Malignant pleural mesothelioma : rationale for a new TNM classification

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Malignant Pleural Mesothelioma : Rationale for a New TNMClassification

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Abstract. *Background :* Malignant pleural mesothelioma (MPM) is a rare but aggressive thoracic malignancy with a poor prognosis. In this regard, a well-defined staging system is of utmost importance in order to correctly diagnose and assign an appropriate treatment to the patient.
Methods : The current TNM-staging system (7th edition) enables to either clinically or pathologically stage the severity of the disease according to extension of the tumor (T), number of nodes (N) and presence of metastases (M). Patients with stage I-III are considered for surgery, while palliative treatment is indicated for stage IV patients according to the current classification.
Results : Despite its widespread use, the validity of this staging system is questioned due to the low prevalence, histological variety and retrospective nature of the previous study design. In addition, the role of specific treatment modalities including surgery, has yet to be determined, especially for treatment of early-stage disease. In this regard, the International Association for the Study of Lung Cancer (IASLC) initiated the multi-centre, prospective "Mesothelioma Staging Project" in order to address limitations of the 7th edition and to optimize the staging system in accordance to current needs.
Conclusions : An improved staging system will contribute to the design of prospective multi-institutional clinical trials investigating novel treatment strategies for mesothelioma. In this way comparison of outcome between different medical centres also becomes feasible.

Abbreviations

MPM, Malignant pleural mesothelioma
T, tumor
N, nodes
M, metastases
IASLC, International Association for the Study of Lung Cancer
IMIG, International Mesothelioma Interest Group
UICC, International Union against Cancer
AJCC, American Joint Committee on Cancer
cTNM, clinical TNM
pTNM, pathological TNM
NSLC, non-small cellular lung cancer
P/D, pleurectomy/decortication
EPP, extra pleural pneumonectomy

Introduction

Malignant pleural mesothelioma (MPM) is a rare and aggressive thoracic neoplasm with a low survival rate (8-14 months) upon diagnosis. The malignancy originates within the parietal pleura of the lung and is predominantly caused by exposure to asbestos, a silicate mineral frequently used as insulation in buildings. However, other carcinogenic factors such as genetic predisposition, ionizing radiation, chemicals and metals have been associated with the disease development (1).

Despite the banishment of asbestos in most European countries and the United States, a peak incidence between 2015 and 2020 has been predicted for MPM due to slow development of the malignancy and the latent and persistent properties of asbestos in the lung upon initial exposure (2, 3). On the other hand, some developing and economic powerful countries such as Russia, India, China and Brazil are still producing large amount of asbestos and are likely to be confronted with a sharp increase in MPM incidence in the near future (1, 4).

In addition to demography (i.e. asbestos-related jobs) prognosis is also affected by other factors such as age, gender and histology. Male patients have a higher risk to develop MPM due to the fact that the disease is correlated with professions predominantly performed by men (i.e. construction workers) (2).

Several histological types of MPM exist with different morphological and growth properties resulting in quite different outcomes. Epithelioid mesothelioma has the best prognosis, while the sarcomatoid mesothelioma is more aggressive due to its fast penetration of the thoracic wall and diaphragm resulting in extensive loco regional disease and poor prognosis. Current prognostic scoring systems make use of negative prognostic factors such as age $\geq$ 75 years, male sex, presence of pain, appetite loss, lactate dehydrogenase $\geq$ 500 IU*L^{-1}, a platelet count

higher than 400×10^{12}*L^{-1}, advanced stages (III-IV) and non-epithelioid histology (5).

