Malignant pleural mesothelioma (MPM) is an aggressive tumor that arises from the pleura and frequently extends to adjacent structures. MPM cells produce and respond to many angiogenic factors, such as vascular endothelial growth factor (VEGF). VEGF expression in MPM is correlated with microvascular density, which is associated with poor survival.

CT has been widely used as the primary imaging modality for the clinical evaluation of MPM. Major findings include nodular pleural thickening, unilateral pleural effusion, and tumor invasion of adjacent structures. CT tends to underestimate early chest wall invasion and peritoneal involvement and has well-known limitations in the evaluation of lymph node metastases. Perfusion CT can evaluate the microvasculature of tumors, while its disadvantages, such as high radiation exposure or side effects from iodinated contrast, limit its use in both research and clinical settings.

MRI can provide additional information to CT. Because of its excellent contrast resolution, MRI is superior to CT, both in the differentiation of malignant from benign pleural disease, and in the assessment of chest wall and diaphragmatic involvement. Perfusion MRI is the most promising technique for the assessment of the tumor microvasculature. In MPM, therapeutic effects of chemotherapy can be monitored with perfusion MRI.

It has been shown that FDG–PET is useful for the differentiation of benign from malignant lesions, for staging and monitoring metabolic response to therapy against MPM, and that it has prognostic value. An initial report on PET/CT imaging of MPM has shown increased accuracy of overall staging, improving the assessment of tumor resectability. PET/CT seems to be superior to other imaging modalities in detecting more extensive disease involvement, and identifying unsuspected occult distant metastases.

Keywords: Malignant pleural mesothelioma; Angiogenesis; CT; MRI; PET; Perfusion; Staging
1. Introduction

Malignant pleural mesothelioma (MPM) is an aggressive neoplasm of mesothelial cell origin that arises mainly from the pleura [1]. The major histologic subtypes are epithelioid, sarcomatoid, and mixed. In addition, osteosarcomatous degeneration within MPM is considered a rare subtype. The majority of MPM cases are associated with asbestos exposure. Although MPM was once uncommon, its incidence is increasing worldwide as a result of widespread exposure to asbestos [1,2].

The tumor can invade both visceral and parietal pleura and frequently extends to adjacent structures, such as the chest wall, mediastinum, and diaphragm. Lymph node spread and/or metastases to distant organs, such as the lungs, liver, kidneys, adrenal glands, and brain, can occur. It has been shown that the overall survival in MPM is related to the extent of the primary tumor [1]. Today, imaging plays an essential role in evaluating the tumor extension of MPM.

Conventional therapies, such as surgery, radiotherapy, and chemotherapy, do not necessarily improve overall survival. On the other hand, there have been a lot of advances in the understanding of the molecular biology of MPM. In particular, it has been shown that angiogenesis is directly associated with prognosis in MPM [1,3–5]. Presently, studies for the treatment of MPM with anti-angiogenesis agents are ongoing [3,6]. Imaging may play an important role in identifying the candidates for anti-angiogenesis therapy, and in documenting early response.

This review discusses the current state of the science of morphologic and functional imaging of MPM in the context of diagnosis, staging, and angiogenesis.

2. MPM and angiogenesis

It is important to understand the molecular biological features of angiogenesis in MPM. MPM cells arise from the pleura and produce many growth factors, such as epidermal growth factor (EGF), platelet-derived growth factor (PDGF), and transforming growth factor β (TGF-β) [1,3,7,8]. Genetic alterations in tumor-suppressor genes, such as p16, p14, and NF2, are common, and the activity of the antiapoptosis molecule Bcl-xL is elevated in MPM [1,9–11]. In addition, MPM cells usually express telomerase, which enables the cells to become immortalized [1,12,13]. Although the host responds to MPM cells with inflammation and immunity, growth signals coupled with the loss of tumor-suppressor genes lead to tumor cell proliferation [1,7–11]. Moreover, antiapoptosis and immortalization render MPM cells resistant to cell death [1,12,13]. The particular molecular processes can be different from patient to patient, but the overall pattern is similar.

