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

A Basis for Checklists

Gerald Nash, MD; Christopher N. Otis, MD; for the Members of the Cancer Committee, College of American Pathologists

This protocol is intended to assist pathologists in providing clinically useful and relevant information as a result of the examination of surgical specimens. Use of this protocol is intended to be entirely voluntary. If equally valid protocols or similar documents are applicable, the pathologist is, of course, free to follow those authorities. Indeed, the ultimate judgment regarding the propriety of any specific procedure must be made by the physician in light of the individual circumstances presented by a specific patient or specimen.

It should be understood that adherence to this protocol will not guarantee a successful result. Nevertheless, pathologists are urged to familiarize themselves with this document. Should a physician choose to deviate from the protocol owing to the circumstances of a particular patient or specimen, the physician is advised to make a contemporaneous written notation of the reason for the procedure followed.

The College recognizes that this document may be used by hospitals, attorneys, managed care organizations, insurance carriers, and other payers. However, the document was developed solely as a tool to assist pathologists in the diagnostic process by providing information that reflects the state of relevant medical knowledge at the time the protocol was first published. It was not developed for credentialing, litigation, or reimbursement purposes. The College cautions that any uses of the protocol for these purposes involve considerations that are beyond the scope of this document.

PROTOCOL FOR THE EXAMINATION OF SPECIMENS FROM PATIENTS WITH MALIGNANT PLEURAL MESOTHELIOMA

I. Cytologic Material
- A. Clinical information
  1. Patient identification
     - a. Name
     - b. Identification number
     - c. Age (birth date)
     - d. Gender
  2. Responsible physician(s)
  3. Date of procedure
  4. Other clinical information
     - a. Relevant history
       - (1) Present/past occupation
       - (2) Asbestos exposure
       - (3) Radiation exposure
       - (4) Previous diagnosis of cancer or active infection
       - (5) Previous treatment
     - b. Relevant findings
       - (1) Pleural effusion(s) (duration)
       - (2) Pleural plaque(s) or thickening
       - (3) Imaging studies
     - c. Clinical diagnosis
     - d. Procedure (eg, thoracentesis, percutaneous fine-needle aspiration, thoracoscopy)
     - e. Operative findings
     - f. Anatomic site of specimen (eg, pleural space, including laterality, pericardial space)
     - g. Type of specimen (eg, pleural fluid, pleural-based mass)
- B. Macroscopic examination
  1. Specimen
     - a. Unfixed/fixed (specify fixative)
     - b. Number of slides received, if appropriate
     - c. Quantity and appearance of fluid specimen, if appropriate (including viscosity)
     - d. Other (eg, cytologic preparation from tissue)
     - e. Results of intraprocedural consultation
  2. Material prepared for microscopic evaluation (eg, smear, cytocentrifuge, thin preparation of fluid, cell block)
  3. Special studies (specify) (eg, immunohistochemistry, electron microscopy) (note A)
- C. Microscopic evaluation
  1. Adequacy of specimen (if unsatisfactory for evaluation, specify reasons)
  2. Tumor, if present
     - a. Histologic type, if possible (note B)
     - b. Other features (eg, nuclear grade, necrosis)
  3. Additional pathologic findings, if present (eg, ferruginous bodies)
  4. Results/status of special studies (specify) (eg, immunohistochemistry, electron microscopy) (note A)
  5. Comments

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From the Department of Pathology, Baystate Medical Center, Springfield, Mass.