Materials and Methods

7th edition of the TNM-classification

Given the clinical necessity to diagnose MPM correctly, different pathologic staging systems have been proposed in the past. Some of these use a classification of stages I to IV without precise TNM descriptors whereas others are based on tumour extension (T), number of affected nodes (N) and metastases (M) (6). Most of the early staging modules were, however, based on small single-centre experience and were lacking validation (5, 7). Given the overall discrepancy between these different systems, the International Mesothelioma Interest Group (IMIG) attempted to develop a universal staging module in 1995 based on an analysis of several retrospective datasets. The working group consisted of pulmonary physicians, thoracic surgeons, medical oncologists, radiotherapists, radiologists, epidemiologists, pathologists and medical scientists. This has led to the first staging system in accordance with the TNM-classification for solid tumours, in which tumour, lymph node status and metastasis are evaluated to predict overall survival (6). Over the years, the staging system has been further revised leading to the current 7th edition, which has been adopted by the International Union against Cancer (UICC) and the American Joint Commission on Cancer (AJCC) (Table 1) (6-8). The current standard enables to determine treatment options and prognosis (8-23 months) based on disease staging using anatomic features (Table 2), and also improves data exchange between clinicians and medical centers (9, 10).

Table 1. Definitions for T, N and M descriptors of the 7th edition of the TNM-classification for MPM (Used with the permission of the Union for International Cancer Control (UICC), Geneva, Switzerland. The original source for this material is *TNM Classification of Malignant Tumours*, *7th Edition*, by L.H. Sobin, M. K. Gospodarowicz and C. Wittekind (eds.), published by Wiley-Blackwell).

T : Primary tumor
TX : Primary tumor cannot be assessed
T0 : No evidence of primary tumor
T1 : Tumor involves ipsilateral parietal pleura, with or without focal involvement of the visceral pleura
T1a : Tumor involves ipsilateral parietal (mediastinal, diaphragmatic) pleura. No involvement of the visceral pleura
T1b : Tumor involves ipsilateral parietal (mediastinal, diaphragmatic) pleura, with focal involvement of the visceral pleura
T2 : Tumor involves any of the ipsilateral pleural surfaces, with at least one of the following : • Confluent visceral pleural tumor (including the fissure) • Invasion of diaphragmatic muscle • Invasion of the lung parenchyma
T3 : Tumor involves any of the ipsilateral pleural surfaces with at least one of the following : • Invasion of endothoracic fascia • Invasion into mediastinal fat • Solitary focus of tumor invading soft tissues of the chest wall • Non-transmural involvement of the pericardium
T4 : Tumor involves any of the ipsilateral pleural surfaces with at least one of the following : • Diffuse or multifocal invasion of soft tissues of chest wall • Any involvement of rib • Invasion through diaphragm to peritoneum • Invasion of any mediastinal organ(s) • Direct extension to contralateral pleura • Invasion into the spine • Extension to internal surface of pericardium • Pericardial effusion with positive cytology • Invasion of myocardium • Invasion of brachial plexus
N : Regional lymph nodes
NX : Regional lymph nodes cannot be assessed
N0 : No regional lymph node metastasis
N1 : Metastases in the ipsilateral bronchopulmonary and/or hilar lymph node(s)
N2 : Metastases in the subcarinal lymph nodes and/or ipsilateral internal mammary or mediastinal lymph node(s)
N3 : Metastases in contralateral mediastinal, internal mammary, or hilar lymph nodes and/or ipsilateral or contralateral supraclavicular or scalene lymph node(s)
M : Distant metastasis
M0 : No distant metastasis
M1 : Distant metastasis

Table 2. Stage grouping of the 7th edition of the TNM-classification for MPM, treatment options and prognosis ('Frequency' and 'Median survival time' based on (1), 'Stage grouping' used with the permission of the Union for International Cancer Control (UICC), Geneva, Switzerland. The original source for this material is *TNM Classification of Malignant Tumours*, *7th Edition*, by L.H. Sobin, M. K. Gospodarowicz and C. Wittekind (eds.), published by Wiley-Blackwell).

