Protocol for the Examination of Specimens from Patients with Merkel Cell Carcinoma of the Skin

Version: 4.2.0.0
Protocol Posting Date: April 2026

CAP Laboratory Accreditation Program Protocol Required Use Date: January 2027
The changes included in this current protocol version affect accreditation requirements. The new deadline for implementing this protocol version is reflected in the above accreditation date.
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 (e.g., following previous excision)
Cytologic specimens

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Glossary:
Author: Expert who is designated by the chair of the Cancer Committee.
Expert Panel Contributors: Includes members of other CAP committees or external subject matter experts who contribute to the current version of the protocol.

Accreditation Requirements
Synoptic reporting with core and conditional data elements for designated specimen types* is required for accreditation.

- Data elements designated as core must be reported.
- Data elements designated as conditional only need to be reported if applicable.
- Data elements designated as optional are identified with "+". Although not required for accreditation, they may be considered for reporting.

This protocol is not required for recurrent or metastatic tumors resected at a different time than the primary tumor. This protocol is also not required for pathology reviews performed at a second institution (i.e., second opinion and referrals to another institution).

Full accreditation requirements can be found on the CAP website under Accreditation Checklists.
A list of core and conditional data elements can be found in the Summary of Required Elements under Resources on the CAP Cancer Protocols website.
**Includes definitive primary cancer resection and pediatric biopsy tumor types.*

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.

Summary of Changes

v 4.2.0.0

- WHO 5th edition updates to content and explanatory notes
- Updates to Tumor Site, Maximum Tumor Dimensions in Centimeters (cm), Tumor Extent, Second Malignancy questions, and MARGINS and REGIONAL LYMPH NODES sections
- Addition of required (core) Locoregional Cutaneous Metastases question
- Addition of Merkel Cell Polyoma Virus (MCPyV) Status, Histologic Subtype, and Mitotic Rate optional questions
- "Lymphovascular Invasion" question updated to "Lymphatic and / or Vascular Invasion"
- Updates to pTNM Classification to include the addition of the N suffix
- Addition of SPECIAL STUDIES section

Reporting Template

Protocol Posting Date: April 2026
Select a single response unless otherwise indicated.
CASE SUMMARY: (MERKEL CELL CARCINOMA OF THE SKIN)
Standard(s): AJCC 8

SPECIMEN

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

Specimen Laterality (select all that apply)
___ Right
___ Left
___ Midline
___ Not specified

TUMOR (Note B)

Tumor Site
If there is more than one synchronous Merkel cell carcinoma, please exclude the possibility of metastasis and complete a separate checklist for each primary site.
___ Face: _____
___ Scalp and / or neck: _____
___ Lip: _____
___ External ear: _____
___ Trunk: _____
___ Upper limb and / or shoulder: _____
___ Lower limb and / or hip: _____
___ Penis: _____
___ Scrotum: _____
___ Vulva: _____
___ Skin, NOS: _____
___ Overlapping lesion(s) of skin (specify site(s)): _____
___ Not specified

Maximum Tumor Dimension in Centimeters (cm) (Note C)
___ Exact dimension: _____ cm
___ At least (specify): _____ cm
___ Cannot be determined (explain): _____

+Method of Measurement
___ Clinical measurement
___ Macroscopic measurement
___ Microscopic measurement

+Histologic Subtype (Note D)
___ Pure Merkel cell carcinoma
___ Combined Merkel cell carcinoma (MCC with morphological diversity or heterologous differentiation)
+Type of Morphological Diverse Component: _____

+Mitotic Rate (Note E)
In combined Merkel cell carcinoma (MCC with morphological diversity), the mitotic rate should be determined in the neuroendocrine / MCC component.
___ None identified
___ Greater than or equal to 1 per square Millimeter (mm)
+Specify Mitotic Rate: _____ mitoses per mm2

Tumor Extent (Note F) (select all that apply)
___ No evidence of primary tumor
___ Invasion not identified (only intra-epithelial / in situ component)
___ Invades dermis
___ Invades subcutis (includes superficial facial muscle involvement)
___ Invades fascia
___ Invades skeletal muscle (except for superficial facial muscle involvement)
___ Invades cartilage
___ Invades bone
___ Other (specify): _____
___ Cannot be determined (explain): _____

+Tumor Thickness in Millimeters (mm) (Note G)
___ Specify in Millimeters (mm): _____ mm
___ At least in Millimeters (mm): _____ mm
+Tumor Thickness Comment: _____

Lymphatic and / or Vascular Invasion (Note H)
___ Not identified
___ Present
+Method of Detection (select all that apply)
___ Immunohistochemical study
___ H&E stain
___ Cannot be determined (explain): _____

