Old Borders and New Horizons in Multimodality Imaging of Malignant Pleural Mesothelioma

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Abstract

Background The purpose of this article is to describe the various imaging techniques involved in detection, staging, and preoperative planning in malignant pleural mesothelioma (MPM) focusing on new imaging modalities.

Methods For this purpose, first a brief summary of the etiology of MPM is given. Second, not only the commonly known, but also novel imaging modalities used in MPM will be discussed.

Results A wide range of imaging methods, from conventional chest radiography, through computed tomography and hybrid imaging to radiomics and artificial intelligence, can be used to evaluate MPM.

Conclusion Nowadays multimodality imaging is considered the cornerstone in MPM diagnosis and staging.

Keywords
- imaging
- mesothelioma
- pleural disease
- tumor

Introduction

Malignant pleural mesothelioma (MPM) is an aggressive tumor entity with a high mortality rate.[1] Since clinical manifestations of MPM comprising chest pain and dyspnea are rather nonspecific, imaging plays a major role in detection, diagnosis, and staging of MPM.[2] The tumor nodule metastasis (TNM) staging system together with tumor factors and patient demographics is used to determine patient outcome and prognosis. Different imaging modalities are used to plan individualized treatment strategies, and for decreasing morbidity and mortality in patients with MPM.[3]

In March 2017, a group of mesothelioma experts from the National Cancer Institute Thoracic Malignancy Steering Committee, the International Association for the Study of Lung Cancer, and the Mesothelioma Applied Research Foundation proposed a consensus statement on radiologic guidelines in mesothelioma imaging.[4] Even though MPM might be visible in conventional chest X-rays, imaging modalities typically used in the context of MPM include contrast-enhanced computed tomography (CT), magnetic resonance imaging (MRI), and positron emission tomography (PET) combined with CT (PET/CT).[5]

There is continuous active research in imaging and treatment of MPM and the clinical implementation of new and emerging imaging techniques are in steady evolvement.

This article aims to describe the various imaging techniques involved in diagnosis, staging, and preoperative planning in MPM with a focus on emerging imaging techniques.

Mesothelioma: Pathophysiology and Pathology

Mesothelioma is a malignant disease of the mesothelium mostly arising from the pleura (~90%).[6]

In most cases, MPM occurs after asbestos exposure, with latency periods of several decades, although it can also be trigged by prior radiation therapy.[3,7,8] Asbestos particles deposit in the bronchi and alveoli and lead to chronic inflammation and subsequently to lung parenchyma remodeling with an increased risk of chronic bronchitis, chronic obstructive pulmonary disease, fibrotic changes, and lately the development of MPM. The gross pathologic finding in lungs after asbestos exposure is focal pleural thickening (the so-called pleural plaques) which first appears 20 to 30 years

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after the first exposure. In imaging, the plaques appear as focal thickening of less than 1 cm in the parietal pleura. Typically, the visceral pleura is not affected. Of note, pleural calcified or noncalcified plaques are only a hint of previous asbestos exposure but are not considered as neoplasm.[9]

There are three different histologic subtypes of mesothelioma: epithelioid, sarcomatoid, and biphasic.[10] Each histologic type of mesothelioma has its own unique characteristics and varies in treatment response. Epithelioid mesothelioma is the most common type of mesothelioma, accounting for 70% of cases. Simultaneously, it is also the histologic type with the best treatment outcomes. Sarcomatoid mesothelioma is the histologic type with the most dismal prognosis due to its poor treatment response. It is luckily also the rarest form of mesothelioma occurring in 7 to 20% of cases.[10] In biphasic mesothelioma, both epithelioid and sarcomatoid cells are present. It is the second most common form of mesothelioma, occurring in 20 to 35% of cases. Simultaneously, it is the most common type of MPM. The prognosis for biphasic mesothelioma depends upon the proportion of epithelioid versus sarcomatoid cells.[10]

Histology is not only essential to define different treatment options and for outlining prognoses and life expectations; the different subtypes might also impact imaging in terms of contrast agent kinetics and last but not least for artificial intelligence algorithms.

Imaging of Malignant Pleural Mesothelioma: A Multimodality Approach

The radiological appearance of MPM is nonspecific and ranges from pleural effusion in early stages to circumferential, lobulated pleural thickening and pleural masses in advanced stages. The tumor can extend into adjacent structures along multiple planes and can have focal chest wall or mediastinal invasion already at the time of presentation. In more advanced stages, the tumor may invade the chest wall, mediastinum and mediastinal structures, pericardium and diaphragm, or metastasize to the lymph nodes, contralateral pleura, bones, lungs, or other distant sites. In cases where the involved hemithorax is significantly contracted with evidence of retraction of ribs, diffuse endothoracic fascial invasion is present, usually rendering these cases inoperable.[4]

To evaluate the disease stage, a multimodality approach is needed to determine resectability and assignment of therapy.

