The International Association for the Study of Lung Cancer (IASLC)
Staging Project
In Malignant Pleural Mesothelioma (MPM)

PROCOTOL
FOR PURPOSE OF GRANT APPLICATION AND ETHICS REVIEW

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1.0 OBJECTIVES

1.1. The primary objectives of this study are:

1.1.1. To assess the prognostic value and validity of components of the eighth edition of the tumor, node, metastasis (TNM) classification for malignant pleural mesothelioma (MPM) [1,2] with respect to the overall survival of patients with newly diagnosed MPM.

1.1.2. To identify and validate additional descriptors for possible inclusion in future revisions to the TNM classification.

1.2. T-Component objectives:

1.2.1. To assess the classification capacity of each descriptor defining T-status.

1.2.2. To study new conditions not included in the present T (e.g., pleural thickness at pre-defined "upper", "middle", and "lower" regions of the pleura).

1.3. N-Component objectives:

1.3.1. To assess the prognostic impact of N-status.

1.3.2. To study alternative definitions of N status conditions (e.g., defining N-status according to number of positive nodes or intrapleural vs extrapleural location of positive nodes).

1.4 M-Component objectives:

1.4.4 To assess the prognostic impact of M-status.

1.4.5 To assess the prognostic impact of single metastasis in a single organ vs multiple metastases in a single organ vs multiple metastases in several organs.

1.5 Specific objectives regarding prognostic factors:

1.5.1 To assess the prognostic impact of histologic type and subtype, with particular interest in epithelial mesothelioma vs other histologies.

1.5.2 To describe the correlation of staging methods utilized in clinical staging (for those patients with pre-treatment and post-surgical assessment).

1.5.3 To assess the prognostic impact of clinical factors, including performance status, co-morbidity as measured by the Colinet scale, [3] weight loss or other symptoms, and pulmonary function tests, among others.

1.5.4 To assess the prognostic impact of pre-treatment laboratory values, such as hemoglobin, white blood cell count, and platelet count, and biomarkers such as mesothelin, which have been suggested by previous research to be predictive of survival of patients with MPM.

1.5.5 To assess the prognostic impact of maximum standard uptake value (SUV max) for those patients with disease scanned by positron emission tomography (PET) scans prior to treatment (including pleurodesis).

2.0 BACKGROUND

During the past 20 years, both the methods of staging and the staging system for malignant pleural mesothelioma (MPM) have changed significantly. PET/CT (including SUV measurements), mediastinoscopy, MRI, laparoscopy, and VATS are now routinely used to enhance the clinical staging information provided by CT scanning. Use of these clinical staging modalities varies across institutions, and future studies should address the most cost-effective approach to clinical staging. Serum markers such as mesothelin may also add information about disease extent and stage but need to be studied further in large data sets.

Prior to 1995, at least six different staging systems had been proposed, none of which was well validated or widely accepted. To address this problem, the Internal Mesothelioma Interest Group (IMIG) developed a TNM staging system in 1995 that was based on published series of patients for whom there was reliable surgical / pathological staging information. [4] The IMIG system was subsequently accepted by the International Union Against Cancer (UICC) and the American Joint Cancer Committee (AJCC) and became the international staging system for MPM in the 6th edition of their staging manuals. However, the surgical series on which the IMIG staging system was based were retrospectively amalgamated and relatively small. In addition, some of the T descriptors in the current staging system are difficult to apply to patients who are managed non-surgically. N staging was nearly identical to what was used for non-small cell lung cancer (NSCLC); however, the patterns of lymphatic drainage for MPM are distinct from those of NSCLC.

Therefore, in collaboration with the IMIG, the International Association for the Study of Lung Cancer (IASLC) Staging and Prognostic Factors Committee (SPFC) developed a staging project to improve the current staging system for malignant pleural mesothelioma. This effort was organized along the same lines as the IASLC staging project in lung cancer, which has been a primary source for evidence-based recommendations for the TNM system for lung cancer, published extensively and accepted by the UICC and AJCC for both the 7th and 8th editions of TNM. [1,2,5,6] The mesothelioma staging project was initiated in 2009 at the IASLC Workshop on Advances in Mesothelioma (26-27 February 2009). [7] The development of an initial, international MPM database of surgically managed cases was planned, which ultimately accrued 3,101 patients with MPM diagnosed from 1995-2009 [8,9] and showed that it was feasible to conduct this study on an international scale. However, it was recognized that the lack of uniformity and granularity in these various data sources would imply the need for prospectively defined endpoints. Thus, data elements for a subsequent database with centralized collection were agreed by consensus, designed to be applicable to radiographic, surgical, or pathologic staging of MPM. With centralized collection, uniform definitions could be applied to previously ambiguous terms such as pleural thickness or the terminology for surgical cytoreductive procedures [10] in mesothelioma.

