The Royal College of Pathologists
Pathology: the science behind the cure

Standards and datasets for reporting cancers

Dataset for the histopathological reporting of mesothelioma

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Foreword

The cancer datasets published by The Royal College of Pathologists (RCPath) are a combination of textual guidance, educational information and reporting proformas. The datasets enable pathologists to grade and stage cancers in an accurate, consistent manner in compliance with international standards and provide prognostic information, thereby allowing clinicians to provide a high standard of care for patients and appropriate management for specific clinical circumstances. This guideline has been developed to cover most common circumstances. However, we recognise that guidelines cannot anticipate every pathological specimen type and clinical scenario. Occasional variation from the practice recommended in this guideline may therefore be required to report a specimen in a way that maximises benefit to the patient.

Each dataset contains core data items that are mandated for inclusion in the Cancer Outcomes and Services Dataset (COSD – previously the National Cancer Dataset) in England. Core data items are items that are supported by robust published evidence and are required for cancer staging, optimal patient management and prognosis. Core data items meet the requirements of professional standards (as defined by the Information Standards Board for Health and Social Care [ISB]) and it is recommended that at least 90% of reports on cancer resections should record a full set of core data items. Other, non-core data items are described. These may be included to provide a comprehensive report or to meet local clinical or research requirements, with appropriate patient consent where required. All data items should be clearly defined to allow the unambiguous recording of data.

The following stakeholders were contacted to consult on this document:

- British Thoracic Oncology Group
- British Thoracic Society
- Society for Cardiothoracic Surgery in Great Britain and Ireland.

The information used to develop this dataset was obtained by undertaking a systematic search of PubMed. Key terms searched included ‘pleura’ and ‘mesothelioma’ and dates searched were between September 2017 and September 2023. Published evidence was evaluated using modified SIGN guidance (see Appendix G). Consensus of evidence in the guideline was achieved by expert review. Gaps in the evidence will be identified by College members via feedback received during consultation. Further evidence was derived from consensus of recognised experts, in particular recent guidelines from an

internationally convened group of pathologists with a particular interest in mesothelioma, many of whom are part of the International Association for the Study of Lung Cancer (IASLC) and International Mesothelioma Interest Group (IMIG),[1] as well as the WHO Classification of Thoracic Tumours.[2]

All cancer datasets are formally revised every 3 years. However, each year, the College will ask the authors of the dataset, in conjunction with the relevant subspecialty adviser to the College, to consider whether or not the dataset needs to be revised. A full consultation process will be undertaken if major revisions are required. This includes all major revision to core data items, apart from changes to international tumour grading and staging scheme that have been approved by the Specialty Advisory Committee on Cellular Pathology and affiliated professional bodies, which will be implemented without further consultation. If minor revisions or changes to non-core data items are required, an abridged consultation process will be undertaken, whereby a short note of the proposed changes will be placed on the College website for 2 weeks for members' attention. If members do not object to the changes, the short notice of change will be incorporated into the dataset and the full revised version (incorporating the changes) will replace the existing version on the College website.

The dataset has been reviewed by the Professional Guidelines team, Working Group on Cancer Services and Lay Advisory Group. It will be placed on the College website for consultation with the membership from 9 November to 7 December 2023. All comments received be addressed by the authors to the satisfaction of the Chair of the Working Group and the Clinical Lead for Guideline Review.

This dataset was developed without external funding to the writing group. The College requires the authors of datasets to provide a list of potential conflicts of interest; these are monitored by the Professional Guidelines team and are available on request. The authors of this document have declared that there are no conflicts of interest.

1 Introduction

Although mesotheliomas may present in the peritoneum and other sites, they most commonly arise in the pleura and this dataset is limited to the reporting of mesothelioma at this site. It is one of the most important occupational diseases, with incidence steadily rising due to its association with exposure to asbestos. Cases in the United Kingdom continue to rise in the elderly.[3]

The pleura is a common site for metastatic disease as well as for other rarer primary tumours, such as sarcomas. However, this document deals only with the data that are required for mesothelioma.

Features in both biopsy and resection specimens should be reported according to the following guidelines, as data are important in:

- deciding on the most appropriate treatment for particular patients, including the need and choice of adjuvant therapy
- providing prognostic information to clinicians and patients
- providing more reliable staging than using clinical data alone
- monitoring clinical effectiveness of therapeutic trials
- providing accurate data for cancer registration.

International guidelines on the reporting of mesotheliomas have been published by an invited group of pathologists under the aegis of IMIG.[1,4] Also, in 2021, the World Health Organisation (WHO) published an updated classification of pleural tumours,[2] and the 8th TNM staging system came into effect from 1 January 2017, with changes to the staging of mesothelioma based on analysis of a large international database.[5–8] This revision, based on the above updates, will also ensure consistency with the International Collaboration on Cancer Reporting (ICCR) dataset.[9,10]

The purpose of this document is to define the core data that should be recorded for all patients with a histological diagnosis of mesothelioma. These are guidelines that are intended to help pathologists provide local clinicians with the necessary information to manage their patients effectively. Consistency in reporting and staging is improved by the use of standard terminology – for example, precise definition of the various subtypes of mesothelioma according to the WHO 2021 classification,[2] together with accurate definition of anatomic parameters related to staging. Given the anatomical complexity of the thorax, when faced with the rare occurrence of a resection specimen, discussion with the surgeon is frequently required to ensure that information about the pathological staging is accurately delivered.

1.1 Target users and health benefits of this guideline

The target primary users of the dataset are trainee and consultant cellular pathologists and, on their behalf, the suppliers of IT products to laboratories. The secondary users are surgeons and oncologists, cancer registries and the National Cancer Intelligence Network.

Standardised cancer reporting and multidisciplinary team (MDT) working reduce the risk of histological misdiagnosis and help to ensure that clinicians have all the relevant pathological information required for tumour staging, management and prognosis. Collection of standardised cancer specific data also provides information for healthcare providers and epidemiologists and facilitates international benchmarking and research.

