# The Staging of Malignant Pleural Mesothelioma

Caleb J. Euhus, MD, R. Taylor Ripley, MD*

**KEYWORDS**

• Staging • Malignant • Pleural mesothelioma • Lung cancer

**KEY POINTS**

- Malignant pleural mesothelioma (MPM) is an extensive tumor that spreads along the pleura and encases the lung. MPM spreads to pulmonary, mediastinal, and chest wall lymph nodes and occasionally to distant organs.
- Patients present at different times along this progression of disease, which is represented in the staging system for MPM.
- Based on the difficult of diagnosis and other tumors that mimic MPM, the staging system for MPM developed slowly until recently.

## INTRODUCTION

Malignant pleural mesothelioma (MPM) is an extensive tumor that spreads along the pleura and encases the lung.[1] Initially, MPM forms small, independent nodules on the parietal pleura surface that convalesce into confluent sheets of tumor. The pleural space becomes obliterated and filled with effusions. As the tumor progresses, it invades chest wall, diaphragm, and pericardium as locally advanced disease. MPM spreads to pulmonary, mediastinal, and chest wall lymph nodes and occasionally to distant organs. Patients present at different times along this progression of disease, which is represented in the staging system for MPM.

Advances in staging of MPM have been hampered by the disease's rarity, late clinical presentation, and the nihilism secondary to poor outcomes regardless of treatment. Surgeons in the mid–twentieth century rarely encountered this disease. Patients who were evaluated usually presented in cardiopulmonary failure caused by complete encasement of all pleural surfaces. Despite Wagner and colleagues[2] establishing a link between asbestos exposure and a fatal cancer of the pleural in 1960, the histologic similarities between epithelial MPM and other diagnoses challenged pathologists and therefore delayed systematic staging.[3,4] Both primary and metastatic tumors of the pleural surface can mimic the pattern of spread of MPM. Lung adenocarcinoma can metastasizes along the pleura.[5] Extrathoracic primary tumors can metastasize to the pleura.[6] Epithelioid hemangioendothelioma is a rare tumor that closely mimics MPM.[7] Similarly, primary carcinoma and sarcoma originating from the pleura can occur. Based on the difficult of diagnosis and other tumors that mimic MPM, the staging system for MPM developed slowly until recently.

Before 1990, at least 5 staging systems were proposed for MPM: Butchart, Mattson, Sugarbaker, Chahinian, and the American Joint Committee on Cancer (AJCC).[8–13] These classification systems were mainly derived from single institutions, based on few cases, and were not externally validated. Whether tumor, node, and metastasis (TNM) descriptors were the basis for stages I through IV was variable. The systems were rarely applied, which hindered evaluation of whether they correlated well with patient survival.

In 1994, the International Association for the Study of Lung Cancer (IASLC) sponsored a workshop in London called the International

Department of Surgery, Division of General Thoracic Surgery, The Michael E. DeBakey Department of Surgery, Baylor College of Medicine, Houston, TX 77030, USA
* Corresponding author.
*E-mail address:* R.Taylor.Ripley@bcm.edu

Thorac Surg Clin 30 (2020) 425–433
https://doi.org/10.1016/j.thorsurg.2020.07.001

Mesothelioma Interest Group (IMIG).[8] This gathering of pulmonologists, thoracic surgeons, oncologists, epidemiologists, radiologists, pathologists, and laboratory scientists analyzed all of the available trials, reports, and databases covering MPM to create a universal staging system based on TNM descriptors. The proposed system was accepted by the Union for International Cancer Control (UICC) and AJCC as the international MPM staging system for the sixth and seventh editions of the staging manuals (Table 1). Shortly after it was adopted in 1996, the IMIG system was validated in 2 surgical series of MPM. Afterward, this system was applied to both retrospective series as well as prospective clinical trials.[14,15]

The system proposed by IMIG offered an international consensus for the staging of MPM but it still had several weaknesses. First, the system was derived from small studies with few patients. Second, most of series used in the system came from surgical reports; therefore, applying it to patients managed nonoperatively was difficult. Also, the type of operation performed for the disease influenced a patient's stage. Third, the system classified nodal disease based on lung cancer staging. Given that the nodal spread of MPM behaved differently than lung cancers, the usefulness of lung cancer staging for MPM was questionable even at the time of this proposal.