Stage	Tumor (T)	Lymph Nodes (N)	Metastasis (M)	Frequency	Treatment	Median survival time
Stage I	T1	N0	M0	8%		23 months
Stage IA	T1a	N0	M0			
Stage 1B	T1b	N0	M0			
Stage II	T2	N0	M0	8%		15 months
Stage III	T1, T2	N1	M0	17%		10 months
	T1, T2	N2	M0			
	T3	N0, N1, N2	M0			
					Potentially Resectable	
					Unresectable	
Stage IV	T4	Any N	M0	67%		8 months
	Any T	N3	M0			
	Any T	Any N	M1			

(1) The International Association for the Study of Lung Cancer (IASLC) Prospective Malignant Pleural Mesothelioma Staging Project; Protocol For Purpose Of Grant Application And Ethics Review 2011. Available from: https://iaslc.crab.org/MPM/MesoProspectiveProtocolRev23Aug2011.pdf.

Results

Despite being the "gold standard", the 7th edition of the TNM-classification is confronted with several important limitations. First of all, the current MPM staging system is generally based on small single institutional retrospective data (9).

From a medical oncological perspective, it is very difficult to clinically distinguish between several tumor descriptors (T1 vs. T2) and specific T3 properties (i.e. endothoracic fascia invasion) using the current imaging techniques, which leads to upstaging based on final pathological outcome in approximately 80% of the cases clinically (c) staged as stage I or II (9). This also highlights the discrepancy between cTNM and pathological (p) TNM staging, especially in early-stage disease. Moreover, MPM is not a spherically but a longitudinally growing tumor with unpredictable spread along the pleural surfaces resulting in a highly variable loco regional extension (9). Therefore standardized algorithms that provide the most accurate and cost-effective approaches to precise clinical staging are needed, although comparison between cTNM and pTNM may help in evaluating the accuracy of the clinical and imaging methods used to determine the cTNM (9, 10). In this regard it is important to retain the clinical as well as the pathological classification in the medical records (10).

The staging of lymph nodes was adopted from non-small cell lung cancer (NSCLC) staging, while lymphatic drainage in MPM is different from the NSCLC. While the absence (N0) and presence (N+) of metastatic nodes is clearly prognostic, no differences have been shown between N1 and N2 disease, neither has the number of affected nodes an influence on prognosis (7, 9). In addition, overall survival did not show any difference between T1 and T2 and between stage I and II, even when prognostic factors (age, sex and histology) were taken into account. This urges the necessity to revise tumor and node descriptors and stages I and II (9).

Although histology is a powerful prognostic factor due to the large difference observed in survival (19 months vs. 8 months for epithelioid and sarcomatoid type, respectively), it is not incorporated in the current staging system, as well as specific pre-treatment laboratory values (hemoglobin, white blood cell count, etc.) and biomarkers (e.g. mesothelin) which have been suggested by previous researchers to be predictive (8).

In order to address these limitations, the International Staging Committee of the International Association for Lung Cancer (IASLC) in collaboration with the International Mesothelioma Interest Group (IMIG) initially collected retrospective data and currently has launched the "Prospective Mesothelioma Staging Project" for the revisions for the 8th edition in January 2017. The project is an international, multi-institutional cohort study led by the Cancer Research and Biostatistics organization (CRAB, Seattle, US) collecting demographic, diagnostic and treatment data from newly diagnosed MPM patients in a prospective manner. Detailed histological, surgical and anatomical information, as well as blood markers are assessed for their prognostic value for the optimization of the current staging system (9).

Treatment according to stage

The curative and palliative intent of MPM treatment is strongly dependent on correct staging. However, the optimal treatment of MPM has not yet been established and is still under investigation (11). Due to the ineffectiveness of single-modality therapy, treatments with curative intent tends to make use of a multimodality approach, combining (neo)adjuvant chemotherapy, surgery and radiotherapy (12, 13). Despite this radical and aggressive approach, recurrence of MPM is almost inevitable and remains the chief barrier to long-term survival (14, 15). In addition, multimodality approaches are reserved for a carefully selected subgroup of patients because of the considerable morbidity and mortality, and the already advanced disease stage in most patients when diagnosed (12, 13). Early disease stages I-III are considered surgically resectable but require extensive cardiopulmonary evaluation and multidisciplinary discussion in order to assess patient's eligibility (Table 2) (19). Stage IV is considered unresectable (Table 2). Treatment options include symptom control, palliative chemotherapy, surgery and radiotherapy (13).