2 Clinical information required on the specimen request form

Name, date of birth, hospital, hospital number, NHS or CHI number, procedure, specimen type, date of procedure and surgeon/physician should be provided. In addition, the laterality and procedure (biopsy, core needle biopsy, thoracoscopic video-assisted thoracoscopic surgery [VATS] biopsy, thoracotomy, incisional biopsy, pleurectomy, or extrapleural pneumonectomy) should be documented. Details of any previous biopsy or cytology, any previous malignancy, previous treatment such as neoadjuvant chemotherapy and/or radiotherapy must also be recorded. Any exposure to asbestos should be documented, if known. If a diagnostic frozen section was performed, this must be recorded and the intraoperative diagnosis must be documented.

3 Preparation of specimens before dissection

The majority of specimens are biopsies and therefore require no more than formalin fixation before processing. The use of electron microscopy has largely been superseded by immunohistochemistry, although the selection of a small piece of tissue for fixation in glutaraldehyde may be undertaken before placing in formalin, if this investigation is going to be undertaken. Small biopsies should be processed in their entirety, with consideration given to using multiple cassettes as cases frequently require extensive immunohistochemistry. Debulking specimens (e.g. pleurectomy/extended pleural decortication [EPD]) should be fixed for at least 24 hours and then sampled thoroughly. Extrapleural pleuropneumonectomy (EPP) specimens are now rarely performed. If undertaken, specimens are ideally placed in formalin after inflation of the lung via the airways in similar fashion to that undertaken for lung cancer resections. Close collaboration with the surgeon is recommended prior to dissection, in order to identify areas of concern regarding completeness of resection and relevant anatomic structures (pericardium, diaphragm, mediastinal fat, etc.)

[Level of evidence D – Expert opinion is that good communication between surgeon and pathologist improves the accuracy of determining completeness of resection.]

4 Specimen handling and block selection

The overall size of biopsies should be measured and documented, and any identifiable tissues included in the specimen (pleura, chest wall adipose tissue and/or skeletal muscle, rib[s], diaphragm, lymph nodes, mediastinal structures, etc.) should be documented. For surgical biopsies, specimens should be sectioned perpendicular to the pleural surface because orientation in this plane facilitates diagnosis, especially of the desmoplastic variant of sarcomatoid mesothelioma. This is because it enables better assessment of variations in cellularity which are obscured by cross-cutting.

In relation to EPD and EPP specimens, the distribution of disease should be described (distribution: diffuse, nodular, localised/solitary), together with the extent of pleural involvement (localised, subtotal, circumferential), together with involvement of the fissures and interlobular septa. If there is a dominant tumour mass, its size should be measured and its location identified. If present, additional nodules within the lung or patterns of spread within the lung should be noted. In rare cases that are localised and there is consideration of complete excision, the distance to the nearest resection margin should be documented (lateral soft tissue [chest wall] margin, bronchus, pulmonary vessels, mediastinal structures if included, diaphragm), inking margins where appropriate. As discussed above, this frequently requires discussion with the surgeon prior to dissection. In relation to radical pleurectomy specimens, it is important to identify and sample appropriate areas to stage the specimen according to the new TNM guidelines, in particular to identify and sample pericardium and diaphragm as well as the pleura.

Abnormalities within the lung parenchyma (e.g. fibrosis, tumour involvement either as nodules or through direct spread) should be noted, as should non-neoplastic abnormalities in pleura and mediastinal tissues (e.g. pleural plaques), although these are not viewed as core items. Asbestos bodies should be looked for. This may be facilitated by Perls' staining on normal thickness or assessing 25 micrometre-thick unstained sections. In radical pleurectomies, any adherent lung tissue needs to be identified and sampled for this purpose. Taking a photograph prior to dissection may be of value, especially in larger specimens.

Finally, if feasible and there is appropriate consent, banking frozen fresh tumour for future research is recommended.

[Level of evidence C – The basis for block selection is extrapolated from the need to provide microscopic confirmation or evaluation of prognostic and predictive factors.]

5 Considerations for microscopy

5.1 Histological type

Histological typing of mesothelioma is recorded according to the WHO 2021 classification with initial division into mesothelioma in situ, localised mesothelioma and diffuse mesothelioma, with subdivision into epithelioid, biphasic and sarcomatoid subtypes.[2] Further documentation of histological patterns and both cytological and stromal variants should also be undertaken as some have clinical relevance such as pleomorphic cytology and solid pattern.[11,12] Pleomorphic and lymphohistiocytic cytological variants may occur in both epithelioid subtypes. The transitional cytological variant is now viewed exclusively as a variant within the sarcomatoid subtype. Major subtypes and variants are classified as core data items.

[Levels of evidence B–D – Histopathological type is important for clinical management and prognosis, with strength of evidence varying for different types.]

Mesothelioma in situ (MIS) has been considered for decades but has only recently been proven to exist, defined through morphology with the addition of molecular analysis. A diagnosis of MIS can only be made in a multidisciplinary setting when there is a mesothelial proliferation limited to the surface which shows *BRCA1-associated protein* (*BAP1)* loss and/or deletion of the cyclin-dependent kinase inhibitor 2A (*CDKN2A)* gene, within the setting of no evidence of invasion at surgery or on imaging.[13,14]

If an epithelioid neoplasm is present, the usual distinction to be made is between mesothelioma and metastatic adenocarcinoma, since these are by far the most common malignant neoplasms at this site. A diastase-PAS or combined Alcian blue/PAS stain for epithelial mucins may therefore be of use. Staining for acidic (connective tissue) mucins alone (Alcian blue +/- hyaluronidase) can also be of value but has largely been superseded by immunohistochemistry.[4]

Diagnosis, however, may be impossible with the small amount of tissue usually present in a pleural needle biopsy and further large biopsies may be required, especially for

distinguishing reactive from neoplastic infiltrates. In the latter situation, broad spectrum cytokeratins (e.g. AE1/3, MNF116, CAM 5.2) may be useful in identifying extent of invasion, including invasion into subpleural fat, when this is difficult to appreciate on H&E. Recent studies have suggested that identification of mutations in the *BAP1* gene, usually through immunohistochemical staining for *BAP1* that shows loss of nuclear staining is of value in distinguishing mesothelioma and reactive mesothelial hyperplasia as an additional consideration in difficult cases.[1,15,16] Assessment of the *CDKN2A (p16)* gene status using FISH is a further marker that may have value in refining diagnosis.[16–19] Both markers may be particularly useful when there is insufficient morphological evidence for a suspected mesothelioma, especially in superficial biopsies. Antibody staining for methylthioadenosine phosphorylase (MTAP) may be used as a surrogate for FISH, if staining is diffusely lost.[20–24] While this suggests neoplasia, loss of staining is not 100% specific or sensitive and should be confirmed by molecular analysis. Clinical and radiological features are also often invaluable in difficult cases, ideally through multidisciplinary discussion. Other neoplasms also arise in or spread to the pleura and should be duly considered.[17]

