ORIGINAL ARTICLE

The IASLC Mesothelioma Staging Project: Proposals for Revisions of the N Descriptors in the Forthcoming Eighth Edition of the TNM Classification for Pleural Mesothelioma

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ABSTRACT

Introduction: Nodal categories for malignant pleural mesothelioma are derived from the lung cancer staging system and have not been adequately validated. The International Association for the Study of Lung Cancer developed a multinational database to generate evidence-based recommendations to inform the eighth edition of the TNM classification of malignant pleural mesothelioma.

Methods: Data from 29 centers were entered prospectively (n = 1566) or by transfer of retrospective data (n = 1953). Survival according to the seventh edition N categories was evaluated using Kaplan-Meier survival curves and Cox proportional hazards regression analysis. Survival was measured from the date of diagnosis.

Results: There were 2432 analyzable cases: 1603 had clinical (c) staging, 1614 had pathologic (p) staging, and 785 had both. For clinically staged tumors there was no separation in Kaplan-Meier curves between cN0, cN1 or cN2 (cN1 versus cN0 hazard ratio [HR] = 1.06, $p = 0.77$ and cN2 versus cN1 HR = 1.04, $p = 0.85$). For pathologically staged tumors, patients with pN1 or pN2 tumors had worse survival than those with pN0 tumors (HR = 1.51, $p < 0.0001$) but no survival difference was noted between those with pN1 and pN2 tumors (HR = 0.99, $p = 0.99$). Patients with both pN1 and pN2 nodal involvement had poorer survival than those with pN2 tumors only (HR = 1.60, $p = 0.007$) or pN0 tumors (HR = 1.62, $p < 0.0001$).

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**See Appendix for the members of the Mesothelioma Domain of the IASLC Staging and Prognostic Factors Committee, advisory boards, and participating institutions.

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Conclusions: A recommendation to collapse both clinical and pN1 and pN2 categories into a single N category comprising ipsilateral, intrathoracic nodal metastases (N1) will be made for the eighth edition staging system. Nodes previously categorized as N3 will be reclassified as N2.

Keywords: Mesothelioma; Cancer staging; Nodal metastases; Database

Introduction

Malignant pleura mesothelioma (MPM) carries a poor prognosis for most patients, and survival is known to be particularly poor in patients with nodal metastases.[1–4] This has been reflected in several staging systems that have developed over the past four decades.[5–8] The current seventh edition of the TNM classification of MPM of the American Joint Committee on Cancer and the Union for International Cancer Control TNM-based staging systems for MPM was developed in 1994 after a staging workshop sponsored by the International Association for the Study of Lung Cancer (IASLC) and the International Mesothelioma Interest Group and was derived from analyses of several single-institution retrospective series as well as from expert opinion.[8–10] This staging system has remained unchanged for two decades and has been criticized because it largely reflects the outcomes of patients who have undergone a cytoreductive operation and uses several staging descriptors that can be determined only by pathologic review. Thus, the general applicability of this staging system for clinical staging of tumors in nonsurgical patients (who form the majority of patients with MPM) is questionable. Furthermore, the nodal categories (N0–N3) in the American Joint Committee on Cancer/Union for International Cancer Control staging system were adopted from those used in lung cancer staging and are based on the Mountain/Dressler–American Thoracic Society (MD-ATS) and Naruke classification systems, without much supporting MPM-specific evidence. In fact, there are significant anatomic differences between the lymphatic drainage pathways of the pleura and the lung parenchyma, and data from several single-institutional retrospective series have yielded conflicting evidence as to whether there is indeed a prognostic difference between patients with pathologic N1 (pN1) and pN2 pleural mesothelioma. These facts warranted further evaluation of the appropriateness of the current nodal categories.[11]

Accordingly, the Mesothelioma Domain of the IASLC International Staging and Prognostic Factors Committee coordinated development of a large international multicenter database to collect data that could inform staging in MPM, much like what had previously been done for lung cancer and led to the seventh edition of the TNM classification.[12] The initial IASLC MPM database amalgamated retrospective data from 15 institutions worldwide on 3101 operatively treated patients with mesothelioma, and initial analyses published in 2012 suggested that certain changes in the TNM-based staging system might be justifiable; however, there was insufficient granularity in the data on individual T, N, and M descriptors to allow evidence-based revisions to be made. Therefore, a second database was created; it contained more detailed data elements for TNM descriptors and was populated prospectively by using a web-based electronic data capture system. Importantly, data on patients treated both operatively and nonoperatively were collected. Additionally, to increase the proportion of patients who were treated nonoperatively, retrospective data that conformed to the common data elements were included from participating centers. These data were used to derive evidence-based recommendations regarding nodal categories.

