Mesothelioma in the Pleura, Pericardium 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.

☐ indicates multi-select values ◯ indicates single select values

SCOPE OF THIS DATASET

CLINICAL INFORMATION (select all that apply) (Note 1)

- ◯ Information not provided
- ☐ Radiological appearance, *specify*
- ☐ History of previous cancer/BAP1 predisposition, *specify*
- ☐ History of recurrent pleural effusion, *specify*
- ☐ Other clinical information, *specify*

NEOADJUVANT THERAPY (Note 2)

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

CLINICAL AND RADIOLOGICAL CORRELATION (Note 3)

Specify

OPERATIVE PROCEDURE (Note 4)

- ◯ Not specified
- ◯ Core biopsy ➡
- ◯ Open biopsy ➡ Number of biopsies
- ◯ VATS biopsy ➡
- ◯ Extrapleural pneumonectomy (EPP)
- ◯ Pleurectomy/decortication
- ◯ Extended pleurectomy/decortication (EPD)
- ◯ Partial pleurectomy
- ◯ Other, *specify*

SPECIMEN(S) SUBMITTED (select all that apply)

◯ Not provided

Pleura/Thoracic

- ☐ Lung
  - ☐ Left
    - ☐ Wedge
    - ☐ Lobe
    - ☐ Entire lung
  - ☐ Right
    - ☐ Wedge
    - ☐ Lobe
    - ☐ Entire lung
- ☐ Diaphragm
- ☐ Mediastinum
- ☐ Pericardium
- ☐ Parietal pleura
- ☐ Contralateral pleura
- ☐ Visceral pleura
- ☐ Chest wall
- ☐ Rib
- ☐ Port site

Peritoneum

- ☐ Peritoneum
- ☐ Omentum
- ☐ Testis
  - ☐ Left ☐ Right ◯ Laterality not specified
- ☐ Ovary
  - ☐ Left ☐ Right ◯ Laterality not specified
- ☐ Fallopian tube
  - ☐ Left ☐ Right ◯ Laterality not specified
- ☐ Uterus
- ☐ Other intra-abdominal organs, *specify*

Other submitted specimens

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

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TUMOUR SIZE (Note 5)

Pleural specimens

MAXIMUM THICKNESS OF ANY MASS ____ mm

◯ Indeterminate

AND

DIMENSIONS OF DOMINANT MASS

____ mm x ____ mm x ____ mm

◯ Indeterminate

Peritoneal specimens

DIMENSIONS OF DOMINANT MASS

____ mm x ____ mm x ____ mm

◯ Indeterminate

OR

DIMENSIONS OF LARGEST NODULE

____ mm x ____ mm x ____ mm

◯ Indeterminate

MACROSCOPIC TUMOUR SITE (select all that apply) (Note 6)

◯ Indeterminate

Pleura/Thoracic

☐ Left
- ☐ Lung
- ☐ Parietal pleura
- ☐ Visceral pleura
- ☐ Chest wall
- ☐ Rib

☐ Right
- ☐ Lung
- ☐ Parietal pleura
- ☐ Visceral pleura
- ☐ Chest wall
- ☐ Rib

☐ Diaphragm
☐ Mediastinum
☐ Pericardium
☐ Port site

Peritoneum

☐ Peritoneum
☐ Omentum
☐ Testis
- ☐ Left ☐ Right ◯ Laterality not specified

☐ Ovary
- ☐ Left ☐ Right ◯ Laterality not specified

☐ Fallopian tube
- ☐ Left ☐ Right ◯ Laterality not specified

☐ Uterus
☐ Other intra-abdominal organs, *specify*

Other

☐ Lymph nodes
☐ Other site, *specify*

BLOCK IDENTIFICATION KEY (Note 7)

(List overleaf or separately with an indication of the nature and origin of all tissue blocks)

HISTOLOGICAL TUMOUR TYPE (Note 8)

(Value list from the World Health Organization, Classification of Thoracic Tumours (2021))