The distinction between epithelioid mesothelioma and metastatic adenocarcinoma cannot be made with confidence on morphological grounds alone and immunohistochemistry is mandatory. Currently no single antigen indicative of mesothelial or adenocarcinomatous differentiation is sufficiently sensitive or specific, so a panel is recommended. This will vary according to the preference of the individual pathologist, but recommended markers of mesothelial differentiation include cytokeratins of classes 5 and 6, calretinin, N-cadherin, Wilm's Tumour-1 (WT1), D2-40 and thrombomodulin.[2–4] However, it is emphasised that the specificity and sensitivity for mesothelioma using these antibodies is significantly reduced in poorly differentiated epithelioid neoplasms and these data should not be interpreted in isolation from other data. For poorly differentiated epithelioid neoplasms, the use of several broad spectrum cytokeratins may be necessary. Suitable markers of glandular differentiation include epithelial glycoprotein (BerEp4 antibody), CEA and the CD15 antigen. Further immunohistochemistry (e.g. TTF-1, cytokeratin subclasses, hormone receptors) may be useful in defining the nature of metastatic adenocarcinoma.[2–4,25,26]

A broader panel of antibodies is required to distinguish sarcomatoid mesothelioma from sarcomas (primary and metastatic), but no antibody is 100% specific or sensitive. The most consistently useful is cytokeratin staining, which is positive in 80–90% of sarcomatoid mesotheliomas.[2,3,25] Genetic analysis may be of diagnostic value in identifying some

sarcomas (e.g. X;18 translocation for synovial sarcoma). Other antibodies such as D2-40, GATA3 and PDL1 are also reported to be of value.[27,28] Staining for SMARCA4 will exclude thoracic SMARCA4-deficient undifferentiated tumours. *BAP1* is less frequently mutated in sarcomatoid mesotheliomas than in epithelioid mesotheliomas, although may still occur. Assessment of *CDKN2A (p16)* status either via FISH or MTAP immunohistochemistry is also of value in cases where there is difficulty distinguishing sarcomatoid mesothelioma from reactive changes.

Referral to regional or national experts is recommended in complex and difficult cases and reporting pathologists should have an interest in thoracic pathology, be routinely reporting thoracic cases and ideally participate in the thoracic pathology external quality assessment (EQA) scheme.

5.2 Grading

Several papers were published during the past decade suggesting prognostication for epithelioid mesotheliomas could be refined using grading, leading to recommendation for its application in the 2021 edition of the WHO classification.[2,29–31] This is now viewed as a core item. Grading is based on nuclear features, mitotic activity and the presence or absence of necrosis. Grading is not required for biphasic or sarcomatoid mesotheliomas.

5.2.1 Grading breakdown

- Nuclear atypia mild = 1, moderate = 2, severe = 3.
- Mitotic rate ≤1 = 1, 2–4 = 2, ≥5 = 3 (per 2 mm^2).
- Nuclear grade = nuclear atypia score plus mitotic rate score.
- 2–3 = Nuclear grade 1, 4–5 Nuclear grade 2, 6 = Nuclear grade 3.
- **Low grade = Nuclear grade 1 +/- necrosis, Nuclear grade 2 without necrosis.**
- **High grade = Nuclear grade 2 with necrosis, Nuclear grade 3 +/- necrosis.**

5.2.2 Staging

Based on expert consensus, pathological staging is undertaken only for EPD and EPP specimens, using the UICC 8th Edition TNM criteria.[1,5–8] All other cases should be clinically staged, although this may include data from pathological specimens.

6 Core data items

6.1 Clinical

Name, date of birth, hospital, hospital number, NHS/CHI number, specimen type, procedure, date of procedure and surgeon/physician should be supplied. Laterality and type of procedure must be documented. Neoadjuvant treatment should be documented, if undertaken.

[Level of evidence – Good practice point (GPP). Clinical information can help guide diagnosis and staging.]

6.2 Relationship of tumour to other intra-thoracic structures

The location of the tumour in the thorax, as well as its relationship to adherent structures, should be recorded. In particular, areas of likely invasion that pertain to staging should be assessed (chest wall, diaphragm, pericardium, lung, great vessels, pericardium, lymph nodes). Separate tumour nodules in the main resection specimen or separately submitted samples (e.g. separate lung or pleural nodules) should also be documented.

[Level of evidence B – Extent of invasion forms part of established staging criteria.]

6.3 Size of tumour and biopsy data

If a single localised mass, the maximum diameter of tumour should be measured to the nearest millimetre. Ideally, 3 dimensions should be recorded. If there is a dominant mass, this should be measured in similar fashion, with description of other localised nodules or extent of more diffuse confluent disease. The number of biopsies should be documented, as well as the size of any single biopsy as this may have relevance to adequacy in relation to subtyping and grading.

[Level of evidence – GPP and C – Observational studies.]

6.4 Pathological

Histological type should be provided (mesothelioma in situ, localised mesothelioma, diffuse mesothelioma), recognising that most cases will be diffuse mesothelioma. Histological subtype should be stated (epithelioid, biphasic, sarcomatoid). Histological variants (architectural patterns, cytological features, stromal features) should also be documented, with percentages given for architectural patterns in pathologically staged specimens (EPD/EPP).[1,2]

Given the need for ancillary investigations to make the diagnosis, the immunohistochemistry panel used should be documented, this being at least 2 'mesothelium-associated' markers and 2 'epithelium-associated' markers for epithelioid and biphasic tumours (discussed in section 5). For sarcomatoid variants, due to the wide differential diagnosis, the full repertoire of antibodies used should be listed. For biphasic mesothelioma, the presence of any amount epithelioid and sarcomatoid components warrants classification as biphasic, with percentages documented in those pathologically staged.