+Tumor-infiltrating Lymphocytes (Note I)
___ Not identified
___ Present, non-brisk
___ Present, brisk

Locoregional Cutaneous Metastases (Note J)
___ Not identified
___ Present
___ Cannot be determined (explain): _____

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

+Second Malignancy (Note L)
Combined Merkel cell carcinoma (MCC with morphological diversity) does not qualify as a second malignancy.
___ Not identified
___ Present
___ Squamous cell carcinoma in situ
___ Invasive squamous cell carcinoma
___ Chronic lymphocytic leukemia / small cell lymphoma
___ Other (specify): _____

+Tumor Comment: _____

MARGINS (Note M)

Margin Status (select all that apply)
Margin involvement by Merkel cell carcinoma in situ should be recorded if in situ disease is present in the specimen.
___ All margins negative for Merkel cell carcinoma (intra-epithelial / in situ, invasive, or metastatic)
Recommend measuring margin distance to carcinoma if less than or equal to 1.0 mm.
+Specify Distance from Merkel Cell Carcinoma to Peripheral Margin in Millimeters (mm):
_____ mm

+Closest Peripheral Margin Location(s) to Merkel Cell Carcinoma: _____

+Specify Distance from Merkel Cell Carcinoma to Deep Margin in Millimeters (mm):
_____ mm
+Closest Deep Margin Location(s) to Merkel Cell Carcinoma: _____

___ Merkel cell carcinoma present at margin
Margin(s) Involved by Merkel Cell Carcinoma (select all that apply)
___ Peripheral: _____
___ Deep: _____
___ Other (specify): _____
___ Cannot be determined (explain): _____
___ In situ / intra-epithelial Merkel cell carcinoma present at margin
Margin(s) Involved by In Situ / Intra-epithelial Merkel Cell Carcinoma (select all that apply)
___ Peripheral: _____
___ Deep: _____
___ Other (specify): _____

___ Cannot be determined (explain): _____

 # Presence of lymphatic or vascular invasion at the margin does not constitute metastasis.

___ Metastatic Merkel cell carcinoma present at margin#

Margin Involvement by Metastases (select all that apply)

___ Peripheral: _____

___ Deep: _____

___ Other (specify): _____

___ Cannot be determined (explain): _____

___ Other (specify): _____

___ Cannot be determined (explain): _____

+Margin Comment (margin comment may be used to document the presence of lymphatic or vascular invasion at the margin): _____

REGIONAL LYMPH NODES (Note N)

Regional Lymph Node Status

___ Not applicable (no regional lymph nodes submitted or found)

___ Regional lymph nodes present

___ All regional lymph nodes negative for tumor

___ Tumor present in regional lymph node(s)

+Method of Detection (select all that apply)

___ Immunohistochemical study

___ H&E stain

Total Number of Lymph Nodes with Tumor

___ Exact number (specify): _____

___ At least (specify): _____

___ Other (specify): _____

___ Cannot be determined (explain): _____

Number of Sentinel Lymph Nodes with Tumor (required only if applicable)

___ Not applicable (no sentinel lymph nodes examined)

___ Exact number (specify): _____

___ At least (specify): _____

___ Other (specify): _____

___ Cannot be determined (explain): _____

+Nodal Site(s) with Tumor (select all that apply)

___ Subcapsular: _____

___ Intraparenchymal: _____

___ Other (specify): _____

___ Cannot be determined: _____

Size of Largest Sentinel Node Metastatic Deposit (required only if applicable)

Specify in Millimeters (mm)

___ Not applicable

___ Exact size (specify): _____ mm

___ Other (specify): _____

___ Cannot be determined (explain): _____

Size of Largest Non-sentinel Node Metastatic Deposit (required only if applicable)

Specify in Millimeters (mm)

___ Not applicable
___ Exact size (specify): _____ mm
___ Other (specify): _____
___ Cannot be determined (explain): _____

Extranodal Extension (ENE)
___ Not identified
___ Present
___ Cannot be determined (explain): _____

Matted Nodes
___ Not identified
___ Present
___ Cannot be determined (explain): _____

___ Other (specify): _____
___ Cannot be determined (explain): _____

Total Number of Lymph Nodes Examined (sentinel and non-sentinel)
___ Exact number (specify): _____
___ At least (specify): _____
___ Other (specify): _____
___ Cannot be determined (explain): _____

Total Number of Sentinel Lymph Node(s) Examined (required only if applicable)
___ Not applicable (no sentinel lymph nodes examined)
___ Exact number (specify): _____
___ At least (specify): _____
___ Other (specify): _____
___ Cannot be determined (explain): _____