Recently, the great importance of angiogenesis in MPM has been proposed [3,6,17]. Previous studies show that the continuous formation of new blood vessels is required to supply MPM cells with nutrients and to support tumor growth by the aforementioned biological factors [1]. MPM cells produce and respond to many angiogenic factors, such as vascular endothelial growth factor (VEGF) [1,3,14,15]. In fact, MPM expresses the highest known VEGF levels of any solid tumors [2]. In addition, interleukin 8, a potent chemokine with proangiogenesis function, has been shown to be an autocrine growth factor in MPM cell lines [3,16]. VEGF expression in MPM is correlated with microvascular density, which is associated with poor survival [1,3]. Demirag et al. investigated the prognostic significance of VEGF expression in 40 MPM patients, demonstrating that VEGF expression is now considered to be an independent prognostic factor in MPM. In addition, there is a positive correlation between VEGF expression and the tumor stage (p<0.05). Moreover, VEGF expression significantly correlates with tumor necrosis, a process known to stimulate angiogenesis (r=0.42, p<0.01) [17].

VEGF inhibitors have been shown to reduce MPM growth in animal models [1,3]. Studies on the treatment of MPM with anti-angiogenesis agents targeting the VEGF pathway are ongoing [2,6]. Examples of these agents are PTK787, an inhibitor of the PDGF/VEGF pathway, and Bevacizumab, a recombinant human anti-VEGF monoclonal antibody [3]. Bevacizumab is now considered to be effective and generally well tolerated as first-line therapy for metastatic colon cancer, and results from clinical studies of Bevacizumab as a single agent or as part of combination regimens for breast cancer, non-small-cell lung cancer, renal cell carcinoma, and other solid malignancies have been promising [18]. Anti-angiogenic therapy inhibits the development of new tumor vessels, and destroys the existing vessels, and reduction in tumor size is not necessarily the main expected outcome. Thus, evaluation of tumor response relying solely on changes in tumor volume can lead to misinterpretation of anti-angiogenic therapeutic effects [6,19,20]. It is therefore also necessary to directly evaluate the perfusion, vascularity, vascular permeability or the biological process of angiogenesis in the tumor to assess therapeutic response.
3. MPM and imaging

3.1. Computed tomography (CT)

CT has been widely used as the primary imaging modality for the diagnosis, staging, and monitoring of therapeutic response in MPM. Typical findings include nodular pleural thickening, unilateral pleural effusion, and tumor invasion of adjacent structures. CT tends to underestimate early chest wall invasion, direct mediastinal invasion, and peritoneal involvement and has well-known limitations in the evaluation of lymph node metastases. In terms of angiogenesis, perfusion CT can evaluate the microvasculature of tumors, while its disadvantages, such as high radiation exposure, and side effects from iodinated contrast media, limit its use in both research and clinical settings.

3.1.1. CT findings of MPM

MPM arises from the pleura and frequently extends to adjacent structures. Both the pleural tumor and its extension beyond the parietal pleura can be visualized by CT. Pleural thickening and/or effusions are the most common CT findings [21,22].

Several studies have illustrated the CT features of MPM. Kawashima et al. evaluated 50 MPM patients with CT and reported pleural thickening (92% of patients), thickening of the interlobular fissures (86%), pleural effusion (74%), pleural calcification (20%), contraction of the involved hemithorax (42%) and contralateral mediastinal shift (14%). They also reported disease beyond the parietal pleura, i.e., chest wall invasion (18%), pericardial effusion (6%), extension of the tumor into the contralateral hemithorax (4%), thoracic lymph nodes of 1 cm or larger in maximum diameter (58%), direct hepatic invasion (4%), and direct retroperitoneal invasion (8%) [21]. On the other hand, Sahin et al. reported CT findings in 84 patients as either unilateral pleural thickening or pleural nodules or masses (100%), pleural effusion (73%), mediastinal pleural involvement (93%), involvement of the interlobar fissures (76%), and volume contraction (i.e., reduced size of the hemithorax involved) (73%) [22].

As demonstrated in the aforementioned studies, pleural thickening and/or effusion are the most common CT findings. In the majority of MPM patients, pleural thickening is present as circumferential (rind-like) pleural involvement with multiple nodules [23] (Fig. 1). In some cases, only pleural effusion is observed by CT [1]. The combination of an unexplained pleural effusion and pleural pain should raise suspicion of MPM, even if the initial cytologic findings are negative [1].

