ORIGINAL ARTICLE

The IASLC Mesothelioma Staging Project: Improving Staging of a Rare Disease Through International Participation

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Received 20 July 2016; revised 30 August 2016; accepted 1 September 2016
Available online - 23 September 2016

ABSTRACT

For nearly 40 years, there was no generally accepted staging system for malignant pleural mesothelioma. In 1994, members of the International Mesothelioma Interest Group, in collaboration with the International Association for the Study of Lung Cancer, proposed a TNM staging system based on analyses of outcomes in retrospective surgical series and small clinical trials. Subsequently accepted by the American Joint Commission on Cancer and the Union for International Cancer Control for the sixth editions of their staging manuals, this system has since been the international staging standard. However, it has significant limitations, particularly with respect to clinical staging and to the categories for lymph node staging. Here we provide an overview of the development of the International Association for the Study of Lung Cancer malignant pleural mesothelioma staging database, which was designed to address these limitations through the development of a large international data set. Analyses of this database, described in papers linked to this overview, are being used to inform revisions in the eighth editions of the American Joint Commission on Cancer and Union for International Cancer Control staging systems.

Keywords: Mesothelioma; Staging; TNM; Registry

Early MPM Staging Recommendations

During the past 40 years, a number of several staging systems for malignant pleural mesothelioma (MPM) have been proposed. As described by Rusch and Venkatraman,[1]

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**See Appendix for the members of the IASLC Staging and Prognostic Factors Committee, Advisory Boards and Participating Institutions.

Disclosure: Ms. Giroux reports personal fees from her employment as a biostatistician at Cancer Research And Biostatistics during the analysis of the studies described in this article. The remaining authors declare no conflict of interest.

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ISSN: 1556-0864
http://dx.doi.org/10.1016/j.jtho.2016.09.123

the staging systems before the International Mesothelioma Interest Group (IMIG) staging system had been "to some extent imprecise and incompletely validated." The classification proposed by Butchart et al. suffered from an absence of TNM descriptors and vague statements regarding lymph node involvement and degrees of chest wall invasion.[2] Mattson's classification defined contralateral tumor involvement as stage II rather than stage III and has been abandoned.[3] Chahinian was the first to devise a TNM-based mesothelioma staging system, with an attempt to qualify the influence of such parameters as locoregional lymph node involvement as well as specific sites and extent of invasion.[4]

Origins of the IMIG Staging System

In 1994, at a workshop sponsored by the International Association for the Study of Lung Cancer (IASLC) and IMIG, MPM investigators analyzed reported surgical databases and the available small clinical trials in this disease. The data were used to create a TNM-based system that could potentially can be applied to the radiographic, surgical, and pathologic staging of MPM.[5] The precise TNM descriptors were developed by consensus during the meeting and were later critically reviewed by a large number of IMIG members, including the originators of previously proposed staging systems for MPM. One of the the key features of the IMIG staging system is that it separated out subsets of patients with early tumors by segregation of T stages according to the extent of disease as it related to the pleural surfaces, as well as according to the degree of invasion into these surfaces, guided by the work of Boutin et al.[6] This proposed staging system (Table 1) was accepted by the Union for International Cancer Control (UICC) and the American Joint Commission on Cancer (AJCC) as the international MPM staging system for the sixth and seventh editions of their staging manuals.[7] As predicted in the original article, the number of potential early-stage mesotheliomas diagnosed by aggresssive use of early thoracoscopy, greater awareness of the risks of abestos exposure, and a rise in the number of international experts in the management of the disease have justified separating Tl and T2NO subsets. Shortly after it was adopted in 1996, the IMIG staging system was validated in two surgical series of MPM and thereafter used in both retrospective analyses and prospective clinical trials.[1,8]

