Malignant pleural mesothelioma: predictors and staging

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Abstract: Malignant pleural mesothelioma remains a rapidly fatal cancer with few effective therapies. Unusual anatomic features complicate determination of stage and prognosis for individual patients. Validation of staging criteria has been difficult given the rarity of the disease and the fact that only a minority of patients undergo surgical resection with pathological examination of their tumors. Thus, additional heuristic factors and algorithms have been taken into account by clinicians to estimate prognosis and inform discussion of appropriate management strategies or clinical research protocols with patients.

Keywords: Mesothelioma; prognosis; staging

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Tumor staging refers to malignancy-specific algorithms that categorically classify individual patients' tumors according to their state of progression through the typical natural history of the disease. Stage classification reflects anatomical properties of the malignancy observed at a point in time, including the size of the primary tumor, its direct invasion through specific tissue planes into adjacent structures or organs, and metastatic dissemination via the lymphatic or systemic circulation to form satellite lesions. If feasible, criteria for combining these observations to establish stage are organized in a tumor-node-metastasis (TNM) framework.

Staging serves the purposes of estimating prognosis, assessing risks and benefits of specific therapies, and selecting or stratifying homogeneous cohorts of patients to study in clinical trials. A half-century ago, Feinstein (1) recognized that anatomical staging alone may be insufficient to fully classify certain tumors for these purposes, as it neglects orthogonal and potentially informative dimensions such as tumor growth over time (indolent to aggressive) and the presence and severity of clinical symptoms. The ensuing decades have seen the development and periodic revision of international consensus staging systems which for most solid tumors [including malignant pleural mesothelioma (MPM)] remain based exclusively on anatomical criteria. However, there has been increasing recognition of the utility and importance of demographic, historical, clinical, molecular, immune and other factors, particularly for malignancies such as MPM for which the prognostic and predictive accuracy of anatomical staging are limited. Therefore, this review considers separately the topics of MPM staging and prognostic/predictive factors, models and biomarkers in relation to current and emerging therapeutic approaches to MPM.

MPM staging

A number of independent staging systems for MPM have been proposed that differ by format and the significance attributed to specific classification criteria [for review, see reference (2)]. Each of the proposed staging systems was derived based on analyzing series of surgically resected cases of MPM. Disappointingly, none stratifies patient outcome accurately enough to provide useful prognosis for individual patients, to guide therapeutic choices, or to select homogeneous cohorts for clinical trials. Efforts to improve MPM staging have been impeded by the rarity of the disease, the complexity of its assessment and the general ineffectiveness of available therapy.

Pathological staging

Pathological staging classifies cases based on gross and microscopic analyses of pathological specimens from surgical resection. TNM criteria for MPM first appeared in the 4th edition Cancer Staging Manuals published by the International Union Against Cancer (UICC) (3) and The American Joint Committee on Cancer (AJCC) (4). The International Mesothelioma Interest Group (IMIG) proposed modifications to classification and stage grouping criteria (5) that were adopted by the AJCC and UICC and have since remained the international standard for MPM staging.

According to AJCC/UICC criteria, T classification is determined based on the extent of tumor invasion within the pleurae and into adjacent thoracic structures. T1 tumors are those that remain confined to unilateral pleural surfaces. The T2 classification includes tumors that have extended to involve interlobar fissures, lung parenchyma or diaphragm muscle. T3 tumors involve endothoracic fascia or mediastinal adipose tissue, extend into but not through the pericardium, or invade chest wall soft tissue at a single focus. T4 includes tumors with diffuse or multifocal chest wall soft tissue involvement, invasion of brachial plexus, bony components of chest wall or spine, mediastinal organs, contralateral pleura, or extension through diaphragm or pericardium. Unlike TNM staging of most solid tumors, criteria for T classification of MPM do not include consideration of tumor size, due to the impracticality of measuring tumors with irregular and highly variable morphology.

