Merkel Cell Carcinoma
Histopathology Reporting Guide

Family/Last name

Given name(s)

Date of birth DD – MM – YYYY

Patient identifiers

Date of request DD – MM – YYYY

Accession/Laboratory number

Elements in **black text** are CORE. Elements in **grey text** are NON-CORE.
☐ indicates multi-select values ◯ indicates single select values

SCOPE OF THIS DATASET

SPECIMEN(S) SUBMITTED (select all that apply)

- ☐ Skin
- ☐ Lymph node(s), *specify sentinel lymph node if known/ applicable*
- ☐ Other, *specify*

PROCEDURE (select all that apply) (Note 1)

- ◯ Not specified
- ☐ Excision (or resection)
- ☐ Biopsy, *specify type of biopsy if possible (e.g., curettage, shave, punch, elliptical)*

ANATOMIC SITE

- ◯ Not specified
- ◯ *Specify site*

If applicable also indicate
- ◯ Left
- ◯ Right
- ◯ Midline

MACROSCOPIC PRIMARY LESION DESCRIPTION (Note 2)

TUMOUR SIZE (Note 3)

Maximum tumour diameter (clinical measurement) mm

Maximum tumour diameter (macroscopic measurement) mm

Maximum diameter of primary tumour (microscopic measurement) mm

◯ Cannot be determined *(e.g., no clinical information provided or submitted slide likely not representative)*

EXTENT OF INVASION (select all that apply) (Note 4)

- ◯ Cannot be assessed
- ◯ Invasion not identified (i.e., only in situ/intra-epithelial neoplastic proliferation)
- ☐ Tumour invades dermis
- ☐ Tumour invades subcutis
- ☐ Tumour invades into skeletal muscle
- ☐ Tumour invades into bone
- ☐ Tumour invades cartilage
- ☐ Other, *specify*

TUMOUR THICKNESS (Note 5)

- ◯ Indeterminate

Measured thickness mm

OR

mm at least

LYMPHOVASCULAR INVASION (Note 6)

- ◯ Not identified
- ◯ Indeterminate
- ◯ Present, *specify if immunohistochemistry is used*

TUMOUR-INFILTRATING LYMPHOCYTES (Note 7)

- ◯ Not identified
- ◯ Brisk
- ◯ Non-brisk

LOCOREGIONAL[a] CUTANEOUS METASTASES (Note 8)

- ◯ Not identified
- ◯ Indeterminate
- ◯ Present

[a] *Satellite or in-transit cutaneous metastasis.*

MERKEL CELL POLYOMA VIRUS (MCPV) (Note 9)

- ◯ Testing for MCPV not performed (or results not known)
- ◯ Testing for MCPV performed, *specify method(s) and result(s)*

MORPHOLOGICAL DIVERSITY (Note 10)

- ◯ Not identified
- ◯ Present - squamous, *specify second phenotypic element*

  ▼
  [ ]
- ◯ Present - other (non-squamous), *specify second phenotypic element*

  ▼
  [ ]

MARGIN/TISSUE EDGES STATUS (Note 11)

Peripheral margin

- ◯ Cannot be assessed
- ◯ Not involved by carcinoma

  ▼
  Distance from margin ◯ <1 mm

  OR

  [ ] mm to nearest 1 mm

  Location, *specify if possible*
  [ ]
- ◯ Involved by carcinoma

  ▼
  Location, *specify if possible*
  [ ]

Deep margin

- ◯ Cannot be assessed
- ◯ Not involved by carcinoma

  ▼
  Distance from margin ◯ <1 mm

  OR

  [ ] mm to nearest 1 mm

  Location, *specify if possible*
  [ ]
- ◯ Involved by carcinoma

  ▼
  Location, *specify if possible*
  [ ]

LYMPH NODE STATUS (Note 12)

- ◯ No nodes submitted or found

OR

Sentinel nodes

Number of sentinel lymph nodes examined [ ]
- ◯ Number cannot be determined

Number of positive sentinel lymph nodes [ ]
- ◯ Number cannot be determined

Extranodal extension[b]
- ◯ Not identified
- ◯ Present
- ◯ Indeterminate

Maximum dimension of largest metastasis in sentinel node[b] [ ] mm

Location of largest sentinel node metastasis,[b] *specify (e.g., subcapsular, parenchymal, both subcapsular and parenchymal)*
[ ]

