# Narrative review of staging and diagnosis of malignant pleural mesothelioma

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**Objective:** Despite the aggressive nature of malignant pleural mesothelioma (MPM) its diagnosis and accurate staging remains elusive.

**Background:** MPM is highly associated with asbestos exposure, but the long latency period makes exposure tracking a challenge. The disease often presents surreptitiously leading to late diagnosis and therefore poor prognosis. Patients often present with symptoms such as dyspnea, chest pain, fatigue, and cough that are suggestive of many thoracic ailments such as lung cancer, pneumothorax, and pneumonia. Consequently, these patients often receive a CT scan as the first step towards diagnosis. If the results of the CT scan are suggestive of mesothelioma, such as if diffuse pleural thickening or a rind is seen, a biopsy is the next intervention sought. A thoracoscopic biopsy is often preferred over a core needle biopsy and is paramount for diagnosis and subsequent treatment plan optimization. PET scans have been useful in determining the spread of the disease while MRI has been a tool in determining respectability. In an effort to optimize care for these patients, staging guidelines have evolved and now align with those utilized with solid tumors such as sarcoma. The current classification system is the eighth edition of the tumor, node, and metastasis (TNM) system published by the International Mesothelioma Interest Group (IMIG) for MPM. This edition incorporates changes in the T and N classifications and differs from previous guidelines that focused on surgical management of the disease. In an effort to improve clinical decision making and prognostication novel staging approaches, including volumetric staging, have been proposed. Diagnosis and treatment of MPM is further complicated by the difference in behavior and tumor marker expression of the epithelioid subtype and the sarcomatoid subtypes.

**Methods:** Utilizing computerized databases, literature pertaining to the diagnosis and staging of MPM was analyzed. We focused on the utility of current imaging strategies, staging systems, and pathologic analysis.

**Conclusions:** MPM remains a challenge to diagnose and treat. The increased integration of advanced imaging modalities will likely aid in diagnosis of MPM. Advancements in diagnosis will predictably go hand-in-hand with more precise staging systems that will overall improve prognostication and survival.

**Keywords:** Mesothelioma; cancer staging; video-assisted thoracoscopic surgery; cancer imaging

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## Introduction

Malignant pleural mesothelioma (MPM) is an aggressive malignancy that remains a challenge to diagnose. Symptoms for patients are usually insidious and frequently mimic other benign and malignant chest diseases. A prudent example is early stage mesothelioma masquerading with symptoms suggestive of primary pneumothorax which may lead to tardy diagnosis. Suspicion must be high for any clinical provider who encounters a patient with respiratory or chest complaints such as dyspnea, pain, unexplained pneumothorax and a history of asbestos exposure. CT is an important imaging modality for evaluating a patient with suspected MPM, but tissue diagnosis is critical, and in some countries is required in order to get compensation for occupational hazard exposure. In addition, tissue diagnosis provides important information for prognostication and treatment decisions. Staging for MPM has undergone many changes over the last few decades, evolving from systems primarily focused on surgical management of the disease to a tumor, node, and metastasis (TNM) system more consistent with other solid tumors.

We present the following article in accordance with the Narrative Review reporting checklist (available at https://asj.amegroups.com/article/view/10.21037/asj-21-71/rc).

## Staging systems

Older mesothelioma staging systems include the Brigham and the Butchart systems. The Brigham staging system was proposed by Sugarbaker and colleagues in the late 1990s in response to perceived problems with the International Mesothelioma Interest Group (IMIG) system at the time and was based on tumor, resectability, and nodal status and was derived from patients who underwent extrapleural pneumonectomies (EPP) at a single institution (1-3). It was not widely accepted due to its reliance on surgical margins in patients undergoing EPP and because it differed from the typical TNM staging guidelines (4). The Butchart system was developed in the 1970s and was more simplistic but nevertheless insightful and defined four stages: (I) tumor only present on the ipsilateral pleura, lung, and pericardium on the ipsilateral side, (II) tumors that invade the mediastinum or mediastinal structures, (III) tumor that traverse the diaphragm and enter the peritoneum or involve extrathoracic lymph nodes, or (IV) distant hematogenous metastases (4). Presently, the IMIG system is the most commonly used.