Grading of epithelioid subtypes should be undertaken according to criteria in section 5.3.

As well as involvement by tumour, background lung should be assessed for the presence of asbestos bodies, although if identified, their presence does not contribute to the diagnosis of mesothelioma, only to its causation. Asbestosis should also be documented, if present, according to CAP-PPS asbestosis criteria.[32] Bronchial and vascular margins of the lung should also be sampled.

[Level of evidence B – Subtyping correlates with prognosis.]

6.5 Resections following therapy

Gross preparation of a resected specimen after preoperative (neoadjuvant) therapy should follow the same principles outlined for primarily resected specimens. However, it is likely that some of the tumour will have become necrotic and more sections will need to be examined in order to have a valid representation of the histologic appearance. A percentage of remaining viable tumour can be noted, but scoring should be limited to 'no or minimal response', 'partial response' or 'complete or near complete response', as recommended for other malignancies.[7]

[Level of evidence – GPP.]

6.6 Lymph node spread

If sampled, the presence or absence of tumour involvement should be recorded:

- regional lymph nodes cannot be assessed (NX)
- no regional lymph node metastases (N0)
- metastases in the ipsilateral bronchopulmonary, hilar or mediastinal (including the internal mammary, peridiaphragmatic, pericardial fat pad or intercostal lymph nodes) lymph nodes (N1)

- metastases in the contralateral bronchopulmonary, hilar or mediastinal lymph nodes or ipsilateral or contralateral supraclavicular lymph nodes (N2).

[Level of evidence B – Nodal involvement forms part of established staging criteria.]

6.7 Margins

Any area where there is concern about completeness of resection should be sampled by the pathologist, ideally in collaboration with the surgeon, with subsequent reporting on whether or not the margins are clear. However excision will rarely be complete in most samples, with the exception of localised mesothelioma.

[Level of evidence B – Completeness of resection may provide important prognostic data that governs post-surgical management.]

6.8 Metastases

The presence of metastases should be documented, if histologically confirmed.

7 Non-core data items

Various additional parameters have been recommended, but as yet there is insufficient evidence with regard to influencing patient management for them to be included as core items. They may be prospectively recorded at a local level, according to patient needs and interest.

Abnormalities within the lung parenchyma (e.g. fibrosis, tumour involvement either as nodules or through direct spread) may be noted, as may have non-neoplastic abnormalities in the pleura and mediastinal tissues (e.g. pleural plaques).

The presence of asbestos bodies and pleural plaques can be documented. Extracapsular spread from involved lymph nodes may also be documented.

Some cases may also have ancillary mutation analysis which, if clinically useful, can be documented in the pathology report. In particular, *BAP1* and *CDKN2A* status is increasingly being requested by some oncologists as well as PD-L1 in relation to potential immune-oncology.[1–3,15–24]

8 Diagnostic coding and staging

The 8th edition of the UICC TNM staging system is recommended for all resected mesotheliomas (Appendix A).

The site, histological diagnosis and procedure should be coded using SNOMED coding (Appendix B).

[Level of evidence D – Recommendation based on UK expert opinion and those of IMIG.]

9 Reporting of cytology specimens

As with biopsies, cytological findings should be correlated with the clinical and imaging findings to establish whether the available cytological material is sufficient to render a specific diagnosis or a clinically relevant differential diagnosis. If a pleural cytology specimen is positive or suspicious for malignancy, and there is no other specimen, then material should undergo the same ancillary investigations as for biopsies in terms of the differential diagnosis, which ideally is via a cell pellet for histology as this allows preservation of residual material. Identification of an epithelial phenotype will allow a definitive diagnosis of metastatic carcinoma. Identification of a mesothelial phenotype will allow further management decisions in terms of a definitive diagnosis of mesothelioma or further sampling, dependent on the clinical scenario (Appendix D). Staining for *BAP1* and/or looking for *CDKN2A (p16)* deletions by FISH or immunohistochemistry for MTAP may be of particular value in cases where malignancy is suspected.[1,2]

[Level of evidence D – Recommendation based on collective opinion of experts.]

10 Reporting of frozen sections

Biopsies of pleura are sometimes sent for frozen section, although there must not be an expectation of a definitive diagnosis due to the requirements for ancillary investigations. However, a diagnosis of malignancy can usually be made which allows the surgeon to undertake intra-operative decisions, such as whether or not to undertake pleurodesis.

[Level of evidence D – Recommendation based on collective opinion of experts.]

11 Prognostic and predictive markers

At present, neither predictive nor prognostic immunohistochemical/molecular markers are recommended for routine use, although trials are ongoing where staining for markers such as *BAP1*, p16 (in relation to *CDKN2A* loss), mesothelin and PD-L1 may have relevance. Screening for germline mutations is not routinely recommended but can be undertaken in selected cases.

12 Criteria for audit

The following are recommended by the RCPath as Key assurance indicators (see *Key assurance indicators for pathology services*, November 2019) and key performance indicators (see *Key Performance Indicators – Proposals for implementation*, July 2013),:

- cancer resections should be reported using a template or proforma, including items listed in the English COSD, which are, by definition, core data items in RCPath cancer datasets. English trusts were required to implement the structured recording of core pathology data in the COSD
  - standard: 95% of reports must contain structured data
- histopathology cases must be reported, confirmed and authorised within 7 and 10 calendar days of the procedure
  - standard: 80% of cases must be reported within 7 calendar days and 90% within 10 calendar days.

The following standards are suggested as some of the criteria that might be used in periodic reviews of the lung cancer pathology service:

- completeness of histopathology reports, including grade for epithelioid subtypes expressed as average proportion of the core data items recorded, or as proportion of the reports that successfully include 100% of the items; the standard is that all contain 100% of the items
- specificity and sensitivity of antibodies in diagnostic use and proposed new markers when available
- inter- and intra-observer studies in relation to epithelioid, biphasic and sarcomatoid variants
- accuracy of cytology diagnosis via histology correlation.