N classification of MPM follows the lung cancer map (6), which assumes that tumors invade pulmonary lymphatics that drain predictably and progressively through intraparenchymal and ipsilateral hilar lymph nodes (classified N1) to ipsilateral and midline mediastinal nodes (classified N2), and finally to contralateral and extrathoracic stations (classified N3). The lung map does not account for some nuances of MPM nodal invasion, however. For example, although MPM that is invasive from visceral pleura into pulmonary parenchyma may follow this metastatic pattern, direct lymphatic drainage from the diaphragmatic pleura to the mediastinal nodal chain has also been demonstrated (7) probably accounting for N2 nodal disease observed without evident N1 involvement in approximately 40% of patients (8-10). Although some studies have demonstrated worse prognosis for N2 than N1 (10,11), current TNM grouping criteria do not distinguish N1 from N2 involvement, each determining at minimum stage III. Indeed, the distinction may be rendered moot with the increasing application of lung-sparing surgery, where intrapulmonary nodal sampling is not generally undertaken. Nevertheless, evidence-based proposals have been made to refine N classification considering combined N1 and N2 involvement versus N1-only or N2-only disease (12), the number of involved nodes (8) or nodal stations (10), or the specific mediastinal stations involved (11).

M classification of MPM is binary. M1 indicates documented blood-borne metastasis. Distant metastases to brain, bone, kidney and adrenal glands have been documented (13), but are only rarely diagnosed (14), likely due to the comparatively rapid and fatal progression of local T4 disease involving vital intrathoracic organs.

The International Association for the Study of Lung Cancer (IASLC) staging committee is tasked with recommending data-driven adjustment of TNM classification and staging criteria for MPM in future AJCC/UICC editions. The committee's approach has been to assemble an international database of MPM cases to support evidence-based recommendations. An initial phase of the analysis focused on pooling existing retrospective databases representing series of patients managed surgically at participating institutions, and essentially confirmed in a large international cohort the practical inadequacy of current staging criteria for MPM (15). The second phase of the IASLC Mesothelioma Staging Project is based on a database of prospective cases, and has resulted in published recommendations for adjustments to criteria for the upcoming 8th edition (16).

Clinical staging

Clinical staging of MPM typically involves radiographic assessment of TNM classification criteria using chest computed tomography (CT), magnetic resonance imaging (MRI), and/or fluorodeoxyglucose positron emission tomography (FDG-PET) (17).

Imaging studies effectively identify areas of apparent extrathoracic tumor, indicating M1 disease and excluding consideration of primary surgical resection. However, among patients with radiographically localized MPM, clinical staging of MPM lacks accuracy to predict either patient outcome or pathological T or N status (18). In particular, significant understaging by clinical (relative to pathological) assessment has been documented (15,19).

Overstaging has also been observed, but less commonly.

Chest CT

Based on considerations of availability and cost (20), CT is the most commonly used imaging modality to initially determine potential resectability by ruling out contralateral or distant metastasis, diffuse involvement of chest wall or direct tumor extension into the abdomen. Published guidelines for clinical workup of MPM patients recommend only CT beyond history, physical, and chest X-ray (21). However, CT is insensitive to detect focal tumor invasion of chest wall, pericardium, diaphragm, mediastinum or intralobar fissures as required for accurate T classification (22,23). Clinical determination of N status based on CT is similarly inaccurate with apparent lymphadenopathy being essentially uncorrelated with pathologically-proven nodal metastasis (24,25). Nodal enlargement is neither sensitive nor specific as an indicator of metastatic involvement, and nodal stations such as hilar and internal thoracic are difficult to distinguish from adjacent primary tumor on CT (24,26). Inter-observer variability with respect to staging parameters is also problematic. In a recent multi-institutional study (27), institutional radiologists understaged cases using CT relative to pathological findings, and two experienced reference radiologists who performed central review differed substantially on CT-based clinical staging.

FDG-PET

FDG-PET is an effective modality for identifying patients who may have metastasis to lymph nodes or extrathoracic sites (28-31). In particular, integrated PET-CT has been found to provide modest improvement to staging accuracy relative to CT, particularly for detection of T4 (32). PET-CT also detects mediastinal lymph node involvement with 75% specificity (but only 50% sensitivity) (33). PET-CT may be more accurate and less variable compared to CT for predicting AJCC/UICC pathological stage following induction chemotherapy (34). A consensus statement from the Austrian Mesothelioma Interest Group recommends that both CT and PET-CT have value for MPM staging (35).

