented at initial presentation for the different tumor histotypes, which can be grossly classified as epithelioid versus non-epithelioid forms. Typically, epithelioid MPM is visualized on [^{18}F]FDG-PET/CT as a more limited disease, affecting frequently only part of the pleura and showing a lower [^{18}F]FDG- uptake (median SUV 5.5) compared to sarcomatoid/biphasic subtypes (median SUV 11,7).[52] The latter ones are in fact more aggressive, thus tend to present at a more advanced stage, involving the parietal and visceral pleura massively, and showing a markedly increased metabolism.

While early stage, epithelioid, MPM can show rather subtle pleural thickening, frequently located in the costodiaphragmatic recess, which makes it difficult sometimes to depict, in more advanced stage we can observe chest wall invasion, infiltration of the mediastinal or vertebral structures, invasion of the pericardium or contralateral pleura, transdiaphragmatic extension to the abdomen as well as the appearance of distant metastases.[53] Not forgetting lung parenchyma, which can be involved directly by MPM when showing lymphangitic carcinomatosis or pathological thickening of the interlobular septa.[53]

Gerbaudo and colleagues[54,55] have tried to shed light on the patterns of MPM presentation by dividing them into four categories (Fig. 6): *focal*, *linear*, *mixed* (focal + linear), and *encasing*. This simple way of depicting MPM appearance is also applicable for recurrent disease.[56]

Pitfalls at Initial Diagnosis

As mentioned in the previous section, MPM can present at different forms and show various patterns of diffusion. During initial presentation, it is therefore important to distinguish those aspects that might be misleading in the correct diagnosis and staging of MPM.

Early Stage Disease

The first obstacle in MPM diagnosis resides in cases with very limited disease, particularly for subcentimetric cancers, for which [^{18}F]FDG-PET/CT has a reduced sensitivity.[57,58] This can be considered as a direct consequence of the spatial resolution limit of the available tomographs, although the continuous improvements of PET technology have reduced the limits to few millimeters. The diagnosis becomes even more challenging in case of MPM location in the costodiaphragmatic recesses, especially the right one. Herein, the physiologically increased metabolism of the liver parenchyma overshadows the pleura, making it difficult to distinguish subtle pathological thickening, especially in case of epithelioid forms. The addition on of respiratory movements determines a misplacement of the uptake into the liver or lung, respectively, reducing furthermore the capability of the modality to detect early stage MPM.

Inflammation/Infection

Difficulties in MPM diagnosis derive also by inflammatory processes affecting the pleura, since [^{18}F]FDG is not a cancer-specific tracer. Clinical history and radiological findings usually help in these cases to address a proper diagnosis, although the pattern of distribution on PET for pleurisy or MPM can be quite resembling (Fig. 7). The use of semiquantitative parameters, such as SUV, might be used to overcome the pitfalls related to inflammation. In fact, most benign processes, including pleuritis, tend to have a lower uptake; that is, mean SUV 6.5 versus 0.8, respectively for malignant and