Non-sentinel lymph nodes (clinically negative)

Number of non-sentinel lymph nodes examined [ ]
- ◯ Number cannot be determined

Number of positive non-sentinel lymph nodes [ ]
- ◯ Number cannot be determined

Extranodal extension[b]
- ◯ Not identified
- ◯ Present
- ◯ Indeterminate

Maximum dimension of largest metastasis in regional node[b] [ ] mm

Clinically apparent lymph nodes

Number of lymph nodes examined [ ]
- ◯ Number cannot be determined

Number of positive lymph nodes [ ]
- ◯ Number cannot be determined

Extranodal extension[b]
- ◯ Not identified
- ◯ Present
- ◯ Indeterminate

Maximum dimension of largest metastasis in regional node[b] [ ] mm

[b] *Required only in the presence of positive nodes.*

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IMMUNOHISTOCHEMISTRY (Note 13)

◯ Not performed, *explain reasons*

◯ Performed, *specify*

PATHOLOGICAL STAGING (UICC TNM 8th edition)[c] (Note 14)

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

☐ m - multiple primary tumours
☐ r - recurrent
☐ y - post-therapy

Primary tumour (pT)

◯ TX Primary tumour cannot be assessed
◯ T0 No evidence of primary tumour
◯ Tis Carcinoma in situ
◯ T1 Tumour 2 cm or less in greatest dimension
◯ T2 Tumour more than 2 cm but not more than 5 cm in greatest dimension
◯ T3 Tumour more than 5 cm in greatest dimension
◯ T4 Tumour invades deep extradermal structures, i.e., cartilage, skeletal muscle, fascia or bone

Regional lymph nodes (pN)

◯ No nodes submitted or found
◯ NX Regional lymph nodes cannot be assessed
◯ N0 No regional lymph node metastasis
◯ N1 Regional lymph node metastasis
◯ N2 In-transit metastasis *without* lymph node metastasis
◯ N3 In-transit metastasis *with* lymph node metastasis

[c] *Reproduced with permission. Source: UICC TNM Classification of Malignant Tumours, 8th Edition, eds by James D. Brierley, Mary K. Gospodarowicz, Christian Wittekind. 2016, Publisher Wiley Blackwell.*

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Definitions

CORE elements

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

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

NON-CORE elements

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

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

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Scope

The dataset has been developed for the reporting of the pathologic findings of primary cutaneous Merkel cell carcinoma (MCC) in excision (resection) specimens containing tumour. It does not apply to partial superficial biopsies or re-excisions with no residual primary tumour. It also does not apply to cytology specimens. For small partial biopsies and cytology specimens, reporting the tumour diagnosis per se is usually sufficient. If there is no residual tumour seen in a re-excision, it suffices to say so. The features of the tumour seen in prior biopsies or excisions do not need to be repeated. In situations in which an initial partial (incisional or excisional) biopsy contains a substantial amount of tumour, completion of the data set may require synthesizing the findings of both the biopsy and subsequent excision with residual tumour.

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Note 1 – Procedure (Core)

Reporting expectations vary depending on procedure type. The full set of staging features can only be captured by an excision with primary tumour.

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Note 2 – Macroscopic primary lesion description (Non-core)

The macroscopic description provides valuable information on the dimensions of the resected tissue and the size of the tumour. On rare occasions it may also help document the presence of a satellite. It is also helpful for assessing the margin status.

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Note 3 – Tumour size (Core)

Tumour diameter is a staging parameter.[2,3]

Tumour diameter has historically been determined by clinical measurements. If that measurement is available, it should be reported as such. If clinical tumour diameter is unavailable, macroscopic and/or microscopic measurements should be used (largest diameter of tumour).

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Note 4 – Extent of invasion (Core)

Relevant to document extent of disease and for staging (invasion of bone, muscle, fascia or cartilage constitutes pT4; except for superficial facial muscle involvement).[2,3]

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Note 5 – Tumour thickness (Non-core)

Tumour thickness is a reproducible/measurable parameter of potential prognostic significance.[4]

When possible, if the specimen includes epidermis and dermis, tumour thickness is to be measured according to the method of Breslow and quantified in millimetres (mm) (rounded to the nearest 0.1 mm).

