COLLEGE of AMERICAN PATHOLOGISTS

Protocol for the Examination of Specimens From Patients With Merkel Cell Carcinoma of the Skin

Version: MerkelCell 4.0.0.1 **Protocol Posting Date:** June 2017
Includes pTNM requirements from the 8th Edition, AJCC Staging Manual

For accreditation purposes, this protocol should be used for the following procedures AND tumor types:

Procedure	Description
Excision	
Tumor Type	**Description**
Merkel cell carcinoma	

This protocol is NOT required for accreditation purposes for the following:

Procedure
Biopsy
Primary resection specimen with no residual cancer (eg, following previous excision)
Cytologic specimens

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With guidance from the CAP Cancer and CAP Pathology Electronic Reporting Committees.

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Accreditation Requirements
This protocol can be utilized for a variety of procedures and tumor types for clinical care purposes. For accreditation purposes, only the definitive primary cancer resection specimen is required to have the core and conditional data elements reported in a synoptic format.

- Core data elements are required in reports to adequately describe appropriate malignancies. For accreditation purposes, essential data elements must be reported in all instances, even if the response is "not applicable" or "cannot be determined."
- Conditional data elements are only required to be reported if applicable as delineated in the protocol. For instance, the total number of lymph nodes examined must be reported, but only if nodes are present in the specimen.
- Optional data elements are identified with "+" and although not required for CAP accreditation purposes, may be considered for reporting as determined by local practice standards.

The use of this protocol is not required for recurrent tumors or for metastatic tumors that are resected at a different time than the primary tumor. Use of this protocol is also not required for pathology reviews performed at a second institution (ie, secondary consultation, second opinion, or review of outside case at second institution).

Synoptic Reporting
All core and conditionally required data elements outlined on the surgical case summary from this cancer protocol must be displayed in synoptic report format. Synoptic format is defined as:

- Data element: followed by its answer (response), outline format without the paired "Data element: Response" format is NOT considered synoptic.
- The data element should be represented in the report as it is listed in the case summary. The response for any data element may be modified from those listed in the case summary, including "Cannot be determined" if appropriate.
- Each diagnostic parameter pair (Data element: Response) is listed on a separate line or in a tabular format to achieve visual separation. The following exceptions are allowed to be listed on one line:
    - Anatomic site or specimen, laterality, and procedure
    - Pathologic Stage Classification (pTNM) elements
    - Negative margins, as long as all negative margins are specifically enumerated where applicable
- The synoptic portion of the report can appear in the diagnosis section of the pathology report, at the end of the report or in a separate section, but all Data element: Responses must be listed together in one location

Organizations and pathologists may choose to list the required elements in any order, use additional methods in order to enhance or achieve visual separation, or add optional items within the synoptic report. The report may have required elements in a summary format elsewhere in the report IN ADDITION TO but not as replacement for the synoptic report i.e. all required elements must be in the synoptic portion of the report in the format defined above.

CAP Laboratory Accreditation Program Protocol Required Use Date: March 2018*

** Beginning January 1, 2018, the 8th edition AJCC Staging Manual should be used for reporting pTNM.*

CAP Merkel Cell Carcinoma Protocol Summary of Changes

Version 4.0.0.1
The following data element was modified:
Tumor Extension

Version 4.0.0.0
The following data elements were modified:
Pathologic Stage Classification (pTNM, AJCC 8th Edition)
Mitotic Rate

Surgical Pathology Cancer Case Summary

Protocol posting date: June 2017

MERKEL CELL CARCINOMA OF THE SKIN:

Select a single response unless otherwise indicated.

Procedure (select all that apply)
___ Excision
___ Re-excision
___ Lymphadenectomy, sentinel node(s)
___ Lymphadenectomy, regional nodes (specify): _____
___ Other (specify): _____
___ Not specified

+ Specimen Laterality
+ ___ Right
+ ___ Left
+ ___ Midline
+ ___ Not specified

Tumor Site
Specify (if known): _____
___ Not specified

Tumor Size
Greatest dimension (centimeters): ___ cm
+ Additional dimensions (centimeters): ___ x ___ cm
___ Cannot be determined (explain): _____

+ Tumor Thickness (Note A)
+ ___ Specify (millimeters): ___ mm
+ ___ At least (millimeters): ___ mm (explain): _____

Margins

Peripheral Margins
___ Cannot be assessed
___ Uninvolved by carcinoma
    Distance of carcinoma from margin (millimeters): ___ mm
    Specify location(s), if possible: _____
___ Involved by carcinoma
    Specify location(s), if possible: _____

Deep Margin
___ Cannot be assessed
___ Uninvolved by carcinoma
    Distance of carcinoma from margin (millimeters): ___ mm
    Specify location(s), if possible: _____
___ Involved by carcinoma
    Specify location(s), if possible: _____

Lymphovascular Invasion
___ Not identified

+ Data elements preceded by this symbol are not required for accreditation purposes. These optional elements may be clinically important but are not yet validated or regularly used in patient management.