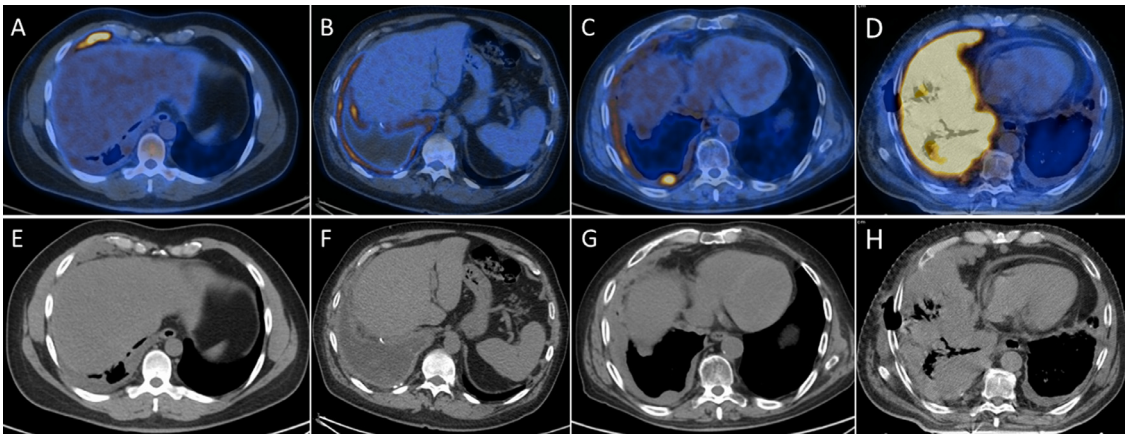

Figure 6 Illustration of the different patterns of MPM presentation on fused PET/CT (A-D) and localization CT (E-H) views. In particular, the focal (A,E), the linear (B, F), the mixed (C, G) and the encasing (D, H) patterns are shown for more clarity.

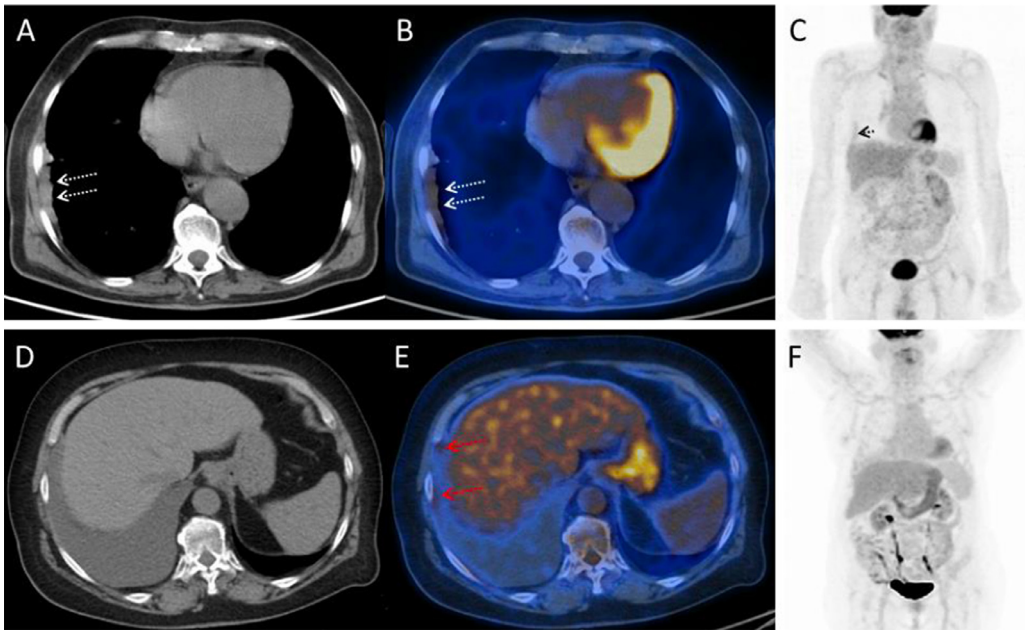

Figure 7 Differential diagnosis between MPM and pleurisy can be sometimes challenging. Herein, two examples are shown to illustrate the appearance of pleural inflammation (A-C; white arrows) compared to early stage epithelioid mesothelioma (D-F; red arrows). The [^{18}F]FDG accumulation is similar, while the major difference is determined by the presence of massive pleural effusion in the MPM example. This sign characterizes up to 95% of meosthelioma presentations.

benign disease.[38,59] Thanks to the use of cut-off points (ranging from 2-3.5),[53] [^{18}F]FDG-PET can differentiate malignant from benign pleural lesions with an accuracy reaching up to 97,5% (range 91%-98%)[53,60–62] Undeniably, some overlap exists since early stage MPM and epithelioid forms have commonly a lower metabolism. Some authors recommend in this regard the use of delayed images at 90-120 minutes after tracer injection.[53,63,64] The rationale is based on the assumption that malignant lesions present an increased tracer accumulation overtime, compared to inflammatory processes.

