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

Standards and datasets for reporting cancers

Dataset for the histological reporting of primary cutaneous Merkel cell carcinoma and regional lymph nodes

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Comments	This dataset has been revised to include educational updates and improved clarity, a reference amendment, redesign of the coding appendix and standardisation of terminology in the reporting proformas. In accordance with the College's pre-publications policy, this document was on the College website for an abridged consultation from 4–18 February 2014. Fifteen items of feedback were received. The authors considered them and amended the document as appropriate. Please email publications@rcpath.org if you wish to see the responses and comments. **Dr Suzy Lishman** **Vice-President for Advocacy and Communications**

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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. It may rarely be necessary or even desirable to depart from the guidelines in the interests of specific patients and special circumstances. The clinical risk of departing from the guidelines should be assessed by the relevant multidisciplinary team (MDT); just as adherence to the guidelines may not constitute defence against a claim of negligence, so a decision to deviate from them should not necessarily be deemed negligent.

Each dataset contains **core data items** that are mandated for inclusion in the Cancer Outcomes and Services Dataset (COSD – previously the National Cancer Data Set) 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 organisations have been consulted during its preparation and approved the dataset:

- British Association of Dermatologists (BAD) (as a co-institutional member of The Royal College of Pathologists' Joint Specialty Advisory Committee on Dermatopathology)
- British Society for Dermatopathology (BSD) (as an institutional member of The Royal College of Pathologists' Joint Specialty Advisory Committee on Dermatopathology)
- National Specialist Dermatopathology External Quality Assessment Scheme (NSDEQA) (as a member of The Royal College of Pathologists' Joint Specialty Advisory Committee on Dermatopathology)
- National Cancer Intelligence Network (NCIN).

This dataset has been constructed taking into account the new strong evidence base that is contained in and forms the basis for the following new national and international publications. All publications have widespread national and/or international peer acceptance and reflect the current accepted professional standards and practice in skin cancer.

- COSD published by NCIN.[5] This relates to the core data items for all skin cancers – a specific dataset for Merkel cell carcinoma is not yet available. The NCIN intends to eventually include rare skin cancers, including Merkel cell carcinoma in COSD as indicated in its 2011 NCIN Data Briefing (www.ncin.org.uk).
- Clinical guidelines published by the British Association of Dermatologists (BAD) and other professional bodies [BAD *National Guidelines on Merkel Cell Carcinoma,* in preparation].
- World Health Organization (WHO) Classification of Skin Tumours.[6]
- Armed Forces Institute of Pathology (AFIP) Atlas of Tumour Pathology.[7]
- National Institute for Health and Clinical Excellence (NICE) Guidance on Cancer Series.[8,9]
- National Cancer Peer Review (NCPR) Program by the Department of Heath Cancer Action Team.[10]
- NHS Evidence.[11]
- National Comprehensive Cancer Network (NCCN).[12]
- College of American Pathologists (CAP).[13,14]

As well as peer-reviewed scientific publications, consideration has also been given to published evidence and expert opinion on the internet, such as on Dermpedia (www.Dermpedia.org).

Evidence for the revised dataset was also obtained by electronically searching medical literature databases for relevant research evidence, systematic reviews and national or international publications on skin cancer up to November 2013. This identified no evidence to alter the views or conclusions of the publications listed above. The evidence has been evaluated according to the modified SIGN guidance and the level of evidence for the recommendations has been summarised according to College guidance (see Appendix E). Most of the supporting evidence is grade C or D or meets the GPP (Good Practice Point) criteria. No major conflicts in the evidence have been identified and any minor discrepancies between evidence have been resolved by expert consensus.

No major organisational changes have been identified that would hinder the implementation of the dataset, which is fully integrated with the COSD, and there are no new major financial or work implications arising from the implementation.

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 sub-specialty 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 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. All changes will be documented in the 'data control' section of the relevant dataset.

The dataset has been reviewed by the WGCS and was placed on the College website for an abridged consultation with the membership from 4–18 February 2014. All comments received from the WGCS and membership were addressed by the authors, to the satisfaction of the WGCS Chair and the Vice-President for Advocacy and Communications.

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 Clinical Effectiveness Department and are available on request.

1 Introduction

1.1 Purpose of the dataset

This document provides the dataset for the histological reporting of primary cutaneous Merkel cell carcinoma (primary cutaneous high grade neuroendocrine carcinoma) and associated regional lymph nodes. Merkel cell carcinoma can very occasionally arise in extracutaneous locations. The proven value of this dataset in that situation must currently be regarded as uncertain.

It results from a new international staging system for Merkel cell carcinoma within the spectrum of non-melanoma skin cancer.[1,2]

The meticulous diagnosis and reporting of Merkel cell carcinoma is important because histological parameters play a significant role in defining patient treatment. Similarly, recording of pathological parameters in the dataset has direct implications for the staging and

prognosis of individual patients. The use of datasets (and the background information that forms part of the datasets) in the context of the multidisciplinary team (MDT) meeting is advocated to optimise decisions related to patient treatment, to facilitate regular audit and review of all aspects of the service, to enable the collection of accurate data for Cancer Registries and to provide feedback for those caring for patients with cancer. It is important to have robust local mechanisms in place to ensure that the MDT Clinical Leads and Cancer Registries are apprised of supplementary or revised histology reports that may affect patient treatment and data collection.

1.2 Staging

A new international staging system for cutaneous Merkel cell carcinoma and regional lymph nodes was introduced in 2010.

Ideally, staging of cutaneous malignancy should be based on the latest published edition of the Tumour, Node and Metastasis (TNM) categorisation of malignant tumours published by the International Union against Cancer (UICC).[1] Internationally, it has been agreed that this should be identical to the same staging edition published by the American Joint Committee on Cancer (AJCC).[2] When published, however, the UICC 7th edition contained significant errors in relation to skin cancer. Unfortunately, some of these remain unaddressed in the subsequent Supplement.[3] On that basis, after widespread consultation, The Royal College of Pathologists had advised its members to use the AJCC 7th edition for skin cancer[4] for staging purposes. For the same reason, a similar decision was made by the NCIN.

