Thoracic Mesothelium

Protocol applies to malignant thoracic mesothelioma.

Protocol revision date: January 2004
Based on AJCC/UICC TNM, 6th edition

Procedures

- **Cytology** (No Accompanying Checklist)
- **Incisional Biopsy**
- **Resection**

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Surgical Pathology Cancer Case Summary (Checklist)

Protocol revision date: January 2004
Applies to malignant mesothelioma only
Based on AJCC/UICC TNM, 6th edition

PLEURA/PERICARDIUM: Biopsy

Patient name:
Surgical pathology number:

Note: Check 1 response unless otherwise indicated.

MACROSCOPIC

Specimen Type
___ Percutaneous needle biopsy
___ Thoracoscopic biopsy
___ Open thoracotomy
___ Lymph node biopsy
___ Other (specify): _____
___ Not specified

Tumor Site (check all that apply)
___ Right pleura
___ Left pleura
___ Pericardium
___ Other (specify): _____
___ Not specified

MICROSCOPIC

Histologic Type
___ Epithelioid (epithelial) mesothelioma
___ Sarcomatoid mesothelioma
___ Biphasic mesothelioma
___ Desmoplastic mesothelioma
___ Other (specify): _____
___ Mesothelioma, type cannot be determined

* Data elements ***with asterisks*** are ***not required*** for accreditation purposes for the Commission on Cancer. These elements may be clinically important, but are not yet validated or regularly used in patient management. Alternatively, the necessary data may not be available to the pathologist at the time of pathologic assessment of this specimen.

Extent of Invasion (as appropriate)
___ Cannot be determined
___ Lung parenchyma
___ Endothoracic fascia
___ Soft tissue of chest wall
___ Diaphragm
___ Other (specify): _____

***Additional Pathologic Findings (check all that apply)**
*___ None identified
*___ Ferruginous bodies
*___ Pleural plaque
*___ Pulmonary interstitial fibrosis
*___ Inflammation (type): _____
*___ Other (specify): _____

***Comment(s)**

Surgical Pathology Cancer Case Summary (Checklist)

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PLEURA/PERICARDIUM: Resection

Patient name:
Surgical pathology number:

Note: Check 1 response unless otherwise indicated.

MACROSCOPIC

Specimen Type
___ Pleural resection
___ Pericardial resection
___ Other (specify): _____
___ Not specified

Tumor Site (check all that apply)
___ Right pleura
___ Left pleura
___ Pericardium
___ Other (specify): _____
___ Not specified

***Tumor Configuration and Size**
*___ Localized
*Greatest dimension: ___ cm
*Additional dimensions: ___ x ___ cm
*___ Diffuse
*Maximum thickness: ___ cm
*___ Cannot be determined (see Comment)

MICROSCOPIC

Histologic Type
___ Epithelioid (epithelial) mesothelioma
___ Sarcomatoid mesothelioma
___ Biphasic mesothelioma
___ Desmoplastic mesothelioma
___ Other (specify): _____
___ Mesothelioma, type cannot be determined

* Data elements ***with asterisks*** are ***not required*** for accreditation purposes for the Commission on Cancer. These elements may be clinically important, but are not yet validated or regularly used in patient management. Alternatively, the necessary data may not be available to the pathologist at the time of pathologic assessment of this specimen.

Pathologic Staging (pTNM)

Primary Tumor (pT)

___ pTX: Primary tumor cannot be assessed
___ pT0: No evidence of primary tumor
pT1: Tumor involves ipsilateral parietal pleura, with or without focal involvement of visceral pleura
___ pT1a: Tumor involves ipsilateral parietal (mediastinal, diaphragmatic) pleura. No involvement of the visceral pleura
___ pT1b: Tumor involves ipsilateral parietal (mediastinal, diaphragmatic) pleura, with focal involvement of the visceral pleura
___ pT2: Tumor involves any of the ipsilateral pleural surfaces with at least 1 of the following: confluent visceral pleural tumor (including fissure), invasion of diaphragmatic muscle, invasion of lung parenchyma
___ pT3: Tumor involves any of the ipsilateral pleural surfaces, with at least 1 of the following: invasion of the endothoracic fascia, invasion into mediastinal fat, solitary focus of tumor invading the soft tissues of the chest wall, non-transmural involvement of the pericardium
___ pT4: Tumor involves any of the ipsilateral pleural surfaces, with at least 1 of the following: diffuse or multifocal invasion of soft tissues of the chest wall, any involvement of rib, invasion through the diaphragm to the peritoneum, invasion of any mediastinal organ(s), direct extension to the contralateral pleura, invasion into the spine, extension to the internal surface of the pericardium, pericardial effusion with positive cytology, invasion of the myocardium, invasion of the brachial plexus