Differential Diagnosis

Pleura can be a localization site not only for MPM or inflammatory processes, but also for other benign and malignant conditions. Some examples are represented by solitary fibrous tumor of the pleura, thymoma with pleural dissemination, epithelioid hemangioendothelioma, sarcoma, and pleural metastases from other cancer types (Fig. 8), such as lung and breast cancer, or lymphoma.[38,53] While thymomas and solitary fibrous tumors can be difficult to distinguish from MPM, metastatic pleural localizations tend commonly to have a higher SUVmax compared to non-metastatic disease (7.1 vs. 4.7, respectively). Additionally, previous clinical history can better address differential diagnosis, since pure radiological findings might not be fully helping. At the very end, however, immunohistochemistry alone on tumor specimen can make the proper differential diagnosis.

Nodal Staging

Approximately, half of MPM cases undergoing surgery will present with intrathoracic nodal involvement.[57,65] Although superior to CT, [^{18}F]FDG-PET/CT has shown suboptimal performance in lymph node detection.[53,66,67] Hence, nodal staging represents a potential source of error. For early stage epithelioid forms, the problem is mostly false positive N1/N2 lymph nodes. In fact, the lower tracer uptake characterizing these forms makes inflammatory nodal reaction misleading. With the increase of MPM extension, particularly in metabolically active subtypes, nodal involvement can be disregarded due to the increased [^{18}F]FDG-uptake in the pleura overshadowing lymph nodes located closed by. This can happen for hilar nodes, undistinguishable from thickened mediastinal pleura, as well as for lymph nodes draining the anterior and posterior parietal pleura. For these advanced cases of MPM, the likelihood of nodal metastases increases proportionally, therefore, much more attention has to be payed to distinguish secondary lymph nodes from primary tumor nodules.

Pitfalls in Treated Patients

Talc Pleurodesis

Most patients with MPM will undergo [^{18}F]FDG-PET/CT after at least one diagnostic or therapeutic procedure. The first in the row are thoracentesis and video-assisted thoracoscopic surgery (VATS), with or without talc pleurodesis. While the pure surgical procedure will determine easily recognizable changes in the thoracic structures, talc pleurodesis undeniably leads to major pitfalls in MPM assessment (Figs. 9 and 10). By definition, pleurodesis represents a chemical irritation of the pleura induced by talc, leading to a fibrotic reaction and subsequent clinging of the layers. The process induces a long lasting inflammatory reaction, that