___ Present
___ Cannot be determined

Tumor Extension (select all that apply)
___ No evidence of primary tumor
___ Not identified
___ Tumor invades bone
___ Tumor invades muscle
___ Tumor invades fascia
___ Tumor invades cartilage
___ Other (specify): _____
___ Cannot be assessed
___ Not applicable

+ Mitotic Rate (Note B)
+ ___ <1/mm^2
+ ___ ≥1/mm^2 (specify number): _____

+ Tumor-Infiltrating Lymphocytes (Note C)
+ ___ Not identified
+ ___ Present, nonbrisk
+ ___ Present, brisk

+ Tumor Growth Pattern (Note D)
+ ___ Nodular
+ ___ Infiltrative

+ Presence of Second Malignancy (Note E)
+ ___ Present (specify type): _____
+ ___ Not identified

Regional Lymph Nodes (Note F)

___ No lymph nodes submitted or found

Lymph Node Examination (required only if lymph nodes are present in the specimen)

Number of Lymph Nodes Involved: ____
___ Number cannot be determined (explain): _____

+ Size of Largest Metastatic Deposit (millimeters): ____mm

+ Extranodal Extension
+ ___ Not identified
+ ___ Present
+ ___ Cannot be determined

Number of Lymph Nodes Examined: ____
___ Number cannot be determined (explain): _____

Number of Sentinel Nodes Examined: ____
___ Number cannot be determined (explain): _____

Pathologic Stage Classification (pTNM, AJCC 8th Edition) (Note G)

Note: Reporting of pT, pN, and (when applicable) pM categories is based on information available to the pathologist at the time the report is issued. Only the applicable T, N, or M category is required for reporting; their definitions need not be included in the report. The categories (with modifiers when applicable) can be listed on 1 line or more than 1 line.

TNM Descriptors (required only if applicable) (select all that apply)
____ m (multiple)
____ r (recurrent)
____ y (posttreatment)

Primary Tumor (pT)

Note: If clinical tumor size is unavailable, gross or microscopic tumor measurement should be used for determining the T category.

___ pTX: Primary tumor cannot be assessed (eg, curetted)
___ pT0: No evidence of primary tumor
___ pTis: In situ primary tumor
___ pT1: Maximum clinical tumor diameter ≤2 cm
___ pT2: Maximum clinical tumor diameter >2 but ≤5 cm
___ pT3: Maximum clinical tumor diameter >5 cm
___ pT4: Primary tumor invades bone, muscle, fascia, or cartilage

Regional Lymph Nodes (pN)

___ pNX: Regional lymph nodes cannot be assessed (eg, previously removed for another reason or *not* removed for pathological evaluation)
___ pN0: No regional lymph node metastasis detected on pathological evaluation
___ pN1: Metastasis in regional lymph node(s)
___ pN1a(sn): Clinically occult regional lymph node metastasis identified only by sentinel lymph node biopsy
___ pN1a: Clinically occult regional lymph node metastasis following lymph node dissection
___ pN1b: Clinically and/or radiologically detected regional lymph node metastasis[#]
___ pN2: In transit metastasis (discontinuous from primary tumor; located between primary tumor and draining regional nodal basin, or distal to the primary tumor) *without* lymph node metastasis
___ pN3: In transit metastasis (discontinuous from primary tumor; located between primary tumor and draining regional nodal basin, or distal to the primary tumor) *with* lymph node metastasis

[#] *Note: The pN1b, subcategory is dependent on clinical information that may be unavailable to the pathologist. If this information is not available, the parent category (pN1) should be selected.*

Distant Metastasis (pM) (required only if confirmed pathologically in this case)

___ pM1: Distant metastasis microscopically confirmed
___ pM1a: Metastasis to distant skin, distant subcutaneous tissue, or distant lymph node(s), microscopically confirmed
___ pM1b: Metastasis to lung, microscopically confirmed
___ pM1c: Metastasis to all other distant sites, microscopically confirmed

Specify site(s), if known: _____

+ Additional Pathologic Findings
+ Specify: _____

+ Comment(s)

Explanatory Notes

A. Tumor Thickness
There are published[1] and unpublished data from 3 independent prospective cohorts of Merkel cell carcinoma (MCC) patients examining tumor thickness (measured in millimeters from the stratum granulosum to the deepest infiltrating tumor cells) as a prognostic indicator for outcome.[1,2] All 3 centers have data that find that tumor thickness is more predictive of outcome than maximum tumor diameter (a current staging parameter). In 2 of the studies, the outcome thus far examined was nodal metastasis; the 3rd study evaluated disease-specific survival.

