COLLEGE of AMERICAN PATHOLOGISTS

Protocol for the Examination of Specimens From Patients With Malignant Pleural Mesothelioma

Version: Mesothelioma 4.0.0.0 **Protocol Posting Date:** June 2017
Includes pTNM requirements from the 8th Edition, AJCC Staging Manual

For accreditation purposes, this protocol should be used for the following procedures AND tumor types:

Procedure	Description
Resection	Includes pneumonectomy, pleurectomy, and decortication procedures
Tumor Type	**Description**
Mesothelioma	

This protocol is NOT required for accreditation purposes for the following:

Procedure
Biopsy
Primary resection specimen with no residual cancer (eg, following neoadjuvant therapy)
Cytologic specimens

The following tumor types should NOT be reported using this protocol:

Tumor Type
Solitary fibrous tumor
Peritoneal mesothelioma
Lymphoma (consider the Hodgkin or non-Hodgkin Lymphoma protocols)
Sarcoma (consider the Soft Tissue protocol)

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With guidance from the CAP Cancer and CAP Pathology Electronic Reporting Committees.

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Accreditation Requirements
This protocol can be utilized for a variety of procedures and tumor types for clinical care purposes. For accreditation purposes, only the definitive primary cancer resection specimen is required to have the core and conditional data elements reported in a synoptic format.

- Core data elements are required in reports to adequately describe appropriate malignancies. For accreditation purposes, essential data elements must be reported in all instances, even if the response is "not applicable" or "cannot be determined."
- Conditional data elements are only required to be reported if applicable as delineated in the protocol. For instance, the total number of lymph nodes examined must be reported, but only if nodes are present in the specimen.
- Optional data elements are identified with "+" and although not required for CAP accreditation purposes, may be considered for reporting as determined by local practice standards.

The use of this protocol is not required for recurrent tumors or for metastatic tumors that are resected at a different time than the primary tumor. Use of this protocol is also not required for pathology reviews performed at a second institution (ie, secondary consultation, second opinion, or review of outside case at second institution).

Synoptic Reporting
All core and conditionally required data elements outlined on the surgical case summary from this cancer protocol must be displayed in synoptic report format. Synoptic format is defined as:

- Data element: followed by its answer (response), outline format without the paired "Data element: Response" format is NOT considered synoptic.
- The data element must be represented in the report as it is listed in the case summary. The response for any data element may be modified from those listed in the case summary, including "Cannot be determined" if appropriate.
- Each diagnostic parameter pair (Data element: Response) is listed on a separate line or in a tabular format to achieve visual separation. The following exceptions are allowed to be listed on one line:
    - Anatomic site or specimen, laterality, and procedure
    - Pathologic Stage Classification (pTNM) elements
    - Negative margins, as long as all negative margins are specifically enumerated where applicable
- The synoptic portion of the report can appear in the diagnosis section of the pathology report, at the end of the report or in a separate section, but all Data element: Responses must be listed together in one location

Organizations and pathologists may choose to list the required elements in any order, use additional methods in order to enhance or achieve visual separation, or add optional items within the synoptic report. The report may have required elements in a summary format elsewhere in the report IN ADDITION TO but not as replacement for the synoptic report i.e. all required elements must be in the synoptic portion of the report in the format defined above.

CAP Laboratory Accreditation Program Protocol Required Use Date: March 2018*

** Beginning January 1, 2018, the 8th edition AJCC Staging Manual should be used for reporting pTNM.*

CAP Malignant Plural Mesothelioma Protocol Summary of Changes

The following data elements were modified:
Pathologic Stage Classification (pTNM, AJCC 8th Edition)

The following data element was deleted:
Specimen Integrity

Surgical Pathology Cancer Case Summary

Protocol posting date: June 2017

MALIGNANT PLEURAL MESOTHELIOMA:

Select a single response unless otherwise indicated.

Procedure (select all that apply) (Note A)
___ Extrapleural pneumonectomy
___ Extended pleurectomy/ decortication
___ Pleurectomy/decortication
___ Partial pleurectomy
___ Other (specify): _____
___ Not specified

Specimen Laterality
___ Right
___ Left
___ Not specified

Tumor Site (select all that apply)
___ Parietal pleura
___ Visceral pleura
___ Diaphragm
___ Other (specify): _____
___ Not specified

+ Tumor Size (for localized tumors only)
+ Greatest dimension (centimeters): ___ cm
+ Additional dimensions (centimeters): ___ x ___ cm
+ ___ Cannot be determined (explain): _____