◯ Mesothelioma in situ
◯ Localized mesothelioma
◯ Diffuse mesothelioma, NOS

Subtype

◯ Epithelioid mesothelioma
◯ Sarcomatoid mesothelioma (including desmoplastic)
◯ Biphasic mesothelioma
- Epithelioid ____ %
- Sarcomatoid ____ %

Architectural pattterns

◯ Tubulopapillary ➡ ____ %
◯ Trabecular ➡ ____ %
◯ Adenomatoid ➡ ____ %
◯ Solid ➡ ____ %
◯ Micropapillary ➡ ____ %

Cytological features

◯ Rhabdoid
◯ Deciduoid
◯ Small cell
◯ Clear cell
◯ Signet ring
◯ Lymphohistiocytoid
◯ Pleomorphic
◯ Transitional

Stromal features

◯ Myxoid
◯ Desmoplastic
◯ Heterologous differentiation

HISTOLOGICAL TUMOUR GRADE (Note 9)

(Applicable to diffuse epithelioid mesotheliomas)

◯ Low grade (nuclear grades I and II without necrosis)
◯ High grade (nuclear grade II with necrosis, nuclear grade III with or without necrosis)

RESPONSE TO THERAPY (Note 10)

COEXISTENT PATHOLOGY (select all that apply) (Note 11)

◯ None identified
☐ Pleural plaque
☐ Other, *specify*

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EXTENT OF INVASION (select all that apply) (Note 12)

- ◯ No evidence of primary tumour
- ◯ Cannot be assessed
- ☐ Parietal pleura without involvement of the
  - ◯ Ipsilateral visceral pleura
  - ◯ Mediastinal pleura
  - ◯ Diaphragmatic pleura
- ☐ Parietal pleura with focal involvement of the
  - ◯ Ipsilateral visceral pleura
  - ◯ Mediastinal pleura
  - ◯ Diaphragmatic pleura
- ☐ Diaphragmatic muscle
- ☐ Lung parenchyma
- ☐ Endothoracic fascia
- ☐ Mediastinal fat
- ☐ Localised focus of tumour invading the soft tissue of the chest wall
- ☐ Into but not through the pericardium
- ☐ Through the pericardium
- ☐ Diffuse or multiple foci invading soft tissue of chest wall
- ☐ Rib(s)
- ☐ Peritoneum through the diaphragm
- ☐ Great vessels/oesophagus/trachea or other mediastinal organ
- ☐ Spine
- ☐ Myocardium
- ☐ Extension into contralateral pleura
- ☐ Other, *specify*

MARGIN STATUS (Note 13)

(Only applicable to EPP and EPD specimens)

- ◯ Cannot be assessed
- ◯ Not involved
- ◯ Involved, *specify margin(s) and their location, if possible*

LYMPH NODE STATUS (Note 14)

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

Lymph node station/location or specimen identification

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

ANCILLARY STUDIES - INVASIVE MESOTHELIOMA (Note 15)

- ◯ Not performed
- ◯ Performed (sellect all that apply)
  - ☐ ALK testing, *specify test(s) and result(s)*
  - ☐ BAP1 testing, *specify test(s) and result(s)*
  - ☐ CDKN2A, *specify test(s) and result(s)*
  - ☐ MTAP testing, *specify test(s) and result(s)*
  - ☐ Immunohistochemistry, *specify test(s) and result(s)*
  - ☐ Other e.g., NF2 (loss or fusion). EWSR1/ATF1, EWSR1/FUS-CREB, EWSR1/ YY fusions, *record test(s), methodology and results*

ANCILLARY STUDIES - MESOTHELIOMA IN SITU (Note 15)

- ◯ Not performed
- ◯ Performed (select all that apply)
  - ☐ BAP1 testing, *specify test(s) and result(s)*
  - ☐ CDKN2A, *specify test(s) and result(s)*
  - ☐ MTAP testing, *specify test(s) and result(s)*
  - ☐ Other, *record test(s), methodology and results*

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REPRESENTATIVE BLOCKS FOR ANCILLARY STUDIES

Specify those blocks best representing tumour and/or normal tissue for further study