Fig. 1. Contrast enhanced axial CT. (A–C) Axial images obtained 6 months following diagnosis of MPM show circumferential pleural abnormality comprising both fluid and extensive nodular thickening, perihilar metastases, mediastinal invasion (white arrow, B), enlarged mediastinal lymph nodes (black arrow, B) and direct tumor extension along a former chest tube tract (white arrow, C). Prior to this study, a staging cervical mediastinoscopy showed metastatic foci of MPM within enlarged 4R and level 7 nodes. The patient was not a candidate for extrapleural pneumonectomy (EPP) and declined pleurectomy/decortication, opting for chemotherapy only.
3.1.2. Differential diagnosis

CT is useful in differentiating malignant from benign disease. The presence of pleural calcifications may suggest a benign process, while that of several of the previously mentioned findings indicate malignancy; for instance, circumferential or nodular pleural thickening, or mediastinal pleural involvement [25,26]. However, MPM cannot be reliably differentiated from other pleural malignancies [27]. Diffuse pleural thickening and effusion can result from not only MPM but also from other pleural diseases, such as asbestosis, infections, and other malignant pleural tumors [24,25].

Leung et al. reviewed CT findings in 74 patients with diffuse pleural disease (11 patients with MPM, 24 with pleural metastases, and 35 with benign pleural disease), and concluded that CT is helpful in the differential diagnosis of diffuse pleural disease, particularly to differentiate malignant from benign conditions [27]. According to the literature, features that are helpful in distinguishing malignant from benign pleural disease are (a) circumferential pleural thickening, (b) nodular pleural thickening, (c) parietal pleural thickening of greater than 1 cm, and (d) mediastinal pleural involvement. Twenty-eight of 39 malignant cases (sensitivity, 72%; specificity, 83%) were identified correctly by the presence of one or more of these criteria [26]. MPM could not be reliably differentiated from pleural metastases, however [26]. On the other hand, Hierholzer et al. investigated 42 cases of pleural disease and found that circumferential pleural thickening, nodularity or irregularity of the pleural contour, mediastinal pleural involvement, and infiltration of the chest wall and/or diaphragm are most suggestive of a malignant cause, while pleural calcification in CT images is suggestive of a benign cause. However, pleural thickness of greater than 1 cm does not reveal a significant difference between malignant and benign pleural disease (p > 0.05) [27].

In general, circumferential or nodular pleural thickening is considered to be consistent with malignancy. Furthermore, infiltration of the adjacent structures may undeniably suggest malignancy. Some infectious processes, such as actinomycosis, tuberculosis and nocardiosis, can invade the chest wall, but usually do so at a single focus rather than at multiple sites, as seen in malignant disease [25]. Of note is that calcified plaques are a sign of asbestos exposure but are not a precursor to MPM [1]. However, calcification does not always indicate a benign cause, because non-calcified MPM can encase calcified plaques and mimic calcified tumors.

It has been difficult to differentiate MPM from other pleural malignancies. However, Metintas et al. suggested in their recent review of 215 patients (99 patients with MPM, 39 with metastatic pleural disease and 77 with benign pleural disease) that CT findings of circumferential pleural involvement, mediastinal pleural involvement, and pleural thickness of more than 1 cm, distinguish MPM from metastatic pleural disease with relatively high sensitivity and specificity (sensitivity/specificity values of 70/85, 85/67, and 59/82, respectively). Of note is that circumferential pleural involvement was observed in 70% of MPM cases as compared to only in 15% of malignant pleural disease cases, 9% of tuberculous pleurisy cases, and 5% of asbestos-related advanced benign pleural disease cases. These findings may be important for patients in serious states or patients who do not desire to undergo invasive biopsy procedures [23].