Traditional Imaging in Malignant Pleural Mesothelioma

Conventional Radiography

Conventional chest radiography (CXR) is pathologic in advanced disease, showing unilateral pleural effusion, with ipsilateral volume loss and pleural thickening. In less advanced cases, the sensitivity of CXR in detecting MPM is low. CXR plays a role in early stages to suspect the disease when the following radiographic rather nonspecific features are present[11]: drug-resistant unilateral pleural effusion, unilateral lobulated pleural thickening with or without thickening of the pleural

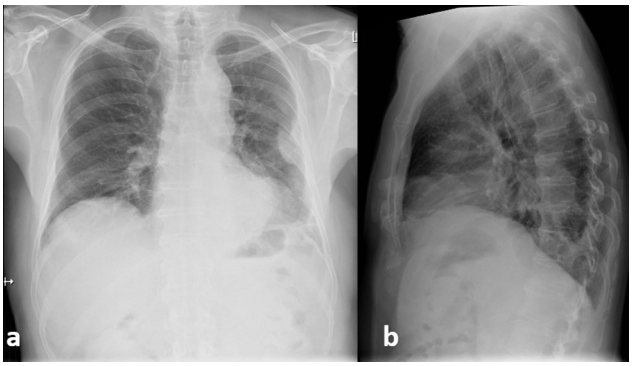

Fig. 1 Conventional chest radiograph of a 58-year-old male patient with malignant pleural mesothelioma showing drug-resistant unilateral pleural effusion, unilateral left-sided lobulated pleural thickening, multiple peripherally distributed intrathoracic masses, and discrete loss of volume in the ipsilateral hemithorax.

fissures, and multiple peripherally distributed intrathoracic masses. The key point is that pleural effusion is not associated with contralateral mediastinal shift. Due to the restrictive action of the pleural tumor rind, there will be ipsilateral volume loss and retraction of the thoracic cage, narrowing of the intercostal spaces, elevation of the hemidiaphragm, and shift of the mediastinum toward the affected side (►**Fig. 1**).[9]

To better depict the extent, amount and distribution of MPM chest CT with intravenous contrast agent should be performed.

Computed Tomography

CT with intravenous contrast agent is the cornerstone in MPM imaging and is used to assess both baseline disease and response to therapy. CT for follow-up of patients with MPM is usually performed every 3 to 4 months in the first year of follow-up if no recurrence is suspected. After the first year, imaging intervals are defined individually for each patient.[12] Typically, the following characteristic features are evident[11]: circumferential pleural thickening, nodular or lobular thickening of the mediastinal pleura, infiltration of the chest wall, mediastinal and pericardial infiltration, and presence of lymphadenopathy in extrapleural fat tissues (►**Fig. 2**). Further, benign calcified or noncalcified plaques may be present. Rib destruction can be seen in advanced stages of bulky MPM. Of note, pleural effusion is rather unspecific; however, 30 to 80% of patients will show unilateral pleural effusion in early-stage disease, masking the underlying neoplasia.[13,14] Therefore, therapy-resistant pleural effusion must alert the treating physician, especially in patients with a history of asbestos exposure. Features which can help to discriminate neoplastic from benign pleural changes include (1) circumferential thickening of the pleura, (2) nodular thickening of the pleura, (3) parietal thickening of the pleura more than 1 cm, an especially (4) the involvement of the mediastinal pleura.[15] Discriminating MPM from other neoplastic causes of pleural changes remains challenging.

On CT, MPM has a similar tissue attenuation to surrounding structures such as muscular tissue, the diaphragm and pericardium, as well as complex pleural effusions, which makes the differentiation of MPM from surrounding structures sometimes