Tumor Focality (Note B)
___ Localized
___ Diffuse
___ Cannot be determined

Histologic Type (Note C)
___ Epithelioid mesothelioma
___ Sarcomatoid mesothelioma
___ Biphasic mesothelioma
___ Desmoplastic mesothelioma
___ Other histologic type not listed (specify): _____

Tumor Extension (select all that apply) (Note D)
___ Tumor limited to parietal pleura without involvement of ipsilateral visceral, mediastinal, or diaphragmatic pleura
___ Tumor limited to parietal pleura with focal involvement of ipsilateral visceral, mediastinal, or diaphragmatic pleura
___ Tumor involves all of the ipsilateral pleural surfaces (including fissure)
___ Tumor involves diaphragmatic muscle
___ Tumor extends into lung parenchyma
___ Tumor involves endothoracic fascia
___ Tumor extends into mediastinal fat

___ Solitary focus extends into the soft tissues of the chest wall
___ Diffuse or multiple foci extend into soft tissue of chest wall
___ Tumor extends into but not through the pericardium
___ Tumor involves rib(s)
___ Tumor involves mediastinal organ(s) (specify): _____
___ Other (specify): _____
___ Cannot be assessed

Margins (Note E)
___ Cannot be assessed
___ Uninvolved by mesothelioma
___ Involved by mesothelioma
Specify margin(s): _____
___ Not applicable

Regional Lymph Nodes

___ No lymph nodes submitted or found

Lymph Node Examination (required only if lymph nodes are present in the specimen)

Number of Lymph Nodes Involved: _____
___ Number cannot be determined (explain): _____

Number of Lymph Nodes Examined: _____
___ Number cannot be determined (explain): _____

Treatment Effect (Note F)
___ No known presurgical therapy
___ Greater than 50% residual viable tumor
___ Less than 50% residual viable tumor
___ Cannot be determined

Pathologic Stage Classification (pTNM, AJCC 8th edition) (Note G)

Note: Reporting of pT, pN, and (when applicable) pM categories is based on information available to the pathologist at the time the report is issued. Only the applicable T, N, or M category is required for reporting; their definitions need not be included in the report. The categories (with modifiers when applicable) can be listed on 1 line or more than 1 line.

TNM Descriptors (required only if applicable) (select all that apply)
___ r (recurrent)
___ y (posttreatment)

Primary Tumor (pT)
___ pTX: Primary tumor cannot be assessed
___ pT0: No evidence of primary tumor
___ pT1: Tumor limited to the ipsilateral parietal pleura with or without involvement of:
- visceral pleura
- mediastinal pleura
- diaphragmatic pleura

___ pT2: Tumor involving each of the ipsilateral pleural surfaces (parietal, mediastinal, diaphragmatic, and visceral pleura) with at least one of the following features:
- involvement of diaphragmatic muscle
- extension of tumor from visceral pleura into the underlying pulmonary parenchyma

___ pT3: Describes locally advanced but **potentially resectable** tumor

Tumor involving all the ipsilateral pleural surfaces (parietal, mediastinal, diaphragmatic, and visceral pleura) with at least one of the following features:
- involvement of the endothoracic 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

___ pT4: Describes locally advanced **technically unresectable** tumor
Tumor involving all the ipsilateral pleural surfaces (parietal, mediastinal, diaphragmatic, and visceral pleura) 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 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

Regional Lymph Nodes (pN)
___ pNX: Regional lymph nodes cannot be assessed
___ pN0: No regional lymph node metastases
___ pN1: Metastases in the ipsilateral bronchopulmonary hilar or mediastinal (including the internal mammary, peridiaphragmatic, pericardial fat pad, or intercostal) lymph nodes
___ pN2: Metastases in the contralateral mediastinal, ipsilateral, or contralateral supraclavicular lymph nodes

Distant Metastasis (pM) (required only if confirmed pathologically in this case)
___ pM1: Distant metastasis present
Specify site(s), if known: _____

+ Additional Pathologic Findings (select all that apply)
+ ___ None identified
+ ___ Asbestos bodies
+ ___ Pleural plaque
+ ___ Pulmonary interstitial fibrosis
+ ___ Inflammation (specify type): _____
+ ___ Other (specify): _____

+ Ancillary Studies (select all that apply) (Note H)
+ ___ Immunohistochemical stain(s) (specify stains and results): _____
+ ___ Histochemical stain(s) (specify stains and results): _____
+ ___ Electron microscopy (specify results): _____
+ ___ Other (specify): _____

+ Clinical History (select all that apply)
+ ___ Neoadjuvant therapy
+ ___ Other (specify): _____