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Reprints: Joe Schramm, College of American Pathologists, 325 Waukegan Rd, Northfield, IL 60093-2750.

a. Correlation with intraprocedural consultation, as appropriate
b. Correlation with other specimens, as appropriate
c. Correlation with clinical information, as appropriate

II. Incisional Biopsy

A. Clinical information
1. Patient identification
a. Name
b. Identification number
c. Age (birth date)
d. Gender
2. Responsible physician(s)
3. Date of procedure
4. Other clinical information
a. Relevant history
(1) Present/past occupation
(2) Asbestos exposure
(3) Radiation exposure
(4) Previous diagnosis of cancer or active infection
(5) Previous treatment
b. Relevant findings
(1) Pleural effusion(s) (duration)
(2) Pleural plaque(s) or thickening
(3) Imaging studies
c. Clinical diagnosis
d. Procedure (eg, percutaneous needle biopsy, thoracoscopic biopsy of pleura and/or lung, open thoracotomy biopsy of pleura and/or lung, lymph node biopsy)
e. Operative findings
f. Anatomic site(s) of specimen (eg, parietal/visceral pleura, lung indicating lobe and laterality, mediastinal node, diaphragm, pericardium)
g. Type(s) of specimen (eg, pleura, lung, lymph node, tumor nodule)

B. Macroscopic examination
1. Specimen
a. Unfixed/fixed (specify fixative)
b. Size (3 dimensions)
c. Descriptive features (color, hemorrhage, necrosis)
d. Results of intraoperative consultation
2. Tissue submitted for microscopic evaluation
a. Submit entire specimen, if possible
b. Frozen section tissue fragment(s) (unless saved for special studies)
3. Special studies (specify) (eg, immunohistochemistry, electron microscopy) (note **A**)

C. Microscopic evaluation
1. Tumor
a. Histologic type (note **B**)
b. Histologic grade (note **C**)
c. Extent of invasion (note **D**)
2. Additional pathologic findings, if present
a. Ferruginous bodies
b. Pleural plaque
c. Pulmonary interstitial fibrosis
d. Other(s)
3. Other tissue(s) present
4. Results/status of special studies (specify)
5. Comments
a. Correlation with intraoperative consultation, as appropriate
b. Correlation with other specimens, as appropriate
c. Correlation with clinical information, as appropriate

III. Resection

A. Clinical information
1. Patient identification
a. Name
b. Identification number
c. Age (birth date)
d. Gender
2. Responsible physician(s)
3. Date of procedure
4. Other clinical information
a. Relevant history
(1) Present/past occupation
(2) Asbestos exposure
(3) Radiation exposure
(4) Previous diagnosis of cancer or active infection
(5) Previous treatment
b. Relevant findings
(1) Pleural effusion(s) (duration)
(2) Pleural plaque(s) or thickening
(3) Imaging studies
c. Clinical diagnosis
d. Procedure
e. Operative findings
f. Anatomic site(s) of specimen

B. Macroscopic examination
1. Specimens
a. Organ(s)/tissue(s) included
b. Unfixed/fixed (specify fixative)
c. Size (3 dimensions)
d. Weight
e. External aspect (extent of resection)
f. Visceral pleura, as appropriate
g. Attached tissue, as appropriate (eg, pleura/pericardium/diaphragm)
h. Orientation, if designated by surgeon
i. Results of intraoperative consultation
2. Tumor
a. Location
b. Size (3 dimensions and minimum/maximum thickness of involved pleura)
c. Descriptive features (eg, color, diffuse/localized/circumscribed, consistency)
d. Extent of invasion, as appropriate (note **D**)
3. Margins (resections performed for surgical cure)
a. Bronchus
b. Pulmonary vessels
c. Parietal pleura
(1) Chest wall
(2) Mediastinal (including pericardium, great vessels, esophagus, trachea, vertebral bodies)
d. Diaphragm
e. Extrapleural chest wall (including excised thoracoscopic site and old scars)
f. Note areas designated by surgeon
4. Other pleura/lung

a. Normal
b. Abnormal (specify)