3.1.3. CT staging

The International Mesothelioma Interest Group proposed a tumor-node-metastasis (TNM) staging system for MPM. This staging system is based on data suggesting that overall survival in MPM is related to the extent of the primary tumor (T status) and to lymph node involvement (N status), and classifies the preoperative patients as follows: patients with early disease and a potentially better prognosis (T1a and b); patients who may potentially benefit from surgery but may not necessarily be cured (T2 and T3); patients for whom surgery may have no benefit because of short survival and extensive local tumor spread (T4); patients with extensive regional node involvement (T4-N1, T4-N2, T4-N3) or distant metastases (M1), for whom surgery is not an option [28,29]. Therefore, it is important to distinguish the T1–T3 stages from the T4 disease for the prediction of resectability. On the other hand, the revised Brigham and Women’s Hospital surgical staging system for MPM considers resectability, tumor histology, and nodal status, and includes four stages [30]: Stage I corresponds to disease confined within the capsule of the ipsilateral parietal pleura without adenopathy, lung, pericardium, diaphragm, or chest wall disease limited to previous biopsy sites. Stage II is the same as stage I with positive resection margins, and/or positive intrapleural lymph nodes. In stage III, there is local extension of disease into chest wall or mediastinum; into the heart; through the diaphragm or peritoneum; or with extrapleural lymph node involvement. Stage IV corresponds to the presence of distant metastatic disease. Stage III and IV tumors are considered unresectable. This staging system has been shown to stratify survival successfully. In fact, Sugarbaker and colleagues studied 183 patients with MPM treated with extrapleural pneumonectomy followed by adjuvant chemotherapy and radiotherapy, and concluded that patients with epithelial histology, margin-negative, and extrapleural node-negative status had extended survival [30].

The assessment of local invasion of the chest wall, mediastinum, and diaphragm is essential for resectability. CT criteria for resectability include (a) preservation of extrapleural fat planes; (b) absence of extrapleural soft-tissue masses; (c) normal CT attenuation values of adjacent structures, and (d) a smooth inferior diaphragmatic surface. CT criteria for unresectability include (a) invasion of extrapleural soft tissue or fat; (b) infiltration, displacement or separation of ribs by tumor; (c) bone destruction, and/or (d) tumor encasing the diaphragm. In the mediastinum, invasion of soft tissue masses without preservation of fat planes indicates unresectability. In addition, a tumor surrounding more than 50% of a mediastinal structure is suggestive of unresectability. In contrast, preservation of normal mediastinal fat without extrapleural soft tissue masses is consistent with resectable disease [31]. At the diaphragm, the most reliable findings indicative of resectability are preservation of the extrapleural fat plane between the inferior diaphragmatic surface and the adjacent abdominal organs, and a smooth inferior diaphragmatic surface. Conversely, a soft tissue mass encasing the hemidiaphragm is considered unresectable [31].
CT does, however, have limitations, as it tends to underestimate the extent of MPM [24,25,32]. Understaging may be less important in the resectable stages (T1–T3), but assumes greater importance in the diagnosis of T4 (unresectable) disease. In addition, the evaluation of nodal involvement (N1–N3) by CT remains suboptimal because enlarged nodes alone do not prove nodal metastases [24,25,32]. Recent multi-detector row CT and multiplanar reformatting techniques may improve the visualization of lymph nodes and tumor extent, especially in regions difficult to assess with axial imaging [32].

3.1.4. Perfusion CT

Perfusion CT using iodinated contrast material can measure blood flow, blood volume and capillary permeability [6]. Perfusion CT can provide sequential acquisition of images with high temporal resolution during the passage of contrast material through tumor tissue, reflecting the microcirculation. In fact, several investigators have used perfusion CT to evaluate microvessel density of tumors [6,33]. The advantage of perfusion CT is its simple quantification and its wide availability. However, the disadvantages, such as high radiation exposure or side effects from iodinated contrast material, limit the use of perfusion CT in both research and clinical settings [34].

3.2. Magnetic resonance imaging (MRI)

MRI provides additional information to CT in some difficult cases [31]. Because of the excellent contrast resolution, MRI is superior to CT both in the differentiation of malignant from benign pleural disease and in the assessment of chest wall and diaphragmatic involvement of MPM [35] (Fig. 2). In addition, perfusion MRI is the most promising technique for evaluating angiogenesis in MPM.

3.2.1. MRI findings in MPM

Compared to adjacent chest wall musculature, MPM has intermediate or slightly high signal intensity on T1-weighted images (T1-WI) and moderately high signal intensity on T2-weighted images (T2-WI) [24,25,32]. MPM signal is enhanced with the use of gadolinium-based contrast material (Gd-CM) [24,25,32]. MRI findings in MPM include diffuse pleural thickening, pleural effusion, and involvement of adjacent structures. Pleural effusion is frequently observed as focal areas of very high signal intensity on T2-WI [25].