When a substantial amount of tumour was removed by a prior procedure, the final report of residual tumour should include a combined tumour measurement taking the findings from both procedures into account.

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Note 6 – Lymphovascular invasion (Core)

Lymphovascular invasion (LVI) is prognostically relevant.[5]

When lymphatic invasion is suspected, but not unequivocal on H&E, the use of immunohistochemistry (e.g., D2-40) is recommended for final determination on the presence or absence of LVI.

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Note 7 – Tumour-infiltrating lymphocytes (Non-core)

Potentially prognostically significant, if further stratified by immunophenotypic findings. Details on the immunophenotype of the tumour microenvironment may also be predictive of response to checkpoint blockade inhibitors. However, currently it is not practical to perform such studies routinely.[6-8]

If tumour-infiltrating lymphocytes (TILS) are reported, we suggest to do so in analogy to melanoma for reasons of familiarity and reproducibility.

TILs not identified: No lymphocytes present, or lymphocytes present but do not infiltrate tumour at all.

TILs non-brisk: Lymphocytes infiltrate tumour only focally or not along the entire base of the vertical growth phase.

TILs brisk: Lymphocytes diffusely infiltrate the entire base of the dermal tumour (Figure 1a) or the entire invasive component of the tumour (Figure 1b).

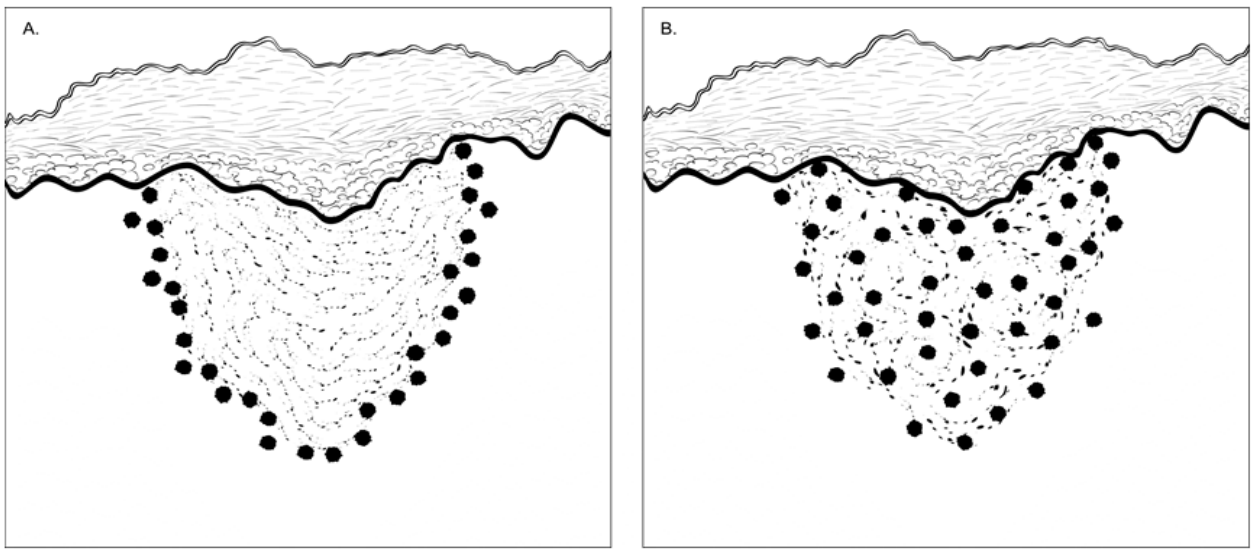

Figure 1. Brisk tumour-infiltrating lymphocytes. a. Lymphocytes diffusely infiltrate the entire base of the invasive tumour; **b.** Lymphocytes infiltrate the entire invasive component of the carcinoma.
Source: Smoller BR, Gershenwald JE, Scolyer RA et al. Protocol for the Examination of Specimens From Patients With Melanoma of the Skin, 2017. Available at www.cap.org/cancerprotocols. Reproduced with permission.