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Appendix A TNM classification (from *Staging Manual in Thoracic Oncology*)[3–6]

Primary tumour (T)

pTX Primary tumour cannot be assessed

pT0 No evidence of primary tumour

pT1 Tumour limited to the ipsilateral parietal ± visceral ± mediastinal ± diaphragmatic pleura

pT2 Tumour involving each of the ipsilateral pleural surfaces (parietal, mediastinal, diaphragmatic and visceral pleura) with at least one of the following features:

- involvement of diaphragmatic muscle
- extension of tumour from visceral pleura into the underlying pulmonary parenchyma.

pT3 Describes locally advanced but potentially resectable tumour

Tumour involving all of the ipsilateral pleural surfaces (parietal, mediastinal, diaphragmatic and visceral pleura) with at least one of the following features:

- involvement of the endothoracic fascia
- extension into the mediastinal fat
- solitary, completely resectable focus of tumour extending into the soft tissues of the chest wall
- non-transmural involvement of the pericardium.

pT4 Describes locally advanced technically unresectable tumour

Tumour involving all of the ipsilateral pleural surfaces (parietal, mediastinal, diaphragmatic and visceral pleura) with at least one of the following features:

- diffuse extension or multifocal masses of tumour in the chest wall, with or without associated rib destruction
- direct transdiaphragmatic extension of tumour to the peritoneum
- direct extension of tumour to the contralateral pleura

- direct extension of tumour to mediastinal organs
- direct extension of tumour into the spine
- tumour extending through to the internal surface of the pericardium with or without a pericardial effusion; or tumour involving the myocardium.

Regional lymph nodes (N)

pNX Regional lymph nodes cannot be assessed

pN0 No regional lymph node metastases

pN1 Metastases in the ipsilateral bronchopulmonary, hilar or mediastinal (including the internal mammary, peridiaphragmatic, pericardial fat pad or intercostal lymph nodes) lymph nodes

pN2 Metastases in the contralateral bronchopulmonary, hilar or mediastinal lymph nodes or ipsilateral or contralateral supraclavicular lymph nodes

Distant metastasis (M)

pM0 No distant metastasis

pM1 Distant metastasis

Stage grouping

	N0	**N1**	**N2**
T1	IA	II	IIIB
T2	IB	II	IIIB
T3	IB	IIIA	IIIB
T4	IIIB	IIIB	IIIB
M1	IV	IV	IV

Appendix B SNOMED coding[2]

Topography

Tumour site	SNOMED 2/3 code	SNOMED-CT terminology	SNOMED-CT code
Pleura	T-29000	Pleural membrane structure (body structure)	3120008

Morphology (align with 2021 classification of tumours with MIS, localised and diffuse)[2]

Morphological codes	SNOMED 2/3 /ICD-O code	SNOMED-CT terminology	SNOMED-CT code
Mesothelioma in situ	M9050/2	Mesothelioma in situ	1179700000
Mesothelioma, NOS	M9050/3	Mesothelioma, malignant (morphologic abnormality)	62064005
Epithelioid mesothelioma	M9052/3	Epithelioid mesothelioma, malignant (morphologic abnormality)	65278006
Sarcomatoid (inc. desmoplastic) mesothelioma	M9051/3	Fibrous mesothelioma, malignant (morphologic abnormality)	54443001
Biphasic mesothelioma	M9053/3	Mesothelioma, biphasic, malignant (morphologic abnormality)	30383009
Well-differentiated papillary mesothelial tumour	M9052/1	No code yet	734100004
Adenomatoid tumour	M9054/0	Adenomatoid tumour (morphologic abnormality)	2348006

Procedure

Local P codes should be recorded. At present, P codes vary according to the SNOMED system in use in different institutions.

Appendix C Reporting proforma for mesothelioma biopsy/cytology specimens

Surname……	Forenames……	Date of birth…….Sex….....
Hospital…….……	Hospital no……..……	NHS/CHI no……..
Date of receipt……	Date of reporting……..……	Report no……...
Pathologist……..…	Surgeon……..…	

Previous treatment (neoadjuvant chemotherapy/radiotherapy)

Yes □ No □

Specimen origin

Laterality

Right □ Left □ Not stated □

Pleura □ Lung □ Other □ ……..……

Sample type* (more than one box may be ticked)

Biopsy

Pleural biopsy □ Core needle biopsy □ VATS biopsy □

Open biopsy □ Lymph node biopsy □ Specify site(s) ……..…….....

Other site(s) □ Details ….....

Number of biopsies …..

Cytology

Pleural effusion □ Pericardial effusion □ Other □ Details……..

FNA □ Details……..

Microscopic features

Histological type of mesothelioma

M**e**sothelioma in situ □

Localised mesothelioma □

Diffuse mesothelioma □

Histological subtype

Epithelioid □ Biphasic □ Sarcomatoid □

If epithelioid, low or high grade Low □ High □

Histological variants

Architectural patterns

Tubulopapillary	Yes □	No □
Trabecular	Yes □	No □
Adenomatoid	Yes □	No □
Solid	Yes □	No □
Micropapillary	Yes □	No □

Cytological features

Rhabdoid	Yes □	No □
Deciduoid	Yes □	No □
Small cell	Yes □	No □
Clear cell	Yes □	No □
Signet ring	Yes □	No □
Lymphohistiocytoid	Yes □	No □
Pleomorphic	Yes □	No □
Transitional	Yes □	No □

Stromal features

Desmoplastic	Yes □	No □
Myxoid	Yes □	No □

Heterologous differentiation Yes □ No □

Ancillary investigations

Not used □

D-PAS mucin staining Positive □ Negative □

Alcian Blue mucin staining Positive □ Negative □

Immunohistochemistry (list antibodies used – minimum of 4 recommended)

Calretinin Positive □ Negative □

Cytokeratin 5/6 Positive □ Negative □

WT-1 Positive □ Negative □

BerEP4 Positive □ Negative □

CEA Positive □ Negative □

(Other: …..... Positive □ Negative □)

Comments:

SNOMED codes:

Signature ….....…… **Date** ……./……./…….