To further refine the IMIG 1994 staging system, IASLC and the Staging and Prognostic Factors Committee (SPFC) formed a database to collect anonymized MPM surgical cases. This effort was an international, multi-institutional cohort study that established a detailed database with broader representation of treatment modalities, new terminology, and an electronic data capture system. Cases with complete anatomic stage information, complete survival information, and diagnosis of MPM met eligibility criteria. Both clinical and pathologic staging information was obtained. Best stage was defined as pathologic stage when available after surgical resection; otherwise, clinical stage was considered as best stage. For patients who receive neoadjuvant chemotherapy, normally, the pathologic stage is denoted ypTNM, in which the y descriptor indicates the surgery was performed after chemotherapy. For the purposes of this study, only clinical staging was analyzed and ypTNM staging was not considered in these reports.

Surgeons from around the world leading programs with a high volume of patients with mesothelioma transferred data to the statistical center, Cancer Research and Biostatistics (CRAB), in Seattle, Washington. CRAB provided the biostatistical support for the analysis. Data for 3101 patients from 15 centers were collected from 1995 to 2009 and first published in 2012.[16] Data collection continued and ultimately 3519 cases from 29 centers on 4 continents were uploaded from January 1995 until June 2013. Cases after June 2013 were excluded to allow a minimum potential follow-up of 18 months by the time of analysis. The data were retrospectively added to the database for 1953 (55%) of the patients and prospectively collected for 1566 (45%) of the patients. Of the 3519 patients, 2460 passed the initial screening based on appropriate data elements and these patients were analyzed for the 2016 IASLC mesothelioma project. From this effort, formal revisions to the T, N, and M descriptors for the eighth edition of the TNM classification system were published. The most recent revisions are discussed later.

## DISCUSSION

### *T Descriptors for Malignant Pleural Mesothelioma*

The T descriptor in other solid tumors is often based on measurement of a concentrically growing primary lesion, which is prognostic of overall survival (OS). MPM's unusual rindlike growth pattern makes measurement for the T category difficult to generate. Therefore, the T category is based on spread from the pleura into other thoracic structures. In the eighth edition of the TNM classifications for pleural mesothelioma, T1 denotes disease limited to the ipsilateral pleura regardless of whether the involvement entails the parietal, visceral, diaphragmatic, or mediastinal pleura (Table 2). T2 signifies tumor of the pleural surfaces on the ipsilateral side in addition to involvement of the diaphragm muscle and/or extension into the pulmonary parenchyma. T3 involves invasion of all of the ipsilateral pleura but also has involvement of the endothoracic fascia, extension into the mediastinal fat, solitary resectable disease extending into the soft tissue of the chest wall, and/or nontransmural involvement of the pericardium. T4 involves all ipsilateral pleural surfaces with 1 or more of the following: diffuse extension or multifocal masses of tumor in the chest with or without rib destruction, direct transdiaphragmatic extension into the peritoneum, direct extension of tumor to the contralateral pleura, direct extension of tumor to mediastinal organs, tumor into the spine, and/or tumor extending through the internal surface of the pericardium with or without pericardial effusion with or without myocardial involvement. T3 disease is considered resectable, whereas T4 disease is considered unresectable. The IASLC mesothelioma project

**Table 1**
**The 1995 international staging system for mesothelioma**

| Stage | Description |
|---|---|
| T1 | T1a; tumor limited to the ipsilateral parietal pleura, including mediastinal and diaphragmatic pleura. No involvement of visceral pleura<br>T1b: tumor involving the ipsilateral parietal pleura, including ipsilateral and diaphragmatic pleura. Scattered foci of tumor also involving the visceral pleura |
| T2 | Tumor involving each of the ipsilateral pleural surfaces (parietal, mediastinal, diaphragmatic, and visceral) with at least 1 of the following features:<br>• Involvement of diaphragmatic muscle<br>• Confluent visceral pleural tumor (including the fissures) or extension of tumor from visceral pleura into the underlying pulmonary parenchyma |
| T3 | Describes locally advanced but potentially resectable tumor. Tumor involving all of the ipsilateral pleural surfaces (parietal, mediastinal, diaphragmatic, and visceral) with at least 1 of the following features:<br>• Involvement of the extrathoracic fascia<br>• Extension into the mediastinal fat<br>• Solitary, completely resectable focus of tumor extending into the soft tissues of the chest wall<br>• Nontransmural involvement of the pericardium |
| T4 | Describes locally advanced technically unresectable tumor. Tumor involving all of the ipsilateral pleural surfaces (parietal, mediastinal, diaphragmatic, and visceral) with at least 1 of the following features:<br>• Diffuse extension or multifocal masses of tumor in the chest wall, with or without associated rib destruction<br>• Direct transdiaphragmatic extension of tumor to the peritoneum<br>• Direct extension of tumor to the contralateral pleura<br>• Direct extension of tumor to 1 or more mediastinal organs<br>• Direct extension of tumor into the spine<br>• Tumor extending through to the internal surface of the pericardium with or without a pericardial effusion, or tumor involving the myocardium |
| N: Lymph Nodes | |
| NX | Regional lymph nodes cannot be assessed |
| N0 | No lymph node metastases |
| N1 | Metastases in the ipsilateral bronchopulmonary or hilar lymph nodes |
| N2 | Metastases in the subcarinal or ipsilateral mediastinal lymph nodes, including the ipsilateral internal mammary nodes |
| N3 | Metastases in the contralateral mediastinal, contralateral internal mammary, ipsilateral, or contralateral supraclavicular lymph node |
| M: Metastases | |
| mX | Presence of distant metastases cannot be assessed |
| m0 | No distant metastases |
| M1 | Distant metastases present |
| Stage | Description |
| Stage I | |
| 1a | T1aN0M0 |
| 1b | T1bN0M0 |
| Stage II | T2N0M0 |
| Stage III | Any T3M0<br>Any N1M0<br>Any N2M0 |
| Stage IV | Any T4<br>Any N3<br>Any M1 |

