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

Version: 4.1.0.0
Protocol Posting Date: June 2021
CAP Laboratory Accreditation Program Protocol Required Use Date: March 2022

The changes included in this current protocol version affect accreditation requirements. The new deadline for implementing this protocol version is reflected in the above accreditation date.

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

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Resection</td>
<td>Includes extrapleural pneumonectomy, pleurectomy, and decortication procedures</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Tumor Type</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mesothelioma</td>
<td></td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Procedure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biopsy</td>
</tr>
<tr>
<td>Primary resection specimen with no residual cancer (eg, following neoadjuvant therapy)</td>
</tr>
<tr>
<td>Cytologic specimens</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Tumor Type</th>
</tr>
</thead>
<tbody>
<tr>
<td>Solitary fibrous tumor</td>
</tr>
<tr>
<td>Peritoneal mesothelioma</td>
</tr>
<tr>
<td>Lymphoma (consider the Hodgkin or non-Hodgkin Lymphoma protocols)</td>
</tr>
<tr>
<td>Sarcoma (consider the Soft Tissue protocol)</td>
</tr>
</tbody>
</table>

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

* Denotes primary author.
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 should 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 ie, all required elements must be in the synoptic portion of the report in the format defined above.
Summary of Changes

v 4.1.0.0

- General Reformatting
- New WHO 5th Edition Histological Updates
- Added Nuclear Atypia Score
- Added Mitotic Count Score
- Added Nuclear Grade
- Added Necrosis
- Added Histologic Grade
- Revised Treatment Effect
- Revised Margins Section
- Revised Lymph Node Section
- Removed pNX Staging Classification
Reporting Template

Protocol Posting Date: June 2021
Select a single response unless otherwise indicated.

CASE SUMMARY: (MALIGNANT PLEURAL MESOTHELIOMA)
Standard(s): AJCC-UICC 8

CLINICAL

+Clinical History (select all that apply)
___ Neoadjuvant therapy performed (specify type, if known): _________________
___ Other (specify): _________________

SPECIMEN (Note A)

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

Specimen Laterality
___ Right
___ Left
___ Not specified

TUMOR

Tumor Focality (Note D)
___ Localized
___ Diffuse
___ Cannot be determined: _________________

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

+Tumor Size (for localized tumors only)
___ Greatest dimension in Centimeters (cm): _______ __________ cm
+Additional Dimension in Centimeters (cm): ____ x ____ cm
___ Cannot be determined (explain): _______________

Histologic Type (Note B)
___ Epithelioid mesothelioma
+Architectural Pattern (may include percentages totaling 100%) (select all that apply)
___ Tubulopapillary: _________________ %
___ Trabecular: _________________ %
___ Adenomatoid: _________________ %
___ Solid: _________________ %
___ Micropapillary: _________________ %
___ Other (specify): _________________

+Cytological Features (select all that apply)
___ Rhabdoid
___ Deciduoid
___ Small cell
___ Clear cell
___ Signet ring
___ Lymphohistiocytoid
___ Pleomorphic
___ Other (specify): _________________

+Stromal Features (select all that apply)
___ Myxoid predominant
___ Other (specify): _________________
___ Sarcomatoid mesothelioma

+Cytological Features (select all that apply)
___ Lymphohistiocytoid
___ Transitional
___ Pleomorphic
___ Other (specify): _________________

+Stromal Features (select all that apply)
___ Desmoplastic
___ With heterologous differentiation
___ Other (specify): _________________
___ Biphasic mesothelioma

Percentage of Sarcomatoid Pattern
___ Specify percentage: _________________ %
___ Other (specify): _________________
___ Cannot be determined
___ Other histologic type not listed (specify): _________________
___ Cannot be determined (explain): _________________

+Histologic Type Comment: _________________

+Nuclear Atypia Score
___ 1 (mild)
___ 2 (moderate)
___ 3 (severe)
___ Cannot be determined: _________________

