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

Protocol applies to Merkel cell carcinoma of cutaneous surfaces only.

Based on:

AJCC/UICC TNM, 8th edition
CAP Cancer Protocol version: MerkelCell 4.0.0.1
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Revision History:

None

Summary of Changes:

This protocol is revised to the 8th edition of the AJCC Cancer Staging Manual and the current version of the CAP Cancer Protocol MerkelCell 4.0.0.1.

Procedures Covered in this Protocol:

- Excision
- Re-excision
- Lymphadenectomy
  - Sentinel Nodes
  - Regional Nodes

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Molecular and Immunohistochemistry Considerations:

Immunohistochemistry for CK20 and most low molecular weight cytokeratins are positive. Additional immunostains to be considered are chromogranin, synaptophysin, CD56, neuron-specific enolase, and neurofilament. Many of the stains show the classic perinuclear dot-like staining pattern.

An MIB-1 proliferation index of greater than 50% is associated with a significantly worse prognosis.

Metastatic Merkel cell carcinoma to the lymph nodes may be difficult to identify on routine hematoxylin-eosin (H&E) stained sections. Before designating a lymph node as negative it is strongly recommended to perform at least one immunostain, including but not limited to AE1/AE3, CK116, Cam 5.2, CD56, CK20, synaptophysin, and/or chromogranin.

These tests can be performed on formalin fixed paraffin embedded tissue sections. The macroscopic description should provide the fixative used. 10% neutral buffered formalin is the preferred fixative. It is recommended that the duration of fixation be provided as well.

PROCEDURES AND GENERAL ANATOMIC CONSIDERATIONS:

- **Procedures Covered by this Protocol:**

  - Excision (ellipse, wide local excision, other)
  - Re-excision (ellipse, wide local excision, other)
  - Lymphadenectomy
    - Sentinel nodes
    - Regional nodes

- **Specimen Size and Extent of Resection:**

  - Excision
    - Measure the length and width of the skin surface and maximum depth/thickness.
  - Re-excision
    - Measure the length and width of the skin surface, and maximum depth/thickness.
  - Lymphadenectomy
    - Sentinel nodes – count and measure each node in three dimensions.
    - Regional nodes – count and give a range in size of lymph nodes submitted.

- **Specimen Integrity and Adequacy:**

  Note if defects to the margin or epithelium are present. Describe the anatomic location of the defect from the tumor and relevant margins. If defects involve the tumor and serve to hinder assessment of the final surgical margin, consultation with the surgeon for clarification should be considered, as well as differential application of ink to the margins in areas affected by defects as this may assist in creating a post-surgical treatment plan.

TUMOR ("T" of TNM)

- **Tumor Site(s):**

  - Specify tumor site on skin if known.

- **Specimen Laterality:**

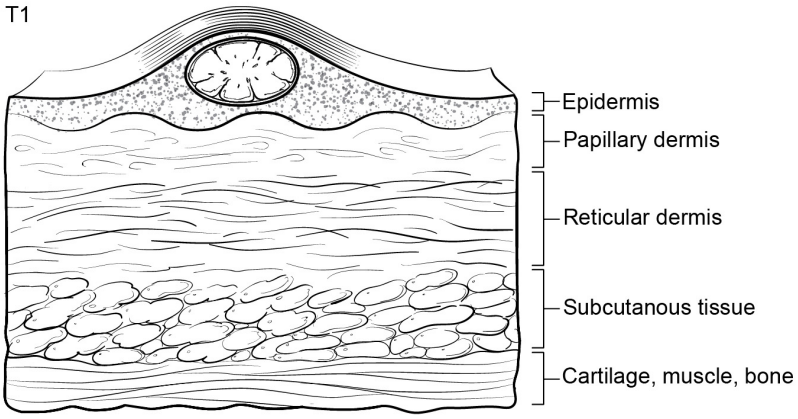
  - Right
  - Left
  - Midline
  - Other, as designated by the surgeon

- **Tumor Size and Thickness: *** *(Figure 1)*

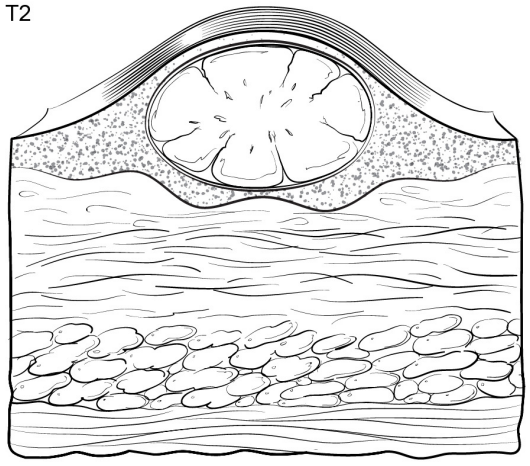
  - Provide three dimensions of tumor; providing thickness in mm. **
  - Maximum tumor diameter is the current staging parameter and an indicator of a high-risk tumor and may upstage the tumor from T1 to T3.

