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

Standards and datasets for reporting cancers

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

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Comments	This document will replace the 4th edition of the dataset published in 2014. This is to incorporate the *TNM Classification of Malignant Tumours (8th edition)* from the Union for International Cancer Control published in 2017. In accordance with the College's pre-publications policy, this document was on the College website for consultation from 6 September to 4 October 2018. Responses and authors' comments are available to view on request. **Dr Brian Rous** **Clinical Lead for Guideline Review (Cellular Pathology)**

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Foreword

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

Each dataset contains core data items (see Appendices D1, D2, E1 and E2) that are mandated for inclusion in the Cancer Outcomes and Services Dataset (COSD – previously the National Cancer Dataset) in England. Core data items are items that are supported by robust published evidence and are required for cancer staging, optimal patient management and prognosis. Core data items meet the requirements of professional standards (as defined by the Information Standards Board for Health and Social Care [ISB]) and it is recommended that at least 95% 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; member of RCPath's Specialty Advisory Committee on Dermatopathology)
- British Society for Dermatopathology (BSD; member of RCPath's Specialty Advisory Committee on Dermatopathology)
- National Specialist Dermatopathology External Quality Assessment (NSDEQA) scheme (member of RCPath's Specialty Advisory Committee on Dermatopathology).

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

- Union for International Cancer Control; previously International Union against Cancer (UICC)[1]
- American Joint Committee on Cancer (AJCC)[2]
- World Health Organization (WHO) Classification of Skin Tumours[3]
- National Institute for Health and Clinical Excellence (NICE) Guidance and Quality Standards on skin cancer and melanoma[4,5]
- NHS Evidence[6]
- BAD Draft National Clinical Guidelines on Merkel Cell Carcinoma (jointly with other professional bodies; draft)
- Public Health England (PHE) COSD.[7] This relates to the core data items for all skin cancers – a site-specific dataset for Merkel cell carcinoma is not yet available. PHE intends to eventually include rare skin cancers, including Merkel cell carcinoma, in the COSD as indicated in the 2011 NCIN Data Briefing (www.ncin.org.uk).
- NHS England Quality Surveillance Programme (QSP; formerly the National Cancer Peer Review Programme)[8]
- National Comprehensive Cancer Network (NCCN)[9]

- College of American Pathologists (CAP)[10,11]
- Armed Forces Institute of Pathology (AFIP) Atlas of Tumour Pathology (noting AFIP disestablished in 2011 and now under American Registry of Pathology [ARP] Press).[12]

Evidence for the revised dataset was obtained from updates to international tumour grading, staging and classification systems and by electronically searching medical literature databases for relevant research evidence, systematic reviews and national or international publications on Merkel cell carcinoma. The level of evidence for the recommendations has been summarised (Appendix F). Unless otherwise stated, the level of evidence corresponds to 'Good practice point (GPP): Recommended best practice based on the clinical experience of the authors of the writing group'. The sections of this dataset that indicate compliance with each of the AGREE II standards are indicated in Appendix G.

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 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 members' attention. If members do not object to the changes, the short notice of change will be incorporated into the dataset and the full revised version (incorporating the changes) will replace the existing version on the College website.

The dataset has been reviewed by the Clinical Effectiveness department, Lay Governance Group and Working Group on Cancer Services (WGCS) and was on the College website for consultation with the membership from 6 September to 4 October 2018. All comments received from the WGCS and membership were addressed by the authors, to the satisfaction of the Chair of the Working Group and Clinical Lead for Guideline Review (Cellular Pathology).

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. The authors of this dataset have declared no conflicts of interest.

1 Introduction

1.1 Target users and health benefits of this guideline

The primary target users of this dataset are consultant and trainee cellular pathologists and biomedical scientists and, on their behalf, the suppliers of IT products to laboratories. Other target users are clinicians in secondary and primary care within the NHS and members of skin cancer multidisciplinary teams (MDT). Secondary users are NHS England and NHS Scotland, each involved in quality surveillance, cancer networks, cancer alliances and those involved in skin cancer data collection via the NHS, including PHE and in particular the National Cancer Registration and Analysis Service (NCRAS).

Standardised cancer reporting and 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. The collection of standardised cancer-specific data also provides information for epidemiologists and facilitates international benchmarking and research.

1.2 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 replaces the edition of the dataset published in 2014.

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 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 NCRAS 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 NCRAS are apprised of supplementary or revised histology reports that may affect patient treatment and data collection.

1.3 Changes since the previous edition

1.3.1 Pathological tumour, node and metastases (pTNM)

UICC TNM 8, rather than AJCC TNM 8, has been selected by the RCPath because this provides TNM staging of the entire skin surface for cutaneous carcinoma compared with only the head and neck in AJCC 8.[1,2]

Although minor differences existed on publication between UICC TNM 8 and AJCC TNM 8 for most skin cancers, many of these have now been corrected under website errata (www.wileyanduicc.com; www.cancerstaging.org). UICC TNM 8 and AJCC TNM 8 both staged Merkel cell carcinoma identically from the outset of their publications.