As well as applying to tumours that arise in the skin, this staging also applies to Merkel cell carcinoma on the penis, vulva and vermilion lip. It does not apply to the eyelid (where Merkel cell carcinoma should be staged as AJCC7 eyelid carcinoma).

1.3 Core and non-core data items

Data items are divided into core and non-core types.

As defined in the Foreword, core items in The Royal College of Pathologists' cancer datasets are robust, evidence-based data items that are required for cancer staging, management and prognosis. These data items are expected to be available routinely for cancer MDT meetings, are recorded by MDT management systems and are used part of the Clinical Lines of Enquiry for the NCPR programme.

As also defined in the Foreword, non-core data items are not considered mandatory on a national basis, but all or part may be included to provide a more comprehensive report or to meet locally agreed clinical or research requirements.

The core pathological data items are summarised in proforma style, which may be used as the reporting format, or combined with free text as required. There is peer support that the use of proformas and checklists contributes substantially to improving the quality of histopathology reports.

1.4 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 of the relevant pathological information required for tumour staging, management and prognosis. Collection of standardised cancer specific data also provides information for healthcare providers, epidemiologists, and facilitates international benchmarking and research.

2 Clinical information required on the specimen request form

Provision of clinical information is the responsibility of the clinician submitting a specimen for pathological examination. The requirement for clinical information is based on the National Clinical Guidelines, the proposed UK National Histopathology Request Form (Appendix C) and COSD.[5] The information is required for MDT discussion and also conforms to NICE requirements[8] for the clinician. For Merkel cell carcinoma, accurate clinical and/or imaging information is required to achieve accurate pN1a *versus* pN1b staging and stage group.

3 Preparation of specimens before dissection

3.1 Skin specimens

The overall size of the submitted specimen must be measured. When appropriate, and in particular with excision specimens, this should incorporate three dimensions. Any unusual features that could be diagnostically important should also be recorded.

The presence, absence or any uncertainty about the existence of a lesion or abnormalities to the naked eye must be recorded. When a lesion is apparent, measurements should include the maximum diameter and elevation.

Consideration should be given to inking the margins of all skin specimens with potential skin cancer. Standard techniques include the use of substances such as Indian ink, silver nitrate, alcian blue, crayon or commercial preparations. Excepting Mohs' surgery, inking is the best way to obtain a reasonably accurate assessment of surgical margins and thereby lesional clearance. Discretion and flexibility should, however, be applied in this decision. The potential for dye to track and give rise to false margins should be taken into account in the final histopathological assessment. Its routine use in large specimens, especially with a clearly visible small central lesion, is debatable. Even in these circumstances, however, inking may be useful because of the possibility of unexpected microscopic extension of the lesion. It is not necessary to ink specimens that are submitted purely for diagnostic purposes, without clinical intent for complete excision.

The examination of specimens submitted to the laboratory with prior designated orientation, by sutures or inking, for example, can be facilitated by the use of different coloured inks on different margins, notching the specimen or the insertion of coloured agar into the processing cassette.

3.2 Regional lymphadenectomy specimens

The generalities of macroscopic neck and axillary block dissection, described for head and neck cancer and breast cancer (www.rcpath.org/publications-media/publications/datasets), apply equally to skin cancer. Inguinal dissections can be approached as axillary dissections.

The overall dimensions of the fixed tissue must be described, with particular note of any designated orientation and any apical node. Nodes should be identified by inspection and palpation. The use of clearing agents is time consuming and increases cost. Accordingly this is not regarded as essential.

3.3 Sentinel lymph node biopsy

The clinical value of sentinel lymph node biopsy for Merkel cell carcinoma, as a potential indicator for survival, recurrence and prognosis, is subject to considerable international debate. In general, this is even greater than for its use in melanoma. AJCC7, however, provides evidence for a prognostic clinical value and accordingly is used as a major staging criterion.

Each individual sentinel lymph node must be examined separately after fixation. Each lymph node should be separated from the surrounding fat, taking care not to damage the capsule or slice into the lymph node.

4 Specimen handling, dissection and block selection

4.1 Skin specimens

The method of handling excisional biopsies depends on the size of the specimen, whether the lesion can be seen, the position of the lesion on the specimen, the uniformity of the lesion and the type of processing technology. It is recommended that a separate judgement is made on each individual case, taking these variables into account, assisted by the following general comments.

Laboratories using rapid processing technology must ensure that trimmed tissue is no more than 2–3 mm in maximum thickness, whereas those using conventional processing technology can increase this to 4–5 mm.

Specimens that need to be trimmed, and in which the lesion can be seen, should be cut at regular intervals so that the nearest naked-eye margin to the lesion can be assessed histopathologically. For many skin ellipses, this will require transverse rather than longitudinal sectioning. When multiple sections are required, this should be undertaken by the ‘sliced bread/toast rack’ method.

The more of the specimen examined, the more accurate the assessment of the surgical margins will be. Accordingly, for specimens under 10 mm, it is recommended that most or all of the lesions are examined. For specimens over 10 mm, the extent of sampling should take into account the proximity of the lesion to the margins, maximum lesional thickness, lesional uniformity and any unusual features. When the lesion can be clearly identified, sampling the polar margins of skin ellipses should be discretionary and based predominantly on whether the lesion is close (under 1–2 mm) to the margin or is less than that in the shorter transverse axis.

When the border of a lesion is indistinct, the whole of the specimen should be sampled. In this situation, the polar ends from the long axis of a skin ellipse should be examined. These can be placed in one or two cassettes, depending on whether orientation of the specimen has been identified clinically.

In some very large specimens, as well as sampling the lesion, the cruciate margins at 3, 6, 9 and 12 o’clock can be sampled, although the limitation in assessing margin clearance should be appreciated.