5. Regional lymph nodes (note E)
   a. Total number*
      * All nodes included in a pulmonary specimen are designated N1 (note E) unless otherwise specified by surgeon.
   b. Number involved by tumor
      (1) Extracapsular extension
      (2) Distinguish metastasis from nodal involvement by direct extension, as appropriate
6. Separately submitted lymph nodes (report each node station separately) (note E)
   a. Location (station) specified by surgeon
   b. Total number
   c. Number involved by tumor
      (1) Extracapsular extension
      (2) Distinguish metastasis from nodal involvement by direct extension, as appropriate
7. Tissues submitted for microscopic evaluation
   a. Tumor relation to pleura
   b. Tumor relation to adjacent lung
   c. Tumor relation to extrapleural tissues
      (1) Chest wall
      (2) Diaphragm
      (3) Pericardium
      (4) Mediastinal tissues
   d. Margins, as appropriate
      (1) Bronchus
      (2) Pulmonary vessels
      (3) Parietal pleura
         i. Chest wall
         ii. Mediastinal (pericardium, great vessels, esophagus, trachea, vertebral bodies)
      (4) Diaphragm
      (5) Extrapleural chest wall
      (6) Areas marked by surgeon
   e. Nonneoplastic pleura/lung
      (1) Normal
      (2) Abnormal
   f. Attached tissue
   g. All lymph nodes
   h. Frozen section tissue fragment(s) (unless saved for special studies)
   i. Other(s) (specify)
8. Special studies (specify) (eg, immunohistochemistry, electron microscopy) (note A)

C. Microscopic evaluation
1. Tumor
   a. Histologic type (note B)
   b. Histologic grade (note C)
   c. Site (laterality, visceral/parietal pleura, pericardium)
   d. Size (from gross description, diffuse/localized)
   e. Extent of invasion (note D)
2. Regional lymph nodes (note E)
   a. Site(s)
      (1) Included in pulmonary specimen
      (2) Separately submitted (report each node station separately, as specified)
   b. Number
      (1) Total number
      (2) Number with metastasis (note extracapsular invasion, if present)
3. Margins
   a. Bronchus
   b. Pulmonary vessels
   c. Parietal pleura
      (1) Chest wall
      (2) Mediastinal
         i. Pericardium
         ii. Great vessels
         iii. Esophagus
         iv. Trachea
         v. Vertebral bodies
   d. Diaphragm
   e. Extrapleural chest wall (including excised thoracoscopic site and old scars)
   f. Areas marked by surgeon
4. Additional pathologic findings, if present
   a. Nonneoplastic lung
   b. Ferruginous bodies
   c. Pleural plaque
   d. Interstitial fibrosis
   e. Other(s)
5. Distant metastasis, specify site(s) (note D)
6. Other tissue(s)/organ(s)
7. Results/status of special studies (specify)
8. Comments
   a. Correlation with intraoperative consultation, as appropriate
   b. Correlation with other specimens, as appropriate
   c. Correlation with clinical information, as appropriate

EXPLANATORY NOTES

A: Special Studies.—Immunohistochemistry and electron microscopy have become important adjuncts to routine microscopic evaluation in the diagnosis and classification of malignant mesothelioma.[1-7]

B: Histologic Type.—For consistency in reporting, the histologic classification published by the World Health Organization is recommended.[8] However, other classifications may be used. The more detailed histologic classification of malignant mesothelioma by Hammar recognizes histologic variations that might be confused with other neoplasms and points out light microscopic similarities to benign pleural cells, including the surface mesothelial cell and the multipotential subserosal spindle cell.[9]

The localized fibrous tumor of the pleura (previously referred to as localized fibrous mesothelioma) is not included in this protocol because it is generally regarded as a benign tumor arising from the subserosal fibrous tissue rather than from the mesothelium.[10]

World Health Organization Classification[8]

Epithelial
Fibrous (spindle cell)
Biphasic

Hammar Classification[9]

Epithelial
  Tubulopapillary
  Epithelioid

Glandular
Large cell/giant cell
Small cell
Adenoid-cystic
Signet ring
Sarcomatoid (fibrous, sarcomatous, mesenchymal)
Mixed epithelial-sarcomatoid (biphasic)
Transitional
Desmoplastic

C: Histologic Grading.—There is no specific recommended histologic grading system for malignant mesothelioma of the pleura.