Extreme caution has been applied by the RCPath in using the UICC prognostic grids as these remain based on UICC TNM 7 and have not yet been updated for TNM 8.

The terms microscopic and macroscopic are often replaced in TNM 8 by the terms ‘clinically occult’ and ‘clinically detected’, respectively. UICC TNM 8, unlike AJCC TNM 8, has continued, in common with UICC and AJCC TNM 7, to place non-melanoma skin cancer (NMSC) of the vermillion (non-hair bearing) lip in the staging chapter for lip and oral cavity and not skin carcinoma.

The main differences between TNM 7 and TNM 8 for cutaneous Merkel cell carcinoma are summarised below.

pTNM stage categories

pT

AJCC states that the maximum dimension for pT1–pT3 categories should be a clinical measurement, on the evidence base available, but a pathological measurement is permitted if the clinical one is not available. UICC states that the measurement should be assessed by physical examination. This dataset therefore recommends use of the clinical measurement but supports use of the pathological measurement if the clinical one is absent. Indicating which one is used for staging is a new dataset item. Preferably, this should be the

macroscopic measurement, unless in a particular case use of a macroscopic and/or microscopic one is unavoidable.

pN1
pT1 subdivision requires clinical information as to whether nodes are clinically occult or clinically detected, but that may not be available at the time of reporting. In this eventuality, the parent category pT1 should be used. Clinical detection of nodal disease is via inspection, palpation and/or imaging.

pN1a is now divided into pN1a (sn) and pN1a, representing clinically occult but positive node(s) on sentinel lymph node biopsy (SLNB) (sn) and lymphadenctomy, respectively (defined as a microscopic metastasis). This reflects a more definitive role for SLNB in Merkel cell carcinoma staging.

pN1b represents a clinically detected node(s) that is confirmed as pathologically positive (defined as a macroscopic metastasis).

pN2 and pN3
In-transit metastasis is now staged as pN2 or pN3 according to whether lymph node(s) are microscopically negative or positive.

pTNM stage group
Stage I, II and III in UICC TNM 8 are new. Stage IIIA includes a specific clinical situation of no known primary tumour (T0) but a clinically detectable and microscopically confirmed nodal metastasis.

1.3.2 Changes in 2018

The authors are mindful that significant changes in skin cancer are likely to be published during 2018. These include a new (second) edition of the WHO Classification of Skin Tumours and new national clinical guidelines on NMSC from the BAD. Any such changes will be captured in the first revision of this dataset. After consideration, rather than await these changes, it was agreed that this new dataset would proceed to facilitate use of the new TNM classification from 1 January 2018.

1.4 Core and non-core data items

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

As defined in the foreword, core items in RCPath's 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 as part of the national QSP.

The foreword also sets out that non-core data items are not considered mandatory on a national basis, but some or all 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 structured proforma style, which may be used as the reporting format, or combined with free text as required. There is peer support for the idea that the use of structured proformas (or protocols/checklists) contributes substantially to improving the quality of histopathology reports.

2 Clinical information required on the specimen request form

The 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 proposed UK National Histopathology Request Form (Appendix C) and COSD.[7] The information is required for MDT discussion and also conforms to NICE requirements[4,5] for the clinician. For Merkel cell carcinoma, it is important to emphasise that T1, T2 and T3 categories are best based, according to available evidence, on the maximum clinical dimension of the tumour. This must be recorded on the request form and in the clinical notes by the clinician. The maximum pathological dimension can be used if the clinical dimension is absent on the request form.

Accurate clinical and/or imaging information is also 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 dimension (usually diameter) in millimetres and possible 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.

During examination of specimens submitted to the laboratory with prior designated orientation, by sutures or inking, for example, different coloured inks must be used on different margins, notching the specimen or inserting coloured agar into the processing cassette.

The dissection of a wedge excision (e.g. ear or lip) can be flexible depending on the nature of the specimen, whether there is a location marker and the position of the lesion. The same flexibility applies to whether the specimen needs to be inked. The selection of blocks taken, however, must be clearly documented and frequently a diagram can be useful. Additionally, if necessary, this should be accompanied by direct liaison between the person dissecting the specimen and the later reporting pathologist. This is the recommended approach to avoid potential problems in block interpretation during subsequent reporting. The blocks selected, however, must be able to measure the lesional margins to the same degree of accuracy stated in the dataset for the type of skin cancer present. Sometimes, there is only one so-called wedge margin and no peripheral and deep margins. If applicable, the presence or absence of cartilage invasion should be stated in the report.

3.2 Regional lymphadenectomy specimens

The generalities of macroscopic neck and axillary block dissection, described for head and neck cancer and breast cancer,[13,14] 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 SLNB for Merkel cell carcinoma as a potential indicator for survival, recurrence and prognosis is subject to considerable international debate. This debate is comparable to the use of SLNB in melanoma. AJCC, however, has provided evidence for a prognostic clinical value and accordingly supports its use as primary staging criterion.[2] The role of SLNB in staging has become even more important in TNM 8 and is the criterion for distinguishing pN1a (sn) and pN1a, although this does not change the stage group.