### Clinical TNM staging

The first widely accepted TNM classification for MPM was published by the IMIG in 1994 as a result of a consensus meeting of the Seventh World Conference of the International Association for the Study of Lung Cancer (IASLC) (5). It was the first MPM staging system that utilized the outcomes of multiple retrospective series. This system was ultimately adopted and revised by the American Joint Commission on Cancer (AJCC) and the Union for International Cancer Control (UICC) (6,7). As of 2021, the TNM system published by the IMIG for MPM is currently on its eighth edition.

Compared to the seventh edition, the T stage in the eighth edition has been simplified based on more recent data (*Table 1*) (6). In the seventh edition, T1a was defined as tumor involving the ipsilateral parietal pleura without involvement of the visceral pleura and T1b was tumor involving the parietal pleura on the ipsilateral side with focal involvement of the visceral pleura. In the eighth edition, this has been condensed and simplified to just T1, which is defined as tumor involving the ipsilateral parietal pleura with or without involving of the visceral pleura. The other stages remain unchanged. T2 refers to tumor that involves the ipsilateral pleural surfaces (parietal, mediastinal, diaphragmatic, or visceral) and one or more of the following: confluent visceral pleural tumor, involvement of the diaphragm muscle, and/or invasion of the lung parenchyma. T3 refers to involvement of all the ipsilateral pleural surfaces with at least one of the following: invasion of the endothoracic fascia, extension into mediastinal fat, solitary completely resectable focus invading soft tissues of the chest wall, and/or non-transmural involvement of the pericardium. T4 refers to involvement of all the ipsilateral pleural surfaces with at least one of the following: diffuse or multifocal invasion of the chest wall's soft tissue, involvement of ribs, invasion through the diaphragm into the peritoneum, invasion of any mediastinal organ, direct extension to the pleura on the contralateral side, invasive of brachial plexus, the spine, or transmural invasion of the pericardium. The transmural involvement may or may not have a concomitant pericardial effusion. Invasion into the myocardium would also classify the tumor as T4. When updating this classification system, the IASLC did review data that showed there was a significant survival benefit when no pleural thickness was greater than 5.1 mm versus any pleural thickness greater than 5.1 mm (median survival 24.2 *vs.* 17.7 months, P=0.0014), however, it was not

**Table 1** Comparison of T characterizes between the eight and seventh editions of the IASLC TNM guidelines

| T Category | Seventh edition classification | Eighth edition classification |
|---|---|---|
| Tx | Primary tumor couldn't be assessed | Primary tumor couldn't be assessed |
| T0 | No evidence of primary tumor | No evidence of primary tumor |
| T1a | Tumor involves the parietal pleura on the ipsilateral side (which includes that of the mediastinum and diaphragm) with no involvement of visceral pleura | Tumor involves the parietal pleura on the ipsilateral side (which includes that of the mediastinum and diaphragm) with no involvement of visceral pleura |
| T1b | Tumor involves parietal pleura on the ipsilateral side (which includes that of the mediastinum and diaphragm) and the visceral pleura has focal involvement | |
| T2 | Tumor involves parietal, mediastinal, diaphragmatic and visceral pleural surfaces on the ipsilateral side and is also can be characterized by any of the listed qualities:<br>• Tumor that impacts the entirety of the visceral pleura (including the fissures)<br>• Tumor that effects the diaphragm<br>• Tumor that has invaded the parenchyma of the lung | Tumor involves parietal, mediastinal, diaphragmatic and visceral pleural surfaces on the ipsilateral side and is also can be characterized by any of the listed qualities:<br>• Tumor that impacts the entirety of the visceral pleura (including the fissures)<br>• Tumor that effects the diaphragm<br>• Tumor that has invaded the parenchyma of the lung |
| T3 | Tumor involves parietal, mediastinal, diaphragmatic and visceral pleural surfaces on the ipsilateral side and is also can be characterized by any of the listed qualities:<br>• Tumor invades that pericardial fascia, but is not transmural<br>• Tumor invades the chest wall in a single location that is amenable to resection<br>• Tumor invades into the mediastinal fat<br>• Tumors invades into the endothoracic fascia | Tumor involves parietal, mediastinal, diaphragmatic and visceral pleural surfaces on the ipsilateral side and is also can be characterized by any of the listed qualities:<br>• Tumor invades that pericardial fascia, but is not transmural<br>• Tumor invades the chest wall in a single location that is amenable to resection<br>• Tumor invades into the mediastinal fat<br>• Tumors invades into the endothoracic fascia |
| T4 | Tumor involves parietal, mediastinal, diaphragmatic and visceral pleural surfaces on the ipsilateral side and is also can be characterized by any of the listed qualities:<br>• Tumor invades the chest wall diffusely or in a way not amenable to resection<br>• Tumor extends to contralateral pleura<br>• Tumor involves a rib<br>• Tumor progresses through the diaphragm<br>• Tumor invades any mediastinal organ, spine, or the brachial plexus<br>• Tumor involves the entire thickness of the pericardium +/– effusion<br>• Tumor with myocardial involvement | Tumor involves parietal, mediastinal, diaphragmatic and visceral pleural surfaces on the ipsilateral side and is also can be characterized by any of the listed qualities:<br>• Tumor invades the chest wall diffusely or in a way not amenable to resection<br>• Tumor extends to contralateral pleura<br>• Tumor involves a rib<br>• Tumor progresses through the diaphragm<br>• Tumor invades any mediastinal organ, spine, or the brachial plexus<br>• Tumor involves the entire thickness of the pericardium +/– effusion<br>• Tumor with myocardial involvement |