HISTOLOGICALLY CONFIRMED DISTANT METASTASES (Note 16)

- ◯ Not identified
- ◯ Present, *specify site(s)*

PATHOLOGICAL STAGING (UICC TNM 8th edition)[a] (Note 17)

(Only EPD/EPP should be pathologically staged; Not applicable to mesotheliomas in situ)

PLEURAL SPECIMENS

TNM Descriptors (only if applicable) (select all that apply)

- ☐ 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

Primary tumour (pT)

- ◯ TX[b] 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)

Regional lymph nodes (pN)

- ◯ NX[b] 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

[a] *Reproduced with permission. Source: UICC TNM Classification of Malignant Tumours, 8th Edition, eds by James D. Brierley, Mary K. Gospodarowicz, Christian Wittekind. 2016, Publisher Wiley. (incorporating any errata published up until 6th October 2020).*

[b] *TX and NX should be used only if absolutely necessary.*

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Definitions

CORE elements

CORE elements are those which are essential for the clinical management, staging or prognosis of the cancer. These elements will either have evidentiary support at Level III-2 or above (based on prognostic factors in the National Health and Medical Research Council (NHMRC) levels of evidence[1]). In rare circumstances, where level III-2 evidence is not available an element may be made a core element where there is unanimous agreement by the Dataset Authoring Committee (DAC). An appropriate staging system e.g., Pathological TNM staging would normally be included as a CORE element.

Non-morphological testing e.g., molecular or immunohistochemical testing is a growing feature of cancer reporting. However, in many parts of the world this type of testing is limited by the available resources. In order to encourage the global adoption of ancillary tests for patient benefit, International Collaboration on Cancer Reporting (ICCR) recommends that some ancillary testing in ICCR Datasets is included as core elements. Where the technical capability does not yet exist, laboratories may consider temporarily using these data elements as NON-CORE items.

The summation of all CORE elements is considered to be the minimum reporting standard for a specific cancer.

NON-CORE elements

NON-CORE elements are those which are unanimously agreed should be included in the dataset but are not supported by level III-2 evidence. These elements may be clinically important and recommended as good practice but are not yet validated or regularly used in patient management.

Key information other than that which is essential for clinical management, staging or prognosis of the cancer such as macroscopic observations and interpretation, which are fundamental to the histological diagnosis and conclusion e.g., macroscopic tumour details, may be included as either CORE or NON-CORE elements by consensus of the DAC.

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Scope

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

The third edition includes changes to align the dataset with the 2021 World Health Organization (WHO) Classification of Thoracic Tumours, 5th edition.[2]

The authors of this dataset can be accessed here.

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Note 1 – Clinical information (Non-core)

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, thus avoiding error.

For 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 immuno-histochemical stains to definitively rule out metastasis from a known tumour, review of previous histology and consideration of a genetic predisposition syndrome.[3,4] 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 of general interest, but not relevant to diagnosis and does not influence sample processing because i) both mesothelioma and lung cancer can be induced by asbestos, so that a history of exposure by itself does not distinguish definitively between these possibilities; ii) mesotheliomas do occur rarely in patients with no known history of exposure to asbestos; and iii) tumours unrelated to asbestos exposure do occur in asbestos-exposed individuals.[5]

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Note 2 – Neoadjuvant therapy (Non-core)

A history of neoadjuvant therapy is of interest in the pathology analysis. However, there is currently no approved system for the assessment of residual tumour, including nodal status, and implications for staging and prognostication in the neoadjuvant setting are not established.[6,7,8]

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Note 3 – Clinical and radiological correlation (Core)

Correlation with clinical, radiological and thoracoscopic findings is always recommended and essential to a diagnosis of in situ mesothelioma, but maybe less critical for a diagnosis of invasive mesothelioma if tissue invasion is demonstrated in the histological specimen. For in situ mesothelioma, it is essential that no mass lesions are identified on imaging or thoracoscopy.[2,9,10]

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Note 4 – Operative procedure (Core)

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 (EPP) or extended pleurectomy/decortication (EPD) 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.