Regional Lymph Nodes (pN)

___ pNX: Regional lymph nodes cannot be assessed
___ pN0: No regional lymph node metastases
___ pN1: Metastases in the ipsilateral bronchopulmonary and/or hilar lymph node(s)
___ pN2: Metastases in the subcarinal lymph node(s) and/or the ipsilateral internal mammary or mediastinal lymph node(s)
___ pN3: Metastases in the contralateral mediastinal, internal mammary, or hilar lymph node(s) and/or the ipsilateral or contralateral supraclavicular or scalene lymph node(s)
Specify: Number examined: ___
Number involved: ___

Distant Metastasis (pM)

___ pMX: Cannot be assessed
___ pM1: Distant metastasis
*Specify site(s), if known: _____

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Venous/Lymphatic (Large/Small Vessel) Invasion (V/L)
___ Absent
___ Present
___ Indeterminate

Margins
___ Cannot be assessed
___ Margins uninvolved by mesothelioma
Distance of tumor from closest margin: ___ mm
Specify margin: _____
___ Margin(s) involved by mesothelioma
Specify margin(s): _____

***Additional Pathologic Findings (check all that apply)**
*___ None identified
*___ Ferruginous bodies
*___ Pleural plaque
*___ Pulmonary interstitial fibrosis
*___ Inflammation (type): _____
*___ Other (specify): _____

***Comment(s)**

* Data elements ***with asterisks*** are ***not required*** for accreditation purposes for the Commission on Cancer. These elements may be clinically important, but are not yet validated or regularly used in patient management. Alternatively, the necessary data may not be available to the pathologist at the time of pathologic assessment of this specimen.

Background Documentation

Protocol revision date: January 2004

I. Cytologic Material

A. Clinical Information

1. Patient identification
   a. Name
   b. Identification number
   c. Age (birth date)
   d. Sex
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, 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
   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. Sex
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. Extent of invasion (Note **C**)
2. Additional pathologic findings, if present
   a. Ferruginous bodies
   b. Pleural plaque(s)
   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. Sex
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, chest wall)
   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, other)
   d. Extent of invasion, as appropriate (Note **C**)
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. Extra-pleural 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
   a. Total number[#]
   b. Number involved by tumor
      (1) extracapsular extension
      (2) distinguish metastasis from nodal involvement by direct extension, as appropriate

      [#] *All nodes included in a pulmonary specimen are designated N1 (Note **E**) unless otherwise specified by surgeon*
6. Separately submitted lymph nodes (report each node station separately)
   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) extra-pleural chest wall
(6) areas marked by surgeon

e. Non-neoplastic 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. Site (laterality, visceral/parietal pleura, pericardium)
c. Size (from gross description, diffuse/localized)
d. Extent of invasion and stage (Note **C**)

2. Regional lymph nodes
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. Extra-pleural chest wall (including excised thoracoscopic site and old scars)
f. Areas marked by surgeon

4. Additional pathologic findings, if present
a. Non-neoplastic lung
b. Ferruginous bodies
c. Pleural plaque
d. Interstitial fibrosis
e. Other(s)

5. Distant metastasis, specify site(s)
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

Histochemistry, immunohistochemistry and electron microscopy have become important adjuncts to routine microscopic evaluation in the diagnosis and classification of malignant mesothelioma.[1-11] These methods are helpful to distinguish malignant epithelioid mesothelioma from metastatic adenocarcinoma and sarcomatoid mesothelioma from metastatic or primary pleural sarcomas. These methods are less helpful to distinguish malignancies from reactive mesothelial hyperplasia.

Histochemistry

Adenocarcinomas can have intracytoplasmic neutral mucin that stains with mucicarmine and D-PAS stains. These reactions are usually negative in malignant mesothelioma. The cells of epithelioid mesotheliomas can contain acid mucopolysaccharides that can be stained with Alcian blue or Colloidal iron stains. These reactions can be blocked with the addition of hyaluronidase, confirming the presence of hyaluronic acid in the cytoplasm of mesothelial cells.