*From* Rusch VW. A proposed new international TNM staging system for malignant pleural mesothelioma from the International Mesothelioma Interest Group. Chest 1995;108(4):1125; with permission.

**Table 2**
**The T descriptors for malignant pleural mesothelioma**

| T Component Staging | T Descriptors |
|---|---|
| TX | Primary tumor cannot be assessed |
| T0 | No evidence of primary tumor |
| T1 | Tumor limited to the ipsilateral parietal ± visceral ± mediastinal ± diaphragmatic pleura |
| T2 | Tumor involving each of the ipsilateral pleural surfaces (parietal, mediastinal, diaphragmatic, and visceral pleura) with at least 1 of the following features:<br>• Involvement of diaphragmatic muscle<br>• Extension of tumor from visceral pleura into the underlying pulmonary parenchyma |
| T3 | Describes locally advanced but potentially resectable tumor<br>Tumor involving all of the ipsilateral pleural surfaces (parietal, mediastinal, diaphragmatic, and visceral pleura) with at least 1 of the following features:<br>• Involvement of the endothoracic fascia<br>• Extension into the mediastinal fat<br>• Solitary, completely resectable focus of tumor extending into the soft tissues of the chest wall<br>• Nontransmural involvement of the pericardium |
| T4 | Describes locally advanced technically unresectable tumor<br>Tumor involving all of the ipsilateral pleural surfaces (parietal, mediastinal, diaphragmatic, and visceral pleura) with at least 1 of the following features:<br>• Diffuse extension or multifocal masses of tumor in the chest wall, with or without associated rib destruction<br>• Direct transdiaphragmatic extension of tumor to the peritoneum<br>• Direct extension of tumor to the contralateral pleura<br>• Direct extension of tumor to mediastinal organs<br>• Direct extension of tumor into the spine<br>• Tumor extending through to the internal surface of the pericardium with or without a pericardial effusion; or tumor involving the myocardium |

*From* Nowak AK, Chansky K, Rice DC, et al. The IASLC Mesothelioma Staging Project: proposals for revisions of the T descriptors in the forthcoming eighth edition of the TNM Classification for Pleural Mesothelioma. J Thorac Oncol. 2016;11(12):2095; with permission.

generated recommendations for the T descriptors based on clinical staging from 509 patients, pathologic staging from 836 patients, and both clinical and pathologic staging from 642 patients (**Fig. 1**).

In the analysis of clinical T staging, a separation in survival curves occurred between all categories except T1a and T1b.[17] However, no survival differences were noted from the pathologic staging between any of the T categories other than T3 and T4. Specifically, no difference in survival was noted between T1b, T2, or T3. In the previous staging system, T1 descriptor was divided into T1a and T1b based on involvement of ipsilateral parietal pleural without or with visceral pleural involvement, respectively. Given the poor discrimination between T1a and T1b on both clinical and pathologic staging, they were merged into a single T1 stage. Therefore, the distinction between invasion of parietal and visceral pleura was eliminated. Given that nodal positivity is a strong predictor of survival, an adjustment for the N component was performed and did not change the results for outcomes based on the T component.