+Regional Lymph Node Comment: _____

DISTANT METASTASIS (Note O)

Distant Site(s) Involved (required only if applicable) (select all that apply)
___ Not applicable
___ Distant skin, distant subcutaneous tissue, or distant lymph node(s): _____
___ Lung: _____
___ Other (specify): _____
___ Cannot be determined (explain): _____

pTNM CLASSIFICATION (AJCC 8th Edition) (Note P)

Reporting of pT, pN, and (when applicable) pM categories is based on information available to the pathologist at the time the report is issued. As per the AJCC (Chapter 1, 8th Ed.) it is the managing physician's responsibility to establish the final pathologic stage based upon all pertinent information, including but potentially not limited to this pathology report.

Prior Procedure Classification

In general, CAP cancer protocol case summaries are intended to guide reporting on the specimen that the pathologist is evaluating at that time. However, Merkel cell carcinoma cases frequently include multiple procedures; and the excision / re-excision specimen(s) may not have any residual carcinoma. Because of this, a prior procedure that was performed may affect the pathologic classification of the tumor. In order to represent this appropriately in the pathology report, information from prior procedures may be incorporated into the assignment of pathologic classification if it is available. When information from a prior procedure is included in this report, details of that procedure should be documented in the report as well.

___ No information from a prior procedure is included in the classification assigned in this report
___ Classification assigned in this report includes information from a prior procedure (explain):
_____

Modified Classification (required only if applicable) (select all that apply)
___ Not applicable
___ y (post-neoadjuvant therapy)
___ r (recurrence)

pT Category
If clinical tumor size is unavailable, gross or microscopic tumor measurement should be used for determining the T category.
___ pT not assigned (cannot be determined based on available pathological information)
___ pT0: No evidence of primary tumor
___ pTis: In situ primary tumor
___ pT1: Maximum clinical tumor diameter less than or equal to 2 cm
___ pT2: Maximum clinical tumor diameter greater than 2 cm but less than or equal to 5 cm
___ pT3: Maximum clinical tumor diameter greater than 5 cm
___ pT4: Primary tumor invades fascia, muscle, cartilage, or bone

T Suffix (required only if applicable)
___ Not applicable
___ (m) multiple primary synchronous tumors in a single organ

pN Category
___ pN not assigned (no nodes submitted or found)
___ pN not assigned (cannot be determined based on available pathological information)
___ 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
 # 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.
___ pN1b: Clinically and / or radiologically detected regional lymph node metastasis, microscopically confirmed#
___ pN1 (subcategory cannot be determined)
___ 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

N Suffix (required only if applicable) (select all that apply)
___ Not applicable
___ (sn) Sentinel node procedure
___ (f) FNA or core needle biopsy

pM Category (required only if confirmed pathologically)
___ Not applicable - pM cannot be determined from the submitted specimen(s)
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
___ pM1 (subcategory cannot be determined)

ADDITIONAL FINDINGS

+Additional Findings (specify): _____

SPECIAL STUDIES
Pending biomarker studies should be listed in the Comments section of this report.

Merkel Cell Polyoma Virus (MCPyV) (Note Q)
___ Not performed
___ Performed
Merkel Cell Polyoma Virus (MCPyV) Status
___ Positive
___ Negative
___ Cannot be determined (explain): _____
Method of Detection (select all that apply)
___ Immunohistochemical study
___ DNA sequencing
___ RNA in situ hybridization
___ Other (specify): _____

Other Special Studies (specify): _____

COMMENTS

Comment(s): _____

Explanatory Notes

A. Procedure

Merkel cell carcinoma (MCC) is typically a rapidly growing tumor located primarily in the dermis and/or subcutis. Exclusively intraepithelial/ in situ MCCs are rare.[1] Therefore, shave, punch, and incisional biopsies that do not include the entire lesion are suboptimal for pathologic evaluation and should be avoided, unless clinically indicated. In patients with localized disease, sentinel lymph node biopsy has been shown to identify subclinical nodal metastasis and thus improve prognostic staging.[2,3,4]

The use of frozen sections for evaluation of margin status in Merkel cell carcinoma resections has gained popularity recently, particularly in the management of eyelid and periocular tumors.[5,6] However, since the tumor cells can mimic lymphocytes to some extent, extreme care is warranted on intraoperative frozen section evaluation of margins.[7]