IASLC, International Association for the Study of Lung Cancer; TNM, tumor, node, and metastasis.

included due to need for further analysis and the somewhat subjective nature of the measurements on the collected data (8).

Just as with lung cancer, the N staging system is important for prognostication for survival in patients with MPM. In the seventh edition, the classification system was N0-3. In the eighth edition, N3 was consolidated with N2 (*Table 2*). N1 correlates with nodal metastases in the ipsilateral bronchopulmonary, hilar, or mediastinal lymph nodes. N2 now correlates with metastases in the contralateral bronchopulmonary, hilar, or mediastinal lymph nodes or any supraclavicular lymph nodes. N3 is no longer used. For the M system, M1 continues to refer to any distant metastases (*Table 3*). Major sites for metastasis include lung, liver, adrenal gland, kidneys, spleen, thyroid, and brain (9).

**Table 2** Comparison of N characterizes between the eight and seventh editions of the IASLC TNM guidelines

| N Category | Seventh edition classification | Eighth edition classification |
|---|---|---|
| Nx | Cannot assess regional lymph nodes | Cannot assess regional lymph nodes |
| N0 | No metastasis to regional lymph nodes | No metastasis to regional lymph nodes |
| N1 | The hilar lymph nodes or the bronchopulmonary nodes on the ipsilateral side show evidence of metastasis | The hilar, mediastinal, or the bronchopulmonary lymph nodes on the ipsilateral side. Show evidence of metastasis (the intercostal, pericardial fat pad, internal mammary, peri-diaphragmatic, lymph nodes are also included here) |
| N2 | The mediastinal lymph nodes, subcarinal lymph nodes, internal mammary nodes on the ipsilateral side, or the peridiaphragmatic lymph nodes show evidence of metastasis | Metastases in the contralateral bronchopulmonary, hilar, or mediastinal lymph nodes or ipsilateral or contralateral supraclavicular lymph nodes |
| N3 | The scalene or supraclavicular lymph nodes on the ipsilateral side or, the hilar lymph nodes, contralateral internal mammary, contralateral mediastinal show evidence of metastasis | N/A |

IASLC, International Association for the Study of Lung Cancer; TNM, tumor, node, and metastasis.

**Table 3** Comparison of M characterizes between the eight and seventh editions of the IASLC TNM guidelines

| M Category | Seventh edition classification | Eighth edition classification |
|---|---|---|
| Mx | Distant metastasis existence cannot be assessed | Distant metastasis existence cannot be assessed |
| M0 | Distant metastases not evident | Distant metastases not evident |
| M1 | Distant metastases evident | Distant metastases evident |

IASLC, International Association for the Study of Lung Cancer; TNM, tumor, node, and metastasis.