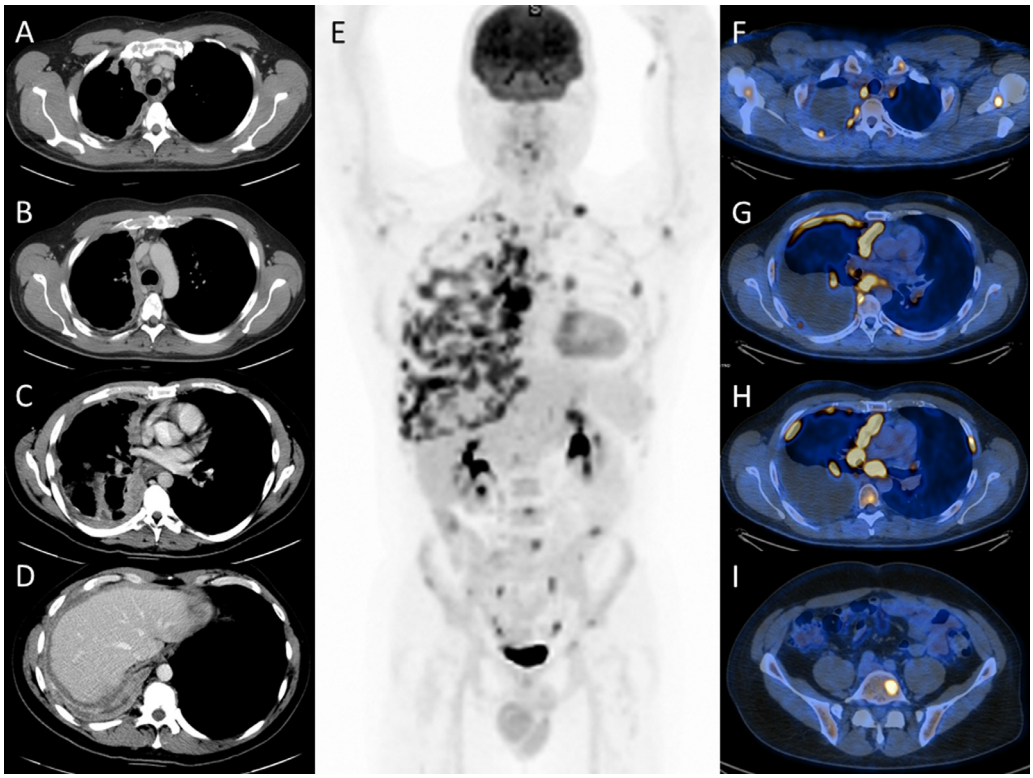

Figure 8 Advanced stage MPM can be undistinguishable from metastatic lung cancer presenting with massive pleural invasion. The example herein illustrated represents a male patient with stage IV adenocarcinoma of the lung. The diffused pleural involvement and the markedly increased [^{18}F]FDG uptake (SUVmax 18), overshadow the primary tumor located in the upper right lobe.

interferes with PET interpretation. In general, the talc effect presents with the appearance of focal or diffuse [^{18}F]FDG accumulation in the pleura, mostly associated to partial calcification on CT of the sites of talc deposit. This aspect can be of help in distinguishing uptake related to talc from pathological uptake due to MPM lesions.[53] Unfortunately, when assessing MPM extent, particularly by means of semiquantitative and volumetric parameters, the sum of talc effect on the overall metabolic activity cannot be removed, thus has to be considered carefully especially at treatment response assessment.[65,67–69]

Postsurgical Evaluation

In limited disease, surgical procedure preceded by induction chemotherapy is the treatment of choice. Given the peculiar location and distribution pattern of MPM, the procedure consisting in either extrapleural pneumonectomy (EPP) or pleurectomy and decortication (P/D) is a major impact of thoracic morphology and function, and are appreciated on PET/CT (Fig. 11). Similar to what described for lung cancer, direct post-surgical rearrangement may last for up to 3 months after the intervention. Some structures though might be permanently impacted by the process of pleural removal, thus determining a persisting tracer accumulation on PET. This is the case of pericardial stretching and myocardial activation. The fibrotic tension created by the healing surgical breach, particularly in delicate structures such as the heart and vasculatures, promotes increased [^{18}F]FDG-uptake along the tensed surface, mimicking MPM recurrence. The lack of pathological thickening and the usual stability of the finding, may help distinguish this pitfall.

Postradiotherapy Assessment

Radiation therapy is part of MPM treatment following surgery. Together with induction chemotherapy, post-operative radiotherapy completes the so-called trimodal treatment in MPM. The field of irradiation is extended to the pleura, which impacts not only the parietal structures of the thorax but also visceral and lung parenchyma in particular. The effects and the duration of radiation therapy resemble those described in previous paragraphs, leading to inflammatory changes to the involved structures visible on PET/CT. A minimum of 3 months should be considered when assessing the neoplastic disease after irradiation.

Postimmunotherapy Assessment

A special place in the context of pitfalls consideration is left for immunomodulatory treatments. Their utilization in MPM is not new, since clinical trials studying interferon alpha, granulocyte-macrophage colony-stimulating factor (GM-CSF), autologous tumor cell vaccines, and tumor growth factor (TGF-beta) blockade have been conducted over three