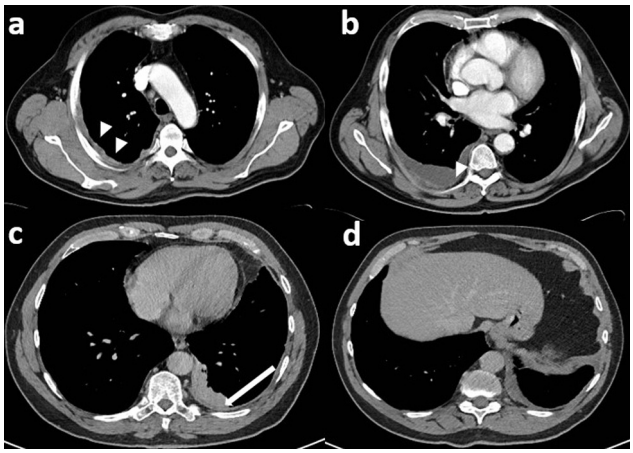

Fig. 2 (**a**, **b**) 64-year-old male patient with right-sided malignant pleural mesothelioma. The tumor is configured circumferential, or rind-like along the right thoracic pleural surface (*white arrow heads*) in contrast to (**c**) and (**d**), where the tumor manifestation is more nodular or mass-like (*arrow*) in this 72-year-old mal patient with asbestos exposure 25 years previous to tumor manifestation.

challenging[16,17] (►**Fig. 3**). Furthermore, the diagnostic accuracy of CT for N-staging is with approximately 50% rather low.

Magnetic Resonance Imaging

Although thoracic MRI is not routinely used to evaluate MPM, the modality has its strengths in the evaluation of suspected chest wall or diaphragmatic infiltration, or in patients in whom iodinated contrast agents are contraindicated.[3] MRI performs better than CT in detecting infiltration of the chest wall, mediastinal and nervous structures (such as the brachial plexus), and invasion of the peritoneum. MRI is generally reserved for surgical candidates to guide treatment/surgery planning. Further, MRI signal is useful in the distinction of MPM from benign pleural fibrous plaque.[9]

Additionally, current data show that diffusion-weighted imaging (DWI) allows for patient-tailored care in MPM: the functional imaging capabilities of MRI through DWI are used to estimate tumor volume and parameters of the tumor pixel-value histogram in an attempt to discriminate between long- and short-term overall survivors.[18]

Even though MRI does have superior soft tissue contrast compared with CT, subtle local invasion can still be challenging to diagnose.

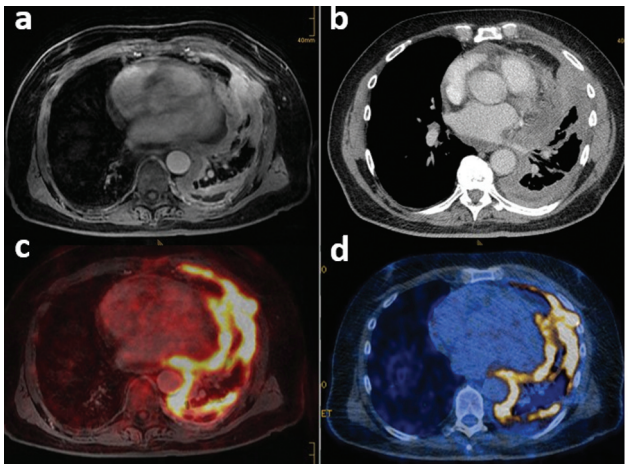

Fig. 3 67-year-old female patient with left-sided malignant pleural mesothelioma with chest wall invasion. While in (**a**) MR and (**c**) PET/MR, it can be nicely appreciated that the intercostal muscles are invaded by the tumor; (**b**) on CT manifestations of MPM have a similar tissue attenuation to the intercostal muscles and the tumor is not distinguishable from the muscular tissue. In (**d**) PET/CT, the intercostal FDG uptake gives a hint for the presence of chest wall infiltration. CT, computed tomography; MR, magnetic resonance; PET, positron emission tomography.

PET/CT

In the last years, 18-fluorodeoxyglucose positron-emission tomography CT (^{18}F-FDG-PET/CT) has become an integrated part of diagnosis and especially preoperative imaging and staging of MPM,[19] especially in cases where aggressive surgical resection is being considered. ^{18}F-FDG-PET/CT adds information about the biochemical activity of the tumor and is very useful in the investigation for extra-thoracic lymphadenopathy and metastatic disease.[3,19,20] Further, ^{18}F-FDG-PET/CT allows for discrimination of MPM from fibrous pathology in most cases. Although ^{18}F-FDG-PET/CT has shown to have a higher sensitivity and lower interobserver variability for clinical intrathoracic staging of MPM compared with CT, it underestimates the tumor stage, especially regarding T-stage.[21]

