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

Based on AJCC/UICC TNM, 7th edition

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Procedures
• Resection

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The College of American Pathologists offers these protocols to assist pathologists in providing clinically useful and relevant information when reporting results of surgical specimen examinations of surgical specimens. The College regards the reporting elements in the "Surgical Pathology Cancer Case Summary" portion of the protocols as essential elements of the pathology report. However, the manner in which these elements are reported is at the discretion of each specific pathologist, taking into account clinician preferences, institutional policies, and individual practice.

The College developed these protocols as an educational tool to assist pathologists in the useful reporting of relevant information. It did not issue the protocols for use in litigation, reimbursement, or other contexts. Nevertheless, the College recognizes that the protocols might be used by hospitals, attorneys, payers, and others. Indeed, effective January 1, 2004, the Commission on Cancer of the American College of Surgeons mandated the use of the required data elements of the protocols as part of its Cancer Program Standards for Approved Cancer Programs. Therefore, it becomes even more important for pathologists to familiarize themselves with these documents. At the same time, the College cautions that use of the protocols other than for their intended educational purpose may involve additional considerations that are beyond the scope of this document.

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CAP Mesothelioma Protocol Revision History

Version Code
The definition of the version code can be found at www.cap.org/cancerprotocols.

Version: Mesothelioma 3.1.0.0

Summary of Changes
The following changes have been made since the October 2009 release.

Resection

Regional Lymph Nodes (pN)
Specify: Number examined / Number involved, has been changed to:

___ No nodes submitted or found

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

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

Surgical Pathology Cancer Case Summary

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PLEURA: Resection

Select a single response unless otherwise indicated.

Specimen
___ Pleura
___ Other (specify): _____
___ Not specified

Procedure
___ Pleural decortication
___ Pleurectomy
___ Extrapleural pneumonectomy
___ Other (specify): _____
___ Not specified

Specimen Integrity
___ Intact
___ Disrupted
___ Indeterminate

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: ___ cm
+ Additional dimensions: ___ x ___ cm
+ ___ Cannot be determined (see Comment)

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

Histologic Type (Note B)
___ Epithelioid mesothelioma
___ Sarcomatoid mesothelioma
___ Biphasic mesothelioma
___ Desmoplastic mesothelioma
___ Other (specify): _____

Tumor Extension (select all that apply) (Note C)
___ Parietal pleura without involvement of ipsilateral visceral pleura
___ Parietal pleura with focal involvement of ipsilateral visceral pleura
___ Confluent visceral pleural tumor (including fissure)
___ Into but not through diaphragm
___ Lung parenchyma
___ Endothoracic fascia
___ Into mediastinal fat
___ Solitary focus invading soft tissue of the chest wall
___ Diffuse or multiple foci invading soft tissue of chest wall
___ Into but not through the pericardium
___ Rib(s)
___ Mediastinal organ(s) (specify): _____
___ Other (specify): _____

Margins (Note D)
___ Not applicable
___ Cannot be assessed
___ Margins negative for mesothelioma
___ Margin(s) involved by mesothelioma
Specify margin(s): _____

Treatment Effect (Note E)
___ Not applicable
___ Cannot be determined
___ Greater than 50% residual viable tumor
___ Less than 50% residual viable tumor

Pathologic Staging (pTNM) (Note F)

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

Primary Tumor (pT)
___ pTX: Primary tumor cannot be assessed
___ pT0: No evidence of primary tumor
___ pT1a: Tumor limited to ipsilateral parietal pleura with or without mediastinal or diaphragmatic pleural involvement. No involvement of the visceral pleura
___ pT1b: Tumor involves ipsilateral parietal pleura with or without mediastinal or diaphragmatic pleural involvement. Tumor also involving the visceral pleura
___ pT2: Tumor involves each of the ipsilateral pleural surfaces (parietal, mediastinal, diaphragmatic, and visceral pleura) with at least 1 of the following features: involvement of diaphragmatic muscle, extension of tumor from visceral pleura into the underlying pulmonary parenchyma
___ pT3: Locally advanced but potentially resectable tumor that involves all of the ipsilateral pleural surfaces (parietal, mediastinal, diaphragmatic, and visceral pleura), with at least 1 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: Locally advanced technically unresectable tumor involving all of the ipsilateral pleural surfaces (parietal, mediastinal, diaphragmatic, and visceral pleura), with at least 1 of the following features: diffuse extension or multifocal masses of tumor in the chest wall with or without associated rib destruction, direct transdiaphragmatic extension to the peritoneum, direct extension to the contralateral pleura, direct extension to mediastinal organs, direct extension into the spine, extension through the internal surface of the pericardium with or without a pericardial effusion, 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 or hilar lymph nodes
___ pN2: Metastases in the subcarinal or the ipsilateral mediastinal lymph nodes including the ipsilateral internal mammary and peridiaphragmatic nodes
___ pN3: Metastases in the contralateral mediastinal, contralateral internal mammary, ipsilateral or contralateral supraclavicular lymph nodes