Appendix D Reporting proforma for mesothelioma resection specimens

Surname……	Forenames……	Date of birth……Sex….....
Hospital…….……	Hospital no……..……	NHS/CHI no……..
Date of receipt……	Date of reporting……..……	Report no……...
Pathologist……..…	Surgeon……..…	

Previous treatment (neoadjuvant chemotherapy/radiotherapy)

Yes □ No □

Laterality

Right □ Left □ Not stated □

Specimen type

Decortication □ Radical pleurectomy □ Local chest wall/pleural resection □

Extrapleuropneumonectomy □ Debulking □

Submitted material

Parietal pleura	Yes □	No □	Visceral pleura	Yes □	No □
Diaphragm	Yes □	No □	Endothoracic fascia	Yes □	No □
Lung	Yes □	No □, details….....			
Mediastinal fat	Yes □	No □	Chest wall	Yes □	No □
Pericardium	Yes □	No □	Rib	Yes □	No □
Peritoneum	Yes □	No □, details….....			
Contralateral pleura	Yes □	No □	Spine	Yes □	No □

Histological type of mesothelioma

Mesothelioma in situ □ Localised mesothelioma □ Diffuse mesothelioma □

Histological subtype

Epithelioid □ Biphasic □ Sarcomatoid □

If epi**thelioid**, grade □ Low □ High

Histological variants

Architectural patterns

Tubulopapillary	Yes □	No □	……%
Trabecular	Yes □	No □	…….%
Adenomatoid	Yes □	No □	…….%
Solid	Yes □	No □	…….%
Micropapillary	Yes □	No □	…….%

Cytological features

Rhabdoid	Yes □	No □
Deciduoid	Yes □	No □
Small cell	Yes □	No □
Clear cell	Yes □	No □
Signet ring	Yes □	No □
Lymphohistiocytoid	Yes □	No □
Pleomorphic	Yes □	No □
Transitional	Yes □	No □

Stromal features

Desmoplastic	Yes □	No □
Myxoid	Yes □	No □
Heterologous differentiation	Yes □	No □

Tumour size (if localised)

…….mm

Ancillary investigations

Not used	□	
D-PAS mucin staining	Positive □	Negative □
Alcian Blue mucin staining	Positive □	Negative □

Immunohistochemistry (list antibodies used – minimum of 4 recommended)

Calretinin	Positive □	Negative □
Cytokeratin 5/6	Positive □	Negative □
WT-1	Positive □	Negative □
BerEP4	Positive □	Negative □
CEA	Positive □	Negative □
(Other: ….....	Positive □	Negative □)

Extent of invasion

□ No evidence of primary tumour

□ Cannot be assessed

□ Parietal involvement without involvement of the

□ Ipsilateral visceral pleura

□ Mediastinal pleura

□ Diaphragmatic pleura

□ Parietal involvement with 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

□ Ribs

□ Peritoneum through the diaphragm

□ Great vessels/oesophagus/trachea or other mediastinal organ

□ Spine

□ Myocardium

□ Extension into contralateral pleura

□ Other, specify …….

Lymph node involvement

No nodes submitted □

Cannot be assessed □

Lymph node stations/location

……. □ Involved □ Not involved

……. □ Involved □ Not involved

……. □ Involved □ Not involved

……. □ Involved □ Not involved

……. □ Involved □ Not involved

If neoadjuvant therapy, % of viable tumour on cross-section …....

Margins

Excision complete (R0)□ Microscopic involvement (R1)□ Macroscopic involvement (R2)□

Sites of involvement if R1 or R2: ……

Closest margin if excision complete: …..... distance ….....mm

Site(s) of incomplete resection: …..... …..... ….....

Metastases

Unknown □ Absent (M0) □ Present (M1) □ Details: ……

Background lung (if sampled)

Asbestos bodies Yes □ No □ N/A □

Asbestosis Yes □ No □ N/A □

Response to neoadjuvant therapy

N/A □ Complete/Near complete □ Partial □ None/Minimal □

Ancillary studies (core for mesothelioma in situ only)

Performed Yes □ No □

BAP1 (specify test(s) and result(s)) …….

Performed Yes □ No □

CDKN2A (specify test(s) and result(s)) …….

Performed Yes □ No □

MTAP (specify test(s) and result(s)) …….

Summary of pathological staging (UICC TNM 8th edition):

□ 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

□ Tx Primary tumour cannot be assessed

□ T0 No evidence of primary tumour

□ T1 Tumour involves ipsilateral pleura, with or without involvement of visceral, mediastinal or diaphragmatic pleura

□ T2 Tumour involves ipsilateral (parietal or visceral) pleura, with at least one of the following:

- Invasion of diaphragmatic muscle
- Invasion of lung parenchyma

□ T3 Tumour involves ipsilateral (parietal or visceral) pleura, with at least one of the following:

- Invasion of endothoracic fascia
- Invasion of mediastinal fat
- Solitary focus of tumour invading the 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 spread)
- Contralateral pleura
- Mediastinal organs (oesophagus, trachea, heart, great vessels)
- Vertebra, neuroforamen(s), spinal cord
- Internal surface of the pericardium (transmural invasion with or without a pericardial effusion)

Regional lymph nodes (pN)

□ NX Regional lymph nodes cannot be assessed

□ N0 No regional lymph node metastasis

□ N1 Metastasis to ipsilateral intrathoracic lymph nodes (includes ipsilateral bronchopulmonary, hilar, subcarinal, paratracheal, aortopulmonary,

paraoesophageal, peridiaphragmatic, pericardial pad, intercostal and internal mammary nodes)

□ N2 Metastases to contralateral intrathoracic lymph nodes. Metastases to ipsilateral or contralateral supraclavicular lymph nodes

SNOMED codes:

Comments:

Signature .....…… Date ……..../……../……...