Methods

Data were submitted from 29 centers around the world, including in Europe (48%), North America (33%), Asia (10%), and Australia (9%). Data were prospectively collected by means of the electronic data capture system in 1566 cases (45%) and by transfer of retrospective data in 1953 (55%) cases. Although cases from as early as 1995 were included, most were diagnosed between 2000 and 2013. Cases diagnosed after June 30, 2013, were excluded and analyses were undertaken at the end of 2014, allowing a minimum potential follow-up of 18 months. Data management and statistical analyses were provided by coinvestigators at Cancer Research And Biostatistics in Seattle, Washington. A total of 3519 cases were collected, 2432 of which had a complete set of TNM data (by either clinical or pathologic staging), known histologic type, and survival follow-up (Table 1). Pretreatment (i.e., clinical) TNM staging information was available for 1603 patients, postoperative (i.e., pathologic) staging data were available for 1614 patients, and both types of data were available in 785 cases. Clinical staging included all tests and imaging studies done for initial extent-of-disease evaluation and information obtained from mediastinoscopy, endobronchial ultrasound transbronchial needle aspiration, or laparoscopy in cases in which these procedures had been performed, but not from thoracotomy. Of the 29 participating centers, 23 submitted data on clinical classification (positive, negative, or not done) for individual nodal stations, comprising a total of 1322 cases. Pathologic nodal sampling results for a total of

Table 1. Summary of Cases Meeting the Requirements for Inclusion in the Primary N Category Analysis

		Available TNM Staging					
		Both		Clinical Only		Pathologic Only	
Characteristic	Total	n	(%)	n	(%)	n	(%)
Region							
Asia	213	85	(39%)	123	(57%)	5	(2%)
Australia	109	1	(0%)	108	(99%)	0	0
Europe	529	61	(11%)	224	(42%)	244	(46%)
North America	695	379	(54%)	287	(41%)	29	(4%)
Turkey	55	46	(83%)	8	(14%)	1	(1%)
Sex							
Female	313	126	(40%)	126	(40%)	61	(19%)
Male	1288	447	(34%)	623	(48%)	218	(16%)
Histologic type							
Biphasic	243	93	(38%)	91	(37%)	59	(24%)
Epithelioid	1150	436	(37%)	507	(44%)	207	(18%)
Other/NOS	133	33	(24%)	93	(69%)	7	(5%)
Sarcomatoid	75	11	(14%)	58	(77%)	6	(8%)
Total	1601	573	(35%)	749	(46%)	279	(17%)

Note: Clinical and/or pathologic stage with supporting nodal station data was required.
NOS, not otherwise specified.

851 patients were available from 20 centers (Fig. 1). There was no standardization regarding method or extent of intraoperative nodal sampling, and this varied significantly across institutions. Node classification was based on the current seventh edition TNM classification, whereby N0 denotes an absence of nodal metastases; N1 denotes metastases to nodes contained within the pleural reflection (hilar and parenchymal, stations 10–14); N2 denotes metastases in ipsilateral mediastinal nodes outside the pleural reflection (stations 2–9)