Comparison of clinical with pathologic T categories revealed that upstaging occurred frequently. Upstaging was recorded in 56% of clinical T1 patients, 54% of clinical T2 patients, and 39% of clinical T3 patients. Only 4% were assigned a lower pathologic stage than the clinical stage. Chest wall fascia, pericardium, or multiple T3 descriptors were the reasons that T1 or T2 were reclassified as T3. Multiple pathologic T4 descriptors were the reason for reclassifying T3 as T4. These findings suggest that clinical staging often underestimates the extent of the disease.

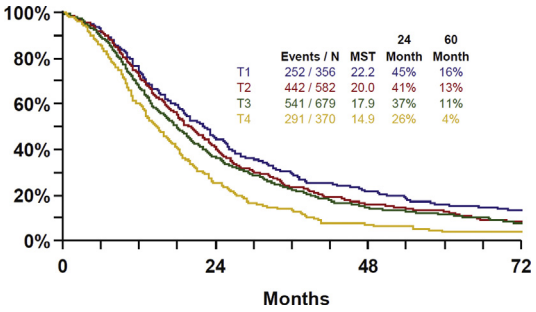


**Fig. 1.** OS of patients with malignant pleural mesothelioma based on the best staging from the combination of clinical and pathologic T descriptors (see Table 2). (*From* Nowak AK, Chansky K, Rice DC, et al. The IASLC Mesothelioma Staging Project: proposals for revisions of the T descriptors in the forthcoming eighth edition of the TNM Classification for Pleural Mesothelioma. J Thorac Oncol. 2016;11(12):2094; with permission.)

Given the frequency that clinical T stage incorrectly predicted pathologic T stage as well as the unusually spread of MPM along pleural surfaces, tumor thickness was analyzed to ascertain its correlation with survival.[17] Measurements of pleural tumor thickness was available in 472 patients. Based on the sum of maximal thickness in upper, middle, and lower pleural measurements, quartiles were generated and survivals were compared as exploratory analyses. OS was inversely correlated with increasing thickness. A data-driven tumor cut point of 5.1 mm was identified. For a single maximal pleural thickness, median survivals of 24.2 and 17.7 months were noted when lesions were less than or greater than 5.1 mm, respectively. The patterns of tumor spread were also categorized as minimal, nodular, or rindlike, which revealed survivals of 23.4, 18.2, and 14.5 months, respectively. Despite efforts to measure pleural thickness or categorize based on imaging patterns, these data are subject to a high degree of interobserver variability. Ultimately, computer-based volumetric analysis may systematize assessment of tumor mass into generating the T stage; however, this technology is not yet widespread enough to incorporate into the staging system. For the eighth edition of the staging system, tumor thickness is not a component of the T descriptor.

### *N Descriptors for Malignant Pleural Mesothelioma*

In the eighth edition of the TNM classifications for pleural mesothelioma, N0 denotes absence of nodal metastasis (Table 3).[18] N1 signifies metastases to the ipsilateral bronchopulmonary, hilar, or mediastinal lymph nodes. The mediastinal lymph nodes include the internal mammary, peridiaphragmatic, pericardial fat pad, and the intercostal lymph nodes. N2 signifies the same nodal areas on the contralateral side in addition to both ipsilateral and contralateral supraclavicular lymph nodes. The IASLC mesothelioma project generated recommendations for the N descriptors based on clinical staging from 1603 patients, pathologic staging from 1614 patients, and both clinical and pathologic staging from 785 patients (Fig. 2).

In the prior staging system, nodal categories of N0 to N3 for MPM were adopted from the lung cancer staging.[8] Despite the recognition that the MPM lymphatic drainage is distinct from drainage in lung parenchymal tumors, this staging system remained for about 20 years. One problem with the lung cancer staging system arose from reports that questioned whether patients with pN1 and

**Table 3**
**The N descriptors for malignant pleural mesothelioma**

| Regional Lymph Nodes(N) | Definition |
|---|---|
| NX | Regional lymph nodes cannot be assessed |
| N0 | No regional lymph node metastases |
| N1 | Metastases in the ipsilateral bronchopulmonary, hilar, or mediastinal (including the internal mammary, peridiaphragmatic, pericardial fat pad, or intercostal lymph nodes) lymph nodes |
| N2 | Metastases in the contralateral bronchopulmonary, hilar, or mediastinal lymph nodes or ipsilateral or contralateral supraclavicular lymph nodes |

*From* Rice D, Chansky K, Nowak A, et al. The IASLC Mesothelioma Staging Project: proposals for revisions of the N descriptors in the forthcoming eighth edition of the TNM Classification for Pleural Mesothelioma. J Thorac Oncol. 2016;11(12):2108; with permission.