Appendix E Reporting proforma for mesothelioma biopsy/cytology specimens in list format

Element name	Values	Implementation notes	COSD v9
Previous treatment (neoadjuvant chemotherapy/ radiotherapy)	Single selection value list: • Yes • No		
Laterality	Single selection value list: • Right • Left • Not stated		pCR0820 • Right = R • Left = L • Not stated = 9
Specimen origin	Single selection value list: • Pleura • Other • Other		
Specimen origin, other	Free text	Only applicable if 'Specimen origin, other' selected	
Sample type	Multiple selection value list: • Pleural biopsy • Core needle biopsy • VATS biopsy • Open biopsy • Lymph node biopsy		pCR0760 • Pleural biopsy = BU • Core needle biopsy = BU • VATS biopsy = BU • Open biopsy = BU • Lymph node biopsy = BU

	• Other biopsy (sites) • Pleural effusion • Pericardial effusion • Other cytology • FNA		• Other biopsy (sites) = BU • Pleural effusion = CY • Pericardial effusion = CY • Other cytology = CY • FNA = CY
Lymph node biopsy, specify site	Size in mm	Only applicable if 'Sample type, Lymph node biopsy' selected	
Other biopsy site(s), details	Free text	Only applicable if 'Sample type, Other biopsy site(s)' selected	
Other cytology, details	Free text	Only applicable if 'Sample type, Other cytology' selected	
FNA, details	Free text	Only applicable if 'Sample type, FNA' selected	
Histologic type of mesothelioma	Single selection value list: • Mesothelioma in situ • Localised mesothelioma • Diffuse mesothelioma		
Histologic subtype of mesothelioma	Single selection value list: • Epithelioid • Biphasic • Sarcomatoid		

Mesothelioma grade	Single selection value list: • Low • High	Only applicable for epithelioid subtype	pCR0860 • Low = G1 • High = G4
Histologic variants of mesothelioma	Multiple selection value list: Architectural patterns • Tubulopapillary • Trabecular • Adenomatoid • Solid • Micropapillary Cytological features • Rhabdoid • Deciduoid • Small cell • Clear cell • Signet ring • Lymphohistiocytoid • Pleomorphic • Transitional Stromal features • Desmoplastic		

	• Myxoid • Heterologous differentiation		
D-PAS mucin staining	Single selection value list: • Positive • Negative		
Alcian blue mucin staining	Single selection value list: • Positive • Negative		
Calretinin	Single selection value list: • Positive • Negative		
Cytokeratin 5/6	Single selection value list: • Positive • Negative		
WT-1	Single selection value list: • Positive • Negative		
BerEP4	Single selection value list: • Positive • Negative		
CEA	Single selection value list: • Positive • Negative		

Other immunohistochemistry	Free text		
Other immunohistochemistry result	Single selection value list: • Positive • Negative • Not applicable	Not applicable if 'Other immunohistochemistry' is blank	
Comments	Free text		
SNOMED-T code	May have multiple codes. Look up from SNOMED tables.		pCR6410
SNOMED-M code	May have multiple codes. Look up from SNOMED tables.		pCR6420

Appendix F Reporting proforma for mesothelioma resection specimens in list format

Element name	Values	Implementation notes	COSD v9
Previous treatment (neoadjuvant chemotherapy/radiotherapy)	Single selection value list: • Yes • No		
Laterality	Single selection value list: • Left • Right • Not stated		pCR0820 • Right = R • Left = L • Not stated = 9
Specimen type	Single selection value list: • Decortication • Radical pleurectomy • Local chest wall/pleural resection • Extrapleuropneumo-nectomy • Debulking		pCR0760 • Decortication = EX • Radical pleurectomy = RE • Local chest wall/pleural resection = EX • Extrapleuropneumo-nectomy = RE

			• Debulking = 99
Submitted material, parietal pleura	Single selection value list: • Yes • No		
Submitted material, diaphragm	Single selection value list: • Yes • No		
Submitted material, lung	Single selection value list: • Yes • No		
Submitted material, mediastinal fat	Single selection value list: • Yes • No		
Submitted material, pericardium	Single selection value list: Yes No		
Submitted material, peritoneum	Single selection value list: • Yes • No		
Submitted material, contralateral pleura	Single selection value list: • Yes • No		
Submitted material, visceral pleura	Single selection value list:		

	• Yes • No		
Submitted material, endothoracic fascia	Single selection value list: • Yes • No		
Submitted material, endothoracic fascia, details	Free text	Only applicable if ‘Submitted material, endothoracic fascia’ is Yes	
Submitted material, chest wall	Single selection value list: • Yes • No		
Submitted material, rib	Single selection value list: • Yes • No		
Submitted material, rib, details	Free text	Only applicable if ‘Submitted material, rib’ is Yes	
Submitted material, spine	Single selection value list: • Yes • No		
Histological type of mesothelioma	Single selection value list: • Mesothelioma in situ • Localised mesothelioma		

	• Diffuse mesothelioma		
Histologic subtype of mesothelioma	Single selection value list: • Epithelioid • Biphasic • Sarcomatoid		
Grade of mesothelioma	Single selection value list: • Low • High		pCR0860 • Low = G1 • High = G4
Histological variants of mesothelioma	Multiple selection value list: • Architectural patterns • Tubulopapillary • Trabecular • Adenomatoid • Solid • Micropapillary Cytological features • Rhabdoid • Deciduoid • Small cell • Clear cell • Signet ring	Document percentages for architectural patterns	

	• Lymphohistiocytoid • Pleomorphic • Transitional Stromal features • Desmoplastic • Myxoid • Heterologous differentiation		
Tumour size (if localised)	Size in mm		pCR0830
D-PAS mucin staining	Single selection value list: • Positive • Negative		
Alcian blue mucin staining	Single selection value list: • Positive • Negative		
Calretinin	Single selection value list: • Positive • Negative		
Cytokeratin 5/6	Single selection value list: • Positive • Negative		
WT-1	Single selection value list: • Positive • Negative		

BerEP4	Single selection value list: • Positive • Negative		
CEA	Single selection value list: • Positive • Negative		
Other immunohistochemistry	Free text		
Other immunohistochemistry result	Single selection value list: • Positive • Negative • Not applicable	Not applicable if 'Other immuno-histochemistry' is blank	
Tumour limited to ipsilateral parietal ± visceral ± mediastinal ± diaphragmatic pleura	Single selection value list: • Yes • No • Not applicable		
Tumour involving all ipsilateral pleural surfaces (parietal, mediastinal, diaphragmatic, visceral)	Single selection value list: • Yes • No • Not applicable		
Involvement of diaphragmatic muscle	Single selection value list: • Yes • No • Not applicable		
Extension of tumour from visceral pleura into the	Single selection value list:		

underlying pulmonary parenchyma	• Yes • No • Not applicable		
Involvement of endothoracic fascia	Single selection value list: • Yes • No • Not applicable		
Extension into mediastinal fat	Single selection value list: • Yes • No • Not applicable		
Solitary, completely resectable focus of tumour extending into the soft tissues of the chest wall	Single selection value list: • Yes • No • Not applicable		
Non-transmural involvement of the pericardium	Single selection value list: • Yes • No • Not applicable		
Diffuse or multiple foci of the tumour invading the soft tissue of the chest wall ± rib destruction	Single selection value list: • Yes • No • Not applicable		

