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

Priya Rao, MD; Bonnie L. Balzer, MD, PhD; Bianca D. Lemos, MD; Nanette J. Liegeois, MD; Jennifer M. McNiff, MD; Paul Nghiem, MD, PhD; Victor G. Prieto, MD, PhD; M. Timothy Smith, MD; Bruce Robert Smoller, MD; Mark R. Wick, MD; David P. Frishberg, MD; for the Members of the Cancer Committee, College of American Pathologists

The College of American Pathologists offers these protocols to assist pathologists in providing clinically useful and relevant information when reporting results of surgical specimen examinations. The College regards the reporting elements in the ''Surgical Pathology Cancer Case Summary (Checklist)'' portion of the protocols as essential elements of the pathology report. However, the manner in which these elements are reported is at the discretion of each specific pathologist, taking into account clinician preferences, institutional policies, and individual practice.

The College developed these protocols as an educational tool to assist pathologists in the useful reporting of relevant information. It did not issue the protocols for use in litigation, reimbursement, or other contexts. Nevertheless, the College recognizes that the protocols might be used by hospitals, attorneys, payers, and others. Indeed, effective January 1, 2004, the Commission on Cancer of the American College of Surgeons mandated the use of the checklist elements of the protocols as part of its Cancer Program Standards for Approved Cancer Programs. Therefore, it becomes even more important for pathologists to familiarize themselves with these documents. At the same time, the College cautions that use of the protocols other than for their intended educational purpose may involve additional considerations that are beyond the scope of these documents.

Accepted for publication October 30, 2009.

From the Department of Pathology and Laboratory Medicine, Cedars-Sinai Medical Center, Los Angeles, California (Drs Rao, Balzer, and Frishberg); the Division of Dermatology, University of Washington Medical Center, Seattle (Drs Lemos and Nghiem); the Department of Dermatology, Johns Hopkins University School of Medicine, Baltimore, Maryland (Dr Liegeois); the Departments of Dermatology and Pathology, Yale University School of Medicine, New Haven, Connecticut (Dr McNiff); the Departments of Pathology and Dermatology, M. D. Anderson Cancer Center, University of Texas, Houston (Dr Prieto); the Department of Pathology and Laboratory Medicine, Medical University of South Carolina, Charleston (Dr Smith); the Department of Pathology, University of Arkansas for Medical Sciences, Little Rock (Dr Smoller); and the Department of Pathology, University of Virginia Health System, Charlottesville (Dr Wick).

The authors have no relevant financial interest in the products or companies described in this article.

Reprints: David P. Frishberg, MD, Department of Pathology and Laboratory Medicine, Cedars-Sinai Medical Center, 8700 Beverly Blvd, Room 8740, Los Angeles, CA 90048-1804 (e-mail: david.frishberg@cshs.org).

PROTOCOL FOR THE EXAMINATION OF SPECIMENS FROM PATIENTS WITH MERKEL CELL CARCINOMA OF THE SKIN

This protocol applies to Merkel cell carcinoma of cutaneous surfaces only. The seventh edition TNM staging system for Merkel cell carcinoma of the American Joint Committee on Cancer (AJCC) and the International Union Against Cancer (UICC) is recommended.

SURGICAL PATHOLOGY CANCER CASE SUMMARY (CHECKLIST)

Merkel Cell Carcinoma of the Skin: Incisional Biopsy, Excision, Reexcision, Lymphadenectomy

Note: Use of checklist is not required for punch or shave biopsies.

Select a Single Response Unless Otherwise Indicated

* Data elements with asterisks are not required. However, these elements may be clinically important but are not yet validated or regularly used in patient management.