Immunohistochemistry

Malignant mesotheliomas usually exhibit cytoplasmic keratin, EMA, thrombomodulin, WT1, cytokeratin 5/6 and calretinin immunoreactivity. Immunostains for CEA, B72.3, BER-EP4, Leu-M1 and other markers for glycoproteins are negative in malignant mesotheliomas and can decorate the cytoplasm of adenocarcinoma cells. Nuclear immunoreactivity for TTF-1 can also be helpful to distinguish malignant mesothelioma, which stains negatively, from pulmonary adenocarcinomas. The tumor cells of sarcomatoid mesotheliomas usually exhibit focal cytoplasmic immunoreactivity for keratin, a finding that can be helpful to distinguish them from pleural sarcomas.

B. Histologic Type

For consistency in reporting, the histologic classification published by the World Health Organization (WHO) is recommended.[8] However, other classifications have been proposed, such as the detailed histologic classification of malignant mesothelioma by Hammar.[12]

WHO Classification of Mesothelial Tumors

Benign
- Adenomatoid tumor

Malignant mesothelioma
- Epithelioid mesothelioma
- Sarcomatoid mesothelioma
- Desmoplastic mesothelioma
- Biphasic mesothelioma
- Others
  - Tumors with heterologous elements (chondroid, osteoblastic, rhabdomyoblastic, neurogenic sarcoma-like)

Adenomatoid tumor-like
Lymphohistocytoid
Myxoid stroma deciduoid
Multicystic
Clear cell
Small cell
Poorly differentiated or anaplastic

C. Tumor Stage

The protocol recommends the American Joint Committee (AJCC) and the International Union Against Cancer (UICC) TNM staging system shown below.[13,14] The AJCC has adopted the staging system proposed by the International Mesothelioma Interest Group (IMIG) in 1995.[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 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 unfeasible) 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.

AJCC/IMIG Staging System for Diffuse Malignant Pleural Mesothelioma[13-15]

Primary Tumor (T)

TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
T1	Tumor involves ipsilateral parietal pleura, with or without focal involvement of visceral pleura
T1a	Tumor involves ipsilateral parietal (mediastinal, diaphragmatic) pleura. No involvement of the visceral pleura
T1b	Tumor involves ipsilateral parietal (mediastinal, diaphragmatic) pleura, with focal involvement of the visceral pleura
T2	Tumor involves any of the ipsilateral pleural surfaces with at least 1 of the following: - confluent visceral pleural tumor (including fissure) - invasion of diaphragmatic muscle - invasion of lung parenchyma
T3[#]	Tumor involves any of the ipsilateral pleural surfaces, with at least 1 of the following:

- invasion of the endothoracic fascia
- invasion into mediastinal fat
- solitary focus of tumor invading the soft tissues of the chest wall
- non-transmural involvement of the pericardium

T4[##] Tumor involves any of the ipsilateral pleural surfaces, with at least 1 of the following:
- diffuse or multifocal invasion of soft tissues of the chest wall
- any involvement of rib
- invasion through the diaphragm to the peritoneum
- invasion of any mediastinal organ(s)
- direct extension to the contralateral pleura
- invasion into the spine
- extension to the internal surface of the pericardium
- pericardial effusion with positive cytology
- invasion of the myocardium
- invasion of the brachial plexus

[#] T3 describes locally advanced, but potentially resectable tumor

[##] T4 describes locally advanced, technically unresectable tumor

Regional Lymph Nodes (N)

NX Regional lymph nodes cannot be assessed
N0 No regional lymph node metastases
N1 Metastases in the ipsilateral bronchopulmonary and/or hilar lymph node(s)
N2 Metastases in the subcarinal lymph node(s) and/or the ipsilateral internal mammary or mediastinal lymph node(s)
N3 Metastases in the contralateral mediastinal, internal mammary, or hilar lymph node(s) and/or the ipsilateral or contralateral supraclavicular or scalene lymph node(s)

Distant Metastasis (M)

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

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.

The “y” prefix indicates those cases in which classification is performed during or following 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 prior to 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.

The “a” prefix designates the stage determined at autopsy: aTNM.

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).

Vessel Invasion
By AJCC/UICC convention, vessel invasion (lymphatic or venous) does not affect the T category indicating local extent of tumor unless specifically included in the definition of a T category. In all other cases, lymphatic and venous invasion by tumor are coded separately as follows.

Lymphatic Vessel Invasion (L)
LX Lymphatic vessel invasion cannot be assessed
L0 No lymphatic vessel invasion
L1 Lymphatic vessel invasion

Venous Invasion (V)
VX Venous invasion cannot be assessed
V0 No venous invasion
V1 Microscopic venous invasion
V2 Macroscopic venous invasion

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