The requirement for step-levels/sections in any type of specimen is dependent on the requirement to identify a lesion, achieve full-face assessment, establish a diagnosis and assess the margins. Requests for levels at cut-up can be used flexibly, but with the proviso that laboratory protocols and technical experience must ensure that sufficient material remains in the paraffin block for further investigations if subsequently proved necessary.

Trimmed pieces of tissue of different thickness or the processing of more than two pieces of tissue in one cassette incurs an increased risk of inaccurate orientation and sectioning, with a resulting potential loss of diagnostic and margin information.

Re-excision specimens are dealt with in section 11.3.

4.2 Regional lymphadenectomy specimens

Each potential lymph node must be removed, blocked and recorded in a manner that permits a microscopic count of lymph nodes and number involved. Nodes can be bisected and any macroscopic deposits recorded and sampled. For each macroscopically normal node, one section from each cut face should be examined. Representative sampling of an apparent large mass of tumour is acceptable. Each lymph node should maintain identifiable independence and nodes should not be mixed in the same cassette.

Any lymph node or tumour deposit near to the surgical margin within a macroscopic distance of 5 mm should be identified and sampled.

The use of inking for the specimen surface is not regarded as essential.

4.3 Sentinel lymph node biopsy

To date, insufficient evidence-based information is available to advise on the most appropriate methodology to achieve the highest diagnostic sensitivity and specificity for Merkel cell carcinoma. In particular, no information is available as to whether a bread-loaf or bivalve dissection technique is preferable. On that basis, until robust information is available, it is considered appropriate that sentinel nodes for Merkel cell carcinoma should be examined in their entirety by the bread-loaf technique. This should be by using the least number of blocks and 4–5 mm tissue slices. Both techniques have been shown to be equally effective for melanoma and, although the bivalve technique is used in EORTC melanoma trials, the bread-loaf technique is technically less complex. However, it is acceptable for centres that carry out sentinel lymph node biopsy for melanoma and use the alternative method, to use the same technique for Merkel cell carcinoma.

For either method, it is essential that H&E sections are supplemented by the use of at least one immunohistochemical marker from the Merkel cell carcinoma histochemistry panel, as described in section 5.2.2 h). It is essential that the immunohistochemical marker chosen is of proven positivity in the primary tumour.

To date, there is no evidence base to support the use molecular technology (as for example with breast cancer) in this situation. Similarly, there is only a very limited evidence base for the use of Merkel cell virus positivity. Immunohistochemical or molecular technology for Merkel cell virus, cannot be used, unless the primary tumour has been shown to be positive for the virus.

5 Core data items

5.1 Clinical

The minimum clinical core data items to be provided by the clinician for the pathology report are the site of origin and the type of specimen.

5.2 Pathological

5.2.1 Macroscopic

The three dimensional size of the specimen and maximum diameter of the lesion should be recorded in millimetres.

[*Level of evidence D.]*

5.2.2 Microscopic

a) Diagnosis- immunohistochemistry

Merkel cell carcinoma is characterised by small blue cells with a high mitotic count and increased apoptosis.

The diagnosis of Merkel cell carcinoma must be supported by immunohistochemistry. Various antibodies can be used including cytokeratin 20, CAM 5.2, AE1/AE3, CD56, CD117, chromogranin, synaptophysin, neurofilament and neurone specific enolase. Positivity can be variable between antibodies and can be perinuclear dot-like, cap-like, cytoplasmic or cell membrane. The majority of these reflect the ultrastructural presence of aggregates of cytoplasmic intermediate filaments and/or dense-core neuroendocrine granules. The cancer should be negative for lymphoid and melanoma markers. Negative thyroid transcription factor (TTF-1) is important to help exclude metastatic small cell lung cancer.[6]

As a minimum, the panel advised includes cytokeratin 20, AE1/AE3 and/or CAM 5.2, TTF-1, CD45, S100 and melan A.

Merkel cell carcinoma has the ability to reflect the biological heterogeneity of normal Merkel cells and accordingly there is no one immunohistochemical profile that applies to all Merkel cell carcinomas. For example, cytokeratin 20 is considered to have a sensitivity of approximately 90%, whereas others claim a greater sensitivity for neurofilament.

Where their laboratories do not hold these antibodies, pathologist should seek a diagnostic opinion from a specialist skin cancer pathologist at a cancer centre. The paraffin block should be submitted to the centre pathologist to permit the immuno-histochemistry to be undertaken.

Ultrastructurally, the presence of surface processes in a neuroendocrine cell is diagnostic for Merkel cell carcinoma. This will, however, generally require glutaraldehyde fixed tissue for its demonstration.

Histochemistry for potential argyrophil positivity is increasingly not available in laboratories (due to EQA and health and safety limitations), although this is still potentially useful to show neuroendocrine differentiation. The best results are achieved after Bouin fixation.

[The diagnosis of Merkel cell carcinoma must be confirmed by appropriate immunohistochemistry – Level of evidence B.]

b) Level of invasion

Although rare, occasional pure *in-situ*/intra-epidermal disease has been described.

Invasion of fascia, muscle, cartilage or bone is a determinant for stage pT4.

[The level of invasion is a primary staging parameter – Level of evidence B.]

c) In-transit metastasis

The presence of an in-transit metastasis indicates stage N2.

In-transit metastasis is defined as tumour distinct from the primary lesion and either: between the primary lesion and the draining regional lymph nodes or distal to the primary lesion.

No separate subclassification of in-transit metastasis based on distance from the primary tumour exists. In contrast to melanoma, there is therefore no satellite/microsatellite classification. AJCC 7 provides no definition of an in-transit metastasis. To achieve international standardisation, there is peer support for this to be defined as any discontinuous nest of metastatic cells greater than 0.05 mm in diameter, but clearly separated by normal dermis (not fibrosis or inflammation) from the main invasive component of carcinoma by a distance of at least 1 mm. AJCC7 is ambiguous whether a lymphatic vessel must be identified and accordingly this is not regarded as absolute.