Procedure
___ Biopsy, incisional
___ Excision
___ Reexcision
___ Lymphadenectomy, sentinel node(s)
___ Lymphadenectomy, regional nodes (specify): _____
_____
___ Other (specify): _____
___ Not specified

Macroscopic Tumor
___ Present
___ Not identified

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

Tumor Size
Greatest dimension: ___ cm
*Additional dimensions: ___ × ___ cm
___ Indeterminate (see ''Comment'')

***Tumor Thickness** (note **A**)
*Thickness: ___ mm
*Thickness: at least ___ mm (see ''Comment'')

Margins

Peripheral Margins

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

Lymph-Vascular Invasion

___ Not identified
___ Present
___ Indeterminate

Invasion of Bone, Muscle, Fascia, or Cartilage

___ Not identified
___ Present (specify structures involved): _____
___ Not applicable (eg, for superficial biopsy)

***Mitotic Index** (note **B**)

*___ $<1/mm^2$
*___ Specify: ___ $/mm^2$

***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

Lymph Nodes (required only if lymph nodes are present in the specimen) (note **F**)

Number of sentinel nodes examined: _____
Total number of nodes examined (sentinel and non-sentinel): ____
Number of lymph nodes with metastases: _____
Macroscopic tumor:
___ Not identified
___ Present
___ Indeterminate
*Size of largest metastatic focus: ___ mm
*Extranodal extension:
*___ Present
*___ Not identified

Pathologic Staging (pTNM) (note **G**)

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

___ m (multiple)
___ r (recurrent)
___ y (posttreatment)

Primary Tumor (pT)

___ pTX: Primary tumor cannot be assessed
___ pT0: No evidence of primary tumor (eg, nodal/metastatic presentation without associated primary)
___ pTis: In situ primary tumor
___ pT1: ≤2 cm maximum tumor dimension
___ pT2: >2 cm but not more than 5 cm maximum tumor dimension
___ pT3: >5 cm maximum tumor dimension
___ pT4: Primary tumor invades bone, muscle, fascia, or cartilage

Regional Lymph Nodes (pN)

___ pNX: Nodes not examined pathologically
___ pN0: Nodes negative by pathologic exam
___ pN1: Metastasis in regional lymph node(s)
*___ pN1a: Micrometastasis
*___ pN1b: Macrometastasis
___ pN2: In transit metastasis

Distant Metastasis (pM)

___ Not applicable
___ pM1: Metastasis beyond regional lymph nodes
*___ pM1a: Metastasis to skin, subcutaneous tissues, or distant lymph nodes
*___ pM1b: Metastasis to lung
*___ pM1c: Metastasis to all other visceral sites

