Mesothelioma in the Pleura and Peritoneum
Histopathology Reporting Guide

Family/Last name

Given name(s)

Date of birth DD – MM – YYYY

Patient identifiers

Date of request DD – MM – YYYY

Accession/Laboratory number

Elements in **black text** are CORE. Elements in **grey text** are NON-CORE.

CLINICAL INFORMATION (Note 1)

- ☐ Radiological appearance ○ Not provided
- ☐ History of previous cancer
- ☐ Other, *describe*

NEOADJUVANT THERAPY (Note 2)

- ○ Not administered ○ Information not provided
- ○ Administered, *describe*

OPERATIVE PROCEDURE (Note 3)

- ○ Core biopsy ○ Not provided
- ○ Open biopsy
- ○ VATS biopsy
- ○ Decortication
- ○ Radical pleurectomy
- ○ Extrapleural pneumonectomy
- ○ Debulking
- ○ Other, *specify*

SPECIMEN(S) SUBMITTED (select all that apply)

- ○ Not provided

Pleura/Thoracic

- ☐ Diaphragm
- ☐ Lung
  - ☐ Right
    - ☐ Wedge
    - ☐ Lobe
    - ☐ Entire Lung
  - ☐ Left
    - ☐ Wedge
    - ☐ Lobe
    - ☐ Entire Lung
- ☐ Mediastinal fat
- ☐ Pericardium
- ☐ Parietal pleura
- ☐ Contralateral pleura
- ☐ Visceral pleura
- ☐ Endothoracic fascia
- ☐ Chest wall
- ☐ Rib
- ☐ Spine
- ☐ Port site

Peritoneum

- ☐ Peritoneum
- ☐ Omentum
- ☐ Left ovary
- ☐ Right ovary
- ☐ Left fallopian tube
- ☐ Right fallopian tube
- ☐ Uterus
- ☐ Other intra-abdominal organs, *specify*

Other submitted specimens

- ☐ Lymph nodes, *specify site(s)*
- ☐ Other submitted specimens, *specify*

TUMOUR SIZE (Note 4)

Pleural specimens

MAXIMUM THICKNESS OF ANY MASS ____ mm

AND ○ Indeterminate

DIMENSIONS OF DOMINANT MASS

____ mm x ____ mm x ____ mm

○ Indeterminate

Peritoneal specimens

DIMENSIONS OF DOMINANT MASS

____ mm x ____ mm x ____ mm

OR ○ Indeterminate

DIMENSIONS OF LARGEST NODULE

____ mm x ____ mm x ____ mm

○ Indeterminate

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MACROSCOPIC TUMOUR SITE (select all that apply)

- ◯ Indeterminate

Pleura/Thoracic

- ☐ Diaphragm
- ☐ Lung
  - ☐ Right
  - ☐ Left
- ☐ Mediastinal fat
- ☐ Pericardium
- ☐ Parietal pleura
- ☐ Contralateral pleura
- ☐ Visceral pleura
- ☐ Endothoracic fascia
- ☐ Chest wall
- ☐ Rib
- ☐ Spine
- ☐ Port site

Peritoneum

- ☐ Peritoneum
- ☐ Omentum
- ☐ Uterus
- ☐ Left ovary
- ☐ Right ovary
- ☐ Left fallopian tube
- ☐ Right fallopian tube
- ☐ Other intra-abdominal organs, *specify*

Other

- ☐ Lymph nodes
- ☐ Other site, *specify*

MITOTIC COUNT (Note 5)
(Applicable to peritoneal specimens only) /mm2

HISTOLOGICAL TUMOUR TYPE (Note 6)

- ◯ Epithelioid (Epithelial)
- ◯ Sarcomatoid (Sarcomatous)
- ◯ Biphasic (Mixed epithelial and sarcomatous)
- ◯ Malignant mesothelioma, NOS

RESPONSE TO NEOADJUVANT THERAPY (Note 7)

- ◯ Cannot be assessed
- ◯ Prior treatment not known
- ◯ No prior treatment
- ◯ No response
- ◯ Positive response ⇒
  - ◯ No or minimal tumour response
  - ◯ Partial tumour response
  - ◯ Complete or near-complete response