Interestingly, the maximal standard uptake value (SUVmax) of the primary tumor correlates with the likelihood of nodal metastasis (30), but not with T classification (33). Given that SUVmax was found to be independently prognostic in a multivariate analysis accounting for TNM stage (36), the utility of FDG-PET may be more evident in prognosis, whereas accuracy, availability and cost considerations may limit its utility for staging per se.

It should be noted that if patients have previously undergone talc pleurodesis, interpreting FDG-PET results is difficult, because areas of PET-avid granulomatous talc reaction may be mistaken as evidence of tumor (37-39) or attributed undue prognostic significance (40).

MRI

MRI has been found more accurate than CT for distinguishing MPM from chest wall muscle and benign pleural disease (41), and to evaluate diaphragmatic invasion (42). Recently published early experience with sequential co-registered PET-MRI for local staging of MPM has been encouraging (43), although availability and cost may inhibit the routine use of these technologies for clinical MPM staging.

Surgical staging

Surgical staging has been used by some groups to detect metastatic disease that would preclude surgical resection and may be missed by imaging. Some authors have argued for surgical staging as a gold standard pre-operative assessment (44). Zielinski and colleagues used aggressive surgical staging to demonstrate that among 18 patients with clinical stage I or II MPM based on CT, 8 had involved mediastinal nodes, 8 had abdominal dissemination, and one had chest-wall invasion (45).

Cervical mediastinoscopy is a critical component of pre-surgical staging of non-small cell lung cancer. However, it has limited sensitivity for N2 classification of MPM because multiple relevant nodal stations are not accessible by the procedure. Although some reports find mediastinoscopy more accurate than CT for determining mediastinal lymph node involvement (25), others report sensitivity as low as 36% (46). Routine mediastinoscopy continues to be recommended for patients with epithelioid tumors (8,24), in accordance with the poor prognosis of patients with epithelioid histology tumors and nodal metastasis to superior N2 or N3 stations (11). Despite the well-documented prognostic value of pathological lymph node status, the mediastinoscopy result unfortunately does not accurately predict patient outcome after surgery (9).

Additional minimally invasive surgical assessment may be

helpful for preoperative identification of advanced disease. For example, one study reported that in 20% of cases, disease extension beyond the ipsilateral hemithorax that had not been detected by CT, MRI, or PET was discovered using a combination of mediastinoscopy, contralateral thoracoscopy and laparoscopy (47). Varying combinations of esophageal ultrasound (EUS), endobronchial ultrasound (EBUS) (10,45,48), mediastinoscopy or transcervical extended mediastinal lymphadenectomy, and laparoscopy with abdominal lavage (45,46) have also been recommended.

In summary, the accuracy and reproducibility of TNM staging for MPM are impeded by lack of a quantitative measure reflecting tumor size, the number and complexity of T classification criteria, the vital nature (and thus pathologic inaccessibility) of many relevant margins and the increasing tendency to employ lung-sparing surgical procedures that leave many margins and lymph nodes unassessed. These facts led the IASLC staging committee to propose the concept of a "best" stage (bTNM) that combines available staging data obtained from multiple assessments (clinical, surgical, pathological) to mitigate incomplete data and improve TNM performance (15). Efforts are underway to further refine criteria (49-51) and to validate 3-dimensional quantitative estimates of tumor size to potentially augment T classification (27,52) in future editions of the staging system.

Prognostic/predictive factors, models and biomarkers

Multiple clinical prognostic indicators may provide additional risk discrimination independent of anatomical stage. In general, such factors have been employed empirically by clinicians to augment stage in support of clinical decision making and patient counseling. Several multivariable models that combine and weight multiple factors have been proposed, and in some cases independently validated.