Overall survival data from the initial database of surgically managed cases largely supported continued use of the IMIG system for the 7th editions of the staging manuals; however, several important areas for improvement were identified, particularly for the T

and N descriptors. The centralized data collection effort, supplemented by external data sources, yielded a database of 2,414 patients diagnosed from January 1995 to June 2013 from 29 centers around the world, from which the IASLC SPFC developed recommendations toward the eighth edition of the TNM staging system. These recommendations were published in 2016 [11,12,13] and were accepted by the UICC and AJCC in 2017 (with AJCC implementation effective in 2018). [1,2] T1a and T1b were collapsed into T1 for both clinical and pathologic T-descriptors, [11] and N1 and N2 were collapsed into a single N category comprising ipsilateral, intrathoracic nodal metastases (M1), and nodes previously categorized as N3 were reclassified as N2. [12] Overall stage groupings were reconfigured, moving from four stage groups (I, II, III, IV) in the 7th edition to six stage groups (I, IIA, IIB, IIIA, IIIB, IV) in the 8th edition. [13] Measurement of pleural thickness at three levels of the pleura, by standardized measurement, was concluded to have prognostic significance and recommended for further study as a potential new T-descriptor. [11] Additionally, computed-tomography based calculations of tumor volume, evaluated in a pilot study involving a subset of patients from this data base, was found to have acceptable correlation between blinded observers, and was recommended to be further explored. [14, 15]

As the project enters its next phase, with the goal of developing recommendations for the 9th edition of TNM, its continued success will depend on the extent of the international participation and the quality of the data. The subset of cases that were centrally collected was instrumental in the development of the 8th edition recommendations due to the level of detail and consistency of the submitted data.

The study population is patients newly diagnosed with cytologically or histologically confirmed, malignant pleural mesothelioma. Broadly, the data to be collected include patient characteristics, baseline laboratory values and pulmonary function tests, SUV max if pleura was assessed by positron emission tomography (PET), pre-treatment tests on which TNM is based, treatment, TNM plus supporting evidence, and survival. Pre-treatment TNM will be collected for all cases; post-surgical TNM, for surgically managed cases. T-descriptors describe the degree of invasion of the pleural surfaces and extension to adjacent structures such as the chest wall, lung, mediastinum, diaphragm, pericardium, heart, and spine, with additional qualification of pleural thickening and pericardial and pleural effusions. M-descriptors characterize discontinuous involvement of the contralateral lung and more distant sites of metastases. Nodal station involvement is described via the IASLC 2009 nodal map. [16]

This document is provided to collaborating institutions so that we may standardize the processes and procedures for collecting these data about patients newly diagnosed with MPM, while ensuring that private information is gathered in compliance with applicable law and with respect and regards for human subjects.

3.0 STUDY DESIGN

This is an international, multi-institutional cohort study that will collect information on the extent of disease, personal and demographic characteristics, comorbid illness status, treatment and survival of newly-diagnosed patients with malignant pleural mesothelioma. Ideally, an inception cohort would be enrolled prospectively at each site, and data will be collected using a standardized abstraction tool. However, we anticipate a substantial number of cases submitted by participating sites may be transferred to the project rather than entered directly into the EDC system. These datasets will vary in terms of data elements, and some may only be used to answer some of the questions that arise as part of the initial analyses.

Data completeness and logic checks will be conducted on an ongoing basis. Analyses will be conducted at CRAB. Each participating institution will have access to its own patients' data and will be eligible to conduct secondary investigations of the larger database subject to approval by the IASLC. [17]

4.0 SAMPLE SELECTION

Based on the experience from the original retrospective study, three types of study samples will be targeted, depending on the nature of the collaborating institution: population-based, institution-based and clinical series. In each case, the intention is to describe the experience of an unselected group of patients. Sample selection for each is described below.