References

1. Truong K, Goldinger SM, Chou S et al. Merkel cell carcinoma in situ: A systematic review of prognosis and management. *Australas J Dermatol.* 2022 Feb;63(1): e6-e12. PMID: 34873684.
2. Lugowska I, Becker JC, Ascierto PA, et al. Merkel-cell carcinoma: *ESMO-EURACAN Clinical Practice Guideline* for diagnosis, treatment and follow-up. ESMO Open. 2024 May;9(5):102977. PMID: 38796285.
3. Wasserberg N, Schachter J, Fenig E, Feinmesser M, Gutman H. Applicability of the sentinel node technique to Merkel cell carcinoma. *Dermatol Surg*. 2000 Feb;26(2):138-41. PMID: 10691943.
4. Sadeghi R, Adinehpoor Z, Maleki M, et al. Prognostic significance of sentinel lymph node mapping in Merkel cell carcinoma: systematic review and meta-analysis of prognostic studies. *Biomed Res Int*. 2014:2014:489536. PMID: 24971335.
5. Yin VT, Merritt HA, Sniegowski M, Esmaeli B. Eyelid and ocular surface carcinoma: diagnosis and management. *Clin Dermatol.* 2015 Mar-Apr;33(2):159-69. PMID: 25704936.
6. Herbert HM, Sun MT, Selva D, et al. Merkel cell carcinoma of the eyelid: management and prognosis. *JAMA Ophthalmol*. 2014 Feb;132(2):197-204. PMID: 24287584.
7. Tatiana V., Camayo TV, Dane A. *Mohs Micrographic Surgery of Uncommon Tumors* (Angiosarcoma, Eccrine, Paget, and Merkel Cell). In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2025 Jan. 2024 Jul 13. PMID: 39163450.

B. Tumor Site

For Merkel cell carcinoma, the management strategies may vary based on the anatomic site of primary tumor.[1] Tumors in certain locations, such as the lip, are often associated with invasion of bone and cartilage and shorter deceased-specific survival,[2] while other anatomic locations, such as the upper limb, may be associated with a lower risk for distant metastasis.[3] Also, patients with multiple primary Merkel cell carcinomas have shorter overall and disease-specific survival.[4]

References

1. Cass S, Cope B, Andrew J Bishop AJ, et al. Primary tumor site for localized Merkel cell carcinoma drives different management strategies without impacting oncologic outcomes. *Radiother Oncol*. 2023 Nov: 188:109892. PMID: 37659660.
2. Smith VA, Camp ER, Eric J Lentsch EJ. Merkel cell carcinoma: identification of prognostic factors unique to tumors located in the head and neck based on analysis of SEER data. *Laryngoscope*. 2012 Jun;122(6):1283-90. PMID: 22522673.

3. Kim EY, Liu M, Giobbie-Hurder A, et al. Patterns of initial distant metastases in 151 patients undergoing surveillance for treated Merkel cell carcinoma. *J Eur Acad Dermatol Venereol.* 2024 Jun;38(6):1202-1212. PMID: 38433521.
4. Luo Z, Sun Y, Guo Z, et al. Disparities in survival and tumor characteristics in patients with single and multiple primary Merkel cell carcinomas. *J Am Acad Dermatol*. 2025 Aug 23: S0190-9622(25)02678-7. PMID: 40854495.

C. Tumor Dimensions

The largest tumor dimension/diameter measured clinically has been a staging parameter.[1,2] If unavailable, macroscopic measurement obtained during grossing of the excision specimen or microscopic measurement obtained during histopathological evaluation may be used.[3]

References

1. Bichakjian CK, Nghiem P, Johnson T, Wright CL and Sober AJ. Merkel cell carcinoma. In *AJCC Cancer Staging Manual.* 8th ed., Amin MB, Greene FL, Byrd DR, et al, editors. Springer, New York. 2017: 549-562.
2. Brierley JD, Gospodarowicz MK and Wittekind C (eds) (2016). *UICC TNM Classification of Malignant Tumours,* 8th Edition, Wiley, USA.
3. Keohane SG, Proby CM, C Newlands C, et al. The new 8th edition of TNM staging and its implications for skin cancer: a review by the British Association of Dermatologists and the Royal College of Pathologists, UK. *Br J Dermatol.* 2018 Oct;179(4):824-828. PMID: 29923189.

D. Histologic Type

During histopathologic evaluation, most MCC may display exclusive neuroendocrine differentiation, in which case they are designated as ‘pure Merkel cell carcinoma’. In some cases, there may be variable extent of morphological diversity or heterologous differentiation, referred to as ‘combined Merkel cell carcinoma’. Of these, squamous differentiation is the most common, while adnexal, and sarcomatoid differentiation are relatively rare.[1,2,3,4] Only divergent differentiation noted within/ admixed with the main mass of MCC should be considered as combined MCC. Adjacent or discontinuous tumors noted in the same specimen should be considered as second malignancy (Note M).