Surgery

There are currently two major surgical procedures to remove or debulk MPM, namely extended pleurectomy/decortication (P/D) and extra pleural pneumonectomy (EPP). Adjuvant chemotherapy and/or radiotherapy then complete the process by eliminating microscopic residual tumor at the surgical margins to prevent local recurrence or widespread hematogenous or lymphatic dissemination. Also, induction therapy may be applied in order to reduce the tumor volume and obtain a more complete resection by a subsequent surgical procedure (12). These concepts form the basis of multimodality therapy in MPM (15). Despite the availability of both surgical procedures, benefit of MPM surgery remains highly controversial due to difficulties to obtain complete resection (R0), high locoregional recurrence rates and considerable morbidity and mortality (16, 17).

In general, surgical resection is considered for stages I to III in patients who are functionally operable and can tolerate extensive surgery (18). Because of significant variation in surgical nomenclature for MPM, a combined working group of the IASLC and IMIG recently established precise definitions of these procedures (19).

Extended pleurectomy-decortication (P/D)

Extended P/D includes parietal and visceral pleurectomy to remove all gross tumours with diaphragmatic or pericardial resection, if involved by tumor. Lung parenchyma is not resected. The procedure can be performed by open thoracotomy or by video-assisted thoracic surgery (VATS), whereby the latter is feasible but not generally applied (1). Complete resection is obtained in early stages, while in more advanced stages P/D is a debulking procedure as it frequently leaves microscopic residual tumor behind. In addition to a lower mortality and morbidity rate compared to EPP, recent data suggest that extended P/D can be effective in patients with operable advanced disease (stages II-III) and mixed (biphasic) histology even in the presence of high-risk factors (poor performance and co morbidities) (1, 18).

Extrapleural pneumonectomy (EPP)

EPP is defined as an en bloc resection of the parietal and visceral pleura with the ipsilateral lung, pericardium and diaphragm, which are reconstructed with a soft tissue patch. This procedure is considered to provide maximal macroscopic tumor resection to obtain a longer disease-free survival, which was demonstrated in stage I disease from the retrospective IASLC database (9, 14, 17). However, no significant benefit was found of this procedure in the Mesothelioma and Radical Surgery 1 (MARS 1) trial, which was a feasibility study randomizing patients between EPP and no EPP after induction chemotherapy. Moreover, the authors even advised against the use of EPP due to the high morbidity and mortality of EPP in this trial (1, 16, 17, 20). However, only a limited number of patients underwent EPP in the MARS 1 trail making this study clearly underpowered. Therefore, EPP is still considered in patients with resectable early-stage disease (stages I-II), epithelioid histology and good performance status without significant morbidities (18).

Discussion

It is important that trials investigating the benefit of surgery in MPM make use of uniform definitions of the different procedures and that these operations are performed as prescribed. Only then it is possible to compare and review trials concerning this aspect of multimodality therapy and draw correct conclusions.

It should be noted that it is challenging to evaluate new therapies for MPM, because of some specific characteristics of this tumor. First of all, many trials are small because of the rareness of the disease, which compromise the statistical conclusions that can be drawn. Also the histological heterogeneity of MPM with different outcomes may affect the results of a trial when this is not taken into account. As outlined before, precise clinical staging is difficult in MPM which may lead to a variety of different pathological stages in the study population. Therefore, it is also difficult to measure the response of a specific treatment modality. Multicenter trials should be designed with a large uniform patient population to obtain the most meaningful data. This again underscores the

importance of an internationally accepted and validated staging system. Hopefully, the prospective IASLC database will collect significant data to create such a valid staging system.

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