4.1. Population-based sample selection will likely involve enhancement of a population-based cancer registry with the data elements required for this study. All patients diagnosed within the study period may be included or a random sample of same. Documentation of the population coverage of the registry will be required for a sample to fall into this category.

4.2. Institution-based sample selection will likely involve the capture of information on all newly-diagnosed patients with malignant pleural mesothelioma seen at that institution during the period of the study. Usually, this involves the use of an institution's tumor registry that will be enhanced with the data elements required for this study. Description of the institution's referral pattern will be required.

4.3. Clinical series sample selection will capture information on an inception cohort of all newly-diagnosed patients presenting to a defined clinical service during the period of the study. All such patients will be tracked with documentation regarding data completeness and losses to follow up.

5.0 STAGING CRITERIA

Disease will be staged according to the eighth edition of the tumor, node, metastasis (TNM) classification for malignant pleural mesothelioma.

6.0 INTERVENTION

Subjects will not be assigned to any specific intervention as a result of inclusion in this observational data base.

7.0 ELIGIBILITY CRITERIA

7.1. Subjects must have newly diagnosed, malignant pleural mesothelioma.

7.2. Mesothelioma must be confirmed by histology or cytology. The data set used to develop the core recommendations for the 9th edition of TNM will primarily include patients diagnosed on or after July 1, 2013. Patients diagnosed between January 1, 1995 and June 30, 2013 may be included in supportive analyses, such as validation, or if there is a need to increase sample sizes for distinct subgroups.

7.3. For a subject to be eligible for inclusion, there must be sufficient information available to classify the subject according to the eighth edition of the TNM classification for pleural malignant mesothelioma.

8.0 DESCRIPTIVE FACTORS

Patients will be described by pretreatment T, N, and M status, treatment (surgically managed vs not), by country of origin and study sample type. Enrollment will be monitored with respect to these descriptive factors to track recruitment of specific subgroups defined by geography, stage, or treatment modality with a view to targeting additional institutions and/or clinical settings if under-representation exists.

9.0 STATISTICAL CONSIDERATIONS

The IASLC SPFC and the Mesothelioma Advisory Board intend to submit recommendations for proposals for change regarding the 9th edition of the TNM classification for the staging of MPM on or before 2024, subject to the review schedules of the UICC and AJCC. However, it is the intention of the IASLC to continue to collect MPM cases beyond this date, to order to inform future revisions of the staging guidelines.

This international database is not a population-based registry and the stage distribution is not expected to reflect the distribution of mesothelioma stages in the general population. In the data set used to inform recommendation for the 8th edition of TNM, five year survival was 16% for Stage IA (356 patients), 13% for Stage IB (906 patients), 10% for Stage II (254 patients), 8% for Stage IIIA (318 patients), 5% for Stage IIIB (473 patients), and 0% for Stage IV (107 patients), by best stage.

Given the previous data base, power calculations are based on the accrual expectation of 2,300 patients diagnosed from July 2013 to end 2019 with an additional year of follow-up, including 300 Stage IA patients, 1100 Stage IB/II patients, 800 Stage IIIA/IIIB patients, and 100 Stage IV patients. For the purposes of sample size justification, Stage IB and II are consolidated into IB/II and Stage IIIA and IIIB into IIIA/IIIB. Power calculations are based on a 6.5 year accrual period with one additional year of follow-up and one-sided tests of size .05. Given median survival of 23 months for Stage I, a hazard ratio of 1.21 (19 months) for Stage IB/II relative to Stage I could be detected with 81% power. Given median survival of 19 months for Stage IB/II, a hazard ratio of 1.36 (14 months) could be detected for Stage IIIA/IIIB relative to Stage IB/II with 99% power. Given median survival of 14 months for Stage IIIA/IIIB, a hazard ratio of 1.4 (10 months) could be detected for Stage IV relative to Stage IIIA/IIIB with 92% power. Based on the method proposed by Bernstein and Lagokos, [18] these power calculations assume uniform accrual over time, no loss to follow-up, exponentially distributed death times, and use of the logrank test.

12.0 DE-IDENTIFICATION OF DATA

All sites must agree to gather identifiable private information of research subjects in compliance with applicable law and with respect and regards for human subjects. Each participating institution will secure approval of the project from its local Research Ethics Board.