Nevertheless, there was unease about the validity of the IMIG staging system because it was derived chiefly from small, retrospective surgical series, making it difficult to apply to clinical staging in patients not managed surgically. Moreover, concerns were raised about the segregation of lymph node involvement in the disease, the influence of the type of operation performed for the disease, and the role of adjuvant therapy before or after resection with the increased use of pemetrexed and cisplatin either in an adjuvant or induction setting. Subsequently, Sugarbaker et al. proposed the alternative Brigham staging system based on tumor, resectability, and nodal status.[9] In 2010, a single-institution reevaluation of the Brigham system was published; it examined pathologic characteristics and explored correlations with outcome among 354 patients with epithelioid MPM who underwent extrapleural pneumonectomy (EPP).[10] T classification criteria were adjusted on the basis of margin status (negative for T1) and were only minimally concordant with the IMIG system with regard to the classification of T4. Nodal stations with internal mammary or inferior mediastinal involvement were grouped in stage I because they were associated with significantly longer duration of survival relative to those with involvement of lymph nodes in superior mediastinal stations (which were grouped as stages II, III, or IV). This raised the issue of whether patients undergoing surgical resections other than EPP and patients with a non-epithelioid tumor histologic type should be staged separately. It was clear that a large international staging database was needed to inform changes to the staging system in this rare disease.[11]

The First IASLC MPM Database

In an effort modeled on the revisions that the IASLC proposed for lung cancer staging for the seventh editions of the UICC and AJCC manuals, the IASLC, in collaboration with members of the IMIG, developed a large international database. Data were initially solicited from surgeons around the world known to care for a high volume of MPM patients and were transmitted to the statistical center, Cancer Research And Biostatistics in Seattle, Washington, as coded data without identifiable private patient information. Common data elements were established after review of each institutional database. The time frame chosen for data was 1995 to 2009, which was considered a contemporary period providing information relevant to potential revisions of the MPM staging system. The project was initiated in 2009 at the IASLC Workshop on Advances in Mesothelioma (26–27 February 2009, London, United Kingdom), at which time a white paper detailing uniform definitions for the use of surgery in mesothelioma was also planned to standardize the description of surgical cytoreductive procedures on account of the increasing interest in lung-sparing MPM operations.[11–14] Because the white paper was being formulated in parallel with the retrospective registry, the surgical procedures in the original database were classified in general terms as operations performed

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
	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 one of the following features: • Involvement of diaphragmatic muscle • 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 one of the following features: • Involvement of the extrathoracic fascia • Extension into the mediastinal fat • Solitary, completely resectable focus of tumor extending into the soft tissues of the chest wall • 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 one of the following features: • Diffuse extension or multifocal masses of tumor in the chest wall, with or without associated rib destruction • Direct transdiaphragmatic extension of tumor to the peritoneum • Direct extension of tumor to the contralateral pleura • Direct extension of tumor to one or more mediastinal organs • Direct extension of tumor into the spine • 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	
Ia	T1aN0M0
Ib	T1bN0M0
Stage II	T2N0M0
Stage III	Any T3M0 Any N1M0 Any N2M0
Stage IV	Any T4 Any N3 Any M1

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with either palliative or curative intent. The former included exploration, no resection, and palliative (i.e., partial) pleurectomy, whereas the latter included EPP, pleurectomy/decortication (P/D) for resection of all gross tumors, and P/D combined with anatomical lung resection other than pneumonectomy. Data on 3101 patients were submitted from 15 centers on four continents, with publication in 2012.[7] Both clinical and

pathological staging data were not available on all patients, and therefore clinical TNM and pathological TNM staging information were combined in 2316 patients to provide "best" staging in accordance with AJCC and UICC guidelines. Most patients (64.5%) had curative-intent procedures, with approximately half undergoing EPP. Upstaging based on final pathological TNM occurred in up to 80% of patients deemed to have clinical stages I or II disease but in only 22.8% of clinical stage III tumors and not at all in stage IV disease. Although overall survival data largely supported continued use of the original IMIG staging system, several important areas for improvement were identified. Key findings of the analyses were that (1) there was *poor* correlation between clinical and pathologic TNM staging, emphasizing the need for improvement in clinical/radiologic/surgical staging, especially in early-stage disease; (2) the stage groupings effectively separated patients by their median survival, but far more detailed data were needed to revise the T and N staging categories; (3) the epithelioid histologic type was associated with the best outcome and the sarcomatoid type with the worst; (4) survival was significantly influenced by whether the surgical procedure was performed with curative versus palliative intent (median survival 18 versus 12 months, $p < 0.0001$) and by the use of adjuvant therapy; and (5) stage I tumors resected by EPP with curative intent were associated with a median survival of 40 months, whereas those managed by P/D (supposedly for curative intent) had a median survival of 23 months but no differences in survival between EPP and P/D were identified in patients with higher-stage disease (Fig. 1). Multivariable analyses (Table 2) identified factors that independently influenced survival, including overall tumor stage ($p < 0.0001$), T category ($p < 0.0001$), N category ($p < 0.0001$), tumor histologic type ($p < 0.0001$), patient sex ($p = 0.0002$) and age ($p = 0.0025$), and type of operation (curative versus palliative, $p < 0.0001$). The multivariable analyses, however, did not show a significant survival difference between stages I and II, highlighting the need to add more precise clinicopathologic features to help clarify what is "early-stage" mesothelioma.