D: Staging.—The protocol recommends the American Joint Committee on Cancer (AJCC) and International Union Against Cancer (UICC) TNM Staging System, as follows.[11,12] However, the protocol does not preclude the use of other staging systems such as the staging system of the International Mesothelioma Interest Group, which is also shown.[13]

TNM and Stage Groupings

Primary Tumor (T)*

- TX Primary tumor cannot be assessed
- T0 No evidence of primary tumor
- T1 Tumor limited to ipsilateral parietal and/or visceral pleura
- T2 Tumor invades any of the following: ipsilateral lung, endothoracic fascia, diaphragm, or pericardium
- T3 Tumor invades any of the following: ipsilateral chest wall muscle, ribs, or mediastinal organs or tissues
- T4 Tumor directly extends to any of the following: contralateral pleura, contralateral lung, peritoneum, intra-abdominal organs, cervical tissues

* By AJCC/UICC convention, the designation "T" of the TNM classification refers exclusively to the first resection of a primary tumor. The prefix symbol "p" refers to the pathologic classification of the TNM (pTNM), as opposed to the clinical classification. Pathologic classification is based on gross and microscopic examination. Therefore, 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.

The absence or presence of residual tumor following preoperative nonsurgical therapy (eg, chemotherapy or radiation treatment) may be described by the symbol "R" and is classified as follows:

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

If residual tumor is present, its extent may be documented by the TNM classification preceded by the symbol "y" (eg, ypT1). Local recurrence following a previous resection should be classified with the prefix "r" (eg, rpT1).

Regional Lymph Nodes (N)

- NX Regional lymph nodes cannot be assessed
- N0 No regional lymph node metastasis
- N1 Metastasis in ipsilateral peribronchial and/or ipsilateral hilar lymph nodes, including intrapulmonary nodes involved by direct extension of the primary tumor
- N2 Metastasis in ipsilateral mediastinal and/or subcarinal lymph node(s)
- N3 Metastasis in contralateral mediastinal, contralateral hilar, ipsilateral or contralateral scalene, or supraclavicular lymph node(s)

Distant Metastasis (M)

- MX Presence of distant metastasis cannot be assessed
- M0 No evidence of distant metastasis
- M1 Distant metastasis

AJCC/UICC TNM Stage Groupings

Stage I	T1	N0	M0
	T2	N0	M0
Stage II	T1	N1	M0
	T2	N1	M0
Stage III	T1	N2	M0
	T2	N2	M0
	T3	N0, 1, 2	M0
Stage IV	Any T	N3	M0
	T4	Any N	M0
	Any T	Any N	M1

International Mesothelioma Interest Group Staging System

Primary Tumor (T)

T1
- T1a Tumor limited to the ipsilateral parietal pleura, including mediastinal and diaphragmatic pleura; no involvement of the visceral pleura
- T1b Tumor involving the ipsilateral parietal pleura, including mediastinal and diaphragmatic pleura; scattered foci of tumor also involving the visceral pleura

T2 Tumor involving each of the ipsilateral pleural surfaces (parietal, mediastinal, diaphragmatic, and visceral pleura) with at least 1 of the following features:
- Involvement of diaphragmatic muscle
- Confluent visceral pleural tumor (including the fissures) or extension of tumor from visceral pleura into the underlying pulmonary parenchyma

T3* Tumor involving 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 the mediastinal fat
- Solitary, completely resectable focus of tumor extending into the soft tissues of the chest wall
- Nontransmural involvement of the pericardium

* T3 describes locally advanced but potentially resectable tumor.

T4† 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 of tumor to the peritoneum
- Direct extension of tumor to the contralateral pleura
- Direct extension of tumor to 1 or more 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

† T4 describes locally advanced technically unresectable tumor.