AJCC7 provides no information to distinguish between multiple primary tumours (that would warrant the descriptor suffix m in pTNM staging) and in-transit metastases. In view of the apparent rarity of multiple Merkel cell carcinomas, it is recommended that deposits conforming to the above definition and not involving the epidermis are regarded as in-transit metastases.

[In-transit metastasis is a determinant of nodal staging – Level of evidence B.]

d) Lymphovascular invasion

This is an AJCC7 descriptor. It is a core item for the COSD[5] and is generally considered the strongest correlate for sentinel lymph node positivity, survival, recurrence and prognosis.[15]

It is defined as extratumoral in location.

[Level of evidence C.]

e) Presence of second malignancy

In a high percentage of cases (over 30%), Merkel cell carcinoma can co-exist with a second malignancy. The second diagnosis, when present in the skin, should be stated as a core item and the additional malignancy then described in free text, or if appropriate, by an additional cancer dataset.

The most common second extracutaneous malignancy is chronic lymphocytic leukaemia.

The second most common cutaneous malignancy incorporates in-situ and/or invasive squamous cell carcinoma. Other second malignancies may represent any cutaneous cancer including basal cell carcinoma, melanoma, adnexal carcinoma or sarcoma.

There is no absolute evidence to say whether prognosis of Merkel cell carcinoma with a second cancer is better, unchanged or worse. Perhaps related to prognosis, however such double cancers tend to be negative for Merkel cell virus.

To date, there is no agreed or standardised terminology. Some consider the second malignancy as combined, dual or synchronous, whereas others consider them displaying aberrant or divergent differentiation from primitive stem cells.

[Merkel cell carcinoma is associated with a high incidence of second cutaneous malignancies – Level of evidence B.]

f) Margins

Tumour recurrence of Merkel cell carcinoma and clinical morbidity are influenced by the completeness and adequacy of primary excision. In general, use of the words ‘complete/ incomplete’ and ‘adequate/inadequate’ should be avoided in routine histopathology reports. Unless all of the margins have been examined, it is difficult to be certain about the

completeness of excision. The term ‘complete’ is more acceptable in the context of Mohs’ surgery, where the peripheral margin has been examined in its entirety. Adequacy implies a degree of clinicopathological judgement and is therefore more applicable in the context of skin cancer MDT discussion. It is well recognised in a significant number of cases where tumour extends to a margin that there is no residual tumour present on re-excision. This confirms that the term ‘incomplete’ can be inappropriate in this situation. In non-excision specimens (such as curettings), the term ‘edge’ may be more appropriate, as the edge may not reflect the true surgical margin.

Although evidence is more robust for peripheral margins, there is broad peer agreement that comments are necessary about clearance of both peripheral and deep excision margins. The word ‘peripheral’ rather than ‘lateral’ is generally preferred, to avoid problems by possible inference of a medial margin. The words ‘lateral’ and ‘medial’ may be applicable to specifically defined and designated orientated specimens.

Careful consideration has been given as to whether the extent of peripheral and deep clearance should be measured histologically for Merkel cell carcinoma in quantitative terms. It is certainly clinically necessary to have information about whether the peripheral and deep excision margins are clear or involved by tumour.

As a core dataset item for all cancers, COSD records whether tumour excision margins are clear by more than 5 mm, clear by greater than 1 mm but less than or equal to 5 mm, or present less than or equal to 1 mm, but without tumour reaching the margin.[5] Skin cancer margins must therefore be measured in relation to both 1 mm and 5 mm breakpoints.

Guidelines on the surgical margins recommended for Merkel cell carcinoma are based on evidence utilising clinical margins. These are either 10 or 20 mm for this cancer.

Histological margins are widely used as a surrogate marker for clinical margins in the context of the skin cancer MDT discussion and quantitative information about margins is important for skin cancer audits. On this basis, this dataset recommends as a core item, histologically measuring peripheral and deep margins for cutaneous Merkel cell carcinoma as being involved (0 mm), less than 1 mm, or at and over 1 mm to the nearest mm.

When appropriate, an approximate estimate of shrinkage of histological tissues can be made by the skin cancer MDT. This is generally recognised to be in the region of 15–20%.

Tumour base transection in a specimen is regarded by AJCC as a site-specific prognostic factor.

[Margin involvement by tumour or the extent of clearance correlates with the risk of clinical recurrence – Level of evidence D.]

g) Maximum diameter

AJCC7 identifies maximum diameter staging breakpoints between pT1, pT2 and pT3 at 20 mm and 50 mm respectively. The evidence base for 20 mm is considerably stronger than that for 50 mm.[16] A pragmatic approach to measuring diameter should be to combine macroscopic and microscopic measurements as appropriate.

[Maximum diameter is the primary staging determinant – Level of evidence B.]

h) Lymph node involvement

Metastatic Markel cell carcinoma to lymph nodes may be difficult to identify in routine H&E-stained sections. The use of immunohistochemistry has been shown to increase the

sensitivity of identifying occult lymph node metastases.[17,18] On that basis, no lymph node should be reported as negative until at least one immunostain has been performed on the node.[12,13,14] A confirmed deposit on H&E with a proven primary tumour excludes this necessity in an individual or group of nodes. As a minimum, either cytokeratin 20, CAM 5.2 or AE1/AE3 must be used in this situation on negative nodes. With the bread-loaf dissection technique it is recommended that each slice of lymph node is examined by one H&E-stained section and if negative, by a further immunostained section. Two immunostains reduce the risk of false-negatives (by 5–10%), but at the moment there is insufficient evidence to justify this practice on a cost-benefit basis.

The definition of positive nodal staging for Merkel cell carcinoma is the presence of a metastatic deposit, although the evidence base for the lowest threshold is not yet established. After peer consultation, it has been considered reasonable in the interim to adopt the same principal as for melanoma, namely that one cell can be regarded as positive, but that this should be restricted to an immunostained section and the nuclear morphology should be consistent.