According to the Recommendations for Uniform Definitions of Surgical Techniques for Malignant Pleural Mesothelioma proposed by the International Association for the Study of Lung Cancer (IASLC) and the International Mesothelioma Interest Group (iMig),[11] the following definitions apply:

- EPP is an en bloc resection of the parietal and visceral pleura with the ipsilateral lung, pericardium, and diaphragm. In cases where the pericardium and/or diaphragm are not involved by tumour, these structures may be left intact.
- Pleurectomy/decortication (P/D) is a parietal and visceral pleurectomy to remove all gross tumour without diaphragm or pericardial resection.
- EPD is a parietal and visceral pleurectomy to remove all gross tumour with resection of the diaphragm and/or pericardium. The IASLC Mesothelioma Domain suggests use of the term 'extended' rather than 'radical' in this instance as the latter implies a completeness of resection with added therapeutic benefit. There is currently insufficient evidence that resection of the pericardium and diaphragm provides either.
- Partial pleurectomy is the partial removal of parietal and/or visceral pleura for diagnostic or palliative purposes but leaving gross tumour behind.

The type of biopsy is important as it affects the extent to which a diagnosis may be made with any certainty. Accurate subtyping of mesothelioma 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 computed tomography (CT)-guided biopsy, when compared with the subtype assessed in a follow-up series of 83 EPP specimens.[12-15]

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Note 5 – Tumour size (Non-core)

For pleural mesotheliomas that are received as radical surgical (EPP or EPD) 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.

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.

Total specimen size and individual fragment sizes, e.g., for core biopsies, are often routinely recorded in a macroscopic description.

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Note 6 – Macroscopic tumour site (Non-core)

The macroscopic tumour site should be recorded if known as it is important for staging, i.e., the presence of diffuse tumour or multifocality. It will also be important for correlation with thoracoscopy findings.

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Note 7 – Block identification key (Non-core)

The origin/designation of all tissue blocks should be recorded. This information should ideally be documented in the final pathology report and is particularly important should the need for internal or external review arise. The reviewer needs to be clear about the origin of each block in order to provide an informed specialist opinion. If this information is not included in the final pathology report, it should be available on the laboratory computer system and relayed to the reviewing pathologist. It may be useful to have a digital image of the specimen and record of the origin of the tumour blocks in some cases, in particular resections.

Recording the origin/designation of tissue blocks also facilitates retrieval of blocks for further immuno-histochemical or molecular analysis, research studies or clinical trials. Identification of a particular block that is suitable for further studies in the report can further aid this process and should be included in the report.

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Note 8 – Histological tumour type (Core and Non-core)

The major histological tumour types of mesothelioma as recognised by the WHO Classification of Thoracic Tumours, 5th edition are epithelioid, sarcomatoid and biphasic/mixed (see Table 1).[2] By convention a biphasic mesothelioma is diagnosed if the tumour includes both epithelioid and sarcomatoid components with the lesser component comprising at least 10% of the tumour examined in resection specimens which included EPP or EPD.[2] However, in small biopsy samples the designation of biphasic is independent of the percentages of each component.[2]

There are a number of histological patterns of mesothelioma which are important to be aware of as they impact prognosis and may lead to diagnostic confusion (refer to Tables 2 and 3).

For epithelioid mesothelioma, each of the architectural patterns present must be recorded and percentages given in a resection specimen. Favourable architectural patterns include tubulopapillary, trabecular and adenomatoid, whereas solid (>50%) and micropapillary are unfavourable.[2] Whereas adenomatoid pattern refers to gland like structures lined by flat to cuboidal cells resembling adenomatoid tumour. The designations of rhabdoid, deciduoid, small cell, clear cell, signet ring, lymphohistiocytoid and pleomorphic are now included as a separate category under cytological features. Predominant myxoid stroma (>50% of tumour with <50% solid pattern) is associated with favourable prognosis and should be reported as such.