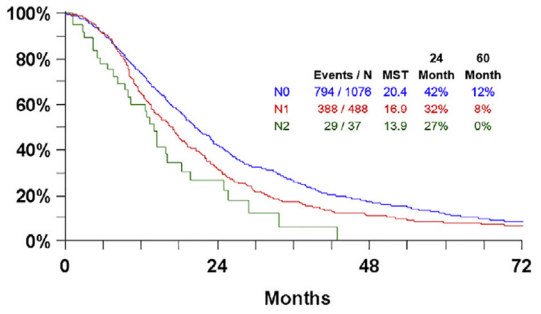


**Fig. 2.** OS of patients with malignant pleural mesothelioma based on the best staging from the combination of clinical and pathologic N descriptor (see Table 3). (*From* Rice D, Chansky K, Nowak A, et al. The IASLC Mesothelioma Staging Project: proposals for revisions of the N descriptors in the forthcoming eighth edition of the TNM Classification for Pleural Mesothelioma. J Thorac Oncol. 2016;11(12):2107; with permission. (Figure 7.C in original).)

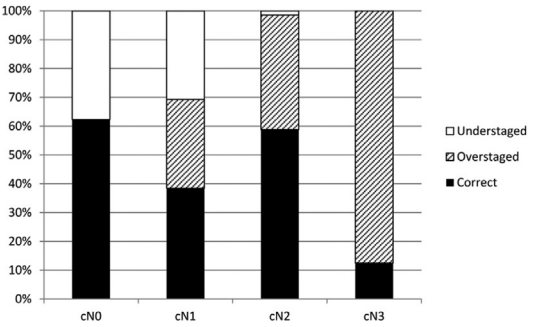


**Fig. 3.** The portion of patients whose N category was understaged, overstaged, or staged correctly when pathologic N staging is compared with clinical N staging. (*From* Rice D, Chansky K, Nowak A, et al. The IASLC Mesothelioma Staging Project: proposals for revisions of the N descriptors in the forthcoming eighth edition of the TNM Classification for Pleural Mesothelioma. J Thorac Oncol. 2016 Dec;11(12):2105; with permission.)

pN2 disease had different survivals.[16] Given that this limitation was known from the first adoption of the IMIG proposals, a data-driven IASLC database was the most anticipated component of this effort.

In total, 1328 patients had complete clinical staging and M0 disease.[18] Among these patients, 78% had cN0, 3% had cN1, 16% had cN2, and 3% had cN3. The median survivals for cN0, cN1, cN2, and cN3 were 19.0, 17.6, 16.2, and 14.5 months, respectively. Surgical assessment of pathologic N disease was obtained for 851 patients with M0 disease. Among these patients, 62% had pN0, 7% had pN1, 30% had pN2, and 1% had pN3. The median survivals for pN0, pN1, and pN2 were 24.0, 16.9, and 17.4 months, respectively. pN3 was excluded secondary to low numbers. Similar to the T descriptor with surgical confirmation, the final pathologic N stage was higher than the clinical N stage in 33% of patients, whereas it was lower in only 6% of the patients (Fig. 3).

The method and extent of nodal sampling were not standardized and varied significantly between institutions, therefore exploratory analyses were performed but not incorporated into the staging system. Exploratory analysis queried whether the number and extent of nodal stations influenced survival.[18] First, given that no difference in OS was noted between pN1 and pN2, these categories were analyzed together (pN+), which revealed a significantly worse survival compared with pN0. In addition, no differences were noted between patients with pN1 or pN2 single-station versus multiple-station disease. To examine the extent of disease, pN2 was compared with pN1 and pN2 combined, which revealed that patients with combined disease (14 months) had significantly worse survival than pN2 only (19 months). Other analyses were performed for the total number of nodes, the lymph node ratios, and distribution. No differences were observed; however, the number of patients with sufficient data for these comparisons was low. Collectively, these findings suggest that anatomic location of nodal metastasis is less important than the cumulative extent of nodal involvement. For this reason, the staging classification was revised such that N1 denotes ipsilateral intrathoracic nodal metastasis and N2 denotes contralateral or any supraclavicular nodal metastasis.

