



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

**Version:** Mesothelioma 4.0.0.1

**Protocol Posting Date:** June 2017

Includes pTNM requirements from the 8<sup>th</sup> 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

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### Version 4.0.0.1

#### The following data element was modified:

Tumor Extension

### Version 4.0.0.0

#### 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**

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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)**

- No evidence of primary tumor  
 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

+ Data elements preceded by this symbol are not required for accreditation purposes. These optional elements may be clinically important but are not yet validated or regularly used in patient management.

- 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 8<sup>th</sup> 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

+ Data elements preceded by this symbol are not required for accreditation purposes. These optional elements may be clinically important but are not yet validated or regularly used in patient management.

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 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

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### 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,  $p < 0.0001$ ).<sup>1</sup> Early stage (stage I) MPM resected by extrapleural 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.<sup>1</sup> 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.<sup>2</sup> 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.<sup>2,3</sup>

### 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.<sup>4</sup>

### C. Histologic Type

For consistency in reporting, the histologic classification published by the World Health Organization (WHO) is recommended.<sup>5</sup> 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.<sup>6,7</sup> 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.<sup>5</sup> The 2015 WHO classification also recognizes well-differentiated papillary mesothelioma (WDPM) as a mesothelioma subtype.<sup>5,8,9</sup> 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.<sup>5</sup> 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.<sup>10</sup> 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.<sup>11,12</sup> The changes introduced in the AJCC Cancer Staging Manual 8<sup>th</sup> edition are based on analyses of the IASLC retrospective and prospective databases.<sup>3,13-15</sup>

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.

### 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.<sup>5</sup> 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.<sup>5</sup> 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%.<sup>16</sup> 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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