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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Comments	This is an update to accommodate the 2015 WHO classification and ensures consistency with the International Collaboration on Cancer Reporting's (ICCR) mesothelioma tumour dataset. In accordance with the College's pre-publications policy, this document was placed on the College website for consultation from 11 July to 8 August 2017. It will replace the Dataset for the histological reporting of mesotheliomas, published in 2013. **Dr Lorna Williamson** **Director of Publishing and Engagement**

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NICE has accredited the process used by The Royal College of Pathologists to produce its cancer datasets. Accreditation is valid for 5 years from July 2017. More information on accreditation can be viewed at www.nice.org.uk/accreditation.

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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. On rare occasions, it may be necessary or even desirable to depart from the guidelines in the interests of specific patients and special circumstances. The guideline has been developed to cover most common scenarios. However it is recognised that guidelines cannot accommodate every pathological specimen type and clinical scenario. Deviation from the guidelines may therefore be required occasionally to report the specimen in a way that maximises the benefit to the patient.

Each dataset contains core data items that are mandated for inclusion in the Cancer Outcomes and Services Dataset (COSD ï 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. All data items should be clearly defined to allow the unambiguous recording of data.

The following stakeholder groups have been consulted:

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

Evidence for the data items in the dataset is 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 Mesothelioma Interest Group (IMIG), together with review of current literature. Evidence has been graded using modified SIGN guidance (see Appendix G). Gaps in the evidence were identified by College Fellows via feedback received from consultation.

No major organisational changes or cost implications have been identified that would hinder the implementation of the dataset.

A formal revision cycle for all cancer datasets takes place on a three-yearly basis. However, each year, the College will ask the author of the dataset, in conjunction with the relevant subspecialty adviser to the College, to consider whether or not the dataset needs to be updated or revised. A full consultation process will be undertaken if major revisions are required, i.e. revisions to core data items (the only exception being changes to international tumour grading and staging schemes that have been approved by the Specialty Advisory Committee on Cellular Pathology and affiliated professional bodies; these changes 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 two weeks for Fellowsô attention. If Fellows 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. All changes will be documented in the ódata controlôsection of the relevant dataset.

The dataset has been reviewed by the Clinical Effectiveness Department, Working Group on Cancer Service and Lay Governance Group. It was placed on the College website for consultation

with the membership from 11 July 2017 to 8 August 2017. All comments received from the Working Group and membership have been addressed by the authors to the satisfaction of the Chair and the Director of Publishing and Engagement. 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 Director of Clinical Effectiveness and are available on request.

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. It is estimated that numbers in the United Kingdom will continue to rise until around 2020 and only then decline.

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:

a) deciding on the most appropriate treatment for particular patients, including the need and choice of adjuvant therapy

b) providing prognostic information to clinicians and patients

c) providing more reliable staging than using clinical data alone

d) monitoring clinical effectiveness of therapeutic trials

e) 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] Also, in 2015, 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.[3ï 6] This revision, based on the above updates, will also ensure consistency with the International Collaboration on Cancer Reporting (ICCR) dataset.[7]

The purpose of this document is to define the core data that must 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 ï for example, precise definition of the various subtypes of mesothelioma according to the WHO 2015 classification,[2] together with accurate definition of anatomic parameters related to staging. Given the 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 [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 must 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 immunohisto-chemistry. Debulking specimens (e.g. pleurectomy) should be fixed for 24 hours and then sampled thoroughly. Pleuropneumonectomy 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 the diagnosis of desmoplastic variants of mesothelioma. This is because it enables better assessment of variations in cellularity which are obscured by cross-cutting.

In relation to radical pleurectomy and pleuropneumonectomy 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. 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 Perlsô 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 2015 classification with initial subdivision into epithelioid, biphasic and sarcomatoid variants. Further subdivision into patterns may also be undertaken as some have clinical relevance such as pleomorphic variants,[8] although these are not 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.]

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.