MARGIN STATUS (Note 8)
(Applicable to extrapleural pneumonectomy specimens only)

- ◯ Not applicable
- ◯ Not involved
- ◯ Involved
- ◯ Cannot be assessed

Specify margin(s), if possible

COEXISTENT PATHOLOGY (Note 9)

- ◯ None identified OR *specify*

EXTENT OF INVASION (select all that apply) (Note10)

- ◯ Cannot be assessed
- ◯ No evidence of primary tumour

- ☐ Parietal pleura without involvement of the ipsilateral visceral pleura
- ☐ Parietal pleura with focal involvement of the ipsilateral visceral pleura
- ☐ Endothoracic fascia (as determined by surgeon/radiologist)
- ☐ Mediastinal fat
- ☐ Localised focus of tumour invading the soft tissue of the chest wall
- ☐ Diffuse or multiple foci invading soft tissue of chest wall
- ☐ Through the pericardium or diaphragm
- ☐ Into but not through the pericardium or diaphragm
- ☐ Rib(s)
- ☐ Peritoneum through the diaphragm
- ☐ Great vessels/oesophagus/trachea or other mediastinal organ
- ☐ Extension into contralateral pleura
- ☐ Spine
- ☐ Myocardium
- ☐ Confluent visceral and parietal pleural tumour (including fissure)
- ☐ Mediastinal organ(s), *specify*
- ☐ Other, *specify*

LYMPH NODE STATUS (Note 11)

- ◯ No nodes submitted or found
- ◯ Cannot be assessed

Lymph node station/location or specimen identification ⇩

	Involved ◯	Not involved ◯
	Involved ◯	Not involved ◯
	Involved ◯	Not involved ◯
	Involved ◯	Not involved ◯

ANCILLARY STUDIES (Note 12)

- ◯ Not performed
- ◯ Performed

⇩

Immunohistochemistry, *List stains*

Other, *specify*

PATHOLOGICAL STAGING (TNM 8th edition)##

PLEURAL SPECIMENS

- ☐ m multiple primary tumours at a single site
- ☐ r recurrent tumours after a disease free period
- ☐ y classification is performed during or following multimodality treatment

T - Primary tumour

- ◯ TX Primary tumour cannot be assessed
- ◯ T0 No evidence of primary tumour
- ◯ T1 Tumour involves ipsilateral parietal pleura, with or without involvement of visceral, mediastinal or diaphragmatic pleura.
- ◯ T2 Tumour involves the ipsilateral pleura (parietal or visceral pleura), with at least one of the following:
  - invasion of diaphragmatic muscle
  - invasion of lung parenchyma
- ◯ T3 Tumour involves ipsilateral pleura (parietal or visceral pleura), with at least one of the following:
  - invasion of endothoracic fascia
  - invasion into mediastinal fat
  - solitary focus of tumour invading soft tissues of the chest wall
  - non-transmural involvement of the pericardium
- ◯ T4 Tumour involves ipsilateral pleura (parietal or visceral pleura), with at least one of the following:
  - chest wall, with or without associated rib destruction (diffuse or multifocal)
  - peritoneum (via direct transdiaphragmatic extension)
  - contralateral pleura
  - mediastinal organs (oesophagus, trachea, heart, great vessels)
  - vertebra, neuroforamen, spinal cord
  - internal surface of the pericardium (transmural invasion with or without a pericardial effusion)

N - Regional lymph nodes

- ◯ NX Regional lymph nodes cannot be assessed
- ◯ N0 No regional lymph node metastasis
- ◯ N1 Metastases to ipsilateral intrathoracic lymph nodes (includes ipsilateral bronchopulmonary, hilar, subcarinal, paratracheal, aortopulmonary, paraesophageal, peridiaphragmatic, pericardial fat pad, intercostal and internal mammary nodes)
- ◯ N2 Metastases to contralateral intrathoracic lymph nodes. Metastases to ipsilateral or contralateral supraclavicular lymph nodes

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Scope

This dataset has been developed for biopsy and resection specimens of Mesothelioma in the pleura and peritoneum.