***Additional Pathologic Findings**

*Specify: _____

***Comment(s):**

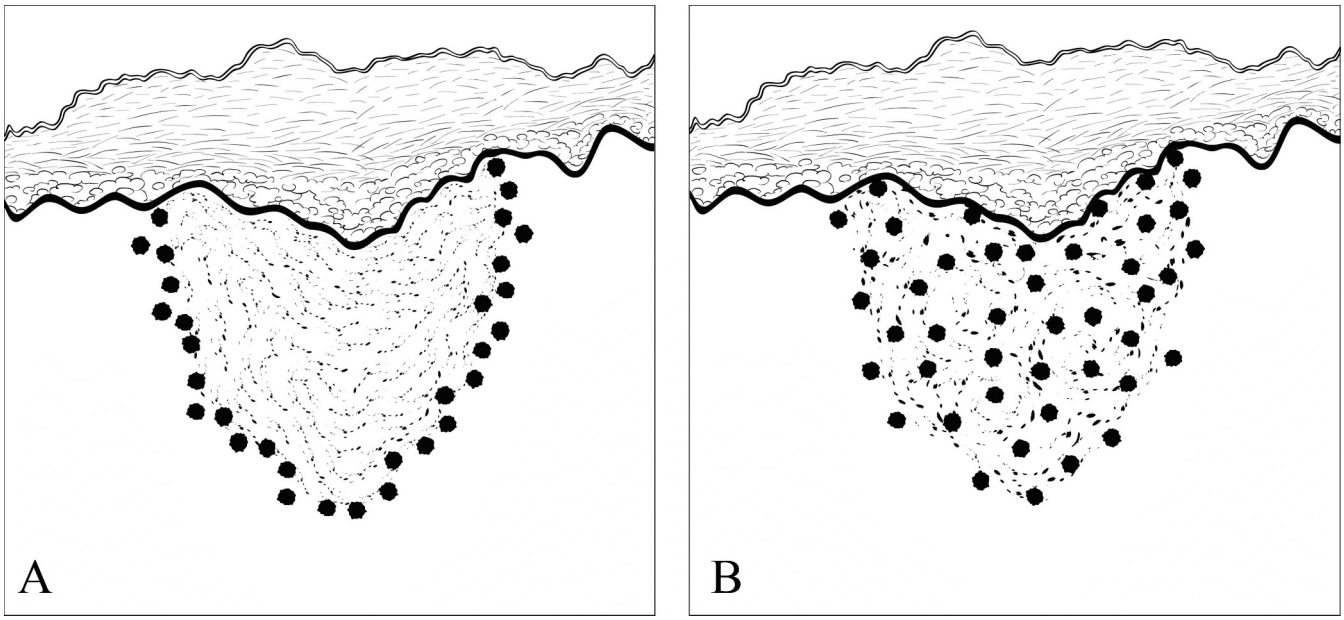
EXPLANATORY NOTES

A: Tumor Thickness.—There are published[1] and unpublished data from 3 independent prospective cohorts of patients with Merkel cell carcinoma examining tumor thickness (measured in millimeters from the stratum granulosum to the deepest infiltrating tumor cells) as a prognostic indicator for outcome. 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 third 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 Index.—The presence of more than 10 mitotic figures per high-power field (HPF) has been shown to correlate with large tumor size as well as a poor prognosis.[2,3] 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 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 checklist item remains optional at this time.

It has also been suggested that a MIB-1 proliferation index of greater than 50% is associated with a significantly worse prognosis.[3]



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. From Frishberg DP et al.[8] Reproduced with permission from Archives of Pathology & Laboratory Medicine. *Copyright 2009. College of American Pathologists.*

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 more than 5 mm.[4] However, there are conflicting data on the subject.[3]

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

Tumor-Infiltrating Lymphocytes Not Identified: No lymphocytes present, or lymphocytes present but they do not infiltrate tumor at all.

Tumor-Infiltrating Lymphocytes Nonbrisk: Lymphocytes infiltrate tumor only focally or not along the entire base of the vertical growth phase.

Tumor-Infiltrating Lymphocytes Brisk: Lymphocytes diffusely infiltrate the entire base of the dermal tumor (Figure, A) or the entire invasive component of the tumor (Figure, B).

D: Tumor Growth Pattern.—In a series of 156 patients with Merkel cell carcinoma, nodular tumor growth pattern was found on both univariate 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.

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.—Merkel cell carcinoma has been shown to be strongly associated with a number of cutaneous and hematologic malignancies, chiefly squamous cell carcinomas and chronic lymphocytic leukemia.[5] The largest series studying the relationship of second neoplasms with Merkel cell carcinoma spanned a period of 16 years and 67 patients and found that the presence of any second neoplasm with Merkel cell carcinoma, whether concurrent or not, conferred a poor prognosis.

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 Merkel cell carcinoma to the lymph node may be difficult to identify on routine hematoxylin-eosin–stained sections. The use of immunostains has been shown to increase the sensitivity of identifying occult lymph node metastases.[6] It is strongly recommended that at least one 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 dotlike staining pattern. All immunohistochemical results should be documented in the final pathology report.

G: TNM Staging.—Recent analysis of more than 4000 patients with Merkel cell carcinoma (MCC) in the National Cancer Database was used to derive a 4-tier staging system to be adopted by the American Joint Committee on Cancer

(AJCC). Primary tumor dimension as a single variable was only weakly correlated with survival. The staging system takes into account tumor size (≤2 cm versus larger), nodal status, and metastatic disease for stratification.[7]

Those patients with MCC presentations that are indeterminate 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 or less (T1), more than 2 cm but 5 cm or less (T2), or more than 5 cm (T3). Extracutaneous invasion by the primary tumor into bone, muscle, fascia, or cartilage is classified as ''T4.''