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 be 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 be 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 peripheral margins at selected points should 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 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 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 done 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 European Organisation for Research and Treatment of Cancer (EORTC) melanoma trials, the bread-loaf technique is technically less complex. However, it is acceptable for centres that carry out SLNB for melanoma and use an appropriate alternative method, to use the same technique for Merkel cell carcinoma. SLNB technical methodology is discussed in the RCPath dataset on cutaneous melanoma.[15]

For either method, it is essential that haematoxylin and eosin (H&E) sections are supplemented by the use of at least one marker from the Merkel cell carcinoma immunohistochemistry panel (as described in section 5.3.1). It is essential that the immunohistochemical marker chosen is of proven positivity in the primary tumour. Cytokeratin 20 with paranuclear dot positivity is highly favoured, but this choice is not absolute or exclusive.

To date, there is no evidence base to support the use of 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, the type of specimen and the clinical maximum dimension of the lesion.

Knowledge of clinical nodal status (i.e. clinically occult or detected) is essential to the pathologist for full pN staging and must be conveyed to the pathologist.

[Level of evidence B – Maximum dimension/diameter of the skin lesion is primary staging determinant.]

5.2 Pathological: macroscopic

5.2.1 Skin

The three-dimensional size of the overall specimen and the maximum dimension/diameter of all lesions must be recorded in millimetres.

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

5.2.2 Lymph node

The three-dimensional size of the overall surgical specimen must be recorded in millimetres and localising markers attached by the clinician should be noted. The presence or absence of dye in sentinel lymph nodes must be recorded to support its sentinel node status, and any macroscopic abnormality should be documented.

[Level of evidence – D.]

5.3 Pathological: microscopic

5.3.1 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 to demonstrate neuroendocrine differentiation and positivity correlates with the ultrastructural presence of dense-core neuroendocrine granules and/or aggregates of cytoplasmic intermediate filaments. Neuroendocrine differentiation can usually be shown by one or more of the following neuroendocrine markers: chromogranin, synaptophysin, neurofilament, neuron-specific enolase or CD56. Various antibodies can be used for the filaments including cytokeratin 20, CAM 5.2 or AE1/AE3. Positivity can be variable between antibodies and can be indicated by perinuclear dot-like, cap-like, cytoplasmic granules or cell membrane deposition. 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.[3]

As a minimum, the panel advised should include at least one neuroendocrine marker, cytokeratin 20, AE1/AE3 and/or CAM 5.2, TTF-1, CD45, S100 and Melan A.

Additional positivity is variable and may include cytokeratin 7, CD117, BerEP4, bcl2, CD99, TdT or PAX-5.

Merkel cell carcinoma has the ability to reflect the biological heterogeneity of normal Merkel cells. 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, pathologists 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 immunohistochemistry 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 unavailable in laboratories (owing to EQA and health and safety limitations), although this is still potentially useful for showing neuroendocrine differentiation. The best results are achieved after Bouin fixation.

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

5.3.2 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. It should be noted that UICC TNM 8 states extradermal invasion and AJCC TNM 8 beyond the subcutaneous fat, although both identify fascia as the first pT4 level.

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

5.3.3 In-transit metastasis

The presence of an in-transit metastasis indicates stage N2 or N3, depending on whether lymph node(s) are negative or positive on microscopy.

In-transit metastasis is defined as a 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 satellite/in-transit metastasis based on distance from the primary tumour exists. In contrast to melanoma, there is therefore no satellite/microsatellite classification. AJCC provides no definition of an in-transit metastasis other than that above. 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. AJCC is ambiguous regarding whether a lymphatic vessel must be identified. Accordingly, this is not regarded as absolute.

AJCC 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.

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

5.3.4 Lymphovascular invasion

This is a core item for the COSD[7] and CAP[10] and is generally considered the strongest correlate for sentinel lymph node positivity, recurrence-reduced survival and prognosis.[16] It is an AJCC registry data collection variable. It may correlate with SLNB positivity.

It is defined as extratumoral in location. The presence of lymphovascular invasion can be facilitated by the use of D2-40 immunohistology.

[Level of evidence – C.]

5.3.5 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.

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

5.3.6 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. However, it is well recognised that in a significant number of cases where tumour extends to a margin, there is no residual tumour present on re-excision. This indicates that the term ‘incomplete’ is inappropriate in this situation. Similarly, lesions not at the margin can occasionally recur and therefore may not be completely excised as originally thought.

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 skin cancers, COSD records whether tumour excision margins are involved, clear by more than 5 mm, clear by at or greater than 1 mm but less than or equal to 5 mm, or clear by less than 1 mm.[7] 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 mm 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. 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 involved (0 mm), less than 1 mm, or at and over 1 mm to the nearest millimetre.

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.

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

5.3.7 Maximum dimension/diameter

TNM 8 identifies maximum dimension staging breakpoints for 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.[17]

AJCC states that the maximum dimension should be a clinical measurement on the evidence base available, but permitting a pathological measurement if the clinical one is not available. UICC are not specific on this point other than recommending that the measurement is assessed by physical examination. This dataset also recommends the use of clinical measurement but supports the use of pathological measurement if the clinical type is absent. Indicating the one used for staging is a new dataset item. Preferably, this should be the macroscopic measurement, unless in a particular case use of a macroscopic and/or microscopic one is unavoidable.