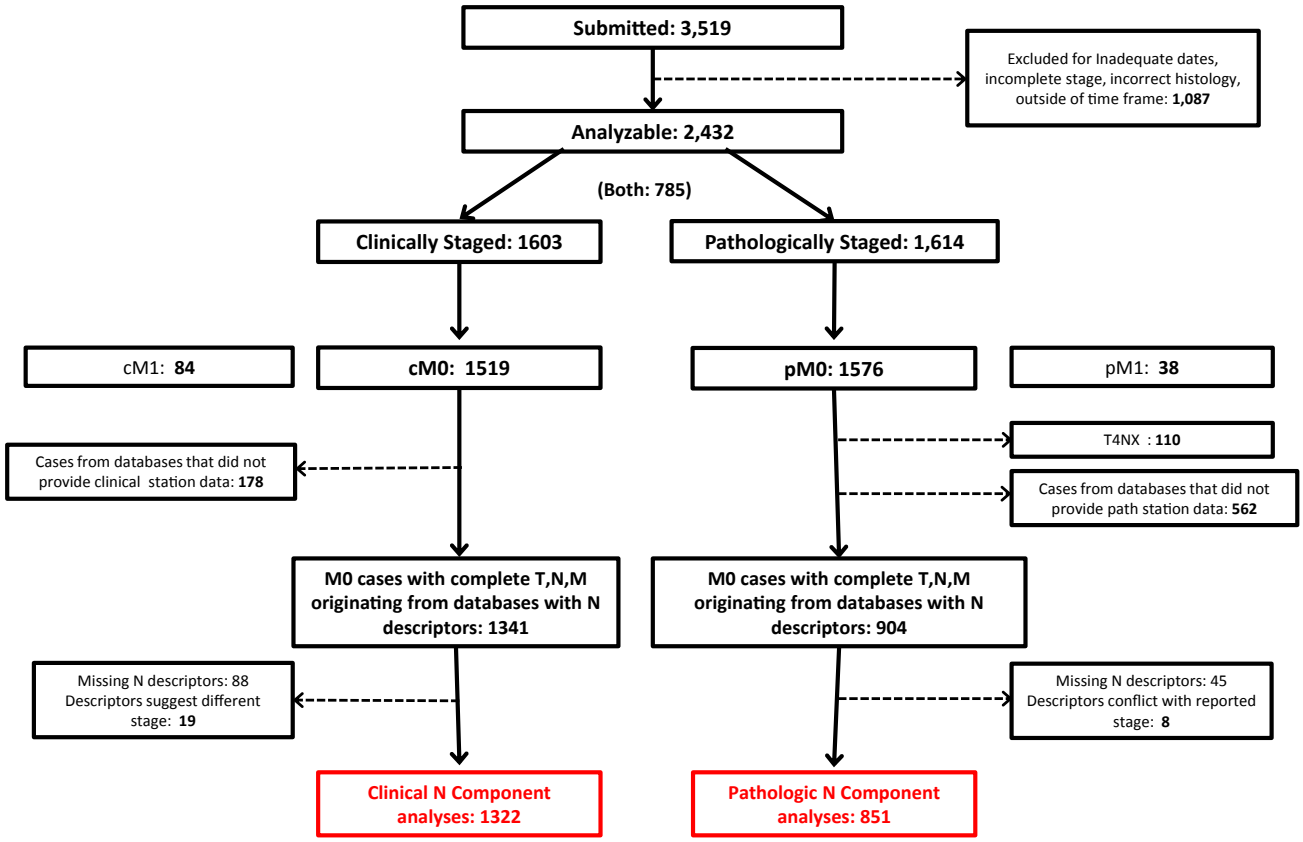

Figure 1. Cases analyzed and reasons for exclusion.

as well as ipsilateral internal mammary, intercostal, diaphragmatic, and pericardial nodes; and N3 denotes supraclavicular (station 1, ipsilateral or contralateral) and all contralateral intrathoracic nodes. Known differences between the Naruke and MD-ATS nodal maps include the designation of nodes along the inferior border of the mainstem bronchus (station 10 versus station 7) and along the upper paratracheal region (stations 1 and 2 versus station 1). As only 10% of cases were submitted from centers in Asia, it is unlikely that these minor differences in nomenclature significantly influenced the overall results. Nodal stations that were excluded from the Naruke and MD-ATS node maps but often involved in MPM, including internal mammary, intercostal, pericardial, and diaphragmatic nodes, were collectively referred to as nonmediastinal intrathoracic nodes.

Statistical Methods

The prognostic capabilities of N categories according to the current system were evaluated using Kaplan-Meier survival curves and Cox proportional hazards regression analysis with and without adjustment for age and geographical region. Alternative N category schemes based on a combination of location and number of positive nodal stations were explored by using Kaplan-Meier survival analysis and Cox proportional hazards regression. Cox regression analyses were performed using the SAS System for Windows Version 9.4 (SAS Institute Inc., Cary, NC).

Results

Overall Survival According to cN Categories

In all, 1322 patients had cM0 tumors and complete information on clinical N (cN) categories with supporting results for individual nodal stations. Most patients had tumors staged as cN0 (78%), with only 16% staged as cN2 and 3% as cN1 or cN3. Median survival for cN0 patients was 19 months versus 17.6 and 16.2 months for cN1 and cN2 patients, respectively (Fig. 2). Perhaps because of the small number of cN1 patients, survival for cN1 patients did not differ significantly from that for cN0 patients (hazard ratio [HR] = 1.15, $p = 0.49$). There was no significant difference between cN1 and cN2 patients (HR = 1.06, $p = 0.78$). When cN1 and cN2 (cN+) patients were combined and compared with cN0 patients with adjustment for region and sex, the median overall survival times were 17.1 versus 19.0 months, respectively (HR = 1.18, $p = 0.04$). No difference in survival was noted between patients with tumors clinically staged as having single-station metastases compared with patients having multiple-station nodal involvement (median 17.1 versus 17.2 months, p = 0.84).

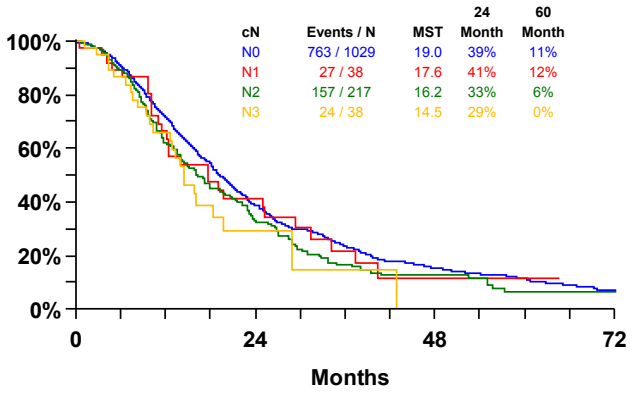

Figure 2. Kaplan-Meier curve for survival by seventh edition American Joint Committee on Cancer clinical N category in cases with N descriptor support. MST, median survival time.

Overall Survival according to pN Staging

Of the 851 patients with pathologic M0 tumors who had surgical confirmation of nodal status, 530 (62%) were classified as pN0, 58 (7%) were classified as pN1, 256 (30%) were classified as pN2, and 7 (1%) were classified as pN3. Because of the small patient numbers, the seven patients with pN3 disease were excluded from further survival analyses. The median survival of patients with pN0 tumors was 24.0 months compared with 16.9 months (HR = 1.51, $p = 0.006$) and 17.4 months (HR = 1.56, $p < 0.001$) for patients with pN1 and pN2 tumors, respectively (Fig. 3). No significant difference in survival was noted between patients with pN1 and pN2 disease ($p = 0.84$). Patients with pN1 or pN2 disease were therefore analyzed together (pN+) which resulted in a significantly worse overall survival prognosis compared with that of patients with pN0 disease (HR = 1.55, $p < 0.0001$).