If the tumor is transected at the deep margin of the specimen, the depth may be indicated as "at least __ mm" with a comment explaining the limitation of thickness assessment.

B. Mitotic Rate
The presence of >10 mitotic figures/high-power field (HPF) has been shown to correlate with large tumor size as well as a poor prognosis.[3,4] The definition of what constitutes a high-power field was not specified in these reports; typically a 10X ocular and a 40X objective will yield a field area of approximately 0.15 mm^2, but this will differ from microscope to microscope and should be determined on an individual basis by direct measurement and calculation of the field or manufacturer's specifications. Reporting mitotic figures per square millimeter should have the advantage of greater reproducibility. The identification of no mitotic figures may be reported as "$<1/mm^2$."

Uniformly accepted thresholds for low- or high-risk mitotic counts are not established for either reporting method (number per HPF versus number per square millimeter), and this case summary item remains optional at this time.

It has also been suggested that an MIB-1 proliferation index of greater than 50% is associated with a significantly worse prognosis.[4]

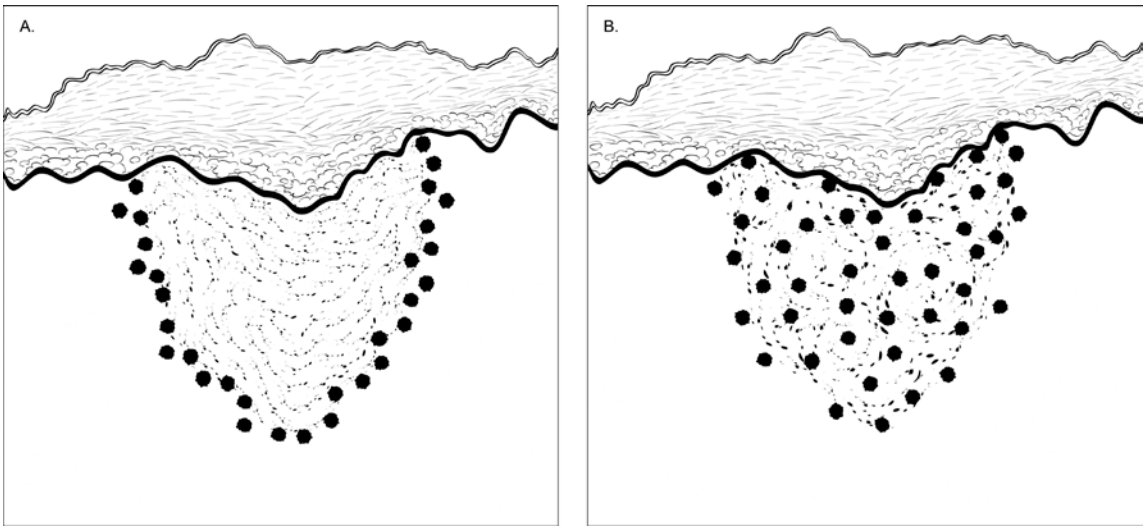
C. Tumor-Infiltrating Lymphocytes
Tumor-infiltrating lymphocytes (TILs) are defined as lymphocytes present at the interface of the tumor and the stroma. Some authors have suggested that the presence of TILs has been shown to portend a poor prognosis, especially when considered in concurrence with a tumor depth of >5 mm.[5] However, there are conflicting data on the subject.[4]

In the absence of specific accepted guidelines for assessment of TILs, it is recommended in this protocol that, for purposes of uniformity, pathologists choosing to report TILs employ guidelines used for assessment of TILs as in cutaneous melanomas, given below:

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

TILs nonbrisk: Lymphocytes infiltrate tumor only focally or not along the entire base of the vertical growth phase.

TILs brisk: Lymphocytes diffusely infiltrate the entire base of the dermal tumor (Figure, A) or the entire invasive component of the tumor (Figure, B).



Brisk tumor-infiltrating lymphocytes. A, Lymphocytes diffusely infiltrate the entire base of the invasive tumor. B, Lymphocytes infiltrate the entire invasive component of the carcinoma.

D. Tumor Growth Pattern
In a series of 156 patients with MCC, nodular tumor growth pattern was found on both uni- and multivariate analysis to correlate with better survival.[1] Nodular pattern is defined as tumors with a relatively well-circumscribed interface with the surrounding tissue, typically composed of one or multiple nodules.[2]

Infiltrative pattern is defined as tumors without a well-circumscribed interface with the surrounding tissue, composed of single cells, rows, trabeculae or strands of cells infiltrating through dermal collagen or deeper soft tissue.