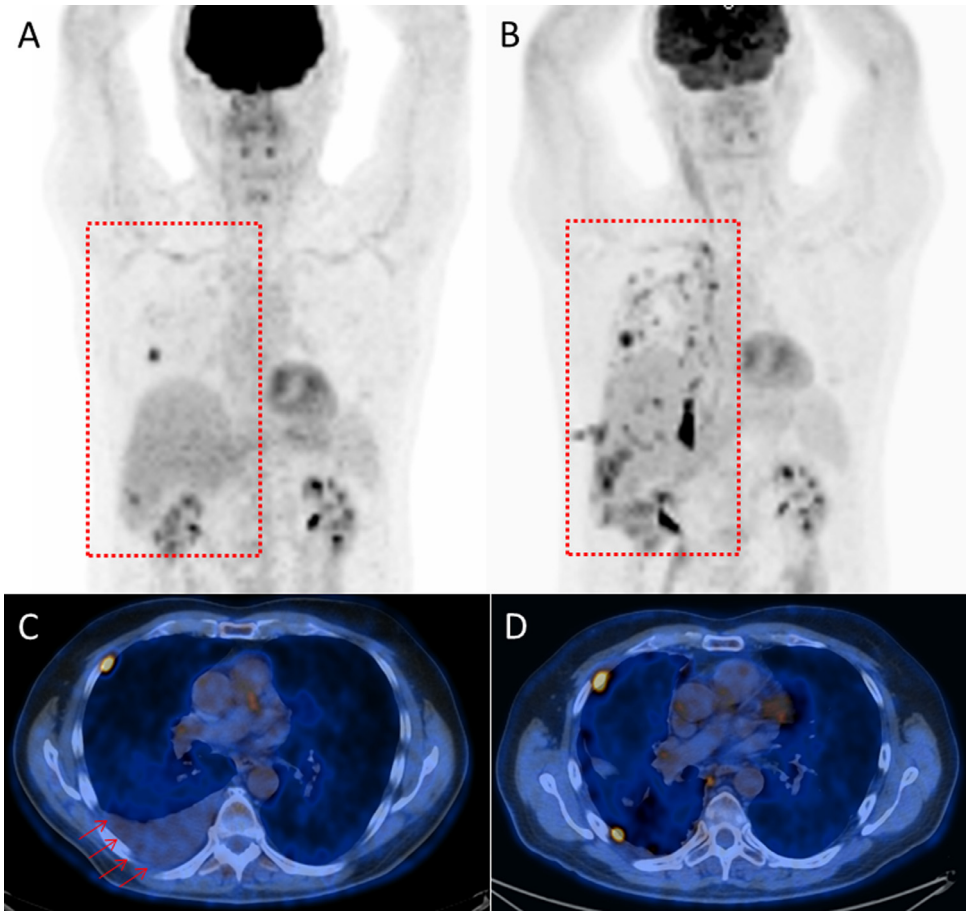

Figure 9 The patient herein illustrated was imaged at baseline (A, C) and after induction chemotherapy (B, D). The areas of tracer accumulation had significantly increased suggesting a possible disease progression (areas inside the red dotted rectangles). However, this aspect was misleading, since the patient had undergone talc pleurodesis in between the two scans, thus determining the increased metabolism. Note how the pleural effusion (C, red arrows) had completely disappeared confirming the procedure.

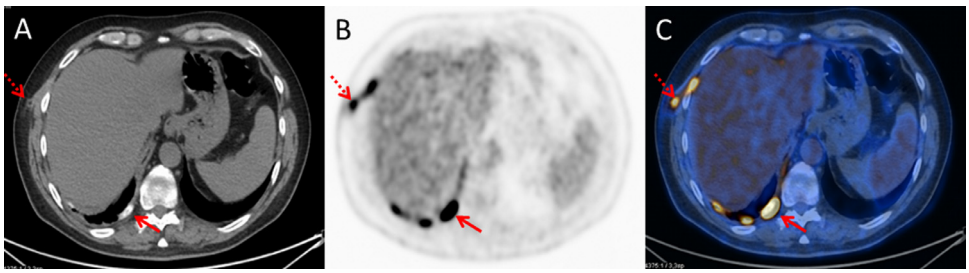

Figure 10 The same patient illustrated in Figure 9, now showing more details of the second PET/CT scan (A-C) at the level of the right costodiaphragmatic recess. Note the transparietal transit of the VATS (dotted red arrows) and the intense uptake in the calcified/ radiopaque lesion in the right costovertebral area (red arrow), documenting the talc pleurodesis.

decades now.[70] The major breakthrough has arrived in the last decade with the introduction of checkpoint inhibitors. Their utility has been investigated in MPM principally for the second/third-line setting, while less data is provided for the upfront or neoadjuvant treatment.[71,72] The limited casuistic is also reflected in the lack of PET data with regards to MPM assessment during immunotherapy.[44] The identification of pseudoprogression can be challenging and is being considered as one of the pitfalls, although the number of cases registered is lower than for other tumor types.[71,73] The problem of immune-related adverse events on the other hand remains valid for MPM as for all other cancers under immunotherapy. Their identification and description is mandatory,[73] with pneumonitis being the mostly interfering with response assessment in MPM.