Regional Lymph Nodes (N)

NX Regional lymph nodes cannot be assessed
N0 No regional lymph node metastasis
N1 Metastasis in the ipsilateral bronchopulmonary or hilar lymph nodes
N2 Metastasis in the subcarinal or the ipsilateral mediastinal lymph nodes, including the ipsilateral internal mammary nodes
N3 Metastasis in the contralateral mediastinal, contralateral internal mammary, ipsilateral or contralateral supraclavicular lymph nodes

Distant Metastasis (M)

MX Distant metastasis cannot be assessed
M0 No distant metastasis
M1 Distant metastasis present

International Mesothelioma Interest Group Stage Groupings

Stage I			
Ia	T1a	N0	M0
Ib	T1b	N0	M0
Stage II	T2	N0	M0
Stage III	T3	N0	M0
	T1	N1	M0
	T2	N1	M0
	T1	N2	M0
	T2	N2	M0
Stage IV	T4	Any N	M0
	Any T	N3	M0
	Any T	Any N	M1

E: Regional Lymph Node Classification.—A classification of regional lymph nodes adapted from Naruke[14] and recommended by the AJCC follows.[11] This anatomic classification of nodal groups is not to be confused with N categories of regional lymph node metastasis of the TNM Staging System detailed in note D.

N2 nodes
- Superior mediastinal nodes
  - Highest mediastinal
  - Upper peritracheal
  - Pretracheal and retrotracheal
  - Lower peritracheal (including azygos nodes)
- Aortic nodes
  - Subaortic (aortic window)
  - Periaortic (ascending aorta or phrenic)
- Inferior mediastinal nodes
  - Subcarinal
  - Periesophageal (below carina)
  - Pulmonary ligament

N1 nodes
- Hilar
- Interlobar
- Lobar
- Segmental

Classification of lymph nodes, as recommended by the American Thoracic Society,[15] is as follows.

Definitions of Lymph Node Stations

2R Right upper peritracheal (suprainnominate) nodes: nodes to the right of the midline of the trachea between the intersection of the caudal margin of the innominate artery with the trachea and the apex of the lung (includes highest R mediastinal node)
2L Left upper peritracheal (supra-aortic nodes): nodes to the left of the midline of the trachea between the top of the aortic arch and the apex of the lung (includes highest L mediastinal node)
4R Right lower peritracheal nodes: nodes to the right of the midline of the trachea between the cephalic border of the azygos vein and the intersection of the caudal margin of the brachiocephalic artery with the right side of the trachea (includes some pretracheal and paracaval nodes)
4L Left lower peritracheal nodes: nodes to the left of the midline of the trachea between the top of the aortic arch and the level of the carina, medial to the ligamentum arteriosum (includes some pretracheal nodes)
5 Aortopulmonary nodes: subaortic and para-aortic nodes, lateral to the ligamentum arteriosum or the aorta or left pulmonary artery, proximal to the first branch of the left pulmonary artery
6 Anterior mediastinal nodes: nodes anterior to the ascending aorta or the innominate artery (includes some pretracheal and preaortic nodes)
7 Subcarinal nodes: nodes arising caudal to the carina of the trachea but not associated with the lower lobe bronchi or arteries within the lung
8 Paraesophageal nodes: nodes dorsal to the posterior wall of the trachea and to the right or left of the midline of the esophagus (includes retrotracheal but not subcarinal nodes)
9 Right or left pulmonary ligament nodes: nodes within the right or left pulmonary ligament
10R Right tracheobronchial nodes: nodes to the right of the midline of the trachea from the level of the cephalic border of the azygos vein to the origin of the right upper lobe bronchus
10L Left peribronchial nodes: nodes to the left of the midline of the trachea between the carina and the left upper lobe bronchus, medial to the ligamentum arteriosum

11 Intrapulmonary nodes: nodes removed in the right or left lung specimen plus those distal to the mainstem bronchi or secondary carina (includes interlobar, lobar, and segmental nodes); postthoracotomy staging may designate 11 interlobar, 12 lobar, 13 segmental, 14 subsegmental

Contributors: the College of American Pathologists Cancer Committee; Karen Antman, MD; Samuel P. Hammar, MD; Eugene Mark, MD; Harvey I. Pass, MD; and Peter B. Schiff, MD, PhD.

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