In order to apply pN staging for involved lymphadenectomy specimens, the pathologist needs to know if clinical examination and imaging were negative (so-called microscopic disease in the context of completion/elective lymphadenectomy specimens) or if clinical or radiological examination were positive (so called macroscopic disease in the context of therapeutic lymphadenectomy specimens). As discussed under tumour burden in Appendix A, a positive node with microscopic disease is stage pN1a and with macroscopic disease pN1b. Only basic pN1 staging can be provided if this clinical and imaging information is not available to the pathologist at the time of reporting.

The number of nodes isolated and number involved by malignancy are core COSD items.[5] The number involved and maximum diameter of a metastatic deposit are not staging criteria.

[Lymph node involvement is the principal nodal staging determinant – Level of evidence B.]

i) Lymph node extracapsular invasion and margin status

For consideration of potential adjuvant radiotherapy, extracapsular invasion and margin status of the whole specimen are listed as core items. Both are widely regarded as adverse prognostic features.

Extracapsular invasion is regarded by AJCC as a site-specific prognostic factor.[2]

[Adjuvant radiotherapy is considered in the presence of extracapsular invasion – Level of evidence D.]

6 Non-core data items

These have been included in national and international guidelines as non-core items or supported during informal consultation.

6.1 Clinical

These are based predominantly on the draft UK National Histopathology Request Form (Appendix C) and can be captured if provided by the clinician.

- Date of surgical procedure.
- Grade of clinician undertaking procedure.
- Clinical diagnosis/description.

- Clinical size of lesion (maximum diameter in mm).
- Procedure intention of clinician.
- Diagnostic/therapeutic biopsy.
- Measured surgical clinical peripheral margin (mm).
- Is this a recurrent tumour?
- Previous histology reference number(s).
- Is the patient immunocompromised? This is one of the most important clinical correlates for both the cause and prognosis of Merkel cell carcinoma.
- Is this a tumour arising is an individual genetically predisposed to cancer?
- Is there clinical and/or imaging evidence of potential nodal involvement?

6.2 Pathological

In general, the following data items have been recorded inconsistently in research publications. The number of patients in different case series is often low and the statistical significance on multivariate analysis variable. Published case series have often been small and end points limited to nodal status or disease-free survival.[17,19,20]

It is recommended that, as a minimum, consideration is given to recording tumour thickness, mitotic index and growth pattern. These three data items are used in centres undertaking research and clinical trials involving Merkel cell carcinoma. The concept of a broad, non-core histological profile is gaining support, but most items do not currently justify inclusion as core data items.[13,14,20]

6.2.1 Skin

a) Tumour thickness

This is regarded by AJCC as a site-specific prognostic factor.[2]

In some series, thickness has been more predictive of outcome than diameter. The good and bad prognostic division points, however, have been variable and included both 5 mm and 10 mm.[15] In occasional series, there appeared to be no correlation between thickness and prognosis.

It is recommended that thickness is measured in millimetres using the method defined for cutaneous melanoma in the College's melanoma dataset (www.rcpath.org/publications-media/publications/datasets).

b) Mitotic index

A mitotic count of more than 10 mitoses per single high-power field has been shown to correlate with large tumour size and poor prognosis.[13,14] Unfortunately, the reports do not specify how 'high power' is defined. Accordingly it is recommended that mitotic index is measured per mm^2, using the standardised method defined for cutaneous melanoma in the College's melanoma dataset, (www.rcpath.org/publications-media/publications/datasets). It is acknowledged, however, that this may be difficult to undertake in practice due to the normally high mitotic rate of Merkel cell carcinoma and distinction from apoptotic nuclei.

A MIB-1 proliferation index of greater than 50% may be associated with a worse prognosis.[13,14]

c) Level of invasion

There is evidence that extension into the subcutaneous fat results in a worse prognosis compared with being limited to the dermis.[15]

It is recommended that the level of invasion, when not extending beyond the subcutaneous fat, can be provided using Clark levels as summarised in the College's cutaneous melanoma dataset (www.rcpath.org/publications-media/publications/datasets).

d) Histological growth pattern

AJCC regards histological growth pattern as a site-specific prognostic factor.[2] There is some evidence that a nodular growth pattern correlates with a better survival.[15] A nodular growth pattern is defined as a relatively well-circumscribed tumour interface with the surrounding tissue. A tumour with an infiltrative growth pattern is defined as one without a well-circumscribed interface and composed of rows, trabeculae or strands of cells extending through the tissue. A tumour with both growth patterns is described as infiltrative.

e) Histological subtype

Intermediate, small cell, trabecular and combined subtypes are described. The intermediate variant has a diffuse, sheet-like growth with relatively large cells. The small cell variant has small, round and dyscohesive cells, and the trabecular variant has columns 2–3 cells thick and possible spindling. The prognostic significance of the subtypes is currently uncertain although the small cell type may have some survival advantage.[19]

f) Tumour infiltrating lymphocytes

These are regarded by AJCC as a site-specific prognostic factor.[2] There is evidence that the presence of tumour-infiltrating lymphocytes (TILs) may portend a worse prognosis.[15] To achieve standardisation, it is recommended that TILs are assessed using the method defined for cutaneous melanoma in the College's melanoma dataset (www.rcpath.org/publications-media/publications/datasets).

g) Regression

Identifiable regression is unusual in Merkel cell carcinoma, but may explain why approximately 10% of Merkel cell carcinomas present as metastatic disease of unknown primary origin. If present, to achieve standardisation, it is recommended that regression is assessed using the method defined for cutaneous melanoma in the College's melanoma dataset (www.rcpath.org/publications-media/publications/datasets).

h) Lymphovascular invasion

Record whether this is intratumoral in location. Section 6.2.2 d records extratumoral lymphovascular invasion. Histochemistry or immunohistochemistry can be used to facilitate the identification of lymphovascular invasion.