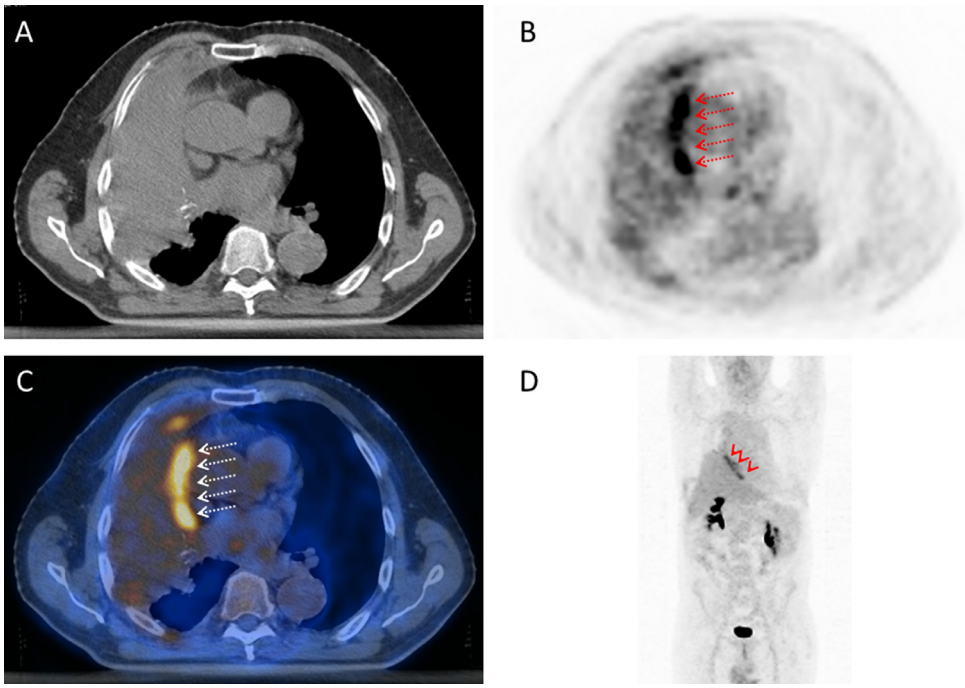

Figure 11 The effect of surgery on the pericardium can lead to misinterpretation. The patient herein illustrated had undergone trimodal treatment, with right pleurectomy and subsequent irradiation. The abnormal [^{18}F]FDG accumulation following the right auricola was initially judged suspicious for recurrence (SUVmax 8.4). Knowing that the patient was originally affected by epithelioid MPM, thus showing lower [^{18}F]FDG uptake, and considering the type of intervention, the finding highlighted with red and white arrows (axial PET and fused views) and red arrowheads (MIP) was readdressed to pericardial stretching.

Special Considerations in Treatment Response Assessment

Response Assessment in Lung Cancer

[^{18}F]FDG-PET is not only used for staging but also for response assessment in solid tumors, such as lung cancer. In addition to morphological characterizations on CT images and visual assessment of [^{18}F]FDG-uptake, quantitative parameters have been discussed to define progression and response to systemic treatment. Formerly, the EORTC had proposed to classify progressive disease as an increase in tumor SUV of greater than 25 % or the appearance of new lesions, while response was seen in decrease of more than 25%.[74] Later on, the so-called "PERCIST criteria" had been introduced. According to "PERCIST" a decrease greater than or equal to 30% in SUVmax is a metabolic response, whereas a SUVmax rise greater than or equal to 30% is considered as progressive metabolic disease.[75]

Number of Lesions

PERCIST has recommended to record the SUVmax in up to five lesions, typically the five hottest lesions for response assessment.[75] Under conventional systemic chemotherapy changes in the SUVmax of primary tumors had been expected to accurately predict the outcomes in their nodal metastases. Under the so-called targeted therapy, a resistant metastasis may become the hottest lesion under ongoing treatment.[76] Both scenarios are reflected in the rationale to measure the single hottest lesion at each time point, which does not necessarily have to be at the same localization. This way the most therapy resistant parts of the tumor can be identified. This measurement of a single lesion is a big advantage of PET based response assessment as compared to all other criteria which had been discussed in the past.