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 staining for BAP1 (BRCA1-assocated protein) is of value in distinguishing mesothelioma and reactive mesothelial hyperplasia as an additional consideration in difficult cases.[9ï12] Assessment of P16 status using FISH is a further marker that may have value in refining diagnosis. These may be particularly useful when there is insufficient morphological evidence for a suspected mesothelioma, especially in superficial biopsies.[13ï15] Clinical and radiological features are often invaluable in difficult cases, ideally through multidisciplinary discussion. Other neoplasms also arise in or spread to the pleura and should be duly considered.[16]

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, Wilmôs Tumour-1 (WT1), D2-40 and thrombomodulin.[1,2] 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.[17] 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 required to further define the nature of metastatic adenocarcinoma.[1]

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 80ï 90% of sarcomatoid mesotheliomas.[1] Genetic analysis may be of diagnostic value in identifying some sarcomas (e.g. X:18 translocation for synovial sarcoma).[2]

Referral to regional or national experts is recommended in complex and difficult cases.

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.

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

If a single localised mass, the maximum diameter of tumour should be measured to the nearest millimetre. Ideally, three 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.

[Level of evidence – Good practice point (GPP).]

6.4 Pathological

Histological type should be stated (epithelioid, biphasic, sarcomatoid [desmoplastic variant if present]). Given the need for ancillary investigations to make the diagnosis, the immunohistochemistry panel used should be documented, this being at least two ómesothelium-associatedô markers and two ó epithelium-associatedô 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.

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. 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 ónoo or minimal responseô, ópartial responseô or ócomplete or near complete responseô, as recommended for other malignancies.[7]

[Level of evidence – GPP.]

6.6 Lymph node spread

If sampled, the presence or absence of tumour 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 after discussion with the surgeon, with subsequent reporting on whether or not the margins are clear. Excision will rarely be complete in radical pleurectomies.

[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 needs and interest.

Further subtyping according to pattern may also be undertaken (tubulopapillary, solid, rhabdoid, pleomorphic, deciduoid etc.) as this may have prognostic value,[8,18,19] although this is not viewed as a core element.

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.

8 Diagnostic coding and staging

The 8th TNM staging system is recommended for all resected mesotheliomas (Appendix A). However, during 2017 whilst there is transition from the 7th TNM staging system to the 8th, in relation to national data collection, it is recommend that both are documented within reports (the 7th TNM being a non-core item), with the staging system(s) used being clearly documented.

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

[Level of evidence D – Recommendation based on UK expert opinion and those of International Mesothelioma Interest Group.]

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 p16 deletions by FISH may be of particular value in cases where malignancy is suspected.[14]

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

10 Reporting of frozen sections

Biopsies of pleura are frequently 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, mesothelin and PD-L1 may have relevance.

12 Criteria for audit of the dataset

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, 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.

In addition, the following audits are recommended by the RCPath as key performance indicators (www.rcpath.org):

- cancer resections must 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 NHS Trusts were required to implement the structured recording of core pathology data in the COSD by January 2016.
  - standard: 95% of reports must contain structured data.
- histopathology cases that are 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.

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Appendix A TNM staging of mesothelioma (from *Staging Manual in Thoracic Oncology,* adapted from references 3–6)

T Descriptors

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.

N Regional lymph nodes

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

M Distant metastasis

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 codes[2]

Topography

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

Morphology

Morphological codes	SNOMED 2/3 /ICD-O code	SNOMED-CT terminology	SNOMED-CT code
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 mesothelioma	M9052/1	No code yet	No code yet
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

Surnameé é é é é .é é é Forenamesé é é é é .é é .é Date of birthé é é é é .. Sexé ....
Hospitalé é é é .é é é .é é Hospital noé é é é é é .é é . NHS/CHI noé é é é é ..
Date of receipté é é é .é é . Date of reportingé é é ..é é .. Report noé é é é é é ...
Pathologisté é é .é é é é é Surgeoné é é é é é .é .é é . Lab noé é é é é é .....