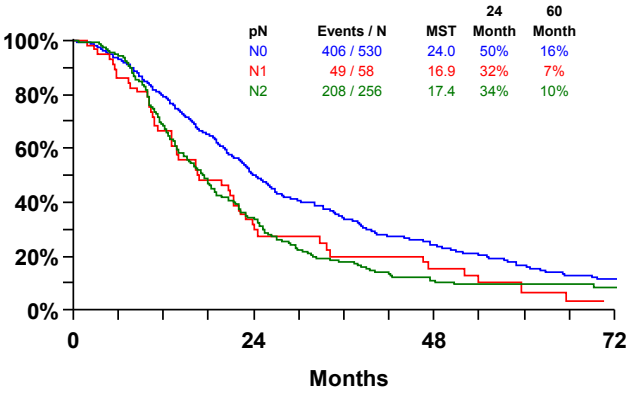

Figure 3. Kaplan-Meier curve for survival by seventh edition American Joint Committee on Cancer C pathologic N category in cases with N descriptor support. MST, median survival time.

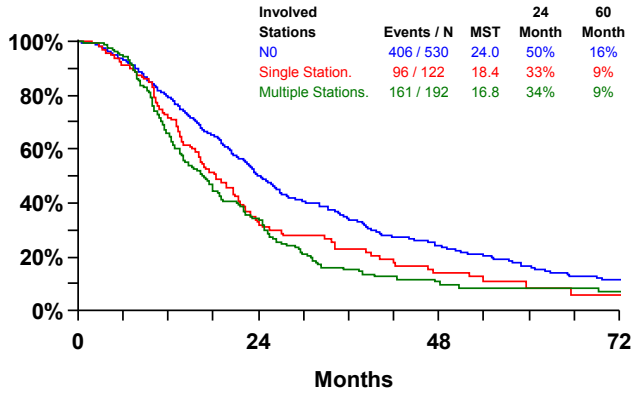

Figure 4. Survival by seventh edition American Joint Committee on Cancer pathologic N category, single versus multiple nodal station involvement. MST, median survival time.

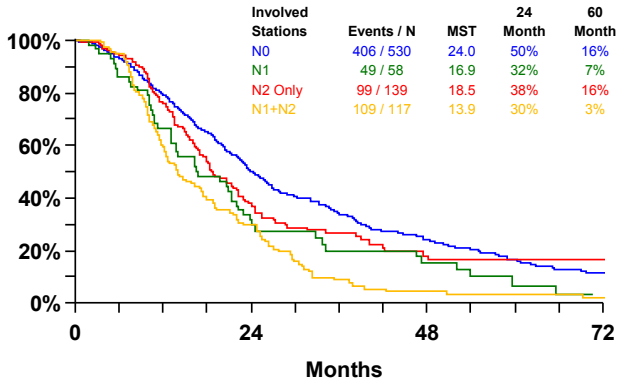

Figure 5. Survival by seventh edition American Joint Committee on Cancer pathologic N category, N1 plus N2 involvement versus N0, pN1 and pN2 only (i.e., without N1). MST, median survival time.

Survival in Relation to the Extent of pN1 and pN2 Metastases

Exploratory analyses were performed to determine whether the pattern or extent of nodal involvement influenced survival in cases with detailed pN category information. No significant survival differences were noted for patients with single-station or multistation pN1 or pN2 metastases (HR = 1.11, $p = 0.44$) (Fig. 4). As the presence of skip metastases (i.e., single-station N2 without N1 metastases) has been associated with improved survival in patients with lung cancer, we examined whether this held true in our patient population. Of the patients with N2 disease, 54% did not have any N1 nodal involvement. Survival for patients with pN0 tumors was significantly different from that for patients with pN2 involvement only (median 24.0 versus 18.5 months, $p = 0.044$). Patients with both N1 and N2 metastases ($n = 117$) had significantly worse survival compared with those with pN0 disease (HR = 1.63, $p < 0.0001$) and those with pN2 disease only (HR = 1.60, $p = 0.0007$) (Fig. 5). No survival difference was noted between patients with pN2-only and pN1-only tumors (HR = 0.83, $p = 0.28$). Analysis of survival by number of involved lymph nodes, lymph node ratio (number of positive nodes to number of nodes on which a biopsy was performed) and nodal distribution (upper mediastinal versus lower mediastinal versus nonmediastinal) did not reveal any significant trends; however, individual patient numbers were small.

Relationship Between Tumor Thickness and Presence of Nodal Metastases

As outlined in the companion manuscript on T categories,[13] prospectively obtained measurements of tumor thickness by axial computed tomography imaging were available for 472 patients who also had complete N category information. These measurements were obtained at three predefined regions within the affected hemithorax (upper, middle, and lower), and running log-rank tests were performed to identify which tumor thickness cutpoints predicted survival. Additionally however, cutpoints based on the maximal thickness of the three levels, or on the sum of the three levels, also predicted risk of nodal metastases. Patients with tumor of maximal thickness less than 5.1 mm had a 14% risk of nodal metastases, whereas this risk rose to 38% in patients with tumors of maximal thickness greater than 5.1 mm ($p < 0.0001$). Similarly, tumor thickness cutpoints (based on three-level summation) of less than 13 mm, 13 to 60 mm, and more than 60 mm were associated with nodal metastases in 14%, 37%, and 47% of cases ($p < 0.0001$). It should be stressed that these findings are exploratory only and will require further investigation and validation with larger patient numbers.