3.2.2. CT versus MRI

MRI is superior to CT in the differentiation of malignant from benign pleural disease. High signal intensity in relation to adjacent musculature on T2-WI and/or significant contrast enhancement on T1-WI is suggestive of malignant disease. Using morphologic features in combination with the signal intensity information, MRI has a high sensitivity and specificity in the detection of pleural malignancy [26]. In addition, contrast-enhanced T1 fat-suppressed sequences are the most sensitive techniques for detecting enhancement of interlobar fissures and tumor invasion of the adjacent structures [35].

![Fig. 2. Gadolinium enhanced coronal T1-weighted and axial LAVA images from the previous patient 5 weeks after the initial chest radiograph reveal enhancing circumferential pleural nodules within the posterior costophrenic sulcus, extending into the major fissure without evidence of diaphragmatic or chest wall invasion. Note the preserved smooth left hemidiaphragm on the coronal image.](image-url)
Fig. 3. (A) T2-weighted coronal MR image showing direct mediastinal invasion (arrow, A); (B and C) noncontrast CT axial images showing mediastinal nodes and encasing pleural rind, but not decisive for direct mediastinal invasion.

The excellent contrast resolution of MRI can improve the evaluation of tumor extension, especially to the chest wall and through the diaphragm, resulting in better prediction of overall resectability than CT [26,36] (Fig. 3). Patz et al. compared the values of the two modalities in predicting resectability. The sensitivity was high for both CT and MRI in evaluating the resectability of MPM in the diaphragm and chest wall (94% and 93% sensitivity for CT, and 100% and 100% for MRI) [31]. CT and MRI provided similar information in most cases. In difficult cases, however, important complementary anatomical information was derived only from MRI. In their review of 95 patients with MPM, Heelan et al. found MRI superior to CT in revealing invasion of the diaphragm (55% accuracy for CT vs. 82% for MRI) and in showing endothoracic fascia or solitary resectable foci of chest wall invasion (46% accuracy for CT vs. 69% for MRI) [35] (Fig. 4).

One of the most important factors influencing the resolution of chest MRI images is artifacts, such as susceptibility artifacts, aliasing, and motion artifacts. Thoracic motion artifacts on MRI images may be minimized with optimal cardiac gating and respiratory compensation. Subtle positive findings on MRI depend on clear resolution of the pleura and adjacent structures, and proper gating is imperative [25,35].

3.2.3. Perfusion MRI

Perfusion MRI using Gd-CM is the most promising technique for the assessment of perfusion, vascularity, and vascular permeability of tumors [34,37–40]. At present, perfusion MRI has been widely used in clinical trials with anti-angiogenic agents to assess early changes in tumor-associated vasculature [6,40]. It has been shown that anti-angiogenic effects of chemotherapy could be successfully monitored with perfusion MRI [34].

Sequential acquisition of images with a temporal resolution of approximately 1 s during intravenous administration of Gd-CM can be obtained by perfusion MRI [6,34,37–40] and the temporal passage of contrast material through tissue, including tumor tissue, reflects the microcirculation [6,34,37–40]. As a result, the pharmacokinetic analysis of perfusion MRI can provide parameters that show significant correlation with angiogenesis [6,34,37]. Gd-CM concentrates in tumors depending on tumor perfusion, vascularity and vascular permeability [6,34,37,40]. During tumor imaging, Gd-CM diffuses passively from the blood vessel into the extracellular space [6]. In the extracellular space, Gd-CM disperses freely without binding and diffuses back into the vascular space [6]. Therefore, if the extracellular space is considered as compartment 1, and the vascular space as compartment 2, a two-compartment model can be applied to the pharmacokinetic analysis of perfusion MRI [6,34]. In this analysis, the redistribution rate constant (Kep) and the elimination rate constant (Kel) are objective measurements [34,37]. Kep is the first-order rate constant for transfer of Gd-CM from compartment 2 to compartment 1 [37]. On the other hand, Kel is the first-order rate constant for elimination of Gd-CM from compartment 1 [37]. Therefore, Kel is a systemic parameter that characterizes perfusion and Kep is a tissue-specific transport parameter that characterizes both perfusion and vascular permeability of the lesion.