[Level of evidence B – Maximum dimension/diameter of the lesion is a primary staging determinant.]

5.3.8 Lymph node involvement

Metastatic Merkel 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.[18,19] On that basis, no lymph node should be reported as negative until at least one immunostain has been performed on the node.[9,11,12] 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 be 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.

To apply pN staging for involved lymphadenectomy specimens, the pathologist needs to know if clinical examination and imaging were negative (so-called clinically occult microscopic disease in the context of completion/elective lymphadenectomy specimens) or if clinical or radiological examination were positive (so-called clinically detected microscopic disease in the context of therapeutic lymphadenectomy specimens). As shown in Appendix A, pT1a (sn) and pT1a represent subcategories with clinically occult nodes that are positive on SLNB or lymphadenectomy, respectively. pT1b represents a subcategory with clinically detected nodes that are confirmed positive on microscopy. 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 and CAP items.[7,10] The number involved and maximum diameter of a metastatic deposit are not staging criteria.

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

5.3.9 Lymph node extranodal extension/invasion and margin status

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

Extranodal extension invasion is regarded by AJCC as a collection variable.[2]

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

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 Non-core clinical items

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

- grade of clinician undertaking procedure
- clinical diagnosis/description
- procedure intention of clinician
- diagnostic/therapeutic biopsy
- measured surgical clinical peripheral margin (millimetres)
- whether this is a recurrent tumour
- previous histology reference number(s)
- whether the patient is immunocompromised; this is one of the most important clinical correlates for both the cause and prognosis of Merkel cell carcinoma
- whether this is a tumour arising in an individual genetically predisposed to cancer
- whether there is clinical and/or imaging evidence of potential nodal involvement.

6.2 Non-core pathological items

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.[16,20,21]

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.[10–12]

6.2.1 Skin

Thickness/depth

In some series, thickness/depth 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.[16] In occasional series, there appeared to be no correlation between thickness/depth and prognosis.

This is regarded by AJCC as a site-specific collection variable.[2]

It is recommended that thickness/depth be measured in millimetres, although no standardised international guidance is available on how this should be undertaken. In the interim, despite its recognised limitations, the RCPath recommend adopting the method used for other types of NMSC, rather than Breslow thickness for melanoma.[15,22]

Mitotic index

A mitotic count of more than ten mitoses per single high power field has been shown to correlate with large tumour size and poor prognosis.[11,12] Unfortunately, the reports do not specify how 'high power' is defined. Accordingly, it is recommended that mitotic index be measured per mm^2, using the standardised method defined for cutaneous melanoma in the College's melanoma datasets.[15] It is acknowledged, however, that this may be difficult to undertake in practice, owing 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.[11,12]

Level of invasion

Section 5.3.2 states that invasion beyond the subcutaneous fat (i.e. at least fascia) is a primary determinant for pT4.

There is evidence that extension into the subcutaneous fat results in a worse prognosis compared with being limited to the dermis.[16]

It is recommended that the level of invasion, when not extending beyond the subcutaneous fat, be provided and if necessary using 'Clark' levels as summarised in the College's cutaneous melanoma dataset.

Histological growth pattern

AJCC regards histological growth pattern as a site-specific collection variable.[2] There is some evidence that a nodular growth pattern correlates with better survival rates.[16] 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.

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, dyscohesive cells, and the trabecular variant has columns two to three cells thick and possible spindling. The prognostic significance of the subtypes is currently uncertain, although the small cell type may have some survival disadvantage.[20]

Tumour-infiltrating lymphocytes
These are regarded by AJCC as a site-specific collection variable.[2] There is evidence that the presence of tumour-infiltrating lymphocytes (TILs) may portend a worse prognosis.[16] By contrast, increased stromal CD8 lymphocytes may have a better prognosis. To achieve standardisation, it is recommended that TILs are assessed using the method defined for cutaneous melanoma in the College's melanoma datasets.[15]

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 datasets.[15]

Lymphovascular invasion
Record whether this is intratumoral in location. Section 5.3.4 records extratumoral lymphovascular invasion. Histochemistry or immunohistochemistry can be used to facilitate the identification of lymphovascular invasion.

6.2.2 Lymph nodes

Maximum tumour dimension/diameter
Diameter of largest deposit is regarded by AJCC as a site-specific collection variable.[2] To date, however, this has no proven staging importance. It is recommended that the largest deposit be measured using the method defined for nodal melanoma in the College's melanoma dataset.[15]

CAP also supports this approach. This includes both sentinel nodes or a lymphadenectomy specimen.

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

Merkel cell polyoma virus (tissue)
Record as present or absent and note 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 of 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 polyoma virus (MCPyV) is limited by being positive in only approximately 80% of cases. Merkel cell carcinoma that is positive for MCPyV tends to have a better prognosis. MCPyV is rarely present in Merkel cell carcinoma combined with a second cutaneous malignancy. MCPyV-negative tumours may have a greater association with a UV light aetiology.