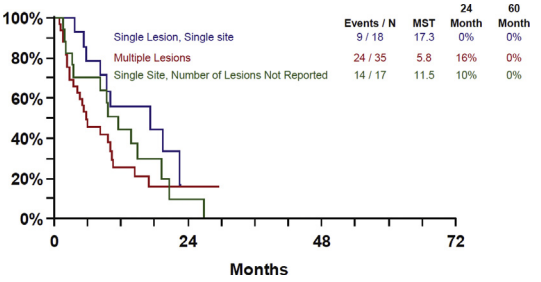


**Fig. 4.** OS of patients with single or multiple metastatic (M1) lesions from malignant pleural mesothelioma. M0, no distant metastasis; M1, distant metastasis present. (*From* Rusch VW, Chansky K, Kindler HL, et al. The IASLC Mesothelioma Staging Project: proposals for the M descriptors and for revision of the TNM staging groupings in the forthcoming eighth edition of the TNM Classification for Mesothelioma. J Thorac Oncol. 2016;11(12):2115; with permission.)

Similar to the T descriptor, whether tumor thickness predicted nodal metastasis was explored with 3 levels (upper, middle, and lower) of cut points based on maximal thickness.[18] Measurements of tumor thickness and complete N disease were available for 472 patients. With the same cut point of 5.1 mm that was generated for the T descriptor, the risks of nodal metastases less than and greater than that thickness were 14% and 38%. These findings were exploratory and require further investigation with more sophisticated technology before incorporation into the staging classifications.

Several weaknesses of nodal staging remain despite the improvements in this revision. First, the incidence of nodal metastasis depends on the extent of nodal sampling, which varies between surgeons, institutions, and the type of resection performed. Second, for patients who were staged both clinically and pathologically, clinical nodal staging did not accurately predict

**Table 4**
**The tumor, node, metastasis staging for malignant pleural mesothelioma**

| Stage | Definition |
|---|---|
| Primary Tumor (T) | |
| TX | Primary tumor cannot be assessed |
| TO | No evidence of primary tumor |
| T1 | Tumor limited to the ipsilateral parietal ± visceral ± mediastinal ± diaphragmatic pleura |
| T2 | Tumor involving each of the ipsilateral pleural surfaces (parietal, mediastinal, diaphragmatic, and visceral pleura) with at least 1 of the following features:<br>• Involvement of diaphragmatic muscle<br>• Extension of tumor from visceral pleura into the underlying pulmonary parenchyma |
| T3 | Describes locally advanced but potentially resectable tumor. Tumor involving all of the ipsilateral pleural surfaces (parietal, mediastinal, diaphragmatic, and visceral pleura) with at least 1 of the following features:<br>• Involvement of the endothoracic fascia<br>• Extension into the mediastinal fat<br>• Solitary, completely resectable focus of tumor extending into the soft tissues of the chest wall<br>• Nontransmural involvement of the pericardium |
| T4 | Describes locally advanced technically unresectable tumor. Tumor involving all of the ipsilateral pleural surfaces (parietal, mediastinal, diaphragmatic, and visceral pleura) with at least 1 of the following features:<br>• Diffuse extension or multifocal masses of tumor in the chest wall, with or without associated rib destruction<br>• Direct transdiaphragmatic extension of tumor to the peritoneum<br>• Direct extension of tumor to the contralateral pleura<br>• Direct extension of tumor to mediastinal organs<br>• Direct extension of tumor into the spine<br>• Tumor extending through to the internal surface of the pericardium with or without a pericardial effusion, or tumor involving the myocardium |
| Regional Lymph Nodes (N) | |
| NX | Regional lymph nodes cannot be assessed |
| NO | No regional lymph node metastases |
| N1 | Metastases in the ipsilateral bronchopulmonary, hilar, or mediastinal (including the internal mammary, peridiaphragmatic, pericardial fat pad, or intercostal lymph nodes) lymph nodes |
| N2 | Metastases in the contralateral mediastinal, ipsilateral, or contralateral supraclavicular lymph nodes |
| Distant Metastasis (M) | |
| MO | No distant metastasis |
| M1 | Distant metastasis present |

*From* Rusch VW, Chansky K, Kindler HL, et al. The IASLC Mesothelioma Staging Project: proposals for the M descriptors and for revision of the TNM staging groupings in the forthcoming eighth edition of the TNM Classification for Mesothelioma. J Thorac Oncol. 2016;11(12):2117; with permission.

pathologic status.[4] The investigators did recommend use of invasive pretreatment nodal sampling to improve accuracy of clinical nodal staging.