### *Pathologic staging*

Thoracentesis and analysis of body fluid cytology is frequently done for pleural effusions of unknown origin. In MPM, diagnosis can be challenging as cytologic features tend to be bland and the tissue invasion that is usually the reliable morphologic criteria for MPM cannot be assessed in a cytology preparation (10). Cytologic diagnosis is also limited to epithelioid subtypes as sarcomatoid subtypes do not shed fluid into the pleural effusions. The American Society of Clinical Oncology practice guidelines published in 2018 by Kindler *et al*. recommend that cytologic evaluation can be an early screening test for mesothelioma but argued against its use as a diagnostic test due to lack of sensitivity (11). Loss of BAP1 and/or deletion of p16 seen in mesothelioma, but not reactive mesothelial cells, could be a useful adjunct for cytologic diagnosis (12).

Core needle biopsy is an option for diagnosis. Image-guided core needle biopsy using ultrasound or CT can have a sensitivity of 77–88% with a needle track seeding rate of 0–4% (13-15). In patients with easily accessible pleural masses or who are higher risk for thoracoscopic biopsy, image-guided core needle biopsy is an appropriate first step. Fine needle biopsy has a sensitivity of only 30% and is not recommended (16).

Thoracoscopic biopsy remains the gold standard for obtaining tissue diagnosis for mesothelioma. It offers advantages over core needle biopsy such as the ability to gather more tissue for evaluation, ability to assess resectability by analyzing invasion and disease extent, and it affords the ability to perform talc pleurodesis to mitigate recurrent pleural effusion (17). VATS pleural biopsy has a sensitivity of 95%, specificity of 100%, and NPV of 94% (18). This is similar to medical pleuroscopy/thoracoscopy, although data directly comparing the two is lacking and there likely isn't a significant difference. Thoracoscopy under purely local anesthetic is a feasible option and pooled evaluation from 1,369 patients from 22 studies by Rahman *et al*. showed a sensitivity of 92% for diagnosing malignant pleural disease (19). A randomized

controlled trial involving 58 patients by Haridas *et al.* showed that medical thoracoscopy had a diagnostic yield of 86% with a complication rate of 10% compared to 62% and 17% respectively for closed Abram needle biopsy (20). Whenever VATS biopsy is performed, incision planning should be performed with possible surgical treatment in mind, and it is generally recommended that the VATS incisions should be performed in line with future thoracotomy sites (21). Tumor spread at resected previous incisions has been described as a negative prognostic indicator for long term survival (22). Occasionally, due to an obliterated pleural space from advanced disease, a muscle-spearing incision within an intercostal space must be used for an open pleural biopsy.

Determining nodal status prior to operative intervention remains a challenge in MPM. Rice *et al.* compared cervical mediastinoscopy with endobronchial ultrasound (EBUS) with or without esophageal endoscopic ultrasound (EUS) (23). In examining 85 patients who underwent mediastinoscopy and/or EBUS, they found that mediastinoscopy had a sensitivity of 28% and negative predictive value (NPV) of 49%, whereas EBUS had a sensitivity of 59% and NPV of 57%. Eleven patients had EUS due to clinical suspicion on CT or PET, of whom infradiaphragmatic nodal metastases were identified in 5. Czarnecka-Kujawa *et al.* examined 48 patients who underwent EBUS only, have found a sensitivity of 16.7%, specificity of 100%, positive predictive value (PPV), and NPV of 70.6% (24). In their group, preoperative mediastinal lymph node staging prevented surgical resection in 18.8% by detection of N2 or N3 disease under the 7th edition IMIG staging system. As with lung cancer, tissue-based mediastinal lymph node evaluation prior to surgical resection should be strongly considered based on clinical suspicion.

Blood based biomarkers have only a limited utility in the diagnosis of MPM presently. Mesothelin is a cell-adhesion glycoprotein typically over-expressed in MPM (25). Mesothelin levels in the serum are elevated in patients compared to control patients with a history of asbestos exposure. Epithelioid tumors are more likely to express mesothelin compared to tumors with sarcomatoid sub-types, which rarely express it. In a meta-analysis by Hollevoet *et al.* of 4,491 patients of whom 1,026 had MPM, the sensitivity of serum mesothelin was 32% with a 95% specificity (26). In another meta-analysis by Cui *et al.*, pleural fluid mesothelin had a sensitivity of 61% and specificity of 87% (27). Serum mesothelin is not used frequently but when elevated should prompt further workup, although a negative test should be regarded skeptically. There has been some interest in using serum mesothelin as a screening tool in asbestos-exposed populations, but prospective studies have failed to demonstrate value for this (26,28,29). Soluble mesothelin-related protein (SMRP) is another plasma biomarker that is FDA approved for diagnosis of MPM, and other biomarkers such as megakaryocyte potentiating factor (MPF), osteopontin, fibulin-3, calretinin, and High-Motility Group Box 1 (HMGB1) are under investigation (30,31).