References

1. Ogawa T, Donizy P, Wu CL, et al. Morphologic Diversity of Merkel Cell Carcinoma. *Am J Dermatopathol.* 2020 Sep;42(9):629-640. PMID: 32833736.
2. Kervarrec T, Appenzeller S, Samimi M, et al. Merkel Cell Polyomavirus–Negative Merkel Cell Carcinoma Originating from In Situ Squamous Cell Carcinoma: A Keratinocytic Tumor with Neuroendocrine Differentiation. *J Invest Dermatol*. 2022 Mar;142(3 Pt A):516-527. PMID: 34480892.
3. Kervarrec T, Appenzeller S, Gramlich S, et al. Analyses of combined Merkel cell carcinomas with neuroblastic components suggests that loss of T antigen expression in Merkel cell carcinoma may result in cell cycle arrest and neuroblastic transdifferentiation. *J Pathol*. 2024 Sep;264(1):112-124. PMID: 39049595.
4. Gaitskell K, Nassar S, Ibrahim H. Merkel cell carcinoma with divergent differentiation. *Clin Exp Dermatol.* 2020 Apr;45(3):327-332. PMID: 31580510.

E. Mitotic Rate

In combined Merkel cell carcinoma (MCC with morphological diversity), the mitotic rate should be determined in the neuroendocrine/MCC component. 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.[1,2] The definition of what constitutes a high-power field was not specified in these reports; typically, a 10× ocular and a 40× 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 recommended approach to enumerating mitoses is to first find the regions in the tumor containing the most mitotic figures, the so-called 'hot spot' or 'dermal hot spot', similar to primary cutaneous melanoma.[3] After counting the mitoses in the initial high-power field, the count is extended to immediately adjacent non-overlapping fields until an area of tissue corresponding to 1 mm^2 is assessed. If no hot spot is found and mitotic figures are sparse and/or randomly scattered throughout the lesion, then a representative mitosis is chosen and, beginning with that field, the count is then extended to immediately adjacent non-overlapping fields until an area corresponding to 1 mm^2 of tissue is assessed. The count then is expressed as the (whole) number of mitoses/mm^2. If the tumor involves an area less than 1 mm^2, the number of mitoses should be assessed and recorded as if they were found within a square millimeter. For example, if the tumor occupies 0.5 mm^2 and only one mitosis is identified, the mitotic rate should be recorded as 1/mm^2 (not 2/mm^2). Only mitotic figures in dermal or subcutaneous tumor cells should be counted. The number of mitoses should be listed as a whole number per square millimeter. If no mitoses are identified, the mitotic rate may be recorded as "none identified" or "0/mm^2". To obtain an accurate measurement, calibration of individual microscopes is recommended using a stage micrometer to determine the number of high-power fields that equate to a square millimeter.

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 currently.

It has also been suggested that proliferative indices, including a Ki67 proliferation index of greater than 50% and pHH3, may correlate with a significantly worse prognosis.[2,4]

References

1. Skelton HG, Smith KJ, Hitchcock CL, McCarthy WF, Lupton GP, Graham JH. Merkel cell carcinoma: analysis of clinical, histologic, and immunohistologic features of 132 cases with relation to survival. *J Am Acad Dermatol*. 1997;37(5 Pt 1):734-739. PMID: 9366819.
2. Llombart B, Monteagudo C, Lopez-Guerrero JA, et al. Clinicopathological and immunohistochemical analysis of 20 cases of Merkel cell carcinoma in search of prognostic markers. *Histopathology*. 2005;46(6):622-634. PMID: 15910593.
3. Scolyer RA, Shaw HM, Thompson JF, et al. Interobserver reproducibility of histopathologic prognostic variables in primary cutaneous melanomas. *Am J Surg Pathol*. 2003;27(12):1571-1576. PMID: 14657718.
4. Iwasaki T, Matsushita M, Nonaka D, et al. Phosphohistone-H3 (PHH3) is prognostic relevant in Merkel cell carcinomas but Merkel cell polyomavirus is a more powerful prognostic factor than AJCC clinical stage, PHH3, Ki-67 or mitotic indices. *Pathol Int.* 2015 Aug;65(8):404-9. PMID: 25982855.