It has been suggested that the malignant cells in the skin of MCPyV-negative cases have more irregular nuclei and more cytoplasm, whereas the nuclei of MCPyV-positive cases are rounder, with less cytoplasm.

Merkel cell carcinoma on the limbs shows a greater frequency of MCPyV positivity compared with the head and neck and, accordingly, indicates a better prognosis.

The role of this virus has been reviewed.[21]

7 Diagnostic staging and coding

TNM and SNOMED are required for the COSD.[8]

7.1 pTNM stage and stage groups

By TNM convention, TNM/cTNM (c meaning clinical) refers to staging a primary tumour that has not been previously treated. Clinical staging can therefore incorporate some pathological diagnostic information, but the T category is still referred to as T and not pT. Similarly, by convention, pTNM (p meaning pathological) refers to staging after surgical treatment. The pathological information for pTNM is designated pT, pN and pM with reference to the three component TNM categories.

pTNM stage/stage group for skin cancer must be recorded according to UICC and not AJCC TNM 8.[1]

pTNM staging/stage grouping must be deferred until all TNM information is available and if appropriate, during or after skin cancer MDT discussion.

A pTNM stage/stage group can be added to a histopathology report as a non-core item, but the report should indicate that this is the minimum stage based on the information in the report.

The pTNM stage categories are conveniently condensed into five stage groups:

- stage 0: in situ
- stage I: localised disease
- stage II: more extensive localised disease
- stage III: regional nodal disease
- stage IV: metastasis.

Although pTNM classically refers to the anatomic extent of disease, more recently this has, at times, incorporated additional non-anatomic prognostic information, giving rise to so-called prognostic groups (UICC) or prognostic stage groups (AJCC).

pTNM stage is based on three anatomical categories: pT (Tumour), pN (Node), M or pM (Metastasis).

- pT – Primary tumour
  - pTx: Primary tumour cannot be assessed
  - pTis: Carcinoma – in situ
  - pT has multiple subcategories, i.e. pT0, pT1, pT2, pT3, pT4
- pN – Regional lymph nodes

- pN has multiple subcategories, i.e. pN0, pN1, pN2, pN3
- for melanoma and Merkel cell carcinoma, isolated tumour cells are defined as N1

- M – Distant metastasis
  - M/pM (if confirmed histopathologically) has two categories, i.e. M0, M1/pM1
  - it should be noted that there is no MX nor pM0
- Additional descriptors can be used:
  - the suffix ‘m’ indicates the presence of multiple synchronous primary tumours in a single organ (i.e. skin) within four months of diagnosis and is recorded in parentheses, e.g. pT1 (m). The highest T category should be used. Over four months they are regarded as new metachronous tumours and staged separately.
  - the suffix 'sn' indicates a SNLB and is shown in parentheses, e.g. pN1 (sn)
  - the prefix 'r' indicates a recurrent tumour with a disease-free interval or disease that has progressed with no interval. This can be designated ‘rp’ if based on pathological information.
  - the TNM R classification for residual tumour is not used as margin status; information is provided in more detail elsewhere in the dataset.

Full details are available 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.

It is noted, however, that SNOMED is now in a practical transition phase, as part of the intended full implementation by the NHS and PHE of SNOMED CT. SNOMED ceased to be licensed by the International Health Terminology Standards Development Organisation from 26 April 2017.

A list of applicable T and M SNOMED and SNOMED CT codes is provided in Appendix B. Mapping SNOMED CT terminology is provided.

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

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.[4,8]

This NICE recommendation relates primarily to inguinal and axillary SNLB and lymph node dissections for skin cancer. Head and neck SNLB 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. However, lymph node dissection of the head and neck and associated reporting must only be undertaken by those with appropriate skills and competence. This is primarily demonstrated by regular practice in the field and participating in an appropriate EQA scheme. 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 RCPath's neck dissection cancer datasets.[13]

11.2 Skin cancer MDT referral

All cases of Merkel cell carcinoma must be referred for specialist skin cancer MDT review.[4] 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 of recording 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 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 one to four 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 be

sampled completely. Specimens over 10 mm can be sampled pragmatically according to the nature of the original margin involvement.

12 Criteria for audit

As recommended by the RCPath as key performance indicators (see *Key Performance Indicators – Proposals for implementation*, July 2013, on http://www.rcpath.org/profession/quality-improvement/kpis-for-laboratory-services.html):

- 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 were required to implement the structured recording of core pathology data in the COSD by January 2016 and to update their systems in line with subsequent COSD updates.
  - standard: 95% of reports must contain structured data
- histopathology cases must be reported, confirmed and authorised within seven to 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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To the late A Bernard Ackerman MD for his infectious enthusiasm for dermatopathology and for facilitating intellectual thought in debating the necessity for, and content of, datasets/checklists.

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Appendix A UICC TNM 8 pathological staging of cutaneous Merkel cell carcinoma, regional lymph nodes and metastasis

Includes:
- vulva
- penis
- hair-bearing lip
- hair-bearing perianal skin.

Excludes:
- eyelid (should be staged as UICC TNM 8 eyelid carcinoma).