Variants of sarcomatoid mesothelioma include desmoplastic mesothelioma and mesothelioma with heterologous elements.[2,16] Mesothelioma with transitional features is included as a cytological variant of sarcomatoid mesothelioma. Transitional mesothelioma is characterised by elongated yet plump cells appearing intermediate between epithelioid and sarcomatoid in morphology, arranged in a sheetlike pattern. The cells typically have moderate amounts of cytoplasm and prominent nucleoli and are more discohesive than epithelioid cells. Reticulin stain can be useful to highlight single cells. Sarcomatoid mesothelioma may contain heterologous (osteosarcomatous, chondrosarcomatous and rhabdomyosarcomatous) elements. Desmoplastic mesothelioma is characterised by atypical spindle cells and dense hyalinised fibrous stroma, the latter comprising at least 50% of the tumour examined in resection specimens which included EPP or EPD.[5] In small biopsy specimens, the term 'with desmoplastic features' should be used. Lymphohistiocytoid cytological features, which may also be present in epithelioid subtypes, should be reported because of favourable prognosis.

In some cases, such as small biopsy specimens or specimens with crush effect, a definitive tumour type cannot be assigned and in this situation a value of 'mesothelioma not otherwise specified (NOS)' should be used.

Table 1: World Health Organization classification of mesothelial tumours of the pleura.[2]

Descriptor	ICD-O code[a]
Adenomatoid tumour	9054/0
Well differentiated papillary mesothelial tumour[b]	9052/1
Mesothelioma in situ	9050/2
Localized mesothelioma	9050/3
Epithelioid mesothelioma	
Sarcomatoid mesothelioma (including desmoplastic)	
Biphasic mesothelioma	
Diffuse mesothelioma, NOS	9050/3
Epithelioid mesothelioma	
Sarcomatoid mesothelioma (including desmoplastic)	
Biphasic mesothelioma	

[a] The morphology codes are from the International Classification of Diseases for Oncology (ICD-O).[17] 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. Subtype labels are indented.
[b] Is a neoplasm of mesothelial origin but is considered distinct from mesothelioma in the 5th edition WHO.[2]

Table 2: Architectural patterns, cytological features and stromal characteristics relevant to reporting of epithelioid mesothelioma.[2]

Description	Pattern/features	Favourable	Unfavourable	Reporting
Composed of round, epithelioid cells, usually with cohesive architecture, but single cells within a fibrous stroma may also be seen	Architectural patterns Tubulopapillary Trabecular Adenomatoid Solid Micropapillary	Architectural patterns Tubulopapillary Trabecular Adenomatoid	Architectural patterns Solid (>50%) Micropapillary	Grade (high or low), architectural patterns present (and in definitive resection specimens such as EPD and EPP[c], percentages of each pattern; for all other specimens, indicate 'with … patterns/features')
	Cytological features Rhabdoid Deciduoid[a] Small cell[a] Clear cell[a] Signet ring[a] Lymphohistiocytoid Pleomorphic	Cytological features Lymphohistiocytoid Low nuclear grade[b]	Cytological features Rhabdoid Pleomorphic High nuclear grade[b]	
	Stromal features Myxoid	Stromal features Myxoid (if predominant, i.e. when >50% solid pattern contains myxoid stroma)	Necrosis (included in grading)	

[a] These cytological features carry no prognostic significance but are important to recognise to avoid misdiagnosis with other entities in the differential diagnosis.
[b] Refer to Table 4 Nuclear grading of pleural diffuse epithelioid mesothelioma.
[C] EPD = extended pleurectomy/decortication; EPP = extrapleural pneumonectomy.