Note 1 - Clinical history (Non-core)

Reason/Evidentiary Support

Clinical information is essential to proper processing and evaluation of pathological specimens as it can influence pre-test probability of a particular diagnosis. This allows the pathology laboratory to accurately triage processing, including extent of sampling. It also informs the pathologist as to decisions ultimately influencing the number of slides to be examined (serial sections, levels) and potential ancillary studies to be performed,[1] thus avoiding error.

For malignant mesothelioma, the radiologic growth pattern and history of previous cancer are important guides to further analysis of a particular specimen. A radiologic nodular growth pattern may prompt correlation with surgical thoracoscopic observations with regard to nodule sampling, while a diffuse growth pattern may lead to a request for deeper or more extensive samples. History of prior cancer could suggest a different panel of immunohistochemical stains to definitively rule out metastasis from a known tumour. A cancer history can prompt a request to review prior outside material or to review an archival in house slide record.[1] Other valuable clinical information includes presence of a pleural effusion and its characteristics (e.g. transudative, bloody, exudative); this can trigger review of and correlation with a concurrent cytological specimen.

A history of asbestos exposure is not relevant for the diagnosis of samples in which malignant mesothelioma is a consideration, as this history does not influence sample processing or ultimate diagnosis.[2]

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Note 2 - Neoadjuvant therapy (Non-core)

Reason/Evidentiary Support

A history of neoadjuvant therapy is important in the pathology analysis. Assessment of residual tumour, including nodal status, is critical to staging and prognostication in the neoadjuvant setting.[3,4]

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Note 3 - Operative procedure (Core)

Reason/Evidentiary Support

Documentation of the operative procedure is useful, as correlation of the type of procedure with the material received can be important for patient safety. In resection specimens, the type of surgical procedure is important in determining the assessment of surgical margins.

Due to advanced age, clinical status, or extent of disease, few mesothelioma patients are suitable for extrapleural pneumonectomy or radical pleurectomy and therefore, diagnosis is usually based upon biopsy alone. Although the volume of tissue sampled is more restricted than for surgical resection specimens, biopsy assessment may contribute significant observations for clinical management and prognosis, in addition to the crucial distinction

between secondary tumours affecting the serosal membranes and mesothelioma, and between mesothelioma and benign reactive mesothelial proliferations.

The type of biopsy is important as it affects the extent to which a diagnosis may be made with any certainty. Accurate typing of mesothelioma[5-8] has been shown to vary by procedure - 83% for open biopsy in comparison to 74% for Video-assisted thoracoscopic surgery (VATS) biopsy, and 44% for X-ray computed tomography (CT)-guided biopsy, when compared with the subtype assessed in a follow-up series of 83 extrapleural pneumonectomy (EPP) specimens.[8]

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Note 4 - Tumour size (Non-core)

Reason/Evidentiary Support

For pleural mesotheliomas that are received as radical surgical (EPP or P/D) specimens, attempting to measure the dimensions of individual tumour nodules is neither simple (because the distinction between tumour and fibrotic reaction may be difficult to assess) nor informative. Rather, measuring the maximum thickness of tumour appears to be a more useful indicator of tumour burden and can often be compared to radiologic measurements.[9]

For peritoneal mesotheliomas, the specimen is normally received in multiple parts and dimensions of the dominant mass should be measured. Where multiple nodules are present, the dimensions of the largest nodule should be recorded.

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Note 5 - Mitotic count (Non-core)

Reason/Evidentiary Support

In pleural malignant mesothelioma, mitotic count has not been definitively established as an independent parameter in the diagnostic setting or as a determinant of prognosis. However among epithelioid peritoneal malignant mesothelioma, increased mitotic count (greater than 4 in 10 HPF[a])[10] was reported as a poor prognostic indicator, and, more recently, was validated in a multi-observer study of an independent group of patients,[11] establishing a lower cut-off of 5 mitoses in 50 HPF.