F. Tumor Extent

Documenting the extent of invasion by tumor is essential for staging of Merkel cell carcinoma.[1,2] Invasion of fascia, skeletal muscle (except for superficial facial muscle), cartilage, or bone constitutes pathologic T-category 4 (pT4). Tumor extension beyond the subcutis has been shown to be a significant prognostic factor in Merkel cell carcinoma of the head and neck.[3]

References

1. Bichakjian CK, Nghiem P, Johnson T, Wright CL and Sober AJ. Merkel cell carcinoma. In *AJCC Cancer Staging Manual*. 8th ed., Amin MB, Greene FL, Byrd DR, et al, editors. Springer, New York. 2017: 549-562.
2. Brierley JD, Gospodarowicz MK and Wittekind C (eds) (2016). *UICC TNM Classification of Malignant Tumours*, 8th Edition, Wiley, USA.
3. Smith VA, Camp ER, Lentsch EJ. Merkel cell carcinoma: identification of prognostic factors unique to tumors located in the head and neck based on analysis of SEER data. *Laryngoscope.* 2012 Jun;122(6):1283-90. PMID: 22522673.

G. Tumor Thickness

Tumor thickness measured like Breslow thickness in melanoma (in millimeters, rounded to the nearest 0.1 mm) from the top of the stratum corneum to the deepest infiltrating tumor cell) is a fairly reproducible parameter that may be of potential prognostic significance in Merkel cell carcinoma. Even though the clinical significance of tumor thickness is still a point of contention, some studies have shown that increasing tumor thickness may correlate with recurrence, sentinel lymph node metastasis, and shorter overall and disease-specific survival.[1,2]

References

1. Lim CS, Whalley D, Haydu LE, et al. Increasing tumor thickness is associated with recurrence and poorer survival in patients with Merkel cell carcinoma. *Ann Surg Oncol*. 2012 Oct;19(11):3325-34. PMID: 22820936.
2. Smith FO, Yue B, Marzban SS, et al. Both tumor depth and diameter are predictive of sentinel lymph node status and survival in Merkel cell carcinoma. *Cancer.* 2015 Sep 15;121(18):3252-60. PMID: 26038193.

H. Lymphatic and/or Vascular Invasion

Lymphovascular invasion may be an early event in Merkel cell carcinoma,[1] and may correlate with large tumor size, infiltrative growth pattern, and non-brisk lymphocytic infiltrate.[2] Prognostically, lymphovascular invasion is associated with shorter recurrence-free and disease-specific survival.[3] While lymphovascular invasion may be easily appreciated on H&E sections, in some cases, immunohistochemical studies using vascular or lymphatic endothelial markers such as D2-40 may be helpful.[2]

References

1. Kukko HM, Koljonen VSK, Tukiainen EJ, et al. Vascular invasion is an early event in pathogenesis of Merkel cell carcinoma. *Mod Pathol.* 2010 Aug;23(8):1151-6. PMID: 20473275.
2. Al-Rohil RN, Milton DR, Nagarajan P, et al. Intratumoral and peritumoral lymphovascular invasion detected by D2-40 immunohistochemistry correlates with metastasis in primary cutaneous Merkel cell carcinoma. *Hum Pathol*. 2018 Jul; 77:98-107. doi: 10.1016/j.humpath.2018.03.017. PMID: 29601841.

3. Jonathan A, Harounian JA, Molin N, Galloway TJ, et al. Effect of Sentinel Lymph Node Biopsy and LVI on Merkel Cell Carcinoma Prognosis and Treatment. *Laryngoscope.* 2021 Mar;131(3): E828-E835. PMID: 32663337.

I. Tumor-Infiltrating Lymphocytes

Tumor-infiltrating lymphocytes (TILs) are defined as lymphocytes present at the interface of the tumor and the stroma. Pattern and density of tumor-infiltrating lymphocytes should be evaluated similar to primary cutaneous melanoma and classified as follows:

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

TILs non-brisk: Lymphocytes infiltrate tumor only focally or not along the entire base/ periphery.

TILs brisk: Lymphocytes diffusely infiltrate the entire tumor or the periphery.