Accuracy of cN Categories

Both cN and pN stage data were available for 572 patients. Although 480 patients had tumors clinically staged as cN0, a minority (38%) had some form of nodal histologic confirmation (endobronchial ultrasound, mediastinoscopy, etc.) before treatment. Overall, clinical staging underestimated N status in 33% of patients and overestimated it in 6% of cases. The κ statistic for agreement between clinical and pathologic stage determinations was 0.16 (95% confidence interval: 0.09–0.22), which indicates only slight agreement (Fig. 6).

Distribution of Nodal Metastases

Complete data on nodal sampling (i.e., when data entry indicated whether nodal stations were positive, negative, or not subjected to biopsy) were available for 642 cases from 16 contributing centers, 274 of which (43%) had positive N1 or N2 nodes. The mean number

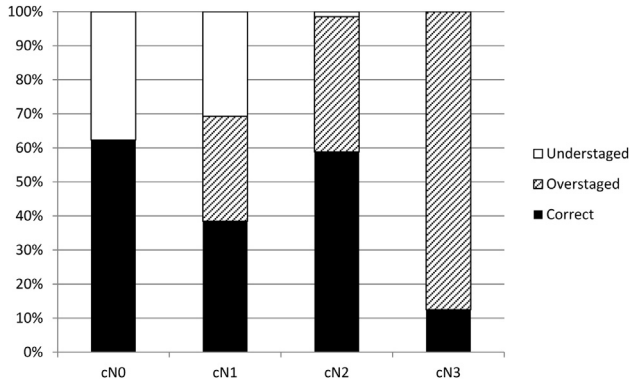

Figure 6. Proportion of overstaged and understaged patients according to pretreatment (clinical) N category in patients with confirmatory data on pathologic N category.

of separate stations on which biopsies were performed per patient was 4.7 (range 1–18), with a mean of 2.7 N1 stations and 2.0 N2 stations sampled. The distribution of nodal stations on which biopsies were performed is shown in Table 2, with stations 4, 7, and 10 being sampled most frequently.

Of 314 patients with N1 or N2 disease, metastases were most frequently identified in the subcarinal (43%), hilar (36%), and lower paratracheal stations (20%); however, these stations were also those most frequently examined by biopsy (see Table 2). On a per station sampled basis, nodes in the internal mammary chain had the highest frequency of positivity, harboring metastases in 24 of 58 stations sampled (41%). More nodal stations were evaluated in patients who underwent extrapleural pneumonectomy (EPP) compared with in those who had pleurectomy/decortication (PD) or extended PD (mean 5.5 versus 3.8 stations, $p < 0.0001$). Patients with the epithelioid histology were more likely to be pathologic node–positive compared with patients with non-epithelioid tumors (41% versus 27%, $p = 0.0003$), although this may have been influenced by differences in the degree of surgical resection, with more aggressive approaches such as EPP (and potentially more thorough node dissections) being favored in patients with epithelioid tumors.

Table 2. Distribution of Sampled Lymph Node Stations

Lymph Node Station	Stations Sampled (n = 642)	Positive Stations (n = 314)	Positive/ Sampled Stations
2	89 (14%)	5 (2%)	6%
3	101 (16%)	15 (5%)	15%
4	292 (45%)	63 (20%)	22%
5	214 (33%)	53 (17%)	25%
6	129 (20%)	22 (7%)	17%
7	500 (78%)	134 (43%)	27%
8	222 (35%)	44 (14%)	20%
9	198 (31%)	36 (11%)	18%
10	361 (56%)	112 (36%)	31%
11	187 (29%)	30 (10%)	16%
12	185 (29%)	33 (11%)	18%
13	119 (19%)	8 (3%)	7%
14	113 (18%)	4 (1%)	4%
Internal mammary	58 (9%)	24 (8%)	41%
Percardial	63 (10%)	5 (2%)	8%
Peridiaphragmatic	61 (10%)	8 (3%)	13%
Intercostal	68 (11%)	10 (3%)	15%
Retrocrural	48 (7%)	2 (1%)	4%

Discussion

The presence of nodal metastases is known to adversely affect outcome in patients with MPM, reducing long-term survival by as much as 50%.[1,2,14] Lymph node metastases are frequent; they are reported in between 35% and 50% of patients undergoing a cytoreductive operation (Table 3), and a recent postmortem study reported the presence of nodal metastases in 76% of autopsies.[30] The seventh edition of the TNM classification classifies any ipsilateral nodal involvement as stage III and categorizes ipsilateral nodes as either N1 (intrapleural including hilar and intraparenchymal nodes) or N2 (extrapleural including mediastinal and nonmediastinal such as internal mammary, peridiaphragmatic, pericardial, and intercostal nodes).[9] Although evidence from most retrospective studies supports assigning tumors with nodal metastases a stage higher than that of N0 tumors of equivalent T category, the current TNM classification system, which has remained unchanged for almost two decades, is not evidence based, having been derived from limited retrospective surgical series. Although the N categories for lung cancer are logical inasmuch as N1 nodes generally become involved with metastatic disease before N2 nodes do, the same orderly progression is not known to occur for mesothelioma, a tumor that chiefly involves the pleura, which is known to have a pattern of lymphatic drainage distinct from that of the lung parenchyma.[31,32] Indeed, it has been postulated that extrapleural nodes (N2) may in fact be the initial site of nodal metastases in patients with mesothelioma, with N1 nodes becoming secondarily involved only when invasion of lung parenchyma occurs.[17] Therefore, a more data-driven assessment of the significance of nodal metastases as they relate to incidence and prognosis was warranted for the upcoming eighth edition of the TNM classification for mesothelioma.[11]