Ki-67 fraction may also have prognostic significance, but its use as an adjunct to mitotic count has not been investigated.

[a] High Powered Field

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Note 6 - Histological tumour type (Core)

Reason/Evidentiary Support

The major histological tumour types of malignant mesothelioma as recognized by the World Health Organisation (WHO) classification (4th edition)[12] are epithelioid, sarcomatoid and biphasic/mixed. By convention a biphasic mesothelioma is diagnosed if the lesser component reaches 10% of the tumour examined.

There are a number of histological patterns of malignant mesothelioma which are important to be aware of primarily because of diagnostic confusion. For epithelioid mesothelioma these include common patterns such as solid, tubulopapillary, and trabecular, also less common forms such as micropapillary, adenomatoid (microcystic), clear cell, transitional, deciduoid, small cell and pleomorphic mesothelioma. It should be noted that, at present, there is no uniformity among pathologists for the definition of many of these patterns nor any clear prognostic significance to most of them, and we do *not* recommend these names be included as part of a diagnosis; their importance lies in the recognition by the pathologist that these are patterns seen in mesotheliomas.

For sarcomatoid mesothelioma these histological variants may comprise heterologous (osteosarcomatous, chondrosarcomatous and rhabdomyosarcomatous) elements, and desmoplastic mesothelioma. Desmoplastic mesothelioma is characterized by atypical spindle cells and dense hyalinised fibrous stroma, the latter comprising at least 50% of the tumour.[2]

The conventional immunohistochemical panel of markers may require modification with some of these patterns to prevent misdiagnosis. Some of these patterns may have prognostic significance; however, until these prognostic patterns are clearly defined and accepted, the current recommendation is to diagnose mesotheliomas as epithelioid, sarcomatoid/desmoplastic, or biphasic/mixed, particularly since radical surgical approaches depend on these general classifications.

In some cases, such as small biopsy specimens, a definitive tumour type cannot be assigned and in this situation a value of "mesothelioma not otherwise specified (NOS)" would be used.

WHO classification of tumours of the pleura[a,b]

Descriptor	ICD0 codes
Diffuse malignant mesothelioma	
Epithelioid mesothelioma	9052/3
Sarcomatoid mesothelioma	9051/3
Biphasic mesothelioma	9053/3

[a] The morphology codes are from the International Classification of Diseases for Oncology (ICD-O). Behaviour is coded /0 for benign tumours; /1 for unspecified, borderline, or uncertain behaviour; /2 for carcinoma in situ and grade III intraepithelial neoplasia; and /3 for malignant tumours.[b] The classification is modified from the previous WHO classification taking into account changes in our understanding of these lesions.

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Note 7 – Response to neoadjuvant therapy (Non-core)

Reason/Evidentiary Support

There is no recommended or agreed system for tumour regression grading of mesothelioma that has been treated with neoadjuvant therapy, however a general indication of residual viable tumour may be useful.

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Note 8 - Margin status (Core)

Reason/Evidentiary Support

In extrapleural pneumonectomy specimens (EPP) the bronchial resection margin status is evaluated by intraoperative frozen section examination. In the surgical pathology specimen, the soft tissue margin status is difficult to assess because the entire pleura represents a margin. Usually in patients with extrapleural pneumonectomy (EPP), the surgeon is performing a blind dissection beneath the endothoracic fascia between the pleura and chest wall.

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Note 9 - Coexistent pathology (Non-core)

Reason/Evidentiary Support

It is recommended that pathologists comment upon any coexistent non-neoplastic findings present in the submitted materials. These include, for extrapleural pneumonectomy specimens, such findings as emphysema, small airways disease, respiratory bronchiolitis, asbestosis, asbestos bodies, talc granulomas and pleural plaques.[13] For diagnosing asbestosis, it is recommended that the criteria published by the asbestosis committee of the College of American Pathologists and Pulmonary Pathology Society be used.[14] For peritoneal resection specimens, additional findings such as endometriosis, endosalpingiosis and mesothelial inclusion cysts should be noted.