Advanced Imaging in Malignant Pleural Mesothelioma

Contrast Agent Kinetics in MPM

Contrast enhancement of neoplastic tissue in CT or MRI has the ability to provide information on tumor vascularity. However, attention has to be paid to the imaging delay after the administration of contrast agent. Recent research has shown that the normally used time delay between contrast medium administration and start of image acquisition might not be sufficient to capture contrast phases optimal for MPM assessment. Patel et al[22,23] showed that enhancement of MPM at the conventional time delay of 40 to 60 seconds did not represent the maximal enhancement. In fact, the group estimated that the peak tumor enhancement occurs at 280 seconds following intravenous (IV) contrast injection (►**Fig. 4**). Improved tumor enhancement leads to an improved tumor-tissue contrast and therefore increases the accuracy in staging and therapy response assessment of MPM. Therefore, postcontrast phase imaging for the evaluation of MPM should be acquired at a time delay longer than typically employed in routine clinical imaging.

Volumetric Assessment in MPM

In the last years, the European Organization for Research and Treatment of Cancer and the Cancer and Leukemia Group B have found several prognostic factors in patients with MPM[24,25]: worse prognosis was associated with not only clinical parameters, advanced stage (stage IV), and metabolic activity, but with tumor volume. Tumor volume measurement has been shown to be a promising, quantitative tool for

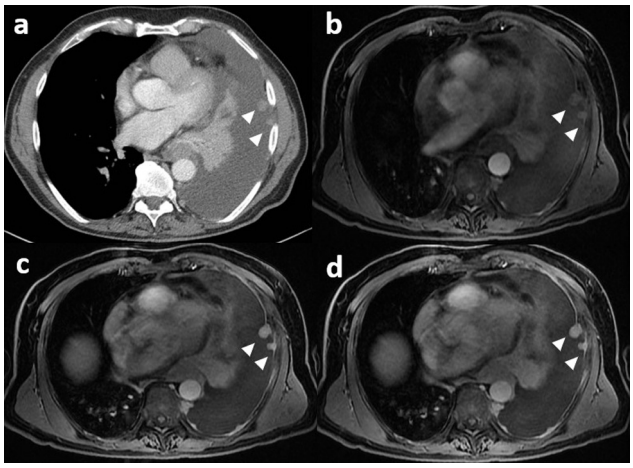

Fig. 4 65-year-old male patient with left-sided malignant pleural mesothelioma and pleural effusion. In (**a**) CT the nodular pleural tumor manifestation is of the same attenuation as the adjacent intercostal muscle. Same goes for the (**b**) T1-weighted MRI with fat saturation obtained 60 seconds after IV contrast administration. Panels (**c**) and (**d**), which were acquired at 120 seconds and 280 seconds after contrast administration, respectively, show a perfect distinction of the enhancing nodular mesothelioma manifestation from the intercostal musculature as well as from the surrounding pleural effusion.

the assessment of MPM tumor burden with prognostic significance[26–28]: it has been shown that tumor volumes of greater than 500 cm^3 were associated with reduced overall survival. Tumor volume can be assessed on CT, PET/CT, or MRI performed for staging or therapy planning purposes without the need of the acquisition of additional images. Tumor volume quantification can be easily performed with commercially available postprocessing tools. Further, volumetric approaches have also been proposed to monitor therapy response.[29]

Before tumor volumetry can be incorporated as an integral part into the clinical staging algorithm, further validation of the role of tumor volumetry is required. Until that, modified RECIST remains the standard for the quantification of MPM in clinical practice, mostly due to its favorable prediction of patient survival and its existing wide acceptance.[30]

PET/MR

Similar to PET/CT, also the interest to integrate MR with PET imaging has increased over the last years due to the superior soft tissue contrast reported for MRI.[31] Nonetheless, to date only a few studies in selected indications have evaluated the feasibility of PET/MR.[8,32–34] PET/MR may facilitate the discrimination of structures located in proximity to each other (for example discriminating lymph nodes from adjacent pleura). Especially in these locations, it is often difficult to distinguish to which structure the FDG-positive signal is related to (►**Fig. 3**).[34]

Metabolic Tumor Volume and Total Lesion Glycolysis

It has been shown that the level of FDG uptake as a surrogate for metabolic activity is associated with median time to tumor progression and survival: while MPM shows a significantly higher FDG uptake than benign lesions, higher FDG uptake indicates a shorter survival time.[35,36]