The current report presents data from the largest multinational, multi-institutional database of patients with MPM established to date. Although most patients underwent some type of operation, a significant proportion (28%) received nonoperative treatment. Because most patients who present with MPM are not candidates for an operation, inclusion of nonoperative patients in this database was of great importance for

Table 3. Series of Patients with Prevalence of Nodal Metastases

Author	Year	EPP/PD (n)	N0 n (%)	N1 n (%)	N1 (Any) n (%)	N1 + N2 n (%)	N2 only n (%)	N2 (Any) n (%)
Edwards[15]	2006	92 EPP	48 (52%)	9 (10%)	30 (33%)	21 (23%)	14 (15%)	35 (38%)
dePerrot[4]	2007	50 EPP	21 (42%)	8 (16%)	21 (42%)	13 (26%)	8 (16%)	21 (42%)
Rice[14]	2007	100 EPP	46 (46%)	12 (12%)	–	–	–	42 (42%)
Rea[16]	2007	21 EPP	14 (67%)	2 (10%)	–	–	–	5 (24%)
Rahman[17]	2008	49 EPP	11 (22%)	7 (14%)	25 (51%)	18 (37%)	13 (27%)	31 (63%)
Flores[3]	2008	223 EPP 125 PD	192 (59%)	22 (7%)	87 (25%)	65 (20%)	45 (14%)	110 (34%)
Buduhan[18]	2009	46 EPP	26 (57%)	4 (9%)	–	–	–	16 (35%)
Richards[19]	2010	353 EPP	162 (46%)	86 (24%)	–	–	–	105 (30%)
Friedberg[20]	2012	38 PD	9 (24%)	4 (11%)	–	–	–	24 (63%)
Nakas[21]	2012	127 EPP 85 PD	94 (44%)	23 (11%)	–	–	–	99 (47%)
Rusch (IASLC)[12]	2012	1191 EPP 299 PD	889 (61%)	179 (12%)	–	–	–	386 (27%)
Bovolato[22]	2014	301 EPP 202 PD	258 (51%)	47 (9%)	–	–	–	100 (20%)
Lang-Lazdunski[23]	2014	102 PD	68 (67%)	8 (8%)	–	–	–	26 (25%)
Lauk[24]	2014	251 EPP	152 (61%)	34 (34%)	–	–	–	62 (25%)
Spaggiari[25]	2014	516 EPP	305 (59%)	65 (13%)	–	–	–	146 (28%)
Sugarbaker[26]	2014	523 EPP	226 (43%)	116 (22%)	256 (49%)	136 (26%)	45 (9%)	181 (35%)
Baldini[27]	2015	169 EPP	86 (51%)	18 (11%)	–	–	–	52 (31%)
Bece[28]	2015	49 EPP	35 (71%)	2 (4%)	–	–	–	12 (24%)
Williams[29]	2015	117 PD	51 (44%)	8 (7%)	–	–	–	37 (32%)
Current		516 EPP 253 PD (82 other)	530 (63%)	58 (6%)	110 (13%)	52 (6%)	204 (24%)	256 (30%)

EPP, extrapleural pneumonectomy; PD, pleurectomy/decortication; IASLC, International Association for the Study of Lung Cancer.

clinical staging, as their outcomes may be more relevant to the population as a whole. In addition, although more than half of the cases were derived from retrospective institutional databases, a significant proportion of them (45%) were prospectively entered electronically by participating centers. These factors, coupled with more detailed information on anatomic N descriptors, make the current database significantly more robust than the previous iteration of the IASLC MPM staging database originally reported by Rusch et al.[12]

Analysis of the original IASLC database, which included 1056 patients with pN-category information, revealed survival differences between patients with node-negative (pN0) versus node-positive (pN1 or pN2) disease but no difference between pN1 and pN2.[12] Additionally, in a small subset of 181 patients on whom data were available, no difference in survival was observed according to the number of nodes harboring metastases. The present study, which included a slightly smaller number of patients with pN-category information (n = 851), corroborated these findings, revealing a significant survival difference between patients with pN0 and pN1 or pN2 disease; but again, no survival difference existed between pN1 and pN2. This supports the current stage grouping, whereby patients with N1 or N2 metastases are assigned the same overall stage (currently stage III). However, because the anatomic location of ipsilateral nodal metastases did not appear to influence prognosis, the data do not support maintaining the anatomic differentiation of current N1 and N2 categories and suggest that intrapleural (N1) and extrapleural (N2) should be collapsed into a single N category (N1) with N3 nodes becoming N2 in the eight edition of the TNM classification for MPM (Fig. 7).