The clinico-pathological implications of TNM 8 for skin cancer have been jointly reviewed by the BAD and RCPath.[23]

Definitions of TNM

Primary tumour (pT)

pTX	Primary tumour cannot be assessed (e.g. curetted and no clinical dimension recorded)
pT0	No evidence of primary tumour (e.g. nodal/metastatic presentation without associated primary)
pTis	In situ primary tumour
pT1	≤20 mm maximum clinical dimension of tumour
pT2	>20 mm to ≤50 mm maximum clinical dimension of tumour
pT3	>50 mm maximum clinical dimension of tumour
pT4	Primary tumour invades fascia, muscle, bone or cartilage (i.e. beyond subcutaneous fat).

NB: Pathological maximum dimension acceptable if clinical dimension not available.

Comment: UICC TNM 8 state pT is identical to T.

Regional lymph nodes (pN)

pNX	Regional lymph nodes cannot be assessed, e.g. previously removed for another reason
pN0	Regional lymph nodes negative by pathological examination
pN1	Regional lymph node(s) positive (i.e. metastasis) by pathological examination
pN1a (sn)	Clinically occult but regional lymph node(s) positive by SLNB (microscopic metastasis)
pN1a	Clinically occult but regional lymph node(s) positive by lymphadenectomy (microscopic metastasis)
pN1b	Clinically detected regional lymph node(s) positive (macroscopic metastasis)
pN2	In-transit metastasis without lymph node metastasis
pN3	In-transit metastasis with lymph node metastasis

NB: Clinical detection of nodal disease is via inspection, palpation and/or imaging. pN1 subdivisions require clinical information that may not be available at the time of reporting. In this eventuality, the parent category pN1 should be used.

In-transit metastasis: a tumour distinct from the primary lesion and located either between the primary lesion and the draining regional lymph nodes, or distal to the primary lesion.
Isolated tumour cells are defined as pN1. The TNM designation for SLNB is (sn).

Distant metastasis (M)

M0	No distant metastases
pM1	Metastasis beyond regional lymph nodes
pM1a	Metastasis to distant skin, subcutaneous tissues or distant lymph nodes confirmed microscopically
pM1b	Metastases to lung confirmed microscopically
pM1c	Metastasis to other visceral sites confirmed microscopically

NB: MX and pM0 do not exist.

pTNM stage group

Stage	**T**	**N**	**M**
Stage 0	Tis	N0	M0
Stage I	T1	N0	M0
Stage IIA	T2, T3	N0	M0
Stage IIB	T4	N0	M0
Stage IIIA	T0	N1b	M0
	T1, T2, T3, T4	N1a(sn), N1a	M0
Stage IIIb	T1, T2, T3, T4	N1b, N2, N3	M0
Stage IV	T0, T1, T2, T3, T4	Any N	M1

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 PHE Skin Site-Specific Reference Group and kindly provided for RCPath dataset information by PHE. Permission for use should be sought from the PHE. This histopathology request form has been approved by the BAD; the mode of national implementation is under consultation. This could be useful to ensure that the maximum clinical dimension of a lesion is always recorded.

The UK National Histopathology Request form for skin biopsies

Date of surgical procedure

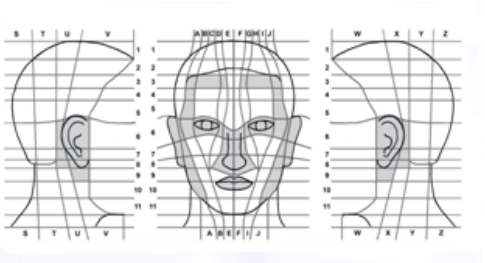
Please attach patient details

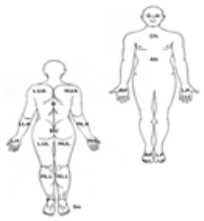
Name of surgeon

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 procedure……..	Date of receipt……..……..	Date of reporting……...
Pathologist…….……	Surgeon…….……	Report no …….

Clinical data

Clinical site: …….

Maximum clinical dimension/diameter†.....mm

Specimen type†:

Not stated □

Incision	Diagnostic □				
Excision	Diagnostic □	Therapeutic □	Uncertain □	Re-excision □	Wider local excision □
Punch	Diagnostic □	Therapeutic □	Uncertain □		
Curettings	Diagnostic □	Therapeutic □	Uncertain □		
Shave	Diagnostic □	Therapeutic □	Uncertain □		
Other	□	Specify ….....			

Macroscopic description

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

Maximum dimension/diameter of lesion†: ……mm Uncertain □ No lesion seen □

Histological data

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

*Indicate positive(s): neuron-specific enolase □ chromogranin □ synaptophysin □ neurofilament protein □ CD56 □

Invasion: Not identified □ (i.e. only in-situ/intra-epidermal disease) Present □

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

Not identified □ Present □ (**pT4**) Uncertain □ Cannot be assessed □

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:

Not identified □ Present □

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 dimension/diameter of lesion

Indicate measurement used:

Clinical (use if provided) □ OR Macroscopic □ OR Microscopic □

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

---

pTNM† **pT ……. (UICC TNM 8)**

SNOMED codes†**……**

Comments

Pathologist…… **Date……..**

†Data items that are part of the Cancer Outcomes and Services Dataset (COSD) version 8.