+ Comment(s)

Explanatory Notes

A. Procedure

The International Association for the Study of Lung Cancer (IASLC) has developed an international malignant plural mesothelioma (MPM) staging database that was designed to address the limitations of the mesothelioma staging. Data analyses revealed that survival was significantly influenced by whether the curative or palliative surgical procedure was performed (median survival 18 versus 12 months, p <0.0001).[1] Early stage (stage I) MPM resected by extraplural pneumonectomy (EPP) with curative intent were associated with a median survival of 40 months, whereas those managed by P/D with curative intent had a median survival of 23 months.[1] Type of surgical procedure did not impact survival in higher stage disease. It was also noted that significant variations regarding surgical nomenclature for procedures for MPM exist among thoracic surgeons.[2] The International Staging Committee of the IASLC and the International Mesothelioma Interest Group (IMIG) recommended that P/D (pleurectomy/decortication) refer to removal of all macroscopic tumor involving the parietal and visceral pleura and that the term extended P/D (or EPD) to be used to describe parietal and visceral pleurectomy together with resection of the diaphragm and /or pericardium.[2,3]

B. Tumor Focality

The majority of malignant mesotheliomas exhibit diffuse growth and may take the form of multiple small nodules, plaque-like masses, or confluent rind-like sheets. However, a small proportion of malignant mesotheliomas are sharply circumscribed. These are designated by the term “localized malignant mesothelioma.” Localized malignant mesotheliomas appear to have a far better prognosis than their diffuse counterpart.[4]

C. Histologic Type

For consistency in reporting, the histologic classification published by the World Health Organization (WHO) is recommended.[5] Major histologic subtypes include epithelioid, sarcomatoid, and biphasic (mixed). Multiple patterns have been described within major subtypes, some of which correlate with overall survival, but their reporting is not required.[6, 7] Desmoplastic mesothelioma is considered to represent a variant of sarcomatoid mesothelioma. Biphasic mesotheliomas, contain both epithelioid and sarcomatoid subtypes, and each component should represent at least 10% of the tumor.[5] The 2015 WHO classification also recognizes well-differentiated papillary mesothelioma (WDPM) as a mesothelioma subtype.[5,8,9] These are noninvasive papillary neoplasms with excellent prognosis, and it is important to distinguish them from architecturally similar but more aggressive papillary pattern of epithelioid MPM.[5] WDPM are not staged according to AJCC staging system.

D. Tumor Extension

Invasion of the endothoracic fascia is categorized as T3. The endothoracic fascia is located external to the parietal pleura beneath the muscles and ribs of the chest wall. Determining the presence or absence of endothoracic fascial invasion can be difficult on pathologic examination, because the endothoracic fascia lacks distinctive gross and histologic features. Assessment of the intactness of the endothoracic fascia is best made by the surgeon at the time of operation.

Although the American Joint Committee on Cancer (AJCC) designates a solitary focus of tumor invading the soft tissues of the chest wall as T3, it does not specifically delineate the elements that constitute the chest wall. According to the surgical literature, the constituents of the chest wall are the ribs, intercostal muscles, and associated supporting connective tissues, the latter 2 of which can be inferred to represent the chest wall soft tissues. Note that this definition does not include the layer of adipose tissue, which is sometimes referred to as extrapleural fat, that lies between the chest wall and the parietal pleura. For specimens that incorporate chest wall structures, it is recommended that the surgeon designate the location(s) of such structures to ensure optimal pathologic assessment.

Although T4 describes locally advanced, technically unresectable tumor, radical extrapleural pneumonectomy specimens may occasionally incorporate structures directly invaded by tumor that fall under the T4 designation. These should be specified under “other” and include tumor extension to the following:
- Peritoneum (through the diaphragm)
- Contralateral pleura
- Spine

- Internal surface of the pericardium
- Myocardium
- Brachial plexus

E. Margins
Because extrapleural pneumonectomy specimens are obtained by dissection of tumor from the thorax with en bloc resection of the lung, pleura, pericardium, and diaphragm, the entire surface of the extrapleural pneumonectomy represents the surgical margin (unless otherwise specified by the operating surgeon).

F. Treatment Effect
Induction chemotherapy before extrapleural pneumonectomy is being used in some centers for locally advanced malignant pleural mesothelioma.[10] Although a formal scheme for grading histologic response to neoadjuvant treatment has not been established, in applicable specimens, a generalized estimate of the amount of residual viable tumor should be reported.