The surgical literature varies with respect to the impact on survival of N1 versus N2 metastases (Table 4). Several authors report no differences in survival between patients with N1 and N2 metastases.[4,12,18,21] In a retrospective analysis of 50 patients undergoing EPP, de Perrot et al. reported the identical median survival of 10 months for patients with N1 (n = 8) and N2 (n = 21) metastases.[4] In a larger series of 212 patients undergoing either EPP or PD, Nakas et al. reported median survival for N1-positive patients (n = 23) of 11 to 12 months, which was not significantly different from the 11- to 14-month survival seen in patients with N2 metastases (n = 99).[21] In contrast, in a series of 348 patients who underwent cytoreduction, Flores et al. reported median survival of 19 months in 22 patients with N1 metastases (similar to pN0 patients), which was significantly better than that of pN2 patients (10 months [n=110]), although notably the number of N1 patients was small.[3] More recently, in the largest series reported to date, which included 529 patients with epithelioid MPM who underwent EPP, Sugarbaker et al. demonstrated significantly better survival in patients with N1 metastases (17 months [n = 116]) compared with that of patients with N2 involvement (13 months [n = 181]).[26]

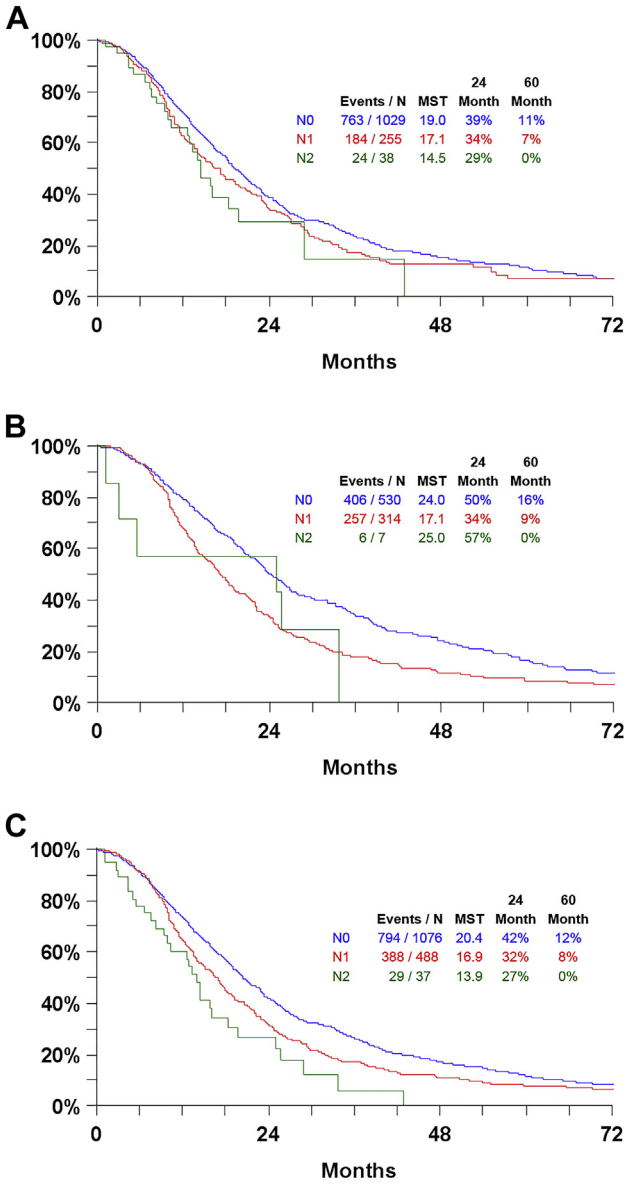

Figure 7. Kaplan-Meier curve for survival by proposed eighth edition N category in cases with N descriptor support: clinical staging (*A*), pathologic staging (*B*), and "best" staging (*C*). MST, median survival time.

It is difficult to interpret the reported literature for many reasons. A minority of patients (approximately 12%) present with isolated N1 disease; therefore, in most retrospective series the true impact of N1 nodes is likely to be statistically insignificant purely because of numerical insufficiency. Additionally, the reported incidence of nodal metastases is dependent on the extent of nodal sampling, which varies between surgeons and institutions (as we observed in the present study) and is also dependent on the type of resection performed—with more N1 nodes typically being evaluated with EPP than with PD. In the present study, only 58 patients (6%) had pN1 tumors, which is similar to the proportion reported by Flores et al. (7%) but low compared with that in many other studies.[3] It is therefore conceivable that N1 nodes may have been undersampled and perhaps included in the group of tumors staged as N0. If this is true, had patients with N1 tumors been identified, overall survival of the pN0 group would perhaps have been better. Additionally, the median survival that we observed in patients with N1 metastases (17 months from date of diagnosis, which preceded date of operation by a median of 3.6 months) is lower than that reported by Flores et al. and Sugarbaker et al., and the median survival of N2 patients (17 months) is on the higher end of the range reported in the literature, which may account for why survival differences were not observed between pN1 and pN2 patients in the present study.[3,26]