Direct trans-diaphragmatic extension of tumour to the peritoneum	Single selection value list: • Yes • No • Not applicable		
Direct extension of tumour to mediastinal organs (great vessels/oesophagus/trachea /other)	Single selection value list: • Yes • No • Not applicable		
Direct extension of tumour to the contralateral pleura	Single selection value list: • Yes • No • Not applicable		
Direct extension of tumour into the spine	Single selection value list: • Yes • No • Not applicable		
Tumour extending through to the internal surface of the pericardium ± pericardial effusion	Single selection value list: • Yes • No • Not applicable		
Direct invasion of the myocardium	Single selection value list: • Yes • No • Not applicable		

Ipsilateral bronchopulmonary, hilar or mediastinal (including the internal mammary, peridiaphragmatic, pericardial fat pad or intercostal lymph nodes) lymph nodes	Single selection value list: • Not submitted • Submitted • Involved		
Contralateral bronchopulmonary, hilar or mediastinal lymph nodes or ipsilateral or contralateral supraclavicular lymph nodes	Single selection value list: • Not submitted • Submitted • Involved		
If neoadjuvant therapy, % of viable tumour on cross-section	Number (range 0–100)		
Excision complete (R0)	Single selection value list: • Yes • No • Not applicable		
Macroscopic involvement (R2)	Single selection value list: • Yes • No • Not applicable		
Sites of involvement if R1 or R2	Single selection value list: • Yes • No • Not applicable	Only applicable if ‘Microscopic involvement (R1)’ is Yes or ‘Macroscopic involvement (R2)’ is Yes	
Closest excision margin	Free text	Only applicable if ‘Excision complete (R0)’ is Yes	

Closest excision margin, distance	Distance in mm	Only applicable if ‘Excision complete (R0)’ is Yes	
Sites of incomplete resection	Free text		
Metastases	Single selection value list: • Unknown • Absent (M0) • Present (M1)		
Metastases, details	Free text	Only applicable if ‘Metastases is Present (M1)’	
Background lung, asbestos bodies	Single selection value list: • Yes • No • Not applicable		
Background lung, asbestosis	Single selection value list: • Yes • No • Not applicable		
pT stage	Single selection value list: • X • 0 • 1 • 2 • 3		pCR0910

	• 4		
pN stage	Single selection value list: • X • 0 • 1 • 2		pCR0920
M stage	Single selection value list: • Unknown • M0 • M1		pCR0930
TNM edition	Single selection value list: • UICC edition 7 • UICC edition 8		pCR6820
Comments	Free text		
SNOMED-T code	May have multiple codes. Look up from SNOMED tables.		pCR6410
SNOMED-M code	May have multiple codes. Look up from SNOMED tables.		pCR6420

Appendix G Summary table – Explanation of grades of evidence

(modified from Palmer K *et al. BMJ* 2008;337:1832)

Grade (level) of evidence	Nature of evidence
Grade A	At least one high-quality meta-analysis, systematic review of randomised controlled trials or a randomised controlled trial with a very low risk of bias and directly attributable to the target population or A body of evidence demonstrating consistency of results and comprising mainly well-conducted meta-analyses, systematic reviews of randomised controlled trials or randomised controlled trials with a low risk of bias, directly applicable to the target cancer type.
Grade B	A body of evidence demonstrating consistency of results and comprising mainly high-quality systematic reviews of case-control or cohort studies and high-quality case-control or cohort studies with a very low risk of confounding or bias and a high probability that the relation is causal and which are directly applicable to the target population or Extrapolation evidence from studies described in A.
Grade C	A body of evidence demonstrating consistency of results and including well-conducted case-control or cohort studies and high- quality case-control or cohort studies with a low risk of confounding or bias and a moderate probability that the relation is causal and which are directly applicable to the target population or Extrapolation evidence from studies described in B.
Grade D	Non-analytic studies such as case reports, case series or expert opinion or Extrapolation evidence from studies described in C.
Good practice point (GPP)	Recommended best practice based on the clinical experience of the authors of the writing group.

Appendix H AGREE II guideline monitoring sheet

The cancer datasets of The Royal College of Pathologists comply with the AGREE II standards for good quality clinical guidelines. The sections of this dataset that indicate compliance with each of the AGREE II standards are indicated in the table.

AGREE standard	Section of guideline
Scope and purpose	
1 The overall objective(s) of the guideline is (are) specifically described	Introduction
2 The health question(s) covered by the guideline is (are) specifically described	Introduction
3 The population (patients, public, etc.) to whom the guideline is meant to apply is specifically described	Foreword
Stakeholder involvement	
4 The guideline development group includes individuals from all the relevant professional groups	Foreword
5 The views and preferences of the target population (patients, public, etc.) have been sought	Foreword
6 The target users of the guideline are clearly defined	Introduction
Rigour of development	
7 Systematic methods were used to search for evidence	Foreword
8 The criteria for selecting the evidence are clearly described	Foreword
9 The strengths and limitations of the body of evidence are clearly described	Foreword
10 The methods for formulating the recommendations are clearly described	Foreword
11 The health benefits, side effects and risks have been considered in formulating the recommendations	Foreword and Introduction
12 There is an explicit link between the recommendations and the supporting evidence	2–11
13 The guideline has been externally reviewed by experts prior to its publication	Foreword
14 A procedure for updating the guideline is provided	Foreword
Clarity of presentation	
15 The recommendations are specific and unambiguous	2–11
16 The different options for management of the condition or health issue are clearly presented	2–11
17 Key recommendations are easily identifiable	2–11
Applicability	
18 The guideline describes facilitators and barriers to its application	Foreword
19 The guideline provides advice and/or tools on how the recommendations can be put into practice	Appendices A–F
20 The potential resource implications of applying the recommendations have been considered	Foreword
21 The guideline presents monitoring and/or auditing criteria	12
Editorial independence	
22 The views of the funding body have not influenced the content of the guideline	Foreword
23 Competing interest of guideline development group members have been recorded and addressed	Foreword