6.2.2 Lymph nodes

a) Tumour diameter

Diameter of largest deposit: this is regarded by AJCC as a site-specific prognostic factor.[2] To date, however, this has no proven staging importance. It is recommended that the

largest deposit is measured using the method defined for nodal melanoma in the College's melanoma dataset (www.rcpath.org/publications-media/publications/datasets).

b) Lymphadenectomy specimens

- Blood vessel invasion.
- Distance of tumour to nearest margin of specimen.

6.2.3 Merkel cell polyoma virus (tissue)

Record as present or absent and the technology used. This can be undertaken by molecular or immunohistochemical techniques. A commercial antibody is available for the large T antigen in transformed cells. Of greatest importance, however, is knowledge whether a designated Merkel cell virus mutation is present. Current evidence suggests that, to date, this mutation is limited to Merkel cell carcinoma. This should be stated if known.

The diagnostic importance of Merkel cell virus is limited by being positive in only approximately 80% of cases. Merkel cell carcinoma that is positive for Merkel cell virus tends to have a better prognosis. Merkel cell virus is rarely present in Merkel cell carcinoma combined with a second cutaneous malignancy.

The role of this new virus is reviewed in reference 20.

6.2.4 TNM stage group

Minimum stage group based on available information.

7 Diagnostic coding and staging

Both TNM and SNOMED codes are required for COSD.[5]

7.1 pTNM status

pTNM status should be recorded according to the 7th edition AJCC.[2]

TNM stage grouping should be deferred until all current TNM information is available and if applicable after skin cancer MDT discussion.

A stage group can be added to a histopathology report as a non-core item, but should usually be stated to be the minimum stage group based on the information in the report.

General principles

pT	Primary tumour.
pTx	Primary tumour cannot be assessed.
pTis	Carcinoma *in-situ.*
pT1, pT2, pT3, pT4	Increasing pT stages.

Additional descriptors can be used:

The suffix 'm' indicates the presence of multiple primary tumours in a single site and is recorded in parentheses: pT(m) N M.

The ‘r’ prefix indicates a recurrent tumour when staged after a documented disease-free interval and is identified by the ‘r’ prefix.

pN	Regional lymph node.
pM	Distant metastasis.

These are described in detail in Appendix A.

7.2 SNOMED codes

SNOMED Topography (T) code should be recorded for the site.

SNOMED Morphology (M) code should be recorded for the diagnosis/tumour morphology.

SNOMED Procedure (P) codes should be recorded for the procedure. P codes vary according to the SNOMED system in use in different organisations, therefore local P codes should be recorded and used for audit purposes.

A list of applicable T and M codes is provided in Appendix B.

8 Small biopsy specimens

These have a particular diagnostic role in cosmetically sensitive or clinically difficult cutaneous areas (e.g. face, digits) where a diagnosis could facilitate skin cancer MDT decision making.

9 Reporting of frozen sections

Frozen sections have no role in the diagnosis of Merkel cell carcinoma in the skin. The diagnosis should be based on paraffin-processed tissue, thereby permitting immunohistochemistry, prospective skin cancer MDT discussion and patient involvement in any decision making process. Frozen sections have no role in lymph node assessment for the same reasons.

10 Cytological diagnosis

Cytology has limited role in the diagnosis of Merkel cell carcinoma. If undertaken for lymph node assessment, it is essential that material is available for immunocytochemistry. Fine needle aspiration cytology can have a role in the investigation of enlarged nodes identified clinically and/or on imaging. A positive sample will reflect stage pN1b (macrometastasis).

11 Specific aspects of individual tumours not covered elsewhere

11.1 Reporting pathologist

NICE recommends that lymph node cytopathology and histopathology resulting from the investigation and treatment of skin cancer should be undertaken by pathologists also involved in reporting of skin histology. In particular, this is to improve the sensitivity and specificity of SLNB or equivalent (ultrasound and cytopathology) and to facilitate skin cancer MDT discussion and audit.[8,10]

This NICE recommendation relates primarily to inguinal and axillary sentinel lymph node biopsy and lymph node dissections for skin cancer. Head and neck sentinel lymph node

biopsy for skin cancer also lies within the competence of specialist dermatopathologists. These topics all lie within the area covered by the National Specialist Dermatopathology EQA. Lymph node dissection of the head and neck and associated reporting, however, must only be undertaken by those having appropriate skills and competence in the area. This is primarily demonstrated by regular practice in the field and participating in an appropriate EQA scheme. In general, this therefore limits head and neck lymph node dissection and reporting to individuals regularly involved in this area of head and neck pathology. Head and neck lymph node dissection must be undertaken and reported according to The Royal College of Pathologists' neck dissection cancer dataset (www.rcpath.org/publications-media/publications/datasets/datasets-TP.htm).

11.2 Skin cancer MDT referral

All cases of Merkel cell carcinoma must be referred for specialist skin cancer MDT review.[8] Referral to an MDT can be included as a non-core item.

11.3 Re-excision specimens

There has been considerable debate as to the extent of the examination that is required of wider local excision specimens for skin cancer. Macroscopic examination is essential. This is the most reliable means to record that the re-excision has been undertaken and also the dimensions of the wider excision specimen. The fixed specimen should also be sliced every 2–4 mm to detect any macroscopic abnormalities such as potential satellite metastases. Each slice with a macroscopic abnormality must be examined histologically, to ensure that margin status can be assessed.

The debate centres on the cost-efficiency of examining an entire specimen that is macroscopically normal when abnormalities were not present at the margins of the index specimen. Some peers consider that this is the only guaranteed way to ensure that residual disease or metastases are not overlooked. Some also consider that the specimen should always be examined in its entirety with a biomedical scientist-led cut-up. There does, however, appear to be considerable latitude for discretion in this area. An acceptable compromise would be to sample the specimen in its shortest transverse axis, incorporating the area where the scar appears closest to the margin. This can generally be achieved in 1–4 cassettes. Clinicians may require information about whether the specimen contains a scar and whether the scar is completely excised.

If abnormalities in the index specimen were reported to extend to the margins, the specimen should be examined more extensively. It is recommended that specimens under 10 mm are sampled completely. Specimens over 10 mm can be sampled pragmatically according to the nature of the original margin involvement.