G. Pathologic Stage Classification
This protocol recommends the AJCC and the International Union Against Cancer (UICC) TNM staging system shown below.[11,12] The changes introduced in the AJCC Cancer Staging Manual 8th edition are based on analyses of the IASLC retrospective and prospective databases. [3,13-15]

By AJCC/UICC convention, the designation “T” refers to a primary tumor that has not been previously treated. The symbol “p” refers to the pathologic classification of the TNM, as opposed to the clinical classification, and is based on gross and microscopic examination. pT entails a resection of the primary tumor or biopsy adequate to evaluate the highest pT category, pN entails removal of nodes adequate to validate lymph node metastasis, and pM implies microscopic examination of distant lesions. Clinical classification (cTNM) is usually carried out by the referring physician before treatment during initial evaluation of the patient or when pathologic classification is not possible.

Pathologic staging is usually performed after attempted surgical resection of the primary tumor. Pathologic staging depends on pathologic documentation of the anatomic extent of disease, whether or not the primary tumor has been completely removed. If a biopsied tumor is not resected for any reason (eg, when technically infeasible) and if the highest T and N categories or the M1 category of the tumor can be confirmed microscopically, the criteria for pathologic classification and staging have been satisfied without total removal of the primary cancer.

Stage Groupings

Stage IA	T1	N0	M0
Stage IB	T2	N0	M0
	T3	N0	M0
Stage II	T1	N1	M0
	T2	N1	M0
Stage IIIA	T3	N1	M0
Stage IIIB	T1-3	N2	M0
	T4	Any N	M0
Stage IV	Any T	Any N	M1

TNM Descriptors
For identification of special cases of TNM or pTNM classifications, the “m” suffix and “y,” “r,” and “a” prefixes are used. Although they do not affect the stage grouping, they indicate cases needing separate analysis.

The “m” suffix indicates the presence of multiple primary tumors in a single site and is recorded in parentheses: pT(m)NM. In actuality, this is not a descriptor that readily applies to diffuse malignant pleural mesothelioma, which often exhibits a multinodular growth pattern but is best considered a single tumor for staging purposes. Because of this, the “m” descriptor is not listed as an option in this protocol case summary.

The "y" prefix indicates those cases in which classification is performed during or after initial multimodality therapy (ie, neoadjuvant chemotherapy, radiation therapy, or both chemotherapy and radiation therapy). The cTNM or pTNM category is identified by a "y" prefix. The ycTNM or ypTNM categorizes the extent of tumor actually present at the time of that examination. The "y" categorization is not an estimate of tumor before multimodality therapy (ie, before initiation of neoadjuvant therapy).

The "r" prefix indicates a recurrent tumor when staged after a documented disease-free interval and is identified by the "r" prefix: rTNM.

Additional Descriptors

Residual Tumor (R)
Tumor remaining in a patient after therapy with curative intent (eg, surgical resection for cure) is categorized by a system known as R classification, shown below.

RX Presence of residual tumor cannot be assessed
R0 No residual tumor
R1 Microscopic residual tumor
R2 Macroscopic residual tumor

For the surgeon, the R classification may be useful to indicate the known or assumed status of the completeness of a surgical excision. For the pathologist, the R classification is relevant to the status of the margins of a surgical resection specimen. That is, tumor involving the resection margin on pathologic examination may be assumed to correspond to residual tumor in the patient and may be classified as macroscopic or microscopic according to the findings at the specimen margin(s).

H. Ancillary Studies
Immunohistochemistry is required for a definitive diagnosis of malignant mesothelioma. The immunohistochemical approach depends on the mesothelioma morphology (epithelioid, sarcomatoid) and the type of tumors that are considered in the differential diagnosis. The 2015 WHO recommends the combined use of a minimum of 2 mesothelial markers and 2 carcinoma markers.[5] Based on the specificity and sensitivity, the best positive mesothelial markers include calretinin, cytokeratins 5/6, WT-1, and D2-40. BerEP4 or MOC31, B72.3, CEA, and BG8 are the most frequently used to diagnose carcinoma.[5] No specific panel is recommended, and the International Mesothelioma Panel recommends that each laboratory should choose antibodies with a sensitivity and specificity of at least 80%.[16] The College of American Pathologists (CAP) does not endorse a specific panel of markers for the evaluation of malignant mesothelioma. If sarcoma is considered in the differential diagnosis appropriate immunohistochemical, cytogenetic and molecular workup should be performed. Diagnostic role of histochemistry and electron microscopy is very limited because immunohistochemistry is widely available and frequently sufficient to establish the diagnosis of malignant mesothelioma.

References
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