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Note 8 – Locoregional cutaneous metastases (Core)

The presence of an in-transit metastasis indicates stage N2.[2,3]

Locoregional cutaneous metastases are metastatic tumour deposits affecting the anatomic region located between the primary tumour and regional lymph node basin. They may be detected clinically or only after microscopic examination. The metastatic deposits may involve the dermis, subcutis or skeletal muscle. In analogy to melanoma, metastases have historically been designated as *microscopic satellite*, *satellite* or *in-transit* lesions. *Satellites* have been defined as metastases occurring within an arbitrarily chosen radius of less than 2 cm of the primary tumour. The term *microscopic satellite* has been used for metastases adjacent to the primary tumour detected upon microscopic examination. Metastatic lesions detected outside a radius of 2 cm are described as *in-transit* metastases. Since there is no apparent prognostic difference between these arbitrary subtypes of metastases, they are grouped together herein as locoregional cutaneous metastases. Diagnostic problems can sometimes occur. An in-transit lesion may be confused with a second primary MCC. A microscopic satellite lesion may be confused with part of the primary tumour that was artifactually separated from the mother lesion by surgery or regression. Thus, for a suspected microscopic satellite to be accepted as bonafide metastasis it must be clearly separated from the main tumour by intervening normal tissue devoid of evidence of prior surgery or regression to avoid overdiagnosis.

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Note 9 – Merkel cell polyoma virus (MCPV) (Core)

The presence or absence of Merkel cell polyoma virus (MCPV) segregates MCC into those of viral pathogenesis (the majority) and those due to UV-mediated genetic damage (the minority).[9] These tumour subsets differ from one another genetically,[9,10] immunohistochemically[11] and biologically.[12] Merkel cell polyoma virus-negative tumours are more aggressive, hence this factor is of prognostic importance.[12] Immunohistochemistry, employing the CM2B4 antibody, is recommended as a reliable method of viral detection.[12]

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Note 10 – Morphological diversity (Core)

Most MCCs exhibit a pure small cell/neuroendocrine phenotype but a minority display morphological diversity. The latter, termed combined MCC, are usually characterized by admixed neuroendocrine and squamous elements, identifiable on routine microscopy (e.g., MCC intimately associated with Bowen's disease or invasive squamous cell carcinoma, or focal squamous differentiation in a MCC). Combined MCCs are uniformly Merkel cell polyoma virus-negative[13-15] and thus belong in an adverse prognostic category.[12]

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Note 11 – Margin/Tissue edges status (Core)

As a core dataset item for all cancers, Cancer Outcomes and Services Dataset (COSD)[16] 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. Skin cancer margins should therefore be measured in relation to both 1 mm and 5 mm breakpoints.

Guidelines on the surgical margins recommended for MCC 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.

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Note 12 – Lymph node status[17] (Core and Non-core)

Metastatic MCC to lymph nodes is usually readily identified, but the detection of rare tumour cells may on occasion be difficult in routine H&E-stained sections. The use of immunohistochemistry (IHC) has been shown to increase the sensitivity of identifying occult lymph node metastases. 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 IHC. If the primary tumour is known to express CK20, one immunostain for CK20 per lymph node tissue block is sufficient. If the immunophenotype of the primary tumour is not known, one may apply two immunostains (e.g., CK20 and NF1 or CK20 and Cam5.2) to reduce the risk of false-negatives. If the primary tumour is known to be negative for CK20, the stain is to be used for which the primary tumour is most strongly and diffusely positive (e.g., Cam5.2, AE1:AE3, INSM1 and CM2B4).

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). 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.[16]

The number involved and maximum diameter of a metastatic deposit are not staging criteria. *Lymph node involvement is the principal nodal staging determinant.*

<u>Lymph node extracapsular invasion and margin status</u>

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 American Joint Commission on Cancer (AJCC) as a site-specific prognostic factor.[2]

Adjuvant radiotherapy is considered in the presence of extracapsular invasion.