12 Criteria for audit of the dataset

Recommended by the RCPath as key performance indicators (KPIs) (see *Key Performance Indicators – Proposals for implementation* (July 2013) on www.rcpath.org/clinical-effectiveness/kpi/KPI):

- 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 Trusts are required to implement the structured recording of core pathology data in the COSD by January 2014.
  Standard: 95% of reports must contain structured data

- Histopathology cases that are reported, confirmed and authorised within seven and ten calendar days of the procedure.

Standard: 80% of cases must be reported within seven calendar days and 90% within ten calendar days.

13 Acknowledgements

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Appendix A AJCC7 pathological staging of cutaneous Merkel cell carcinoma, regional lymph nodes and metastasis

(includes penis, vulva and vermillion lip; eyelid is excluded and should be staged as AJCC7 eyelid carcinoma)

Definitions of TNM

Primary tumour (T)

TX	Primary tumour cannot be assessed
T0	No evidence of primary tumour (e.g. nodal/metastatic presentation without associated primary)
Tis	*In-situ* primary tumour
T1	Less than or equal to 20 mm maximum tumour dimension
T2	Greater than 20 mm but not more than 50 mm maximum tumour dimension
T3	Over 50 mm maximum tumour dimension
T4	Primary tumour invades bones, muscle, fascia or cartilage

Regional lymph nodes (N)

NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
cN0	Nodes negative by clinical exam* (no pathologic node exam performed)
pN0	Nodes negative by pathologic exam
N1	Metastasis in regional lymph node(s)
N1a	Micrometastasis**
N1b	Macrometastasis***
N2	In-transit metastasis****

* Clinical detection of nodal disease may be via inspection, palpation and/or imaging.

** Micrometastases are diagnosed after sentinel or elective lymphadenectomy.

*** Macrometastases are defined as clinically detectable nodal metastases confirmed by therapeutic lymphadenectomy or needle biopsy.

**** In-transit metastasis: a tumour distinct from the primary lesion and located either (1) between the primary lesion and the draining regional lymph nodes or (2) distal to the primary lesion.

Distant metastasis (M)

M0 No distant metastases

M1 Metastases beyond regional lymph nodes

M1a Metastasis to skin, subcutaneous tissues or distant lymph nodes

M1b Metastases to lung

M1c Metastases to all other visceral sites

Anatomic stage/prognostic groups

Stage 0	Tis	N0	M0
Stage IA	T1	pN0	M0
Stage IB	T1	cN0	M0
Stage IIA	T2/T3	pN0	M0
Stage IIB	T2/T3	cN0	M0
Stage IIC	T4	N0	M0
Stage IIIA	Any T	N1a	M0
Stage IIIB	Any T	N1b/N2	M0
Stage IV	Any T	Any N	M1

Tumour burden

A staging definition exists with regard to nodal tumour burden, namely microscopic *versus* macroscopic disease.

Clinically occult nodal metastases (microscopic disease) are defined as those in patients with no clinical or imaging evidence of nodal disease but having pathological evidence of nodal involvement (pN1a).

Clinically apparent nodal metastases (macroscopic disease) are defined as those in patients with clinical or imaging evidence of nodal disease that is confirmed by pathology (pN1b).

Both clinical and imaging findings are relevant to stage grouping. If these are not provided to the pathologist, only basic pN0 or pN1 staging can be provided and not stage group.

Clinically positive but pathologically negative nodes are staged as pN0
Clinically positive nodes but with no pathology undertaken are staged as N1b

Appendix B Merkel cell carcinoma SNOMED coding

Topographical codes	SNOMED	SNOMED CT terminology	SNOMED CT code
Skin	T01000	Skin structure (body structure)	39937001
Lymph node	TC4000 (SNOMED 3) T08000 (SNOMED 2)	Structure of lymph node (body structure)	59441001

Morphological codes	SNOMED	SNOMED CT terminology	SNOMED CT code
***In situ* Merkel cell carcinoma**	M82472	No code	No code
Primary invasive merkel cell carcinoma	M82473	Merkel cell carcinoma (morphologic abnormality)	5052009
Metastatic merkel cell carcinoma	M82476	No code	No code

Procedure

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

Appendix C Draft UK National Histopathology Request Form for Skin Biopsies

Devised by the NCIN Skin Site Specific Reference Group and kindly provided by the NCIN for inclusion in this dataset. Permission for use should be sought from the NCIN. Approved by the BAD. The mode of national implementation is under consultation.

The UK National Histopathology Request form for skin biopsies

Date of surgical procedure

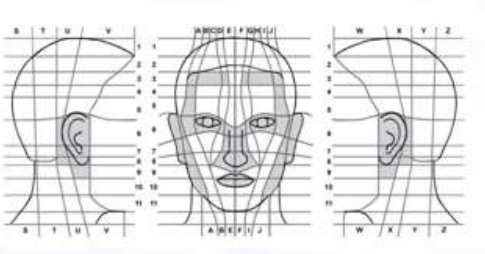
Please attach patient details

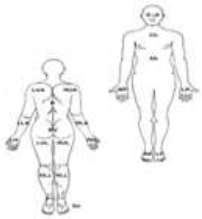
Name of surgeon

Grade of surgeon: Nurse, Specialist trainee, Consultant, Hospital Practitioner, Other

Clinical diagnosis: free text

Mandatory for Clinician to complete:	First biospy	Second	Third	Fourth
Site Code as per image (insert LUL etc)				
Clinical Diagnosis (select either BCC, SCC, Melanoma, Atypical Mole, other tumour or other). For inflammatory lesions add clinical details as free text.				
Clinical size of lesion sampled (max diameter) (mm)				
Intention of the surgeon (select *biopsy, excision or curative curettage*				
Procedure (select *curettage, shave biopsy, punch, incisional biopsy or excision)*				
For tumours give measured surgical clinical margin (mm)				
Is this a recurrent tumour?	Y/N	Y/N	Y/N	Y/N
Is the pateint immunocompromised?	Y/N			
Is this a tumour arising in areas of radiation or thermal injury, chronic draining sinuses, chronic ulcers, chronic inflammation or Bowen's Disease	Y/N	Y/N	Y/N	Y/N
Is this a tumour arising in a genetically predisposed individual?	Y/N			