Further, metabolic ^{18}F-FDG-PET/CT has been proposed as an alternative technique for response evaluation in MPM.[37] Standard uptake value (SUVmax), tumor volume (PETvol), and tumor lesion glycolysis (TLG) can be evaluated. TLG constitutes SUVmean times PETvol, and thus represents a combined metabolic–morphologic tumor burden parameter. Veit-Haibach et al,[37] for example, evaluated MPM patients after three cycles of therapy with pemetrexed and platinum-based chemotherapy and could show that both TLG and PETvol measurements were predictive of overall survival. Zucali et al[38] found that percentage changes from baseline and at interim FDG-PET of SUVmax (ΔSUV) and TLG (ΔTLG) in patients receiving pemetrexed-based chemotherapy are prognostic of treatment outcome and patient response. Interestingly, neither ΔSUV nor ΔTLG showed similar association with survival outcomes in patients treated with pleurodesis.[38]

Radiomics in Mesothelioma

In the last years, radiomics has continuously gained importance in the field of radiology and radiologic imaging and showed promising results in prognosis and diagnosis of various diseases, especially malignancies.[39]

The poor survival rate of MPM necessitates a correct differentiation from other etiologies such as hyperplastic mesothelium and metastatic disease.[40] Studies evaluating radiomic and texture features of pleural plaques showed that quantitative textural and shape analysis might help to discriminate neoplastic from benign lesions: Pena et al, for example, evaluated radiomics, texture, and shape analysis to MR and CT images of pleural disease to assess their ability to distinguish benign from malignant lesions, using histopathology as the reference standard.[41] The group could show that radiomics is able to distinguish benign from malignant lesions on contrast-enhanced CT and MR.

Radiomics has the potential to become a major player in patient management: subjects with higher risk for invasive diagnostic procedures who demonstrate radiomic features, suggesting a benign lesion could be selected to undergo follow-up imaging rather than biopsy.[41,42]

Staging and Evaluation of Therapy Response

Staging

To evaluate the treatment options and to achieve the best clinical outcomes, accurate tumor staging and characterization of therapy response are important. In 1994, the first widely accepted TNM classification for MPM was published by the International Mesothelioma Interest Group.[43] This classification has gone through several important revisions, being now in the eighth edition.[44] For the clinical staging of MPM, different imaging techniques are used: beside contrast-enhanced CT, PET/CT is used to exclude metastases located outside the thorax or to prove that lymph node metastases are present.

Different TNM stages are used to divide patients into different disease stages (►**Table 1**).[44]

Table 1 Stage grouping for eighth edition.

Stage	Stage grouping		
	T	N	M
I			
IA	T1	N0	M0
IB	T2, 3	N0	M0
II	T1, 2	N1	M0
III			
IIIA	T3	N1	M0
IIIB	T1–3	N2	M0
IV	T4	N0–2	M0
	Any T	Any N	M1

Note: Detailed information on the imaging characteristics of the different stages of malignant pleural mesothelioma can be found in the eighth tumor nodule metastasis (TNM) classification for malignant pleural mesothelioma.[44]

Evaluation of Therapy Response

Conventional response criteria are CT-based and constitute normally in measuring size changes of tumor lesion. These criteria are difficult to apply to MPM due to its unique pattern of growth, not producing conventional spherical lesions with bidimensionally measurable diameters.[29] Thus, World Health Organization criteria are poorly suited to evaluate treatment response in MPM, as they were principally developed to assess bidimensionally measurable disease. Modified RECIST criteria have been introduced to address the growth pattern and therapy response in MPM and can be used either with CT or MRI.[29] The process involves measurements of tumor thickness perpendicular to the chest wall or mediastinum obtained at defined locations within the thorax.[45] Further, Plathow et al[29] found evidence that therapy response can be evaluated at a very early stage of chemotherapy. This would be beneficial in individualizing therapy responders early, and preventing useless chemotherapy and its side effects in nonresponders.[29]

Role of Surgery and Surgical Approach

Surgical techniques are used for either (1) diagnosis confirmation or (2) treatment.

Since the appearance of MPM on imaging is relatively unspecific and the discrimination between benign and neoplastic pleural changes can be tricky, tissue sampling for diagnosis confirmation is required.[13,14] This can be done by (1) thoracoscopy or by (2) CT- or ultrasound-guided core needle biopsy if the masses are accessible and large enough (i.e., bulky disease). In cases, where MPM is suspected clinically or radiologically, the diagnostic accuracy of thoracoscopy exceeds 90%. The complication rate of thoracoscopy, in contrast, is with less than 10% of cases, reported to be very low.