### *M Descriptors for Malignant Pleural Mesothelioma*

In the eighth edition of the TNM classifications for pleural mesothelioma, M0 and M1 denote absence and presence of distant metastases, respectively.[18] No changes were recommended to the M descriptor in the 2016 revision of MPM staging; however, the M descriptor was validated based on sufficient differences in OS between clinical M0 and M1. Importantly, the OS of patients with cM1 disease was compared with cM0 with locally advanced disease (T4 or N3) and showed a survival difference, which provided the rationale for including only cM1 in the stage IV group. The median OSs for cM1 versus T3 or N3 patients were 9.7 months versus 13.4 months, respectively. These data were generated from 2414 analyzable cases, although only 84 had cM1 disease.

Evaluation of the prognosis based on the location and number of metastatic sites was limited to exploratory analysis given the small group of 84 patients. In addition, only 70 patients had data regarding the site of disease. The differences in OS between patients with a single sites versus multiple sites suggested that patients with a single site have a better prognosis (Fig. 4). Additional data may confirm these findings and prompt revision to the M descriptor in the future.

### *Tumor, Node, Metastasis Staging for Malignant Pleural Mesothelioma*

The staging for MPM based on the revised eighth edition of the TNM classifications includes T1N0M0 as stage IA, T2-3N0M0 as stage IB, T1-2N1M0 as stage II, T3N1M0 as stage IIIA, T1-2N2M0 and T4N0-2M0 as stage IIIB, and M1 as stage IV (Table 4).[18] These staging categories represent a substantial revision for the UICC/AJCC staging system of robust survival data among 3519 submitted cases. The OSs based on these stages are presented in Fig. 5.

Although this system is developed from an international, multi-institutional cohort study, the committee for IMIG and IASLC/SPFC stress the continued need for data collection and additional revisions for future revisions. At present, the staging project continues with the goal to develop recommendations for the ninth edition of the TNM. The study population for the ongoing project includes patients with newly diagnosed MPM. The data elements are more extensive than the prior databases and will include patient characteristics, laboratory values, pulmonary function tests, and standard uptake values from PET imaging to obtain pretreatment clinical TNM data. Pathologic TNM data will be obtained for surgically managed patients. The surgical data specifically will include data on extension into other structures for refinement of the T stage, nodal station involvement based on the IASLC 2009 nodal map for N stage refinements, and details for the M descriptor. Survival data will be obtained as expected. Collaborating institutions will receive data element lists to help standardize processes for collecting this information.

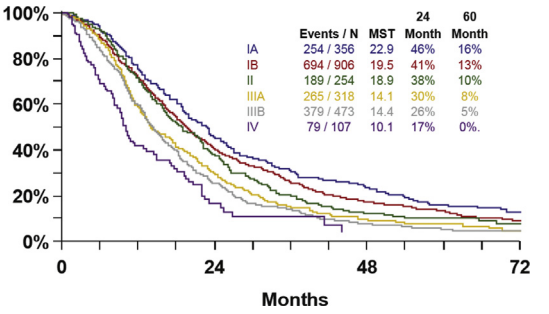


**Fig. 5.** OS of patients with malignant pleural mesothelioma based on the best staging for the eighth edition of the staging system. (*From* Rusch VW, Chansky K, Kindler HL, et al. The IASLC Mesothelioma Staging Project: proposals for the M descriptors and for revision of the TNM staging groupings in the forthcoming eighth edition of the TNM Classification for Mesothelioma. J Thorac Oncol. 2016;11(12):2116; with permission.)

## SUMMARY

MPM is a rare and deadly cancer of the thoracic serous membranes. The staging of this disease is challenging secondary to the low incidence and poor survival. At least 5 staging systems were proposed before 1990, before the first consensus system in 1994 by the IASLC. This system used TNM designations and borrowed heavily from parenchymal lung cancer descriptors. The IASLC formed a database to prospectively collect complete patient data and obtained more than 3000 cases from 1995 to 2013. In 2016, evidence-based revisions to the 1994 IASLC staging classification were released. Clinical staging now is based on findings from patients with MPM rather than lung cancer. However, several limitations still exist; therefore, ongoing efforts are underway at IASLC to improve staging with the next edition.

## CLINICS CARE POINTS

- In 1995, IASLC published a universal TNM system for staging MPM based partially on lung cancer staging paradigms.