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 procedure……..	Date of receipt……..……..	Date of reporting……...
Pathologist…….……	Surgeon…….……	Report no …….

Clinical details

Site	Inguinal ……..	Axillary……..	Other ……
Localisation	Ipsilateral □	Contralateral □	

Clinical nodal status	Clinically occult	(SLNB/completion lymphadenectomy)	□ or
	Clinically detected	(therapeutic lymphadenectomy)	□ or
	Clinical status unknown		□

Macroscopic description

Sentinel lymph node biopsy (for each node)

Dimensions of specimen …… mm x .....mm x .....mm

Macroscopic abnormality present: Not identified □ Yes □ If yes: maximum dimension.....mm Uncertain □

Dye seen in tissue: Not identified □ Yes □

Localising marker: Not identified □ Yes □ If yes: details.....

Lymphadenectomy

Dimensions of specimen …….mm x .....mm x .....mm

Macroscopic abnormality present: Not identified□ Yes □ If yes: maximum dimension.....mm Uncertain □

Localising marker: Not identified □ Yes □ If yes: details.....

Microscopic data

Sentinel lymph node biopsy

Number of sentinel nodes identified† ……

Number of sentinel nodes positive† ……

If positive: extranodal extension No □ Yes □ Uncertain □ Cannot be assessed □

Lymphadenectomy

Number of nodes identified†	…..…			
Number of nodes positive†	…..…			
Highest/most apical node involved:	No □	Yes □	Not identified □	
Extranodal/capsular extension	No □	Yes □	Uncertain □	
Margin of specimen	Involved □	Not involved □	Uncertain □	Not applicable □

pTNM† pN……. (UICC TNM 8)

SNOMED codes†……

Comments

Pathologist…….. Date……

Notes:

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'.

†Data items that are part of the Cancer Outcomes and Services Dataset (COSD) version 8.

Appendix E1 Reporting proforma for cutaneous Merkel cell carcinoma in list format

Element name	Values	Implementation comments
Clinical site	Free text	
Maximum clinical dimension	Size in mm	
Specimen type	Single selection value list: • Not stated • Incision, Diagnostic • Excision, Diagnostic • Excision, Therapeutic • Excision, Uncertain • Re-excision • Wider local excision • Punch, Diagnostic • Punch, Therapeutic • Punch, Uncertain • Curettings, Diagnostic • Curettings, Therapeutic • Curettings, Uncertain • Shave, Diagnostic • Shave, Therapeutic • Shave, Uncertain • Other	
Specimen type, Other, Specify	Free text	Only applicable if 'Specimen type, Other' is selected.
Dimension of specimen, Length	Size in mm	
Dimension of specimen, Breadth	Size in mm	
Dimension of specimen, Depth	Size in mm	
Dimensions of lesion	Size in mm	
Lesion dimension not given, reason	Single selection value list: • Uncertain • No lesion seen • Not applicable	Not applicable if value given for 'Dimensions of lesion'.
Immunohistochemistry, Neuroendocrine marker	Single selection value list: • Positive • Negative	

	• Not tested	
Immunohistochemistry, Cytokeratin 20	Single selection value list: • Positive • Negative • Not tested	
Immunohistochemistry, AE1/AE3	Single selection value list: • Positive • Negative • Not tested	
Immunohistochemistry, CAM 5.2	Single selection value list: • Positive • Negative • Not tested	
Immunohistochemistry, TTF-1	Single selection value list: • Positive • Negative • Not tested	
Immunohistochemistry, CD45	Single selection value list: • Positive • Negative • Not tested	
Immunohistochemistry, S100	Single selection value list: • Positive • Negative • Not tested	
Immunohistochemistry, Melan-A	Single selection value list: • Positive • Negative • Not tested	
Invasive component	Single selection value list: • Not identified (in situ) • Present	
Level of invasion beyond subcutaneous fat	Single selection value list: • Not identified • Present • Uncertain • Cannot be assessed	Not applicable if 'Invasive component, Not identified' is selected.

	• Not applicable	
Level of invasion beyond subcutaneous fat, Specify	Multiple selection value list: • Fascia • Muscle • Perichondrium • Cartilage • Paratendon • Tendon • Periosteum • Bone • Not applicable	Only applicable if 'Level of invasion beyond subcutaneous fat, Present' is selected.
In-transit metastasis	Single value selection list: • Not identified • Present • Uncertain • Cannot be assessed	
Lymphovascular invasion (extratumoral)	Single value selection list: • Not identified • Present • Uncertain • Cannot be assessed	
Presence of second malignancy with MCC in skin	Single value selection list: • Not identified • Present	
Presence of second malignancy with MCC in skin, specify	Free text	Only applicable if 'Presence of second malignancy with MCC in skin, Present' is selected.
Margins, Peripheral	Single selection value list: • Involved • Not involved but <1 mm • Not involved ≥1 mm • Uncertain • Not applicable	
Margins, Peripheral, distance	Size in mm	Only applicable if 'Margins, Peripheral, Not involved ≥1 mm' is selected.
Margins, Deep	Single selection value list: • Involved	