A tumor exhibiting both nodular and infiltrative patterns should be classified as infiltrative.

E. Presence of Second Malignancy
There is the occasional association of MCC and in situ SCC: primarily a histologic finding.[6] There is some question whether this is inversely correlated with merkel cell polyomavirus (MCPyV) detection. There is also an association of MCC with an immunosuppressed status, which may iatrogenic (transplant) or due an underlying malignancy that affects T cell immunity. The poor prognosis of MCC patients with underlying chronic lymphocytic leukemia (CLL) is therefore not necessarily due to the malignancy, but rather the associated immunosuppression.[7]

F. Lymph Node Examination
Clinical detection of nodal disease may be via inspection, palpation, and/or imaging. “Micrometastases” are defined by identification of metastasis on pathologic examination of sentinel or regional lymphadenectomy specimens. “Macrometastases” are defined as clinically detectable nodal metastases, confirmed by pathologic examination of therapeutic lymphadenectomy specimens. Because the pathologist may not have this clinical information, subdivision of N categories in the pathology report is optional.

In-transit metastasis is defined as a tumor distinct from the primary lesion and located either (1) between the primary lesion and the draining node bed or (2) distal to the primary lesion.

Metastatic MCC to the lymph node may be difficult to identify on routine hematoxylin-eosin (H&E)-stained sections. The use of immunostains has been shown to increase the sensitivity of identifying occult lymph node metastases.[8] It is strongly recommended that at least 1 immunostain be performed before designating a lymph node as negative. Depending on the experience or preference of the laboratory, stains may include but are not limited to AE1/AE3, CK116, Cam 5.2, CD56, CK20, synaptophysin, and/or chromogranin, many of which show a perinuclear dot-like staining pattern. All immunohistochemical results should be documented in the final pathology report.

Isolated tumor cells in a lymph node are classified as micrometastases (pN1a).

G. TNM Staging
An MCC-specific 4-tier staging system was first adopted by the American Joint Committee on Cancer (AJCC) in 2010. Recent analysis of more than 9300 patients with MCC was used to validate and revise the staging system for the 8th edition of the AJCC *Cancer Staging Manual* published in 2017.[9] Primary tumor dimension (≤2 cm versus >2 cm), nodal status, and stage at presentation remain the primary predictors of survival.[10] The most important changes in the updated 8th edition staging system include:

- Separation of clinical and pathological stage groupings, consistent with other AJCC staging systems
- Elimination of stage I and II subgroups based on pathologic nodal status
- Inclusion of category pN1a(sn) into stage group IIIA for pathologically detected, clinically occult nodal metastasis identified only by sentinel lymph node biopsy without completion lymphadenectomy
- Inclusion of category T0 pN1b M0 in pathologic stage group IIIA, to identify patients with clinically detected nodal MCC metastases with unknown primary tumor
- Separation of patients with in-transit metastases into category pN2 without and pN3 with nodal metastases

Those patients with MCC in whom the primary tumor cannot be assessed (eg, curetted) should be categorized as TX. Merkel cell carcinoma in situ (ie, 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 tumor with a threshold of ≤2 cm (T1), >2 cm but ≤5 cm (T2), or >5 cm (T3). Extracutaneous invasion by the primary tumor into bone, muscle, fascia, or cartilage is classified as T4.

Histologic measurement of tumor diameter is subject to underestimation due to shrinkage of formalin-fixed tissue and inaccuracy of measurement of the largest diameter of oval tumors. If clinical tumor size is unavailable, histopathologic gross or microscopic measurement should be used.[10]

Regional metastases most commonly present in the regional lymph nodes. Nodal staging is primarily based on nodal tumor 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.

Stage Groupings
Patients with primary Merkel cell carcinoma with no evidence of regional or distant metastases (either clinically or pathologically) are divided into 2 stages: stage I for primary tumors ≤2 cm in size and stage II for primary tumors >2 cm in size (IIA) or with extracutaneous invasion (IIB). Stage III is divided into stage groups IIIA for patients with microscopically positive and clinically occult nodes, and patients with clinically detected lymph node metastases with unknown primary tumor (T0), and IIIB for patients with clinically and/or radiologically detected regional lymph node and/or in-transit metastases. There are no subgroups of stage IV Merkel cell carcinoma.

References
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7. Brewer JD, Shanafelt TD, Otley CC, et al. Chronic lymphocytic leukemia is associated with decreased survival of patients with malignnt melanoma and Merkel cell carcinoma in a SEER population-based study. *J Clin Oncol.* 2012;30(8):843-849.
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