Tumor histology

The World Health Organization (53) distinguishes three major histological subtypes of MPM: epithelioid, sarcomatoid and biphasic (comprising both epithelioid and sarcomatoid elements). The distinction between epithelioid and non-epithelioid (sarcomatoid or biphasic) histology is the single most consistently reported prognostic factor, regardless of stage or treatment. Patients with epithelioid tumors have the more favorable outlook in terms of clinical course, tumor growth rate, resectability, severity of symptoms, responsiveness to chemotherapy, time to progression/recurrence and overall survival. Among 5,038 MPM cases in the SEER database with reported subtype, 65% were epithelioid, 13% were biphasic and 22% were sarcomatoid (54). Because regional heterogeneity of biphasic tumors results in low sensitivity of pleural biopsy to detect non-epithelioid disease (55), SEER data may overestimate the proportion of epithelioid tumors. Only 23% of patients underwent any cancer directed surgery and fewer still would have had definitive surgical resection and pathological determination of histology (54). There is mounting evidence based on comprehensive molecular profiling that MPM may self-sort into four subgroups roughly corresponding to the spectrum of histology and reflecting expression of biomarkers related to epithelial-mesenchymal transition (56).

The widely divergent clinical behavior and biology of epithelioid and non-epithelioid MPM have led some authors to advocate that staging and other prognostic criteria may need either to be specified separately or to otherwise account for histology. For example, analysis of prognosis in relation to TNM staging criteria considering epithelioid (11) and biphasic (57) histology separately reveals that among epithelioid tumors, patient survival is significantly related to both T- and N-status, whereas among biphasic tumors, OS is more strongly driven by T-status. Nodal metastasis is rarely if ever observed among sarcomatoid tumors.

Patient factors

Multiple demographic, historical, and clinical factors apart from histology have been reported to have prognostic relevance for patients with MPM. Factors portending poor prognosis include poor performance status (58-61), advanced age, male sex (15,54,58,59,62-64), preoperative anemia (65,66), high white blood cell count (58,66), high platelet count (66), weight loss (59,61,66), chest pain (59,66), low serum albumin (61,67) and high neutrophil/lymphocyte ratio (68,69).

Functional imaging

High metabolic activity associated with the primary tumor at diagnosis has been correlated to shorter OS. Benard and colleagues (70) found that SUVmax cut at the median value of 4 was associated with OS among 17 patients with MPM,

although high SUVmax patients also had predominantly non-epithelioid tumors, confounding interpretation. Flores and colleagues (30,36,71) have reported that SUVmax and histologic subtype were independently prognostic, although subsequent work supports an association of very high SUVmax (>10) with pleomorphic epithelioid and non-epithelioid histology (72). Among patients who have undergone surgical resection, higher tumor SUVmax observed at the time of tumor recurrence has been associated with shorter subsequent OS (73).

Diffusion-weighted MRI can quantitatively predict biphasic histology (74). Higher apparent diffusion coefficient values are associated with epithelioid histology, while lower values are indicative of non-epithelioid tumor. In particular, diffusion-weighted MRI may be helpful to guide biopsy in areas of suspected sarcomatoid differentiation.

Type of treatment

Several large studies report on the association of specific therapeutic interventions with prognosis. Application of cancer-directed surgery, but not radiation therapy, is associated with good prognosis among 14,228 cases in the SEER dataset (54), as is curative- (*vs.* palliative-) intent surgery among surgical patients constituting the IASLC dataset (15). Nakas (64) identified neoadjuvant or adjuvant chemotherapy as factors independently associated with favorable prognosis among 252 surgically treated (extrapleural pneumonectomy or extended PD) patients, as did Bovolato and colleagues (19) in a retrospective analysis of 1,227 surgical and non-surgical cases from six institutions. When interpreting such studies, it is important to acknowledge the potential influence of selection bias (i.e., that patients who undergo surgery, chemotherapy or radiation therapy, by virtue of being fit enough to do so, may have better prognosis than those that do not, independent of any anti-tumor effect of the therapy) and guarantee time bias (i.e., that patients who die soon after diagnosis, before therapy can be delivered, will always be counted in the "No Treatment" group, regardless of treatment efficacy).