Previous treatment (neoadjuvant chemotherapy/radiotherapy) Yes □ No □

Specimen origin

Laterality Right □ Left □ Not stated □

Pleura □ Lung □ Other □ é é é é é é ..é .é é é .

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) é é ..é é é .....
Other site(s) □ Details .....

Cytology

Pleural effusion □ Pericardial effusion □ Other □ Detailsé é é é é é é ..
FNA □ Detailsé é é é ..

Microscopic features

Histological type of mesothelioma

Epithelioid □ Biphasic □ Sarcomatoid □

Desmoplastic variant Yes □ No □

Ancillary investigations

Not used □

D-PAS mucin staining Positive □ Negative □
Alcian Blue mucin staining Positive □ Negative □

Immunohistochemistry (list antibodies used ï minimum of four 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

Surnameé é é é é .é é é	Forenamesé é é é é .é é .é	Date of birthé é é é é .. Sexé ....
Hospitalé é é é .é é é .é é	Hospital noé é é é é é .é é .	NHS/CHI noé é é é é ..
Date of receipté é é é .é é .	Date of reportingé é é ..é é ..	Report noé é é é é é ...
Pathologisté é é .é é é é é	Surgeoné é é é é é .é .é é .	Lab noé é é é é é .....

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

Epithelioid □ Biphasic □ Sarcomatoid □

Desmoplastic variant Yes □ No □

Tumour size (if localised) é é .mm

Ancillary investigations

Not used □

D-PAS mucin staining	Positive □	Negative □
Alcian Blue mucin staining	Positive □	Negative □

Immunohistochemistry (list antibodies used ï minimum of four recommended)

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

Staging features

Tumour limited to ipsilateral parietal ± visceral ± mediastinal ± diaphragmatic pleura Yes □ No □ N/A □

Tumour involving all ipsilateral pleural surfaces (parietal, mediastinal, diaphragmatic, visceral) Yes □ No □ N/A □

Involvement of diaphragmatic muscle	Yes □ No □ N/A □
Extension of tumour from visceral pleura into the underlying pulmonary parenchyma	Yes □ No □ N/A □
Involvement of endothoracic fascia	Yes □ No □ N/A □
Extension into mediastinal fat	Yes □ No □ N/A □
Solitary, completely resectable focus of tumour extending into the soft tissues of the chest wall	Yes □ No □ N/A □
Non-transmural involvement of the pericardium	Yes □ No □ N/A □
Diffuse or multiple foci of the tumour invading the soft tissue of the chest wall, +/- rib destruction	Yes □ No □ N/A □
Direct trans-diaphragmatic extension of tumour to the peritoneum	Yes □ No □ N/A □
Direct extension of tumour to mediastinal organs (great vessels/oesophagus/trachea/other)	Yes □ No □ N/A □
Direct extension of tumour to the contralateral pleura	Yes □ No □ N/A □
Direct extension of tumour into the spine	Yes □ No □ N/A □
Tumour extending through to the internal surface of the pericardium +/- pericardial effusion	Yes □ No □ N/A □
Direct invasion of the myocardium	Yes □ No □ N/A □

Lymph node involvement

Ipsilateral bronchopulmonary, hilar, or mediastinal (including the internal mammary, peridiaphragmatic, pericardial fat pad, or intercostal lymph nodes) lymph nodes	Not submitted □	Submitted □	Involved □
Contralateral bronchopulmonary, hilar, or mediastinal lymph nodes or ipsilateral or contralateral supraclavicular lymph nodes	Not submitted □	Submitted □	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: é é é é é é é é é é

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

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

Metastases

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

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 □

Summary of pathological staging (select highest stage from above data) including version:

SNOMED codes:

Comments:

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

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

Element name	Values	Implementation notes
Previous treatment (neoadjuvant chemotherapy/radiotherapy)	Single selection value list: • Yes • No	
Specimen origin	Single selection value list: • Pleura • Other • Other	
Specimen origin, other	Free text	Only applicable if ôSpecimen origin, Otherôselected
Sample type	Multiple selection value list: • Pleural biopsy • Core needle biopsy • VATS biopsy • Open biopsy • Lymph node biopsy • Other biopsy (sites) • Pleural effusion • Pericardial effusion • Other cytology • FNA	
Lymph node biopsy, specify site	Size in mm	Only applicable if ôSample type, Lymph node biopsyôselected
Other biopsy site(s), details	Free text	Only applicable if ôSample type, Other biopsy site(s)ôselected
Other cytology, details	Free text	Only applicable if ôSample type, Other cytologyôselected
FNA, details	Free text	Only applicable if ôSample type, FNAô selected
Histologic type of mesthelioma	Single selection value list: • Epithelioid • Biphasic • Sarcomatoid	

Desomplastic variant	Single selection value list: • Yes • No	Only applicable if 'Histologic type of mesothelioma, Sarcomatoid' selected
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.	
SNOMED-M code	May have multiple codes. Look up from SNOMED tables.	

Appendix F Reporting proforma for mesothelioma resection specimens in list format

Element name	Values	Implementation notes
Previous treatment (neoadjuvant chemotherapy/radiotherapy)	Single selection value list: • Yes • No	
Laterality	Single selection value list: • Left • Right	
Specimen type	Single selection value list: • Decortication • Radical pleurectomy • Local chest wall/pleural resection • Extrapleuropneumo-nectomy • Debulking	
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	
Histologic type of mesthelioma	Single selection value list: • Epithelioid • Biphasic • Sarcomatoid	
Desomplastic variant	Single selection value list: • Yes • No	Only applicable if 'Histologic type of mesothelioma, Sarcomatoid' selected
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 ôOther immuno-histochemistryô 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 underlying pulmonary parenchyma	Single selection value list: • 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 0ï 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 ôMicroscopic involvement (R1)ôis Yes or ôMacroscopic involvement (R2)ôis Yes
Closest excision margin	Free text	Only applicable if ôExcision complete (R0)ôis Yes
Closest excision margin, Distance	Distance in mm	Only applicable if ôExcision complete (R0)ôis Yes
Sites of incomplete resection	Free text	
Metastases	Single selection value list: • Unknown • Absent (M0) • Present (M1)	
Metastases, Details	Free text	Only applicable if ôMetastases is Present (M1)ô

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

Appendix G Summary table – explanation of levels of evidence

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

Level of evidence	Nature of evidence
Level 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 cancer type 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.
Level 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 cancer type or Extrapolation evidence from studies described in A.
Level 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 cancer type or Extrapolation evidence from studies described in B.
Level 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 compliance monitoring sheet

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

AGREE standard	Section of dataset
Scope and purpose	
1 The overall objective(s) of the guideline is (are) specifically described	1
2 The clinical question(s) covered by the guidelines is (are) specifically described	1
3 The patients to whom the guideline is meant to apply are specifically described	1
Stakeholder involvement	
4 The guideline development group includes individuals from all the relevant professional groups	Foreword, 2
5 The patientsô views and preferences have been sought	Foreword
6 The target users of the guideline are clearly defined	Foreword, 1ï 2
7 The guideline has been piloted among target users	1
Rigour of development	
8 Systematic methods were used to search for evidence	Foreword
9 The criteria for selecting the evidence are clearly described	Foreword
10 The methods used for formulating the recommendations are clearly described	Foreword
11 The health benefits, side effects and risks have been considered in formulating the recommendations	Foreword
12 There is an explicit link between the recommendations and the supporting evidence	4ï 9,13
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	4ï 11
16 The different options for management of the condition are clearly presented	4ï 11
17 Key recommendations are easily identifiable	4ï 11
18 The guideline is supported with tools for application	Appendices Aï D
Applicability	
19 The potential organisational barriers in applying the recommendations have been discussed	Foreword
20 The potential cost implications of applying the recommendations have been considered	Foreword
21 The guideline presents key review criteria for monitoring and/audit purposes	12
Editorial independence	
22 The guideline is editorially independent from the funding body	Foreword
23 Conflicts of interest of guideline development members have been recorded	Foreword