+Mitotic Count Score
___ 1 (low, up to 1 mitosis per 2 mm2)
___ 2 (intermediate, 2 to 4 mitoses per 2 mm2)
___ 3 (high, 5 or more mitoses per 2 mm2)
___ Cannot be determined: _________________
**Nuclear Grade** (sum of nuclear atypia and mitotic count scores)
- **1** (sum score of 2 or 3)
- **2** (sum score of 4 or 5)
- **3** (sum score of 6)
- Cannot be determined: ___________________

**Necrosis**
- Not identified
- Present
- Cannot be determined: ___________________

**Histologic Grade**
- Low grade (nuclear grades 1 and 2 without necrosis)
- High grade (nuclear grade 2 with necrosis, or nuclear grade 3 with or without necrosis)
- Cannot be determined: ___________________

**Tumor Extent (Note E) (select all that apply)**
- Limited to parietal pleura without involvement of ipsilateral visceral, mediastinal, or diaphragmatic pleura
- Limited to parietal pleura with focal involvement of ipsilateral visceral, mediastinal, or diaphragmatic pleura
- All ipsilateral pleural surfaces (including fissure)
- Diaphragmatic muscle
- Lung parenchyma
- Endothoracic fascia
- Mediastinal fat
- Soft tissues of chest wall in a solitary focus
- Soft tissues of chest wall diffusely or in multiple foci
- Into but not through the pericardium
- Rib(s)
- Mediastinal organ(s) (specify): ___________________
- Other (specify): ___________________
- Cannot be determined: ___________________
- No evidence of primary tumor

**Treatment Effect (Note F)**
- No known presurgical therapy
- Not identified
- Present

**Percentage of Residual Viable Tumor**
- Specify percentage: ___________________%
- Other (specify): ___________________
- Cannot be determined
- Cannot be determined: ___________________

**Tumor Comment:** ___________________
MARGINS (Note G)

Margin Status
___ All margins negative for mesothelioma
___ Mesothelioma present at margin

Margin(s) Involved by Mesothelioma
___ Specify involved margin(s): _____________________
___ Cannot be determined (explain): _____________________
___ Other (specify): _____________________
___ Cannot be determined (explain): _____________________
___ Not applicable

+Margin Comment: _____________________

REGIONAL LYMPH NODES

Regional Lymph Node Status
___ Not applicable (no regional lymph nodes submitted or found)
___ Regional lymph nodes present
___ All regional lymph nodes negative for tumor
___ Tumor present in regional lymph node(s)

Nodal Site(s) with Tumor (select all that apply)
___ Bronchopulmonary: _____________________
___ Hilar: _____________________
___ Ipsilateral mediastinal (including internal mammary, peridiaphragmatic, pericardial fat pad, or intercostal nodes): _____________________
___ Contralateral mediastinal (including internal mammary, peridiaphragmatic, pericardial fat pad, or intercostal nodes): _____________________
___ Supraclavicular: _____________________
___ Other (specify): _____________________
___ Cannot be determined: _____________________

Number of Lymph Nodes with Tumor
___ Exact number (specify): _____________________
___ At least (specify): _____________________
___ Other (specify): _____________________
___ Cannot be determined (explain): _____________________
___ Other (specify): _____________________
___ Cannot be determined (explain): _____________________

Number of Lymph Nodes Examined
___ Exact number (specify): _____________________
___ At least (specify): _____________________
___ Other (specify): _____________________
___ Cannot be determined (explain): _____________________

+Regional Lymph Node Comment: _____________________
DISTANT METASTASIS

Distant Site(s) Involved, if applicable (select all that apply)
___ Not applicable
___ Non-regional lymph node(s): _____________________
___ Other (specify): _____________________
___ Cannot be determined: _____________________

PATHOLOGIC STAGE CLASSIFICATION (pTNM, AJCC 8th Edition) (Note H)

Reporting of pT, pN, and (when applicable) pM categories is based on information available to the pathologist at the time the report is issued. As per the AJCC (Chapter 1, 8th Ed.) it is the managing physician’s responsibility to establish the final pathologic stage based upon all pertinent information, including but potentially not limited to this pathology report.