Standardized Uptake Value (SUV)

For quantitative analyses, the single hottest voxel of a tumor, the SUVmax is in growing use and is the *de facto* standard. Intuitively, other parameters seem more attractive because they use more information than what is included in the single hottest voxel. The SUVpeak has been repeatedly discussed to this regard. As compared to SUVmax, SUVpeak appears to be less sensitive to noise and affected by imaging characteristics for example, voxel size. For the measurement of the SUVpeak, by definition a 1.2 cm diameter volume of interest (VOI) is centered on the tumor area with the maximum uptake. Subsequently, quantification measurements may be compromised, because the automatically generated VOI may include other organs with a much higher or lower physiological uptake. Manual corrections are necessary to exclude intrusion of no tumor structures or organs. However, manual definition is associated with a higher degree of observer variability. This is why the use of SUVpeak should be recommended with caution. However, no parameter has shown convincingly better response prediction as compared to

SUVmax in the respective single hottest lesion, which is mostly used for response assessment.[76]

New Technologies and Scanners

It is well known that quantitative parameters obtained by [^{18}F]FDG PET are highly dependent on scanners and technologies. In order to obtain standardized and harmonized PET results it has been proposed to perform all response assessment and follow-up examinations on the same scanners. As compliance with this recommendation would prevent any progress in scanners and technologies, more realistic coping strategies are required. Unfortunately, SUV changes between different scanner generations and reconstruction methods cannot be reduced by normalization to a reference region such as the liver.[77]

A solution could be to use two datasets for visual and quantitative image interpretation for both daily routine and clinical trials:

1. A dataset for optimal sensitivity and visual assessment, using all available imaging technologies in the scanner.
2. A dataset for standardized quantitative image interpretation, which is highly recommended by the EANM procedure guidelines for tumor imaging: version 2.0.[78]

Response assessment in mesothelioma

Response assessment in malignant pleural mesothelioma is notoriously more challenging compared to other solid tumors, mostly because of the peculiar ring-like shape and the diffuse pattern of growth throughout the pleura.[53,57,79] Consequently, response assessment is commonly based on modified Response Evaluation Criteria in Solid Tumors (RECIST), firstly adapted by Burne and Novak in 2004,[80] and recently adjusted with new recommendations based on RECIST 1.1 criteria.[81] The use of metabolic criteria for MPM response assessment has mostly been limited to the EORTC criteria[74] and at some extent to volumetric analyses, including metabolic tumor volume (MTV) and total lesion glycolysis (TLG), prompted to better delineate the variation of tumor burden during the course of treatment.[49–51,65,68,69,82] Semi-automated iterative threshold-based region-growing algorithm[49] or liver-based threshold method[68] have been used for contouring. These volumetric parameters, especially TLG, have been proposed also as prognostic markers for MPM.[82] The major advantage of [^{18}F]FDG PET over morphological imaging is the possibility to assess tumor viability changes during treatment earlier in time (Fig. 12) and to better quantify tumor burden, thanks to volumetric analyses. Up to now, however, no specific metabolic criteria have been validated for response assessment in MPM, leaving room for future studies to fill the gap.

Conclusions and Future Perspectives

The role of [^{18}F]FDG-PET/CT is well-established in lung cancer and mesothelioma imaging as it provides more reliable and accurate information compared to anatomic imaging. The mediastinal staging is relatively superior with [^{18}F]FDG-PET/CT compared to CT in both lung cancer and MPM.[83,84] [^{18}F]FDG-uptake patterns are relatively heterogeneous in lung cancer, and histological subtypes act as independent predictors in the outcome.[83,85,86] In general, standardized uptake values (SUVs) in clinical [^{18}F]FDG-PET/CT oncology imaging are