Several authors have reported differences in survival outcomes related to the pattern and extent of nodal involvement. Both Edwards et al. and Flores et al. observed that the number of metastatically involved nodes was predictive of survival; however, there was no survival difference among patients with pN1 plus pN2 nodes involved compared with among those with N2 metastases only, or between patients with nodal metastases in the paratracheal and subcarinal nodes versus in other sites.[3,15] Conversely, Richards et al. suggested that patients with metastases to paratracheal nodal stations[2–4] had worse survival than patients with involvement of internal mammary or lower mediastinal[5–9] stations (median survival 13 versus 7 months).[19] The same group subsequently reported worse outcomes in patients who had N1 plus N2 metastases (median survival 13 months) compared with in those with either N1 or N2 involvement only (median survival 17 and 16 months, respectively).[25] Although we did not collect information regarding nodal number (because of the inherent inaccuracies of reporting node number on account of fragmentation), we analyzed survival according to whether single or multiple stations were metastatically involved and observed no difference (median survival 18 versus 17 months, $p = 0.44$). However, like Sugarbaker et al. we found significantly worse survival in patients with N1 plus N2 involvement versus in those with involvement of only N1 or N2 nodes alone (median survival 14 months versus 17 and 19 months, respectively, $p = 0.0007$).[26] No significant survival differences existed between the latter (pN1 only or pN2 only), suggesting that anatomic location of nodal metastases per se may not influence prognosis as much as the cumulative extent of metastatic nodal involvement. However, definitive recommendations regarding the appropriateness of reclassifying N1 plus N2 as a separate N category will need to be based on future larger studies that standardize prospectively

Table 4. Survival of Patients Undergoing Cytoreductive Surgery with Respect to N1 and N2 Involvement

Author	Year	n	N0 (mo)	N1 (mo)	N2 (m0)	N1 vs. N2	Comment
Edwards[15]	2006	92 EPP	28 (N1, N0)		14	NS	No. positive nodes significant
dePerrot[4]	2007	50 EPP	29	10	10	NS	
Flores[3]	2008	324	19	19	10	<0.001	No. positive nodes significant
Buduhan[18]	2009	46 EPP	34	10	12	NS	
Richards[19]	2010	354 EPP	26	19	11	<0.0001	Superior mediastinal (stations 2-4) N2 had worse prognosis
Nakas[21]	2012	127 EPP	22	12	14	NS	
	2012	85 PD	16	11	11		
Rusch (IASLC)[a12]	2012	1191 EPP/299 PD	21	17	13	NS	
Sugarbaker[26]	2014	529 EPP	26	17	13	<0.05	N1 only and N2 only had similar survival. N1 + N2 had worse survival
Current[a]		516 EPP/253 PD	24	17	17	NS	

[a]Survival calculated from date of diagnosis (median 3.6 months before surgery).
EPP, extrapleural pneumonectomy; IASLC, International Association for the Study of Lung Cancer; PD, pleurectomy/decortication.

the extent of nodal sampling or dissection across institutions.

The present study also highlighted the known inaccuracies of cN staging.[12,33] Only 22% of tumors in 1029 patients were clinically staged as having nodal metastases, whereas the incidence of positive nodes in patients who underwent an operaiton was 38% (321 of 851 patients with surgical stage information). In fact, clinical assessment of N categories did not predict outcome, as survival curves for all cN categories were superimposed. In the subset of patients in whom both cN and pN categories were known, clinical staging was inaccurate in predicting pN status (κ statistic = 0.16), which underscores the inability of current staging modalities to reliably determine N categories preoperatively. Of note, only 56% of clinically staged patients had positron emissin tomography imaging and only 7% had mediastinoscopy. A more liberal use of invasive pretreatment nodal sampling is therefore recommended to improve accuracy of clinical nodal staging, although a significant proportion of positive nodes are located in anatomic regions inaccessible to mediastinoscopy or even to endoscopic techniques such as endobronchial and esophageal ultrasound (e.g., internal mammary nodes, peridiaphragmatic, etc.).[34] Other noninvasive predictors of nodal involvement (and hence survival) would also be highly useful, and in this regard the exploratory analysis we performed, which showed association between tumor thickness and nodal involvement, is very intriguing.

In conclusion, the data do not support maintaining the current anatomical-based classification of ipsilateral intrathoracic nodes as N1 and N2, as these nodal categories are not associated with different survival. Rather, survival appears to be influenced more by the extent of nodal involvement than by the specific location of the involved nodes. For these reasons, we recommend redefining any ipsilateral, intrathoracic node with metastatic involvement as N1 for the upcoming eighth edition of the TNM classification of MPM. Ipsilateral supraclavicular or contralateral nodes (previously N3) should be reclassified as N2 (Table 5). Electronic capture of reliable and detailed data documenting tumor involvement at specific nodal stations is planned to continue and may allow more accurate analysis regarding the prognostic significance of anatomic location and pattern of node metastases, which may lead to further refinement of N categories in the future. For now, because metastatic involvement of any lymph nodes is associated with poor prognosis, and especially in cases in which both intrapleural and extrapleural nodes harbor metastases, surgeons should be encouraged to perform detailed node dissections for all patients undergoing a cytoreductive

Table 5. Final Recommendations for N Descriptors for the Eighth Edition of the AJCC/UICC Staging Handbook

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

AJCC/UICC, American Joint Committee on Cancer/Union for International Cancer Control.

operation and to document precise locations of any metastatically involved lymph nodes. This will facilitate more accurate analyses to be performed in future iterations of the TNM classification system for pleural mesothelioma.

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Appendix

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