Extracapsular invasion is present when tumour cells are seen outside the lymph node capsule, typically in perinodal adipose tissue, in contiguity with intranodal disease (e.g., not related to contamination of

perinodal tissue with tumour cells during processing of the tissue specimen in the pathology laboratory). Matted nodes (defined as two or more nodes adherent to one another through involvement by metastatic disease, identified at the time the specimen is examined macroscopically in the pathology laboratory) often suggest the presence of extranodal extension but the latter must be confirmed microscopically.

A) Diameter of largest deposit is regarded by AJCC as a site-specific prognostic factor.[18] To date, however, this has no proven staging importance, and the reproducibility of assessing this parameter is not known. It is recommended that guidelines provided for the measurement of sentinel node tumour burden in the AJCC Melanoma Staging System be use.[18] The single largest maximum dimension (measured in millimetres to the nearest 0.1 mm using an ocular micrometer) of the largest discrete metastatic MCC deposit in sentinel nodes should be measured and recorded. To be considered a discrete deposit, the tumour cells must be in direct continuity with adjacent tumour cells. In some instances, multiple small tumour aggregates may be disbursed within a lymph node and separated by lymphoid cells. In this circumstance, the size of the largest discrete single deposit (not the nodal area over which the multiple deposits are contained) should be recorded. In addition, a descriptive comment on the distribution of tumour cells would also be appropriate. The measurement may be made either on H&E-stained sections or on sections stained immunohistochemically.

B) Extranodal extension is defined as the presence of a nodal metastasis extending through the lymph node capsule and into adjacent tissue, which may be apparent macroscopically but must be confirmed microscopically.[19] Matted nodes (defined as two or more nodes adherent to one another through involvement by metastatic disease, identified at the time the specimen is examined macroscopically in the pathology laboratory) often suggest the presence of extranodal extension, but the latter must be confirmed microscopically.

C) Clinically apparent lymph nodes are defined as those detected on palpation (clinical examination) or on radiological investigations.

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Note 13 – Immunohistochemistry (Non-core)

The use of IHC is recommended to confirm the diagnosis of MCC. It is invaluable, whenever the clinical and histopathologic findings are such that other tumours need to be considered in the differential diagnosis (e.g., lymphoma, metastatic neuroendocrine carcinoma of extracutaneous origin, Ewing's sarcoma). IHC is also helpful for the detection of micrometastatic tumour deposits in sentinel lymph nodes.[20] Various antibodies can be used including, but not limited to cytokeratin 20, CAM 5.2, AE1/AE3, chromogranin, synaptophysin, CM2B4, INSM1 and neurofilament. Positivity can be variable between antibodies and can be perinuclear dot-like, cap-like, cytoplasmic or cell membranous. The tumour should be negative for lymphoid and melanoma markers. Strong and diffuse labelling for thyroid transcription factor (TTF-1) favours metastatic neuroendocrine carcinoma of extracutaneous origin.

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 MCC. For example, cytokeratin 20 is considered to have a sensitivity of approximately 90%, whereas others claim a greater sensitivity for neurofilament.

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Note 14 – Pathological staging[2,3] (Core)

Those patients with MCC in whom the primary tumour cannot be assessed (e.g., curetted) should be categorized as TX. Merkel cell carcinoma in situ (i.e., completely limited to epidermis or adnexal epithelium) is categorized as Tis. The T category of MCC is classified primarily by measuring the maximum dimension of the tumour with a threshold of ≤2 cm (T1), >2 cm but ≤5 cm (T2), or >5 cm (T3). Extracutaneous invasion by the primary tumour into bone, muscle, fascia, or cartilage is classified as T4.

Regional metastases most commonly present in the regional lymph nodes. Nodal staging is primarily based on nodal tumour burden: microscopic versus macroscopic. Therefore, patients without clinical or radiologic evidence of lymph node metastases, but who have pathologically documented nodal metastases, are defined by convention as exhibiting “microscopic” or “clinically occult” nodal metastases. In contrast, MCC patients with both clinical evidence of nodal metastases *and* pathologic examination confirming nodal metastases are defined by convention as having “macroscopic” or “clinically apparent” nodal metastases.

Distant metastases are defined as metastases that have spread beyond the draining lymph node basin, including cutaneous, nodal, and visceral sites.

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