### *Volumetric staging*

Though cTNM staging is the current modality by which we assess MPM patients it has been shown to be unreliable and suboptimal. In a study of 472 patients cTNM and pTNM were concordant in 36.2% with 44.2% and 19.4% of patients being overstaged or understaged respectively (32). A possible alternative suggests the utilization of volumetric analysis of the patient's CT scan, VolCT. VolCT involves the creation of a 3D model of tumor burden derived from data acquired from CT scans (32). VolCT was shown to have better correlation between different radiologists than cTNM (33). VolCT was also shown to have improved prognostic performance when compared to cTNM (P=0.001) (32).

## Image modalities for diagnosis and staging

With the staging parameters in mind, the importance of imaging in the non-invasive staging of MPM becomes paramount. As with most solid malignancies, imaging provides crucial information for determining the extent of disease.

CT is the most commonly and widely using imaging modality for the diagnosis and staging of mesothelioma. Unilateral pleural effusion, pleural thickening, and invasion of structures such as the chest wall or mediastinum are the usual findings. Limitations of CT imaging include difficulty estimating chest wall and mediastinal invasion and involvement of the peritoneal cavity. An additional limitation is that CT imaging cannot often differentiate between pleural effusion secondary to benign or malignant causes. Involvement of lymph nodes is also difficult to estimate with CT scan alone.

In 1990, Kawashima *et al.* wrote a pictorial essay that examined the pretreatment CT findings of 50 patients

(mostly men) with MPM (34). The most common CT images that group found included in order of decreasing frequency: pleural thickening (92%), thickening of the interlobar fissure (86%), unilateral pleural effusion (74%), thoracic lymph nodes 1 cm or larger in maximum diameter (58%) contraction of the involved hemithorax (42%), pleural calcification (which is not a manifestation of mesothelioma, but one of benign asbestos exposure) (20%), chest wall invasion (18%), contralateral mediastinal shift (14%), direct retroperitoneal invasion (8%), pericardial effusion (6%), and extension of tumor to the contralateral hemithorax (4%). Sahin *et al.* in 1993 examined 82 patients in Turkey with MPM and history of exposure to asbestos or zeolite and reported similar CT findings and frequency including pleural thickening, nodules, or masses (100%), mediastinal pleural involvement (93%), involvement of intralobar fissures (76%), volume contraction of the involved hemithorax (73%), pleural effusions (73%), pleural calcifications (62%), contralateral hyaline plaques (26%), rib erosion (19%), and pneumothorax (4%) (35).

Whenever the above findings are found without an explanation, suspicion must be raised for MPM, even with negative cytologic findings (36). It is difficult to differentiate MPM from other malignancies or even benign disease based only on the above findings, however. There is the risk for false positive cases such as biopsy proven disease in a patient who is very unlikely to have mesothelioma such as a young woman with a spontaneous pneumothorax. Results should be analyzed critically with patient specific information in mind. Leung *et al.* analyzed 74 patients (39 malignant, 35 benign) and found that patients with malignant pleural disease were more likely to have circumferential pleural thickening or rind (sensitivity 41%, specificity 100%), nodular pleural thickening (sensitivity 51%, specificity 94%), parietal pleural thickening of more than 1 cm (sensitivity 36%, specificity 94%), and mediastinal pleural involvement (sensitivity 56%, specificity 88%) (37). That group found all of those features were significantly more common in patients with malignant rather than benign pleural thickening. Certain infectious processes such as actinomycosis, tuberculosis, and nocardiosis can invade the chest wall, but usually do so in a single area rather than in multiple areas (38).