	• Not involved but <1 mm • Not involved ≥1 mm • Uncertain • Not applicable	
Margins, Deep, distance	Size in mm	Only applicable if 'Margins, Deep, Not involved ≥1 mm' is selected.
Basis of diameter measurement	Single selection value list: • Clinical • Macroscopic • Microscopic	
Dimension	Single selection value list: • ≤20 mm • >20 – ≤50 mm • >50 mm • Uncertain • Cannot be assessed	
pT category	Single selection value list: • X • 0 • is • 1 • 2 • 3 • 4	
TNM version	UICC8	UICC8 automatically selected.
SNOMED codes	May have multiple codes. Look up from SNOMED tables.	

Appendix E2 Reporting proforma for regional lymph nodes associated with Merkel cell carcinoma in list format

Element name	Values	Implementation comments
Anatomical site	Single selection value list: • Inguinal • Axillary • Other	
Anatomical site, Other	Free text	Only applicable if 'Anatomical site, Other' is selected.
Localisation	Single selection value list: • Ipsilateral • Contralateral	
Clinical nodal status	Single selection value list: • Clinically occult • Clinically detected • Clinical status unknown	
Specimen type	Single selection value list: • Sentinel lymph node biopsy • Completion lymphadenectomy • Lymphadenectomy	
LN[*n*] Dimension of specimen, dimension 1	Size in mm	Repeating data item – repeat *n* for each in 'Number of sentinel nodes identified' if 'Specimen type, Sentinel lymph node biopsy' is selected. Otherwise n=1 only.
LN[*n*] Dimension of specimen, dimension 2	Size in mm	Repeating data item – repeat *n* for each in 'Number of sentinel nodes identified' if 'Specimen type, Sentinel lymph node biopsy' is selected. Otherwise n=1 only.
LN[*n*] Dimension of specimen, dimension 3	Size in mm	Repeating data item – repeat *n* for each in 'Number of sentinel nodes identified' if 'Specimen type, Sentinel lymph node biopsy' is selected. Otherwise n=1 only.
LN[*n*] Macroscopic abnormality present	Single selection value list: • Not identified • Yes • Uncertain	Repeating data item – repeat *n* for each in 'Number of sentinel nodes identified' if 'Specimen type, Sentinel lymph node biopsy' selected. Otherwise n=1 only.

LN[*n*] Maximum dimension of macroscopic abnormality	Size in mm	Only applicable if LN[*n*] 'Macroscopic abnormality present, Yes' is selected. Repeating data item – repeat *n* for each in 'Number of sentinel nodes identified' if 'Specimen type, Sentinel lymph node biopsy' is selected. Otherwise n=1 only.
LN[*n*] Dye seen in tissue	Single selection value list: • Not identified • Yes	Only applicable if 'Specimen type, Sentinel lymph node biopsy' is selected. Repeating data item – repeat *n* for each in 'Number of sentinel nodes identified'.
LN[*n*] Localising marker	Single selection value list: • Not identified • Yes	Repeating data item – repeat *n* for each in 'Number of sentinel nodes identified' if 'Specimen type, Sentinel lymph node biopsy' is selected. Otherwise n=1 only.
LN[*n*] Localisation marker, details	Free text	Only applicable if 'LN[*n*] Localising marker, Yes' is selected. Repeating data item – repeat *n* for each in 'Number of sentinel nodes identified' if 'Specimen type, Sentinel lymph node biopsy' is selected. Otherwise n=1 only.
Number of sentinel nodes identified	Integer	Only applicable if 'Specimen type, Sentinel lymph node biopsy' is selected.
Number of sentinel nodes positive	Integer	Only applicable if 'Specimen type, Sentinel lymph node biopsy' is selected.
Extranodal extension	Single value selection list: • No • Yes • Uncertain • Cannot be assessed	Only applicable if 'Number of sentinel nodes positive' >0.
Number of nodes identified	Integer	Only applicable if 'Specimen type, Lymphadenectomy' is selected.
Number of nodes positive	Integer	Only applicable if 'Specimen type, Lymphadenectomy' is selected.
Highest/most apical node involved	Single value selection list: • No • Yes	Only applicable if 'Specimen type, Lymphadenectomy' is selected.

	• Not identified • Not applicable	
Extranodal/capsular extension	Single value selection list: • No • Yes • Uncertain • Not applicable	Only applicable if ‘Specimen type, Lymphadenectomy’ is selected and ‘Number of nodes identified’ >0.
Margin of specimen	Single selection value list: • Involved • Not involved • Uncertain • Not applicable	Only applicable if ‘Specimen type, Lymphadenectomy’ is selected and ‘Number of nodes identified’ >0.
pN category	Single selection value list: • X • 0 • 1a (sn) • 1a • 1b • 1c • 2 • 3	
TNM version	UICC8	UICC8 automatically selected.
SNOMED codes	May have multiple codes. Look up from SNOMED tables.	

Appendix F 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 G AGREE II compliance monitoring sheet

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

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