Please mark site of samples taken on the above images. For head and neck skin cancers the site code will be made up of the number in the horizontal grid and the letter from the vertical grid (e.g. for a tumour in the middle of the nose that might be code 8E). Where a lesion lies across grid lines then that grid reference in which the greater part of the tumour lies should be used OR if the lesion impacts on a grey shaded area or on the lips then that code should be used. Where the tumour is on the marked lips then the code LIP should be used. For tumours outside the head and neck the letters are indicated on the body map. e.g. a tumour on the left lower arm is LLA).

Free text

Appendix D1 Reporting proforma for cutaneous Merkel cell carcinoma

Surname ……. Forenames …….. Date of birth…… Sex ……..

Hospital ……... Hospital no …….. NHS/CHI no ……

Date of receipt …… Date of reporting ……. Report no ……

Pathologist …….. Clinician ……

Clinical data

Clinical site: …….

Specimen type: Excisional biopsy □ Incisional (diagnostic) biopsy □ Punch biopsy □ Shave □
Curettings (Diagnostic) □ Curettings (Excisional) □ Curettings (Not specified) □
Other (please specify)……

Macroscopic description

Size of specimen: Length ……..mm Breadth…….mm Depth ..…..mm

Maximum diameter of lesion: ……mm Uncertain □ No lesion seen □

Histological data

Immunohistochemistry	Positive	Negative	Not tested
Cytokeratin 20	□	□	□
AE1/AE3	□	□	□
CAM 5.2	□	□	□
TTF-1	□	□	□
CD45	□	□	□
S100	□	□	□
Melan-A	□	□	□

Invasion: No □ (i.e. only *in-situ*/intra-epidermal disease) Yes □

If invasion is present, depth of invasion > subcutaneous fat (Clark Level 5):

No □ Yes (pT4) □ Not assessable □

If yes, specify tissue: fascia□ /muscle□ /perichondrium□ /cartilage□ / paratendon□ /tendon□ /periosteum□ /bone□

In-transit metastasis: Not identified □ Present □ Uncertain □ Cannot be assessed □

Lymphovascular invasion (extratumoral): Not identified □ Present □ Uncertain □ Cannot be assessed □

Presence of second malignancy with MCC in skin: No □ Yes □

If yes, specify diagnosis (provide relevant dataset if appropriate)……

Margins

Peripheral: Involved □ Not involved but <1 mm □ Not involved ≥1 mm □…..mm (to nearest 1 mm)
Uncertain □ Not applicable □

Deep: Involved □ Not involved but <1 mm □ Not involved ≥1 mm □…..mm (to nearest 1 mm)
Uncertain □ Not applicable □

Maximum diameter (Macroscopic and/or microscopic)

≤20 mm □ >20–50 mm □ >50 mm □ Uncertain □ Cannot be assessed □

TNM pathological (p) stage …….

SNOMED code……

Comments

Pathologist…… **Date……..**

Appendix D2 Reporting proforma for regional lymph nodes associated with Merkel cell carcinoma

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

Clinical details

Site Inguinal ……. Axillary…….. Other ……

Sentinel lymph node biopsy

Number of sentinel nodes present	……			
Number of nodes positive	……			
If positive: extracapsular invasion	No □	Yes □	Uncertain □	Cannot be assessed □

Lymphadenectomy

Number of nodes identified	……			
Number of nodes positive	……			
Highest/apical node involved	No □	Yes □	Uncertain □	Cannot be assessed □
If positive: extracapsular invasion	No □	Yes □	Uncertain □	Cannot be assessed □
Margin of specimen clear	No □	Yes □	Uncertain □	Cannot be assessed □

TNM pathological stage (AJCC7) N…….

SNOMED code……

Comments

Pathologist…….. **Date……**

Note

If no previous biopsy details, clinical or radiological information about the presence or absence of abnormal nodes is provided, only basic pN1 staging can be applied. It will not be possible to provide pN1a *versus* pN1b staging or a stage group. This should be recorded under 'Comments'.

Appendix E 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 F AGREE compliance monitoring sheet

The cancer datasets of The Royal College of Pathologists comply with the AGREE standards for good quality clinical guidelines (www.agreecollaboration.org). 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.	Foreword, 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, 1
5. The patients' views and preferences have been sought.	Not applicable*
6. The target users of the guideline are clearly defined.	1
7. The guideline has been piloted among target users.	Local pilot and Skin NSSCRG consultation
RIGOUR OF DEVELOPMENT	
8. Systematic methods were used to search for evidence.	Foreword, 1
9. The criteria for selecting the evidence are clearly described.	Foreword, 1
10. The methods used for formulating the recommendations are clearly described.	Foreword, 1
11. The health benefits, side effects and risks have been considered in formulating the recommendations.	Foreword, 1
12. There is an explicit link between the recommendations and the supporting evidence.	Foreword, 5
13. The guideline has been externally reviewed by experts prior to its publication.	1
14. A procedure for updating the guideline is provided.	Foreword
CLARITY OF PRESENTATION	
15. The recommendations are specific and unambiguous.	3,4,5
16. The different options for management of the condition are clearly presented.	4,5
17. Key recommendations are easily identifiable.	3,4,5
18. The guideline is supported with tools for application.	Appendices A–E
APPLICABILITY	
19. The potential organisational barriers in applying the recommendations have been discussed.	Foreword, 1
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

* The Lay Advisory Committee (LAC) of The Royal College of Pathologists has advised that there is no reason to consult directly with patients or the public regarding this dataset because it is technical in nature and intended to guide pathologists in their practice. The authors will refer to the LAC for further advice if necessary.