TNM Descriptors (select all that apply)
___ Not applicable
___ r (recurrent)
___ y (post-treatment)

pT Category
___ pT not assigned (cannot be determined based on available pathological information)
___ 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 of 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 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 of 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

pN Category
___ pN not assigned (no nodes submitted or found)
___ pN not assigned (cannot be determined based on available pathological information)
___ 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

pM Category (required only if confirmed pathologically)
___ Not applicable - pM cannot be determined from the submitted specimen(s)
___ pM1: Distant metastasis present
ADDITIONAL FINDINGS

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

SPECIAL STUDIES
Ancillary Studies (Note I)
  +Immunohistochemistry (specify stains and results): _________________
  +Histochemistry (specify stains and results): _________________
  +Electron Microscopy (specify results): _________________
  +Other Ancillary Studies (specify types and results): _________________

COMMENTS

Comment(s): _________________
Explanatory Notes

A. Specimen
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 a curative or palliative surgical procedure was performed (median survival 18 versus 12 months, \( p < 0.0001 \)). 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 Pleurectomy/decortication (P/D) with curative intent had a median survival of 23 months. 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. The International Staging Committee of the IASLC and the International Mesothelioma Interest Group (IMIG) recommended that P/D 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.

References

B. Histologic Type
For consistency in reporting, the histologic classification published by the World Health Organization (WHO) is recommended. Mesotheliomas are classified as epithelioid, sarcomatoid (including desmoplastic) or biphasic. Recognition and reporting of various architectural patterns, cytological features and stromal features is encouraged because of their prognostic value. 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.

The 2021 WHO classification recommends using well-differentiated papillary mesothelial tumor (WDPMT) over well-differentiated papillary mesothelioma (WDPM). These are noninvasive papillary neoplasms associated with slow growth and recurrences. Survival is better than that for diffuse mesotheliomas. WDPMTs are not staged according to AJCC staging system and do not require a synoptic report.

The 2021 WHO classification introduced the concept of mesothelioma in-situ as a preinvasive single-layer surface proliferation of neoplastic mesothelial cells. The diagnosis may be suspected in patients with recurrent effusions. The WHO considers essential diagnostic criteria to be (a) non-resolving pleural effusion, (b) no thoracoscopic or imaging evidence of tumor, and (c) a single layer of mesothelial cells (with or without atypia) on the pleural surface with loss of BAP1 and/or MTAP by immunohistochemistry and/or CDKN2A homozygous deletion by fluorescence in-situ hybridization. Multidisciplinary discussion of these cases is encouraged. Mesothelioma in-situ is not staged according to AJCC staging system and does not require a synoptic report.
References


C. Histologic Grade

The 2021 WHO classification recommends grading of diffuse epithelioid mesothelioma to identify tumors that may behave aggressively. A nuclear grade is assigned based on nuclear atypia and mitotic count and subsequently combined with the presence or absence of necrosis. Low grade tumors are those exhibiting nuclear grade 1 (with or without necrosis) or nuclear grade 2 without necrosis. High grade tumors are those exhibiting nuclear grade 2 with necrosis, or nuclear grade 3 with or without necrosis.

Grading should be performed based on the areas showing the highest-grade features.

References


D. 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.

References


E. Tumor Extent

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

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

References

G. 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).

H. Pathologic Stage Classification
This protocol recommends the AJCC and the International Union Against Cancer (UICC) TNM staging system shown below. The changes introduced in the AJCC Cancer Staging Manual 8th edition are based on analyses of the IASLC retrospective and prospective databases.

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.

<table>
<thead>
<tr>
<th>RX</th>
<th>Presence of residual tumor cannot be assessed</th>
</tr>
</thead>
<tbody>
<tr>
<td>R0</td>
<td>No residual tumor</td>
</tr>
<tr>
<td>R1</td>
<td>Microscopic residual tumor</td>
</tr>
<tr>
<td>R2</td>
<td>Macroscopic residual tumor</td>
</tr>
</tbody>
</table>

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).

References


I. 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 2021 WHO classification continues to recommend the combined use of a minimum of two mesothelial markers and two carcinoma markers. 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. 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%. The College of American Pathologists 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