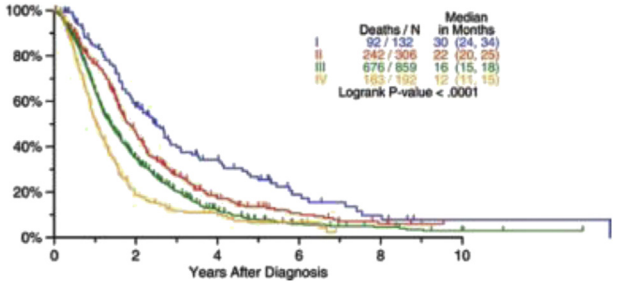

Figure 1. Overall survival by best staging for patients undergoing surgery with curative intent. The 95% confidence interval is shown in parentheses. Reprinted with permission from Rusch et al.[7]

Table 2. Cox Regression Model of Survival, Including Best Stage, Histologic Type, Sex, and Age (N = 2017)

Variable	Hazard Ratio	*p* Value
II vs. I	1.16	0.1153
III vs. II	1.47	<0.0001
III vs. II	1.27	0.0002
IV vs. I	1.86	<0.0001
IV vs. III	1.26	0.0008
Other histologic type vs. epithelial	1.70	<0.0001
Male vs. female sex	1.28	0.0002
Age, y		
50-45 vs. < 50	1.23	0.0058
≥65 vs. <50	1.31	0.0006
≥65 vs. 50-64	1.07	0.2500
Palliative vs. curative operation	1.71	<0.0001

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The white paper, published in 2011, was a premeditated strategy to deal with cytoreductive classification issues for the future.[15] Ultimately, procedure-based definitions emanated from a web-based survey of 62 experienced thoracic surgeons from 39 medical centers in 14 countries who operated on MPM for diagnosis, staging, palliation, or cytoreduction. The mean annual number of cytoreductive procedures performed per surgeon was eight. P/D was defined as resection of parietal and visceral pleura with the aim of achieving macroscopic complete resection by more than 70% of respondents. The term *radical P/D* was often used if the diaphragm or pericardium required resection, in contrast to P/D, in which these structures were not removed. Most surgeons believed that EPP (90%) or radical P/D (68%) could provide adequate cytoreduction, whereas only 23% thought that P/D could. The white paper led the International Staging Committee of the IASLC and the IMIG to recommend that P/D describe removal of all macroscopic tumor involving the parietal and visceral pleura and that the term *extended P/D* (or EPD) be used to describe parietal and visceral pleurectomy in conjunction with resection of the diaphragm and/or pericardium (Fig. 2).

Analyses of Supplementary Prognostic Variables in the First IASLC MPM Database

There was information in the database on supplementary clinical variables for MPM that included the use of chemotherapy or radiotherapy at any time (adjuvant therapy), smoking history, history of asbestos exposure,