Perfusion MRI and angiogenesis parameters can predict the therapeutic efficacy of chemotherapy in MPM. Recently, Giesel et al. evaluated the feasibility of perfusion MRI to monitor the effect of chemotherapy on MPM by comparing pharmacokinetic parameters, including Kep and Kel, to early clinical response and survival. A pharmacokinetic two-compartment model was used to analyze perfusion MRI. The study found that non-responders had a higher Kep value (3.6 min) than clinical responders (2.6 min), which correlated with shorter survival (460 days vs. 780 days, respectively). In other words, a high pre-therapeutic Kep correlated with a poor overall response to
3.3. Positron emission tomography (PET) and PET/CT

Functional imaging with PET has facilitated the non-invasive evaluation of tumor pathophysiology, metabolism and proliferation. The most common PET tracer used in clinical practice is 18F-Fluorodeoxyglucose (FDG), due to its favorable half-life of 18F (109 min). The basis for the use of FDG is the increased glucose metabolism of cancer cells compared to normal tissues [41]. Lesion uptake of FDG reflects the alteration of glycolytic metabolism in various tumors, including MPM. In addition, FDG–PET imaging captures alterations in tissue metabolism that generally precede morphologic change. Today, FDG–PET has achieved wide availability not only in research, but in the clinical setting as well. Preliminary reports describing the role of FDG and PET in pleural malignancies are limited but very encouraging. It has been shown that FDG–PET is useful for the differentiation of benign from malignant lesions, for staging and monitoring metabolic response to therapy of MPM, and that it has prognostic value [42–46].

3.3.1. Benign versus malignant pleural disease

FDG–PET imaging has been shown to accurately differentiate benign pleural lesions from MPM. Bénard et al. [42] described encouraging results in 28 patients referred for the evaluation of pleural disease and suspected MPM. Using FDG–PET with visual analysis, the sensitivity was 92%, with a specificity of 75%, and an accuracy of 89% for the detection of MPM. By using semi-quantitative analysis they concluded that a standardized uptake value of tracer (SUV) greater than 2.0 differentiated between benign from malignant disease, increasing the sensitivity, specificity, and overall accuracy to 91%, 100%, and 92%, respectively. Schneider et al. [43] reported the results of a retrospective analysis of 18 consecutive patients with biopsy-proven MPM who underwent FDG–PET for staging. All primary lesions were FDG-avid, distinguishing between benign and malignant pleural disease. Our results have been similar [44]. In our hands, the overall sensitivity, specificity, and accu-
racy of FDG imaging for the differential diagnosis of MPM has been 97%, 80% and 94%, respectively, compared to 83%, 80%, and 82% for diagnostic CT. Thirty-four lesions were biopsied, and FDG imaging correctly identified 28 out of 29 malignant tumors, yielding negative results in 4 out of 5 benign lesions. The smallest lesion detected was 0.8 cm. The only false-positive finding was an area of diffusely low uptake in the right costophrenic sulcus of a patient treated with talc pleurodesis due to recurrent, symptomatic pleural effusions.

Other reported sources of false-positive findings include benign inflammatory pleuritis; benign asbestos-related plaques; parapneumonic effusion, and tuberculous pleuritis [42,43,45]. True-negative findings have been reported in mild pleural inflammatory reactions, benign angiolipoma, benign asbestos pleural disease, chronic fibrosing pleuritis, and pleural fibroma [42,44,45]. Although most mesotheliomas are highly FDG-avid, mild or lack of tracer uptake has been reported in patients with mesothelioma of the epithelial subtype [42].

Neither the pattern nor the intensity of FDG lesion uptake is able to differentiate between subtypes of malignant pleural mesothelioma, or differentiate MPM from adenocarcinoma or from sarcoma. Therefore, invasive techniques are still warranted.