Regional metastases most commonly present in the regional lymph nodes. A second staging definition is related to 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 with both clinical evidence of nodal metastases *and* pathologic examination confirming nodal metastases is defined by convention as ''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.

Primary Tumor (T)

TX Primary tumor cannot be assessed
T0 No evidence of primary tumor (eg, nodal/metastatic presentation without associated primary)
Tis In situ primary tumor
T1 Less than or equal to 2 cm maximum tumor dimension
T2 Greater than 2 cm but not more than 5 cm maximum tumor dimension
T3 More than 5 cm maximum tumor dimension
T4 Primary tumor invades bone, muscle, fascia, or cartilage

Regional Lymph Nodes (N)

cN0 Nodes not clinically detectable
cN1 Nodes clinically detectable
pNX Regional lymph nodes not examined pathologically
pN0 Nodes negative by pathologic examination
pN1 Metastasis in regional lymph node(s)
  pN1a Micrometastasis
  pN1b Macrometastasis
pN2 In transit metastasis

Distant Metastasis (M)

M0 No distant metastasis
M1 Metastasis beyond regional lymph nodes
M1a Metastasis to skin, subcutaneous tissues, or distant lymph nodes
M1b Metastasis to lung
M1c Metastasis to all other 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 that are 2 cm or less in size and stage II for primary tumors greater than 2 cm in size. Stages I and II are further divided into A and B substages based on method of nodal evaluation. Patients who have pathologically proven node-negative disease (by microscopic evaluation of their draining lymph nodes) have improved survival (substaged as ''A'') as compared with patients who are only evaluated clinically (substaged as ''B''). Stage II has an additional substage (''IIC'') for tumors with extracutaneous invasion (T4) and negative node status regardless of whether the negative node status was established microscopically or clinically. Stage III is also divided into A and B categories for patients with microscopically positive and clinically occult nodes (''IIIA'') and macroscopic nodes (''IIIB''). There are no subgroups of stage IV Merkel cell carcinoma.

Stage Groupings

Stage 0	Tis	cN0, pN0/pNx	M0
Stage IA	T1	cN0, pN0	M0
Stage IB	T1	cN0, pNx	M0
Stage IIA	T2/T3	cN0, pN0	M0
Stage IIB	T2/T3	cN0, pNx	M0
Stage IIC	T4	cN0, pN0/pNx	M0
Stage IIIA	Any T	cN0, pN1	M0
Stage IIIB	Any T	cN1, pN1/N2	M0
Stage IV	Any T	Any N	M1

References

1. Andea AA, Coit DG, Amin B, Busam KJ. Merkel cell carcinoma: histologic features and prognosis. *Cancer*. 2008;113(9):2549–2558.
2. 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.
3. Llombart B, Monteagudo C, López-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.
4. Mott RT, Smoller BR, Morgan MB. Merkel cell carcinoma: a clinicopathologic study with prognostic implications. *J Cutan Pathol*. 2004;31(3):217–223.
5. Brenner B, Sulkes A, Rakowsky E, et al. Second neoplasms in patients with Merkel cell carcinoma. *Cancer*. 2001;91(7):1358–1362.
6. Allen PJ, Busam K, Hill AD, Stojadinovic A, Coit DG. Immunohistochemical analysis of sentinel lymph nodes from patients with Merkel cell carcinoma. *Cancer*. 2001;92(6):1650–1655.
7. Merkel cell carcinoma. In: Edge SB, Byrd DR, Carducci MA, Compton CC, eds. *AJCC Cancer Staging Manual*. 7th ed. New York, NY: Springer; 2009.
8. Frishberg DP, Balch C, Balzer BL, et al. Protocol for the examination of specimens from patients with melanoma of the skin. *Arch Pathol Lab Med*. 2009; 133(10)1560–1567.