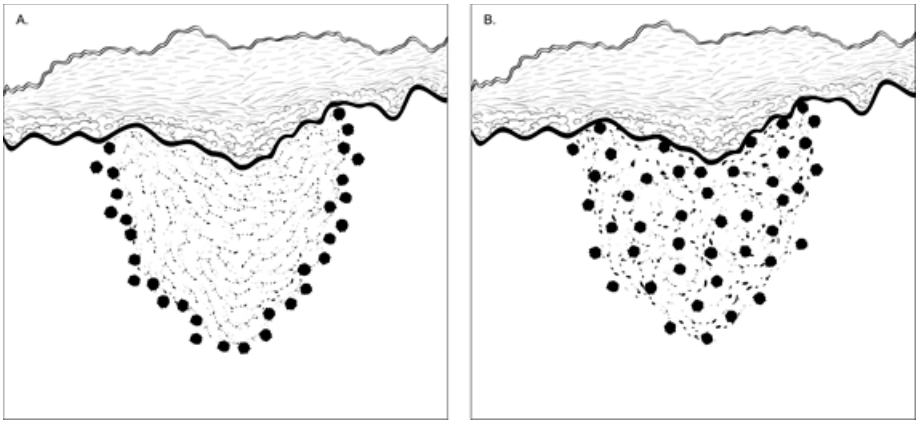

Figure 1: Brisk tumor-infiltrating lymphocytes. A. Lymphocytes diffusely infiltrate the entire base of the invasive tumor. **B**. Lymphocytes infiltrate the entire invasive component of the carcinoma.

Studies have revealed that the distribution density and composition of TILs may have prognostic significance in Merkel cell carcinoma, with respect to response to immunotherapy as well as patient survival.[1,2,3,4,5]

References

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J. Locoregional Cutaneous Metastases

Similar to primary cutaneous melanoma, locoregional metastasis in Merkel cell carcinoma is defined as a discontinuous tumor deposit that is separated from the primary mass and surrounded by normal stroma but restricted to the same anatomic region. Such tumor deposits may be located between the primary tumor and the draining nodal basin or distal to the primary tumor. It may be detected clinically or by microscopic examination and may be located within the dermis, subcutis, or skeletal muscle. Presence of locoregional metastasis (in-transit metastasis or satellitosis) upstages the pN category to at least N2 (depending on lymph node status).[1,2] The possibility of a second primary should be excluded before making a diagnosis of locoregional cutaneous metastasis.[3] Presence of locoregional metastasis will alter the management of the patient.[4]

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K. Tumor Growth Pattern

The growth pattern in Merkel cell carcinoma may be classified as either nodular, in which the tumor contour is relatively well-circumscribed (multiple nodules may be present), or infiltrative, in which the peripheral edge of the tumor is composed of cells arranged singly, in small clusters, cords, or trabeculae between the surrounding dermal collagen bundles or fibroadipose fibroconnective tissue. A tumor exhibiting both nodular and infiltrative patterns should be classified as infiltrative.

Patients with an infiltrative pattern of growth may have a shorter overall 5-year survival rate.[1] Tumor with an infiltrative growth pattern may also show higher mitotic activity,[2] as well as increased rates of sentinel lymph node positivity.[3]

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L. Presence of Second Malignancy

The occurrence of a malignancy that is unrelated to and/or discontinuous from the primary Merkel cell carcinoma in the same specimen is defined as the presence of a second malignancy. This should be distinguished from 'combined Merkel cell carcinoma' in which the second/heterologous component is intimately admixed with the neuroendocrine tumor cells. In sun-exposed skin, squamous cell carcinoma (in situ or invasive) and basal cell carcinomas are known to co-occur adjacent to primary Merkel cell carcinomas.[1,2] In addition, cutaneous involvement by chronic lymphocytic leukemia (CLL) may also be noted.[3] CLL is the most common hematologic disorder noted in association with Merkel cell carcinoma and is related to immunosuppression and sometimes worse prognosis.[4,5,6]

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M. Margin Status

Similar to other cancers, involvement of the margin by Merkel cell carcinoma should be documented in the pathology report. It is recommended that the distance from carcinoma to margin should be documented if the tumor is present at or less than 1 mm from the closest (peripheral or deep) margin. However, in patients with localized MCC, a clinical margin greater than 10 mm correlated with longer overall survival as well as lower rates of relapse.[1,2] Other studies have shown that surgical margins greater than 20 mm were not associated with better outcomes.[3]

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N. Regional Lymph Nodes

Regional lymph nodes are the most common site of metastasis in MCC, which occurs relatively frequently and early, even in the absence of deep local extension or large primary tumor size.[1] Lymph nodes containing metastases of any size, including isolated tumor cells, whether identified in H&E-stained slides or by immunohistochemistry, should be considered positive, similar to melanoma.[1] Reporting should include the number of sentinel and non-sentinel lymph nodes involved, the size of the largest metastatic deposit (in mm), and the presence or absence of extranodal extension.[2]

Metastatic MCC to the lymph node may be difficult to identify on routine H&E-stained sections. The use of multiple H&E-stained levels and immunohistochemical stains has been shown to increase the sensitivity of identifying occult lymph node metastases. For sentinel lymph nodes, it is strongly recommended that at multiple H&E levels (at least 2) and at least 1 immunohistochemical stain be performed before designating a lymph node as negative.[2] 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.[3] A recent study has shown that INSM1 is highly sensitive for metastasis, especially when used in combination with pankeratin.[4] All immunohistochemical results should be documented in the final pathology report.