Table 3: Architectural patterns, cytological features and stromal characteristics relevant to reporting of sarcomatoid mesothelioma including desmoplastic pattern.[2]

Description	Pattern/features	Favourable	Unfavourable
Composed of elongated/spindle cells (>2 times longer than wide) arranged in solid sheets or within a fibrous stroma	Cytological features Lymphohistiocytoid Transitional Pleomorphic	Cytological features Lymphohistiocytoid	Cytological features Transitional
	Stromal features Desmoplastic With heterologous differentiation		

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Note 9 – Histological tumour grade (Core)

A two-tiered grading system (low and high grade) that combines nuclear grade (mitotic count and nuclear atypia) and the presence of necrosis, has been demonstrated to be strongly predictive of survival in patients with epithelioid mesothelioma.[18-20,21,22]

Areas showing the highest-grade features should be used to assign tumours to low grade (any nuclear grade I and nuclear grade II without necrosis) or high grade (nuclear grade II with necrosis and any nuclear grade III). Grade should be reported in both biopsy and resection specimens of diffuse epithelioid mesotheliomas. Refer to Tables 2-4.

The use of Ki-67 proliferation index as an adjunct to mitotic count has not been validated and mitotic count is determined at 40x on haematoxylin and eosin (H&E) stained sections.

Table 4: Nuclear grading of pleural diffuse epithelioid mesothelioma.[2]

Nuclear grade	Nuclear atypia score	1 for mild 2 for moderate 3 for severe
	Mitotic count score	1 for low (≤1 mitosis/2 mm^2) 2 for intermediate (2-4 mitoses/2 mm^2) 3 for high (≥5 mitoses/2 mm^2)
	Sum	2 or 3 = nuclear grade I 4 or 5 = nuclear grade II 6 = nuclear grade III
Necrosis	Present/Absent	
Overall tumour grade	Low grade = nuclear grades I and II without necrosis High grade = nuclear grade II with necrosis, nuclear grade III with or without necrosis	

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Note 10 – Response to therapy (Non-core)

There is no recommended or agreed system for tumour regression grading of mesothelioma that has been treated with neoadjuvant chemotherapy or immunotherapy. Although currently no data support the recording of this information, it may be useful to capture this for research purposes or for future consideration.

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Note 11 – Coexistent pathology (Non-core)

It is recommended that pathologists comment upon any coexistent non-neoplastic findings present in the submitted materials. These include, for EPP specimens, such findings as pleural plaques, asbestosis, asbestos bodies, emphysema, small airways disease, respiratory bronchiolitis, and talc granulomas.[23] 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.[24] For peritoneal specimens, additional findings such as endometriosis, endosalpingiosis and mesothelial inclusion cysts should be noted.

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Note 12 – Extent of invasion (Core)

Extent of invasion is part of staging for radical pleural surgical specimens. In biopsies, the presence of invasion is important for separating benign from malignant mesothelial proliferations, but staging is dependent on multidisciplinary clinical review.

Invasion into the endothoracic fascia is a staging parameter and is usually determined by the surgeon intraoperatively.[25]

The endothoracic fascia represents a connective tissue plane that lies between the parietal pleura and the innermost intercostal muscle. This can be difficult to appreciate histologically.[25] In some circumstances the Elastin van Gieson stain may be helpful.[26] Sections from parietal pleura that oppose 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 13 – Margin status (Core)

In the surgical pathology specimen, the soft tissue margin status is difficult to assess because the entire pleura represents a margin. Therefore, margin status is only applicable to EPP and EPD specimens. Usually in patients with EPP the surgeon is performing a blind dissection beneath the endothoracic fascia between the pleura and chest wall. Any identified positive margins and their location must be recorded.

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Note 14 – Lymph nodes status (Core)

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. They may rarely represent incidental inclusions.[27,28] The diagnosis of metastatic mesothelioma should only be made when there is good evidence of a serosa based tumour whether diffuse or, very rarely, localised.