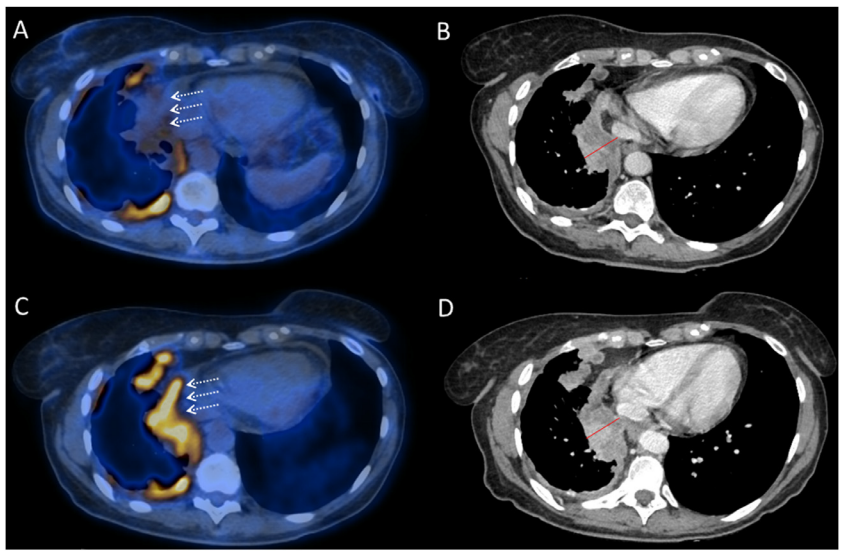

Figure 12 Response assessment performed for an advanced biphasic mesothelioma patient investigated at baseline (A, B) and after chemo-immunotherapy with carboplatin, pemetrexed and pemborlizumab (C, D). Herein, parallel findings on contrast-enhanced CT (B, D) and fused axial [^{18}F]FDG-PET/CT images (A, C) are shown, documenting the discrepancies in response assessment between the two imaging modalities. In fact, progression on right paramediastinal masses (white arrows) is perfectly detectable on metabolic imaging with [^{18}F]FDG PET (A, C), while a comparable diameter on transversal measurements (red lines) is seen on thoracic CT (B, D).

often useful in characterizing the lesions. However, benign lesions can often have high SUVs, as discussed previously. Several studies have discussed the potential role of SUVmax in lung cancers in various clinical scenarios such as diagnosis, prognostication, and time to recurrence. However, the conclusions reported in these studies are variable, given the tracer uptake depends on multiple factors.[74] In general, the SUVmax is often lower in adenocarcinomas in comparison to squamous or other subtypes. Besides, the size and type of the lesions often lead to false-negative results, such as lesions under 10mm in size, lesions with reduced amounts of cells (e.g., invasive mucinous adenocarcinomas, and minimally invasive adenocarcinomas).[83,87] False positive PET/CT findings are reported in 7% of patients with lung cancers,[88] mostly secondary to infectious or inflammatory pathologies. As the nodal status in lung cancer is a vital factor in staging, treatment, and assessment of prognosis, invasive mediastinal staging might be deferred in these patients as the negative predictive values (NPV) of mediastinal lymph node metastases in T1 and T2 tumors might be high. However, on the contrary, caution in interpretation is suggested in patients with higher disease stages, even in patients with non-tracer avid mediastinal lymph nodes.[83,89] Secondly, the SUV values for interpretation are debatable, and the values should not be directly implemented as reported in the literature, unless your local protocols match the one described. Besides, the results should be audited locally to avoid faulty changes in management.

In the assessment of treatment response, it is essential to gain information on the type of treatment as the introduction of immunotherapy has changed the way we analyze and interpret the studies. Finally, artificial intelligence techniques and radiomics might be used to predict the disease type, outcome, and response to therapies soon. Several algorithms, workflow methods, and settings have been tried, however it is beyond the scope of this article to discuss them in detail.[83,90–92]

While reporting scans, it is essential to gain adequate clinical information and a history of previous interventions and comparison to previous imaging should be made. The findings should be discussed in multi-disciplinary meetings, where image interpretation is optimized based on additional clinical information.

In general, standardized protocols that include patient preparation, injected tracer activity, image acquisition, reconstruction, and quantitation might reduce pitfalls.

Finally, [^{18}F]FDG-PET/CT scan reports should be able to provide information that helps in accurate staging and help the team in deciding appropriate treatment in a multidisciplinary setting.

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