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O. Distant Metastasis

Distant metastases are defined as metastases that have spread beyond the draining lymph node basin. MCC can metastasize to virtually any organ or site, but the most commonly involved locations include distant skin, lung, liver, bone, and central nervous system. All applicable sites of microscopically confirmed distant metastasis should be recorded.[1]

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P. pTNM Classification

An MCC-specific 4-tier staging system was first adopted by the American Joint Committee on Cancer (AJCC) in 2010. An 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.[1] Primary tumor dimension, nodal status, and stage at presentation remain the primary predictors of survival.[2]

Pathological stage is normally assigned following definitive surgical treatment. However, a patient with MCC may sometimes not undergo additional surgery after narrow excision of the primary tumor with or without sentinel lymph node biopsy, as further treatment may consist only of radiation therapy. In such cases, provided the entire clinically apparent primary tumor has been excised, a pathological stage may be assigned.[2]

TNM Descriptors

For identification of special cases of pTNM classifications, the “m,” “r,” and “y” prefixes are used. Although they do not affect the stage grouping, they indicate cases needing separate analysis. In the rare instance that more than one separate primary tumors are identified, the “m” prefix should be used. The “y” prefix should be used for specimens from patients who have received systemic and/or radiation therapy prior to surgery. The “r” prefix is used for specimens examined at time of retreatment for recurrence or disease progression.

T Category Considerations

T classification of MCC is determined by a combination of pathological evaluation and clinical measurement of the largest diameter of the primary tumor. Those patients with MCC in whom the primary tumor cannot be assessed (e.g., because of curettage or other form of destruction) should be classified at T category not assigned. Although uncommon, Merkel cell carcinoma in situ (i.e., completely limited to epidermis or adnexal epithelium) is categorized as pTis. The remainder of the T category of MCC is classified primarily by the maximum dimension of the tumor in centimeters. If available, the largest clinical diameter should be used for this measurement, as histologic measurement of tumor diameter is subject to underestimation due to shrinkage of formalin-fixed tissue and inaccuracy of measurement of the largest dimension of oval tumors. However, if clinical tumor size is unavailable, pathologic gross or microscopic measurement should be used. The T category thresholds are as follows: ≤2 cm (pT1), >2 cm but ≤5 cm (pT2), or >5 cm (pT3). Extracutaneous invasion by the primary tumor into bone, muscle, fascia, or cartilage is classified as pT4.[2]

N Category Considerations

Pathological N classification is determined by tumor burden in regional lymph nodes. If no regional lymph nodes are biopsied or removed for pathologic evaluation, or if the status of pathologically evaluated lymph nodes cannot otherwise be determined, pN category is not assigned. Category pN0 is assigned if no evidence of regional lymph node metastasis is identified microscopically.

If a clinically occult regional lymph node metastasis is identified by sentinel lymph node biopsy and additional complete lymph node dissection is not performed, category pN1a(sn) is assigned. In contrast, all patients with occult regional lymph node metastasis who have undergone lymph node dissection with or without prior sentinel lymph node biopsy are assigned pN1a. Regional lymph node metastasis that is clinically detected via inspection, palpation, and/or radiographic imaging and is microscopically confirmed

is categorized as pN1b. Because the pathologist may not have this clinical information, subdivision of pN1 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. In the absence of lymph node metastasis, in-transit metastasis confirmed by pathological examination is assigned category pN2. If both in-transit and lymph node metastases are pathologically confirmed, category pN3 is assigned.[2]

M Category Considerations
Distant metastases are defined as metastases that have spread beyond the draining lymph node basin. The pM category is based on the location of microscopically confirmed distant metastases. Those involving distant skin, subcutis, or lymph nodes are classified as pM1a. Lung metastases are classified as pM1b. All other distant sites of metastasis are classified as pM1c.[2]

The category “MX” has been eliminated from the AJCC TNM system. pM should only be reported when metastases have been documented by pathologic examination (pM1 disease). pMX and pM0 should not be reported by the pathologist.

References

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Q. Merkel Cell Polyoma Virus (MCPyV) Status
Association with or presence of Merkel cell polyoma virus (MCPyV) classifies MCC into 2 groups of viral or ultraviolet light etiology.[1,2] MCPyV-positivity is associated with better outcome.[3,4] Various modalities including RNA in situ hybridization, DNA sequencing and serologic studies may be used to evaluate for MCPyV status,[5] of which immunohistochemical detection using the CM2B4 or Ab3 antibodies is most widely used.

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