Participating sites must agree unequivocally to prohibit release of individually identifiable private data to CRAB for research purposes. CRAB will receive only 'coded' data for analysis. The 'coded' data sent to CRAB must not be able to be linked to individual research subjects, either directly or indirectly through the coding system, by any member of CRAB's research team. Where personal identifiers might inadvertently be included with data received, CRAB will delete/destroy this identified data, and immediately notify the site to replace with de-identified data.

While visiting the site, CRAB staff may access or utilize individually private information but these activities become subject to the oversight of the site's Institutional Review Board. At no time will CRAB employees record any private information.

Because only de-identified data are submitted to CRAB, as an institution, CRAB is not considered to be "engaged" in human subjects' research for this project.

13.0 DATA COLLECTION PROCESSES

With the exception of the outcome data, most of the data collected for this study will occur around the time of diagnosis and treatment. The last date of follow up and vital status of each study subject will be updated at each follow-up visit with a frequency of at least once per year.

Institutions approved by the SPFC for participation in this project will enter the data online using a secure, web-based data entry system or transfer data from an existing database. Designed and administered by Cancer Research and Biostatistics (CRAB), the system will incorporate between-field logic checks and provide a query system enabling communication between CRAB and the institutions regarding the data. The system will provide users the ability to download data entered by that institution.

It is the intent of the project to follow each subject until death.

14.0 SITE APPLICATION MATERIALS

This section lists the necessary application materials for any site interested in contributing data to the staging project. These application materials and other supportive documentation, including the data dictionary for the project, can be accessed online at https://iaslc.crab.org/MPM/MPMStagingProject.pdf .

14.1 IASLC Data Use Agreement
14.2 CRAB Data Use Agreement
14.3 Account Request Form
14.4 Site Cohort Description Form

15.0 PROPERTY OF THE DATA BASE AND PUBLICATION POLICY

Each institution will retain full access and publishing rights to its own data; however, the collective database will be the property of the IASLC, and CRAB will be responsible for its management, storage, and analysis.

Publications related to the objectives of this Staging Project of the IASLC SPFC (i.e., publications providing recommendations for changes in the TNM classification) will be planned, researched, analysed, and written by the members of the Committee.

16.0 SECONDARY USE OF THE IASLC DATA BASE

The IASLC Staging Project has a duty to ensure that the data within its database are used to maximum benefit for the good of patients and the thoracic oncology research community, within ethical constraints and the agreements entered into with individual databases. All requests for the secondary use of the database will be subjected to the following review mechanism:
An initial, outline proposal should be submitted to the chair of the committee. This will be reviewed by e-mail by a subcommittee consisting of the chair person, a CRAB member of the committee, and the chair of the relevant subcommittee. If the request is considered to be a reasonable proposal, the applicant will be asked to submit a full application containing the following, additional documents:

a) A full proposal setting out the details of the study, methods, population under study, data required from the database and proposed time lines.
b) A full list of the participants to the study and proposals for involvement by members of the committee and CRAB. The study should include as primary authors at least one medical member of the committee and one CRAB member of the committee.
c) A supportive letter from CRAB confirming that the necessary data is obtainable from the data base and that the quality and volume of that data is adequate to answer the question posed.
d) Confirmation that the applicant and all other parties who may be considered to hold intellectual property rights will adhere to the highest scientific and ethical standards, including but not exclusively:
    a. Will respect the IASLC ownership of the data and will not seek to use the information provided for any other use without the agreement of the IASLC.
    b. Will respect the anonymity of the clinical data.
    c. Will submit any publication or presentation for scrutiny by the committee, and in addition, by those database proprietors with whom there exists prior

agreements, before submission. The committee reserves the right to deny publication in extreme situations.

d. Will publish any submission in a format agreed with the committee, including the format of the title, and acknowledging the participation of the IASLC, the committee members, CRAB and the database proprietors. The acknowledgment of our sponsors will be recognized in a format agreed with them from time to time.
e. Will submit publications, in the first place, to the Journal of Thoracic Oncology, the official journal of the IASLC.

The full proposal will be circulated to the full committee by e-mail and the committee's view collected by the chairman. If consensus is not reached the proposal will be discussed at the next meeting of the committee. Revisions or additional material may be requested before a final decision is reached. The committee's decision is final and there will be no appeal structure.

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