Tumor size

Similar to many solid tumors, the size of an MPM tumor is prognostic, but is challenging to measure. The prognostic value of tumor volume, estimated from 3-dimensional reconstruction of CT scans (27,65,75) or measured directly as fluid displacement by pleurectomy specimens (76), has been established. Prognosis attributed to "glycolytic volume", a hybrid metric that weights radiographic volume by FDG-PET SUV (40), likely derives in significant part from tumor volume itself, because SUV alone was not found to be independently prognostic. As an anatomical attribute of the tumor, tumor size technically should constitute an element of staging. Efforts are underway to determine the feasibility of incorporating tumor volume into future editions of staging systems (27,52), but meanwhile, tumor size measurements remain useful to augment staging based on current criteria when estimating prognosis.

Molecular classification

The advent and clinical validation of high-throughput platforms for molecular analysis has provided the potential for assessment of immune (77) and molecular (78) biomarkers relevant to response prediction and prognosis. These assays often can utilize specimens obtained using percutaneous or endoscopic fine-needle biopsies (79,80). Such minimally-invasive procedures, while applicable to a broader proportion of patients with MPM, yield specimens that usually are inadequate for pathologic prognostic assays that require intact tissue architecture, such as determination of histological subtype or evaluating prognostic immunohistochemical markers such as merlin and survivin (81) or CD9 (82). Some tumor-related mutations and expression levels of specific genes are associated with known prognostic factors such as histology and sex (82,83). In addition, though, molecular analysis may have sensitivity to detect prognostic features of the tumor that are orthogonal to established factors. For example, tumors that are classified histologically as epithelioid cluster into several subgroups that are associated with distinctly different patient prognosis, based on expression levels of genes related to epithelial-mesenchymal transition (56).

Prognostic models

A number of distinct prognostic classification systems have been proposed, reflecting the variety of patient populations observed, treatment strategies applied and statistical modeling approaches taken. For example, two long-standing prognostic MPM classifiers based on, and therefore specific to, patients enrolled on clinical trials of chemotherapy were derived by the EORTC (58) and the CALGB (59). Both

systems were subsequently validated in similar (i.e., enrolled on chemotherapy clinical trials) patient cohorts (84,85). Performance status, a strong driver of both classifiers, is less relevant for patients undergoing surgery-based therapy, for which marginal functional status would be a disqualifier.

For patients undergoing surgical therapy, the IASLC Staging Committee derived a prognostic classifier based on analysis of a large international database. The model identified sex, age, histology, "best" TNM stage, and palliative vs curative intent surgery as independently prognostic (15). Further analysis of the same dataset identified additional prognostic factors including weight loss, chest pain, low hemoglobin, high platelet and white blood cell counts that were found to independently contribute to poor prognosis when added to the baseline model (66). Opitz and colleagues (86) proposed a prognostic score that is specific to patients undergoing neoadjuvant platinum-based chemotherapy followed by surgery, as objective response to neoadjuvant chemotherapy constitutes a component of the score.

Several proposed prognostic models target specific histological subgroups. A prognostic nomogram that considers weight loss and glycolytic volume (PET SUV integrated with tumor volume) is proposed for prognosis of patients with non-sarcomatous tumors undergoing chemotherapy (40). Gill and colleagues found CT-derived tumor volume and preoperative anemia to be independently prognostic among surgically-treated patients with epithelioid tumors (65).

Among prognostic models derived in unselected cohorts, some include application of specific therapies as factors and as such are potentially subject to aforementioned interpretive biases (19), whereas others focus exclusively on patient factors (61).

Predictive models

Bille and colleagues (60) found that for patients with unresectable MPM, epithelioid histology, good performance status and elevated lymphocyte count at diagnosis were associated with clinical benefit from 1st line chemotherapy.

Summary

MPM presents significant challenges to meaningful classification by anatomical staging systems such as TNM. Determining and validating reliable indicators of disease course, efficacy of particular therapeutic options, and expected overall survival has been hampered by the relative rarity and anatomical complexity of the disease. Historical, demographic, clinical, and pathological factors can improve prognostic assessment of patients in cases where staging information is equivocal or unavailable. However, prognostic algorithms involving these parameters tend to be developed and validated in the context of specific management strategies, and accordingly exhibit substantial variability. To date, no consensus approach has emerged to effectively classify, prognosticate and rank management options within unselected populations of patients with MPM.

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Footnote

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