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Note10 - Extent of invasion (Core)

Reason/Evidentiary Support

Extent of invasion is part of staging for radical pleural surgical specimens. In biopsies the presence of invasion is the most important parameter for separating benign from malignant mesothelial proliferations.

Invasion into the endothoracic fascia is a staging parameter and should be determined only by the surgeon or radiologist, since there are no characteristic pathological features appreciable by gross or microscopic examination.

The endothoracic fascia represents a connective tissue plane that lies between the parietal pleura and the innermost intercostal muscle. Its histology is not well defined. Sections from parietal pleura that appose the chest wall showing histologic involvement of skeletal muscle is the best surrogate indicator that the endothoracic fascia has been breached.

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Note 11 - Lymph nodes status (Core)

Reason/Evidentiary Support

Thoracic or abdominal lymph nodes may be sampled to obtain a diagnosis or for the staging of an already diagnosed tumour. If thoracic, they should be identified by standard station; for abdominal lymph nodes, a suitable specimen identifier or descriptor should be used. A lymph node station should be regarded as positive for mesothelioma regardless of the number of malignant mesothelial cells present or the number of lymph nodes involved provided one node contains malignant mesothelial cells. However, the identification of mesothelial cells in

lymph nodes does not necessarily indicate metastasis. Rarely may they represent incidental inclusions.[15,16] The diagnosis of metastatic mesothelioma should only be made when there is good evidence of a serosa based tumour whether diffuse or, very rarely, localized.

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Note 12 - Ancillary studies (Non-core)

Reason/Evidentiary Support

The three most common molecular alterations in malignant mesothelioma are loss of neurofibromin 2 (Merlin, NF2), cyclin-dependent kinase inhibitor 2A (CDKN2A, p16), and BRCA1 associated protein-1 (BAP1). While to date NF2 loss has not been exploited diagnostically, p16 Fluorescence in situ hybridization (FISH) and BAP1 appear to be useful markers for separating benign from malignant mesothelial proliferations.[17] Thus far both these markers have been reported as only lost in malignant mesotheliomas when strict cut-offs are applied. One outcome of the strict cut-off is the major problem of low sensitivity. Overall, studies reporting loss of p16 by FISH in mesotheliomas show a sensitivity around 50%, albeit significantly higher in pleural (67%) than peritoneal mesothelioma (25%).[17]

Loss of p16 by FISH in pleural mesothelioma is correlated with adverse survival.[18,19] Retention of p16 by immunohistochemistry is a useful prognostic indicator in peritoneal epithelioid malignant mesothelioma, with a significantly prolonged survival in that group.[10]

The sensitivity for loss of nuclear expression of BAP1 is not well defined but probably on the order of 50 to 70% for epithelioid mesotheliomas, and very low for sarcomatoid mesotheliomas.[17] But these markers are only useful when lost; positive staining does not rule out a mesothelioma.

BAP1 immunohistochemistry in addition is useful as a screening tool for BAP1 germline mutation syndromes, in which there are familial aggregations of mesotheliomas, melanomas including ocular melanomas, renal cell carcinomas, and probably a variety of other tumours.[20] Interestingly, patients with BAP1 germline mutation mesotheliomas are reported to have dramatically better survival rates.[21] However, BAP1 immunohistochemistry is no more than a screening tool in this context, since the vast majority of mesotheliomas that show BAP1 loss only have somatic mutations, and formal genetic analysis is required to confirm germline tumours.

Positive immunohistochemistry for EMA[a], Glut1[b], IMP3[c] and CD[d]146 have all been proposed as single markers for malignant mesothelioma when compared to benign proliferations.[17] Since small but significant proportions of benign proliferations are positive for each of these markers, combinations of markers have been proposed, but the correlations are weak.[22-25] Therefore in the absence of morphologic invasion (cytology, small biopsy, or cellular atypia alone) these markers should not be relied upon as the sole determinant of malignancy.

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[a] Epithelial Membrane Antigen
[b] Glucose transporter -1
[c] Human U3 small nucleolar ribonucleoprotein protein
[d] Cluster of differentiation

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