RECOMMENDATION

On the basis of the survey data, which represented the opinions of experienced MPM surgeons from multiple centers in different geographical regions, the IASLC Mesothelioma Domain and the IMIG have recommended the following terminology to be used in the forthcoming Mesothelioma Staging Project:

a. EPP: en bloc resection of the parietal and visceral pleura with the ipsilateral lung, pericardium, and diaphragm. In cases where the pericardium and/or diaphragm are not involved by tumor, these structures may be left intact.
b. Extended P/D: parietal and visceral pleurectomy to remove all gross tumor with resection of the diaphragm and/or pericardium. The IASLC Mesothelioma Domain suggests use of the term "extended" rather than "radical" in this instance as the latter implies a completeness of resection with added therapeutic benefit. There is currently insufficient evidence that resection of the pericardium and diaphragm provides either.
c. P/D: parietal and visceral pleurectomy to remove all gross tumor without diaphragm or pericardial resection.
d. Partial pleurectomy: partial removal of parietal and/or visceral pleura for diagnostic or palliative purposes but leaving gross tumor behind.

Figure 2. Recommendations for uniform classification of MPM cytoreduction. MPM, malignant pleural mesothelioma; IASLC, International Association for the Study of Lung Cancer; IMIG, International Mesothelioma Interest Group; EPP, extrapleural pneumonectomy; P/D, pleurectomy/decortication. Reprinted with permission from Rice et al.[15]

history of weight loss (defined as more than 5% versus less than 5% in the previous 6 months), Eastern Cooperative Oncology Group performance status, chest pain, and dyspnea. Laboratory parameters that were also analyzed included hemoglobin, white blood cell count and platelet count, and many of these had been alluded to in single-institutional series studying MPM. A total of 2141 patients with best TNM stages (pathologic with or without clinical staging) could be used to develop prognostic models for the patient having cytoreductive surgery (scenario A), the individual with only clinical TNM (scenario B), and the patient with newly diagnosed disease and limited data.[16] Three prognostic models were defined. *Scenario A* (cytoreduced patients with surgical staging) was defined on the basis of best pathologic stage, histologic type, sex, age, type of surgery, induction or adjuvant treatment, white blood cell count (WBC) ($\geq$15,500 per mm^3), and platelets ($\geq$400,000 per mm^3) (n = 550). *Scenario B* (no surgical staging) was defined by clinical stage, histologic type, sex, age, type of surgery, adjuvant treatment, WBC, hemoglobin ($<$14,600 per mm^3), and platelets (n = 627,000 per mm^3). *Scenario C* (limited data, but available at MPM diagnosis) was defined by histologic type, sex, age, WBC, hemoglobin, and platelets (n = 906,000 per mm^3). The analyses were limited by missing data for key clinical parameters, including weight loss and presence of pain; however, the prognostic importance of laboratory-based tests alluded to in many previous reports was validated.

The Second IASLC MPM Database

In planning for the eighth editions of the AJCC and UICC staging manuals, an expansion of the IASLC mesothelioma database to address the controversies raised by the initial analysis was started in July 2013. Enhanced information to improve the T, N, and M descriptor analyses was formulated into an electronic data capture (EDC) system developed at Cancer Research And Biostatistics, through which additional MPM cases could be submitted electronically to the database with an appropriate level of staging detail. Additional investigators who could provide valid information on patients with tumors staged clinically and managed nonsurgically were recruited. The EDC included all of the descriptors for the T and N categories in order to determine whether any of those descriptors should be realigned into different categories, whether any of the T and N categories should be expanded or deleted, and whether any of the TNM stage groupings should be changed.[17] As of the data submission of June 1, 2014, a total 3519 MPM cases, 2460 of which were considered eligible for analysis after data review, were submitted from 29 centers spanning four continents. Cases diagnosed as early as 1995 were included provided they met data quality standards, but 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.

It must be pointed out that clinical databases have limitations. The most obvious problems for the MPM database include a predominance of surgical cases in a disease for which most patients are treated medically and lack data for nonsurgical staging tools such as positron emission tomography, endobronchial ultrasound, and endoscopic ultrasound. It is through continued refinement by the IASLC that these potential limitations will be minimized.

The articles linked to this overview[18,19,20] provide detailed analyses of this second IASLC MPM database that serve as the primary source supporting changes to the eighth editions of the AJCC and UICC staging systems. They also emphasize the importance of continuing to accrue staging information to this international database and identify areas for improvement for the ninth edition of the staging systems.

Appendix

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