In contrast to this, the sensitivity of percutaneous CT or ultrasound-guided core needle biopsy is between 50 and 85% —and so lower than in thoracoscopy. Therefore, ultrasound or CT-guided biopsy is normally not used for definitive diagnosis of MPM, except in individuals who are not suitable for thoracoscopy.[12]

In the last decades, various surgical techniques have been advocated in MPM. The main goal of surgery is a macroscopic complete resection and currently there are two surgical techniques with a curative intent: (1) the extrapleural pneumonectomy (EPP) which consists of an en-bloc resection of the lung, pleura, pericardium, and diaphragm and (2) pleurectomy/decortication (P/D), a lung-sparing surgery. At first P/D was considered only if the situation was palliative, but during the last decades, the role of P/D has changed and the technique has gained an important position in MPM treatment.[12] Recent studies have shown that while survival time after extrapleural EPP and P/D is similar, the mortality and morbidity after EPP is higher than after P/D.[12] Of note, individuals undergoing P/D seem to have better options for additional therapies after surgery, in case of MPM recurrence. Further, individuals undergoing P/D have higher survival rates.[12] P/D is very promising, in cases where a macroscopic complete resection can be achieved. In cases of expanded tumor manifestation with invasion of lung parenchyma, a complete macroscopic resection seems to be only feasible in the form of an EPP. Even though there is no treatment recommendation standardized for MPM, it is generally accepted that a monotherapy alone is insufficient for this aggressive tumor. Most of the centers combine macroscopic complete resection with a neoadjuvant or adjuvant chemotherapy with cisplatin and pemetrexed.[46]

Risk Assessment and Screening for MPM

Since clinical manifestations are relatively nonspecific, diagnosis of MPM is made relatively late and patients are often found at advanced disease stages[2] with consecutive high mortality rates.[1] Around 80% of MPM occur in individuals with a history of asbestos exposure; the lifetime risk for the development of MPM in asbestos workers is 10%. As the population at risk is relatively well defined and early-stage disease is potentially curable, screening for asbestos-related disease with low-dose CT was considered in the literature. However, two main reasons make MPM screening difficult: (1) early signs such as pleural effusion are rather nonspecific and calcified or noncalcified pleural plaques are indicators of asbestos exposure but not of neoplastic pathology,[47] and (2) MPM is a fast-growing tumor with a high mortality rate within short time which would make very short screening intervals necessary. Because of this, even if the main risk factor is well known it is difficult to elaborate a suitable screening protocol.

Of note, studies have shown that patients exposed to asbestos have not only higher risk for developing MPM but also for developing lung cancer, and the risk for developing lung cancer is higher than that for MPM.[48]

Future Prospects

Differentiating benign from malignant pleural changes remains one of the biggest issues in MPM imaging. There are several approaches in research used to assess pleural

plaques with the aim to get a better understanding of the features, which suggest malignancy.

Dynamic contrast-enhanced CT is an imaging strategy in which a selected lesion is scanned at multiple time points after IV contrast injection. The dynamic tissue enhancement reveals information on tissue vascularity and perfusion. These parameters have been shown to not only being useful in the assessment of therapy response, but can also give hints on tumor histology in different malignancies.[49,50] It is hoped that the same approach can also be useful for MPM evaluation and preliminary studies could already show promising initial results.[51]

Another approach for tissue characterization and perfusion evaluation is dual-energy CT (DE-CT) scanning where iodine concentration in tissue can be quantified. Measurement of iodine concentration has been shown to improve CT specificity and sensitivity for differentiating between malignant and benign tissues in several tumor entities, including those metastasizing to the pleura.[52] The downside of the technique is that a special DE scanner is needed for image acquisition.

Finally, with the introduction of photon-counting CT we will have another promising technique for tissue characterization, with which we might be able in the future to better characterize pleural lesions.[53]

Currently, these promising techniques are evaluated in clinical studies; however, to date there is not enough evidence to recommend them for routine clinical use in MPM.

Conclusion

Several imaging techniques are used in the diagnosing, staging, and follow-up of MPM. Each of them has its strengths and weaknesses. Therefore, a combined use is important in determining optimal treatment options for patients with MPM. Dynamic contrast-enhanced CT is the imaging modality of choice for imaging diagnosis, staging, and follow-up. Contrast enhancement in MRI provides additional information before surgical treatment, concerning chest wall invasion and mediastinal and nervous structures. PET/CT is better than CT and MRI in the assessment of lymph node involvement and for the investigation of metastatic disease. New evolving postprocessing methods, like volumetry or texture analysis will further enhance a patient-specific treatment strategy.

Conflict of Interest
None.

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