___ No nodes submitted or found

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

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

Distant Metastasis (pM)
___ Not applicable
___ pM1: Distant metastasis
+ Specify site(s), if known: _____

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

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

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

+ Comment(s)

Explanatory Notes

A. Tumor Focality
The majority of malignant mesotheliomas exhibit diffuse growth and may take the form of multiple small nodules, plaque-like masses, or confluent rindlike 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.[1]

B. Histologic Type
For consistency in reporting, the histologic classification published by the World Health Organization (WHO) is recommended.[2] However, other classifications have been proposed, such as the detailed histologic classification of malignant mesothelioma by Hammar.[3] In these other schema, epithelioid mesothelioma is sometimes referred to as epithelial, sarcomatoid mesothelioma is also referred to as fibrous, biphasic mesothelioma is also referred to as mixed, and desmoplastic mesothelioma is considered a variant of sarcomatoid mesothelioma. As defined by the WHO, at least 50% of a tumor should be composed of dense collagenized tissue separated by atypical cells arranged in a storiform or "patternless" pattern in order to designate it as desmoplastic mesothelioma, whereas in biphasic mesotheliomas, which contain both epithelioid and sarcomatoid patterns, each component should represent at least 10% of the tumor.[2]

C. 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 two 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

D. 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).

E. Treatment Effect

Induction chemotherapy before extrapleural pneumonectomy is being used in some centers for locally advanced malignant pleural mesothelioma.[4] 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.

F. Pathologic Staging

This protocol recommends the AJCC and the International Union Against Cancer (UICC) TNM staging system shown below.[5,6] The AJCC has adopted the staging system proposed by the International Mesothelioma Interest Group (IMIG) in 1995.[7]

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 I	T1	N0	M0
Stage IA	T1a	N0	M0
Stage IB	T1b	N0	M0
Stage II	T2	N0	M0
Stage III	T1,T2	N1	M0
	T1,T2	N2	M0
	T3	N0,N1,N2	M0
Stage IV	T4	Any N	M0
	Any T	N3	M0
	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.

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).

Other staging systems for malignant pleural mesothelioma, such as the Brigham Staging System, as shown below, have also been devised.[8] Use of this protocol does not preclude reporting of tumor stage as determined by other systems concurrent with the TNM designation.

Brigham Staging System for Malignant Pleural Mesothelioma[8]

Stage	Definition
I	Disease confined to within capsule of the parietal pleura: ipsilateral pleural, lung, pericardium, diaphragm, or chest wall disease limited to previous biopsy sites
II	All of stage I with positive intrathoracic (N1 or N2) nodes
III	Local extension of disease into chest wall or mediastinum, heart, or through diaphragm, peritoneum; with or without extrathoracic or contralateral (N3) lymph node involvement
IV	Distant metastatic disease

According to the Brigham Staging System, stage I represents resectable patients with negative nodes, whereas stage II patients are resectable but have positive nodal status.[8]

G. Ancillary Studies
Histochemistry, immunohistochemistry, and electron microscopy have become important adjuncts to routine microscopic evaluation in the diagnosis and classification of malignant mesothelioma. These methods are helpful in distinguishing malignant epithelioid mesothelioma from metastatic adenocarcinoma and sarcomatoid mesothelioma from metastatic or primary pleural sarcomas, but they are less helpful in distinguishing malignant mesothelioma from reactive mesothelial hyperplasia. Because there is no uniformly sensitive and specific immunohistochemical marker for malignant mesothelioma, a panel of stains is generally warranted. The College of American Pathologists (CAP) does not endorse a specific panel of markers for the evaluation of malignant mesothelioma. The International Mesothelioma Panel recommends a broad-spectrum cytokeratin, at least two mesothelial-

associated markers, such as calretinin, cytokeratins 5/6, and D2-40, and at least two markers that are typically positive in pulmonary adenocarcinoma and negative in pleural malignant mesothelioma, such as TTF-1, CEA, Ber-Ep4, Leu-M1, and MOC-31.[9,10]

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