3.3.2. PET staging

Accurate staging of MPM is imperative to ascertain prognosis and to elect the appropriate therapeutic algorithm that should follow. PET imaging is an accurate and useful imaging technique for the staging and preoperative evaluation of disease extent. In most instances, PET imaging correctly defines the metabolic extent of intrathoracic involvement, providing complementary information to anatomical imaging modalities for the assessment of tumor resectability [44,46]. Generally, there is good agreement between FDG images and the extent of disease determined surgically. PET images correctly predict unresectability by detecting or confirming the presence and extent of metabolically active tumor invading mediastinal organs, transdiaphragmatic spread, and distant metastatic disease [42–46]. The typical appearance is that of moderate to high \(^{18}\text{F}-\text{FDG}\) uptake involving the areas of thickened pleura. Gerbaudo et al. [46] described different patterns of FDG uptake in MPM, which could be present as focal, linear, mixed or encasing distributions of the tracer [44,46] (Fig. 5). These patterns closely reflect the extent of pleural and parenchymal involvement observed in anatomical imaging and surgery. Tumors at an earlier stage tend to have focal or linear patterns of uptake, whereas the mixed and encasing patterns are indicative of more advanced disease. These investigators also reported the results of semi-quantitative analysis of serial dual-phase FDG images, which showed that radiotracer uptake increases over time in normal tissue, and in MPM [46]. In the normal lung, the rise in FDG uptake between early and late images was 6 ± 4% in 2 h. On the other hand, the rise in FDG uptake in MPM was higher in stage IV patients (97 ± 25%), when compared to stage I (13 ± 1%), stage II (34 ± 2%), and stage III patients (57 ± 3%).

Bénard et al. [42] evaluated the diagnostic value of FDG–PET in 28 patients with suspected MPM. The SUV in FDG–PET was significantly higher in malignant \((n = 24; \text{SUV} = 4.9 ± 2.9)\) than in benign lesions \((n = 4; \text{SUV} = 1.4 ± 0.6)\) \((p < 0.01)\). Nine out of 12 hypermetabolic lymph nodes were detected on FDG–PET images that appeared normal on CT scans. The study concluded that FDG–PET imaging is a sensitive method to identify malignant mesothelioma and to determine the extent of the disease process.

Recently, integrated PET/CT systems have been introduced, and their use has rapidly been incorporated at the forefront of cancer imaging [47–49]. PET/CT imaging combines metabolic with anatomical information in a single imaging procedure. Recent reports suggest that integrated PET/CT scanning improves the diagnostic and staging accuracy over PET or CT alone in different malignancies [50–52].

The advantages of integrated PET/CT imaging for staging and assessing resectability of MPM have recently been reported by Erasmus et al. [53]. The authors concluded that PET/CT increases the accuracy of overall staging and improves the selection of patients for extrapleural pneumonectomy. PET/CT was superior to other imaging modalities, as it detected more extensive disease involvement, and identified occult distant
metastases not suspected after conventional imaging. The main limitation of the technique was its inaccuracy in the detection of nodal MPM metastases.

N1 disease with mild or low FDG uptake could be a source of false-negative results [53,54]. Uptake in N1 nodes might be difficult to distinguish from uptake in the adjacent pleural tumor. N2 nodes affected with micrometastatic disease could yield false-negative findings as well. In addition, false-positive results could occur in granulomatous lymphadenitis. These are certainly very important limitations, considering that N2 positive nodes are always associated with poor survival, and that N2, rather than N1 disease, carries the worst prognosis [30,55]. Both false-negative and false-positive findings in extrapleural nodes contribute misleading information with regard to outcome, and optimal treatment strategy [30].

In our experience, the use of FDG–PET/CT imaging has been very useful for the selection of the most metabolically active site for needle or thoracoscopic biopsy in patients with MPM. This approach tends to increase the yield of positive biopsies, especially in those cases with diffuse pleural thickening, or with distorted anatomy after treatment and suspected recurrent disease [56].

The main limitation of PET is its limited anatomical landmarks, especially in the setting of MPM [42,44,46]. Thus, it still remains to be shown if the use of PET/CT and fusion imaging could improve the assessment of local invasion into the chest wall, pericardium, and diaphragm, during the initial staging of patients with MPM.

3.3.3. Predicting and monitoring therapeutic response with PET

Patients with lesions that are highly FDG-avid have a poor prognosis.