Positron emission tomography (PET) has an important role to play in the staging of MPM and should be used routinely. PET utilizing fludeoxyglucose (FDG) is the most commonly studied and used radionuclide imaging agent for mesothelioma and most thoracic malignancies

and is a powerful diagnostic tool (39). MPM usually shows intense FDG uptake that matches the thickened pleura seen on CT or MRI. It will also demonstrate involvement of the chest wall, fissure, and lymph node metastases. In a study by Bénard *et al.* in which 28 patients received FDG-PET followed by thoracoscopy, they demonstrated excellent overlap/matching between the burden of disease seen on PET and the burden of disease found on thoracoscopy, although in two cases FDG-PET significantly underestimated the burden of disease (one epitheloid, one biphasic) (39). Overall, they demonstrated that FDG-PET had a sensitivity of 92% and specificity of 75% for demonstration of malignant disease. They also performed semiquantitative analysis of 26 of their subjects and concluded that an SUV >2.0 was a reasonable cutoff to distinguish between malignant and benign pleural disease, with a sensitivity of 91% and a specificity of 100%. Another study by Yildirim *et al.* demonstrated similar findings, evaluating 31 patients with pleural disease (17 MPM, 14 benign), and finding that FDG-PET had a sensitivity of 88% and specificity of 93% for malignant disease and was able to identify 13 out of 14 cases of benign disease (40). If correlated with patient specific information such as exposure history these metrics may improve further. Their mean SUV values were 6.5±3.4 for MPM cases and 0.8±0.6 for benign pleural diseases. Their analysis showed an SUV cutoff of 2.2 with a 94% sensitivity and 100% specificity. For post-surgery surveillance, FDG-PET may also be superior to contrast-enhanced CT for demonstrating recurrence and may have an impact on treatment algorithms (41).

Though not routinely utilized in surgical trails due to the requirement of an experienced radiologist, the role of MRI in diagnosis of MPM is primarily focused on determining resectability. MRI enables differentiation of tumor from normal adjacent tissue by using different pulse sequences and imaging in multiple planes but due to the motion of heart and breathing muscles, cardiac gating and respiratory compensation should be utilized (42,43). MPM shows moderately increased signal on T2-weighted images that can be helpful for differentiation. Use of gadolinium-based IV contrast may also be helpful by increasing enhancement and contrast enhanced T1 fat-suppressed sequences are sensitive for detecting enhancement of the interlobar fissures and tumor invasion of surrounding structures (36,44). MRI is superior to CT in terms of evaluating invasion of the diaphragmatic muscle (accuracy 0.82 *vs.* 0.55) and endothoracic fascia or single chest wall focus (accuracy

0.69 *vs.* 0.46) (43). PET MRI may also play an increased role in the future to help more accurately stage patients particularly regarding their T stage, although widespread availability is likely the biggest limiting factor (45,46).

Ultrasound has a limited role to play in the diagnosis of MPM but may be one of the first tests performed by a bedside physician when assessing a pleural effusion of unknown origin. Ultrasound can be used to assess volume and location of pleural fluid, nodular pleural thickening, irregular thickening in the fissures, or a localized mass (25). Pleural thickening greater than 1 cm, nodular pleural thickening, pleural-based masses, and diaphragm nodules or thickening greater than 7 mm should all raise the suspicion for malignancy. In a series of 52 patients with suspected malignant pleural effusions, Qureshi *et al.* report a sensitivity for ultrasound of 73%, specificity 100%, PPV 100%, NPV 73% for diagnosis of malignant disease (47). When ultrasound raises concern for MPM, cross sectional imaging and biopsy should be performed. Ultrasound can play a key role in image-guided thoracentesis for cytology of malignant effusion or core needle biopsy of suspicious pleural-based lesions.

## Conclusions

MPM is a complex disease that causes significant morbidity and mortality and remains a challenging disease to diagnose and stage accurately, particularly as the different subtypes can behave differently. Nevertheless, accurate diagnosis of subtypes and diligent staging are important for making treatment decisions. Clinicians must also be mindful of how their diagnostic techniques may affect future treatment options. Higher resolution diagnostic imaging combined with functional imaging will likely play a greater role in future diagnosis and staging, and future updates to the staging system may incorporate some of this tumor thickness or volumetric data.

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