- In 2016, IASLC published revisions to the TNM system based on MPM cases collected from 1995 to 2013.
- Given the poor discrimination between T1a and T1b on both clinical and pathologic staging, a single T1 stage was adopted, and T1a and T1b were eliminated.
- The pathologic T stage was higher in 56% of clinical T1 patients, 54% of clinical T2 patients, and 39% of clinical T3 patients. Only 4% were assigned a lower pathologic stage than the clinical stage.
- The nodal staging classification was revised such that N1 denotes ipsilateral intrathoracic nodal metastasis and N2 denotes contralateral or any supraclavicular nodal metastasis. The distinction of N1 and N2 based on intraparenchymal versus mediastinal lymph nodes, similar to lung cancer staging, was eliminated. The N3 descriptor was removed.
- The pathologic N stage was higher than the clinical N stage in 33% of patients, whereas it was lower in only 6% of patients.
- No changes were recommended to the M descriptor, which was validated based on sufficient differences in OS between clinical cM0 and cM1.
- The revised eighth edition of the TNM classifications include T1N0M0 as stage IA, T2-3N0M0 as stage IB, T1-2N1M0 as stage II, T3N1M0 as stage IIIA, T1-2N2M0 and T4N0-2M0 as stage IIIB, and M1 as stage IV.
- Ongoing international efforts are underway to revise the current staging system with recommendations for the ninth edition of the TNM.

## DISCLOSURE

The authors have nothing to disclose.

## REFERENCES


1. Corson JM. Pathology of diffuse malignant pleural mesothelioma. Semin Thorac Cardiovasc Surg 1997;9(4):347–55.
2. Wagner JC, Sleggs CA, Marchand P. Diffuse pleural mesothelioma and asbestos exposure in the North Western Cape Province. Br J Ind Med 1960;17:260–71.
3. Attanoos RL, Gibbs AR. Pathology of malignant mesothelioma. Histopathology 1997;30(5):403–18.
4. Husain AN, et al. Guidelines for pathologic diagnosis of malignant mesothelioma: 2012 update of the consensus statement from the International Mesothelioma Interest Group. Arch Pathol Lab Med 2013;137(5):647–67.
5. Hammar SP, et al. Mucin-positive epithelial mesotheliomas: a histochemical, immunohistochemical, and ultrastructural comparison with mucin-producing pulmonary adenocarcinomas. Ultrastruct Pathol 1996;20(4):293–325.
6. Attanoos RL, Gibbs AR. 'Pseudomesotheliomatous' carcinomas of the pleura: a 10-year analysis of cases from the Environmental Lung Disease Research Group, Cardiff. Histopathology 2003;43(5):444–52.
7. Crotty EJ, et al. Epithelioid hemangioendothelioma of the pleura: clinical and radiologic features. AJR Am J Roentgenol 2000;175(6):1545–9.
8. Rusch VW. A proposed new international TNM staging system for malignant pleural mesothelioma. From the International Mesothelioma Interest Group. Chest 1995;108(4):1122–8.
9. Pass H, et al. The IASLC mesothelioma staging project: improving staging of a rare disease through international participation. J Thorac Oncol 2016;11(12):2082–8.
10. Tammilehto L, et al. Evaluation of the clinical TNM staging system for malignant pleural mesothelioma: an assessment in 88 patients. Lung Cancer 1995;12(1–2):25–34.
11. Butchart EG, et al. Pleuropneumonectomy in the management of diffuse malignant mesothelioma of the pleura. Experience with 29 patients. Thorax 1976;31(1):15–24.
12. Sugarbaker DJ, et al. Node status has prognostic significance in the multimodality therapy of diffuse, malignant mesothelioma. J Clin Oncol 1993;11(6):1172–8.
13. Chahinian AP, et al. Diffuse malignant mesothelioma. Prospective evaluation of 69 patients. Ann Intern Med 1982;96(6 Pt 1):746–55.
14. Pass HI, et al. Preoperative tumor volume is associated with outcome in malignant pleural mesothelioma. J Thorac Cardiovasc Surg 1998;115(2):310–7 [discussion: 317–8].
15. Rusch VW, Venkatraman E. The importance of surgical staging in the treatment of malignant pleural mesothelioma. J Thorac Cardiovasc Surg 1996;111(4):815–25 [discussion: 825–6].
16. Rusch VW, et al. Initial analysis of the international association for the study of lung cancer mesothelioma database. J Thorac Oncol 2012;7(11):1631–9.
17. Nowak AK, et al. The IASLC mesothelioma staging project: proposals for revisions of the T descriptors in the forthcoming eighth edition of the TNM classification for pleural mesothelioma. J Thorac Oncol 2016;11(12):2089–99.
18. Rusch VW, et al. The IASLC mesothelioma staging project: proposals for the M descriptors and for revision of the TNM Stage Groupings in the Forthcoming (Eighth) Edition of the TNM classification for mesothelioma. J Thorac Oncol 2016;11(12):2112–9.