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Note 15 – Ancillary studies (Core and Non-core)

All mesothelial tumours

The use of ancillary studies is essential to confirm mesothelial phenotype. All variants of epithelioid mesothelioma react with multiple mesothelial-related antibodies.[29,30] There is some variation among laboratories as to which antibodies are selected for testing but at least two mesothelial and two carcinoma markers with greater than 80% sensitivity and specificity should be used with additional markers to be added if necessary. The most useful mesothelial markers are calretinin, WT-1, cytokeratin 5/6 (CK5/6), and D2-40 (podoplanin). The most useful general carcinoma markers are claudin 4,[31] MOC31, BG8[29,32] and BerEp4.[33,34] The sarcomatoid component of biphasic tumours and pure sarcomatoid mesotheliomas may lose immunoreactivity for most markers but most retain some labelling for cytokeratins,[35] D2-40[36] is the most likely marker to remain immunoreactive.[29,32] The usefulness of GATA 3 for sarcomatoid mesothelioma is still under investigation but promising.[35,37-40]

The three most common molecular alterations in mesothelioma are loss of cyclin-dependent kinase inhibitor 2A (*CDKN2A*, p16), neurofibromin 2 (Merlin, NF2), and BRCA1 associated protein-1 (BAP1). Assessment of hemizygous NF2 loss by FISH[41-43] shows promise but is not widely used diagnostically to date. However, homozygous loss of *CDKN2A*, e.g., by fluorescence in situ hybridization (FISH), and immunohistochemistry for MTAP (as a surrogate for loss of *CDKN2A*), and BAP1 are useful markers for separating benign from malignant mesothelial proliferations, e.g., in small biopsies.[41,44-50]

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, whereas *CDKN2A* homozygous loss is present in the majority of sarcomatoid mesotheliomas.[51] These markers are only useful when lost; positive staining or no deletion do not rule out a mesothelioma, and these alterations are not specific to mesothelioma and may be present in other neoplasms.

BAP1 immunohistochemistry is also 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.[52] 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 not all patients with germline mutations show nuclear loss.[53] Formal genetic analysis is required to confirm germline tumours and can be initiated in cases where there is significant clinical concerns regardless of immuno-histochemical results.

ALK rearrangements have rarely been identified in peritoneal and pleural mesothelioma.[54,55] Assessment for *ALK* rearrangements should especially be considered in peritoneal mesothelioma where treatment implications are more established.[56] If screened by histology, use of the ALK (D5F3) antibody is most established.

Mesothelioma can harbour EWSR1/FUS-ATF1. This mesothelioma subset is observed in pleura and peritoneum and features include young age at presentation, lack of asbestos exposure and retained BAP1 expression. Diagnosis can be made by RNAseq and FISH but treatment implications are not established.[57] The role of SMARCA4 deletion in the diagnosis of mesothelioma is uncertain.[58]

Immunohistochemistry for PD-L1 may be performed if clinically relevant.

Mesothelioma in situ

Loss of nuclear labelling for BAP1 and/or loss of MTAP labelling (cytoplasmic) or homozygous loss of *CDKN2A* by FISH is required for a diagnosis of mesothelioma in situ. The diagnosis requires an adequate biopsy correlation with clinical features (recurrent unexplained pleural effusions in a high risk patient are typical) and thorascocopic and radiological findings that do not demsontrate a mass lesion is essential for diagnosis.[2,59-61]

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Note 16 – Histologically confirmed distant metastases (Core)

Documentation of known metastatic disease is an important part of the pathology report. Such information, if available, should be recorded with as much detail as available including the site and reference to any relevant prior surgical pathology or cytopathology specimens.

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Note 17 – Pathological staging

The pathological primary tumour (T) and regional lymph node (N) categories are considered core elements in the majority of ICCR datasets. The 8th edition of the Union for International Cancer Control (UICC)[62] and American Joint Committee on Cancer (AJCC)[25] Staging Systems is based on retrospective analysis of a large series of patients accumulated by the IASLC, and applies to both clinical and pathological staging. Definitive resection specimens (EPD/EPP) should be pathologically staged, with smaller specimens being clinically staged via multidisciplinary review. It is recommended to discuss intraoperative findings with the surgeon before completion of pathological staging.[63-66]

The 8th edition UICC/AJCC Staging Systems[62,25] do not incorporate a category for mesothelioma in situ. There is currently limited data to suggest inclusion of mesothelioma in situ as a stage.[60]

The reference document: TNM Supplement: A commentary on uniform use, 5th edition (C Wittekind et al. editors) may be of assistance when staging.[67]

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