Bénard et al. [57] followed up 17 MPM patients for survival analysis. An overall median SUV of 4.03 was chosen as a cutoff to establish two patient groups: those with low-SUV lesions and those with high-SUV lesions. The investigators found a wide variability in SUV measurements in patients with malignant disease, and demonstrated that high levels of FDG uptake in mesothelioma were associated with an unfavorable prognosis. The mean SUV of survivors was 3.2 (1.6), compared to 6.6 (2.9) for the non-survivors. The cumulative survival estimate of the high SUV group (0.17 at 12 months) was significantly shorter than that of the low SUV group (0.86 at 12 months) \( (p < 0.01) \) [57]. Recently, Flores et al. [58] reported on the prognostic value of PET imaging in 137 patients with MPM. The authors concluded that a lesion with SUV >10, mixed histology, and stages III and IV carry the worst prognosis.

Fig. 6. Coronal MIP image 90 minutes post injection of FDG. (A) Pre-treatment; (B) Post-treatment, Fused axial PET CT images; (C) Pre-treatment and (D) Post-treatment images of the same patient showing encasing pattern of distribution in malignant pleural mesothelioma with probable diaphragmatic involvement. Note reduced post-treatment FDG avidity of the right pleural mass. The patient subsequently underwent successful EPP.
The use of FDG–PET for the assessment of response to treatment in MPM appears promising. Ceresoli et al. [59] studied the predictive value of FDG–PET in 20 patients to assess treatment efficacy after 2 cycles of single agent pemetrexed, or pemetrexed in combination with carboplatin. The authors defined complete metabolic response as total resolution of FDG uptake within the tumor volume between the pre- and the post-therapeutic scans (Fig. 6). Partial response was defined as a reduction in tumor FDG uptake of 25% or more, whereas progressive disease corresponded to an increase in tumor SUV of ≥25%, or the appearance of any new FDG-avid lesions. Stable metabolic disease was classified as an increase or decrease in tumor SUV of <25%. Early metabolic response was significantly correlated to median time-to-tumour progression (TTP); 14 months for metabolic responders, compared to 7 months for non-responders (p < 0.05). In addition, patients with a metabolic response had a trend toward longer overall survival. Of note is that no correlation was found between TTP and radiologic response assessed by CT.

4. Future directions

In MPM, perfusion MRI is valuable for predicting the therapeutic efficacy of chemotherapy, although, this concept requires further examination in a larger population. In addition, direct comparison between perfusion MRI parameters and angiogenesis factors, such as VEGF expression, is necessary. Furthermore, the ability of perfusion MRI to monitor the therapeutic effect of combination chemotherapy and anti-angiogenesis drugs remains to be assessed.

Other perfusion parameters, such as maximum enhancement ratio, time at maximum enhancement ratio, and slope may be associated with angiogenesis [39,60]. In fact, the usefulness of dynamic MRI and of these parameters in differentiating benign from malignant solitary pulmonary nodules has already been suggested [39,60]. In MPM, these parameters should be studied in the context of angiogenesis factors and prognosis.

MRI state-of-the-art technology and imaging techniques are developing rapidly, as shown by the advent of 3T MRI and parallel imaging. Further refinement of MRI techniques and equipment may improve the temporal resolution of sequential data acquisition. In addition, three-dimensional MRI (3D-MRI), with multi-channel surface coils and/or parallel imaging techniques may be used to evaluate whole lung perfusion. These state-of-the-art techniques will be validated in future studies.

PET is able to study the biological processes of tumor angiogenesis in vivo. Tracers of blood flow, vascular volume, microvessel density, hypoxia and even cell proliferation and apoptosis have already been developed and analyzed [6]. Furthermore, results from recent investigations of molecular processes and targets are being used to design new compounds. For example, the anti-VEGF monoclonal antibody, VG76e, has been labelled with the PET tracer 124I, and its imaging potential was validated successfully in a mouse model [6,61]. In addition, a radiolabelled ligand of αVβ3 integrin receptor, which is expressed specifically in endothelial cells of tumor vessels, has been used successfully to image tumor-associated angiogenesis [6]. These tracers may represent the future of in vivo molecular imaging of angiogenesis. However, their availability is still very limited, and to the best of our knowledge, there are no studies assessing the role of these tracers in MPM.

5. Conclusion

In conclusion, CT plays a primary role in the diagnosis and staging of MPM. MRI and PET can provide additional information to help overcome the limitations of CT. Complementing CT with these other imaging techniques is promising for the assessment of angiogenesis and the prognosis of MPM.

References