  *Histologic measurement of tumor diameter is subject to underestimation secondary to shrinkage of formalin-fixed tissue and inaccuracy of measurement of the largest diameter of oval tumors. If the clinical tumor size in not available, macroscopic or microscopic measurement should be used.

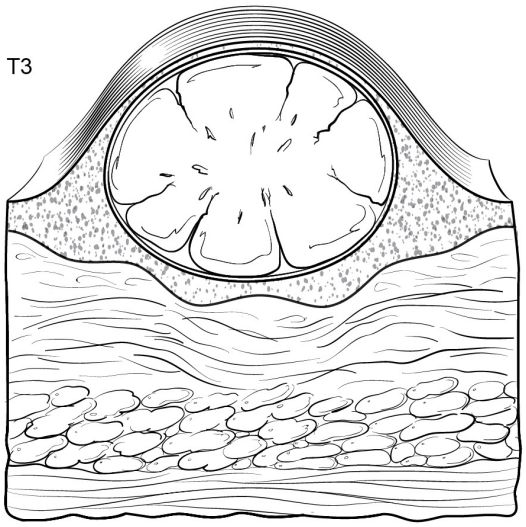
  **Based on the spherical shape of a primary Merkel cell carcinoma, one would expect tumor thickness to correlate with tumor diameter, which is an established prognostic factor currently required for the T category. Several studies have demonstrated a correlation between tumor thickness and prognosis in Merkel cell carcinoma.



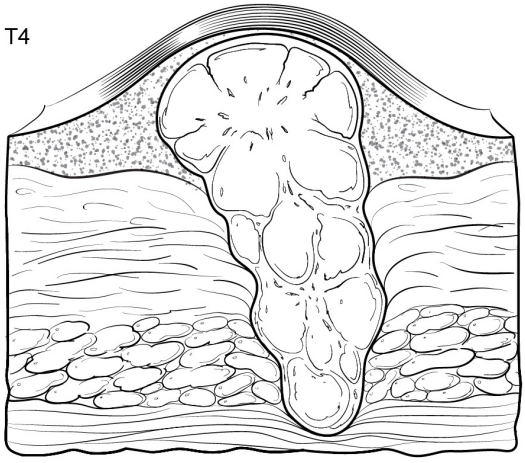
T1 - Maximum clinical tumor diameter 2 cm or less



T2 - Maximum clinical tumor diameter >2 cm but 5 cm or less



T3 - Maximum clinical tumor diameter >5 cm



T4 - Primary tumor invades fascia, muscle, cartilage or bone

Figure 1: Merkel Cell Carcinoma Tumor Size and T Criteria

- **Tumor Depth of Invasion and Relationship to Attached Organs/Structures:**

  - Recent studies suggest thickness of the tumor (Breslow) (measured in mm from the stratum granulosum to the deepest infiltrating tumor cells) may be an indicator of a high-risk tumor with deeper tumors being more likely to involve the lymph nodes.
    - The upper reference point is the top of the epidermis of the overlying skin.
    - The lower reference point is the deepest point of tumor invasion.

  - Indicate if the tumor is:
    - Confined to the epidermis
    - Extends into the subcutaneous tissue
    - Is transected at the deep resection margin
      - If the tumor is transected at the deep margin of the specimen, the depth is indicated as "at least ___mm" with a comment explaining the limitation of thickness assessment (specific to a final diagnosis comment).

  - Describe if the tumor invades into attached underlying organs / structures, (fascia, muscle, cartilage, or bone).

- **Tumor Growth pattern:**

  - Describe the tumor growth pattern.
    - Nodular pattern - well-circumscribed interface with the surrounding tissue
    - Infiltrative pattern - without a well-circumscribed interface with the surrounding tissue
    - Both nodular and infiltrative pattern - classified as infiltrative

Definition of Primary Tumor (pT)

pT Category	pT Criteria
pTX	Primary tumor cannot be assessed (e.g., 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 fascia, muscle, cartilage, or bone

***TNM Descriptors**:*

pT: The designation "T" refers to primary tumor that has not been previously treated. The symbol "p" refers to the pathologic classification of the TNM, as opposed to the clinical classification, and is based on gross and microscopic examination.
pT entails a resection of the primary tumor or biopsy adequate to evaluate the highest pT category.

pT(m)NM: For multiple primary tumors, the T score is modified, with the suffix "(m)" recorded in parentheses following the pT indicator (pT indicating primary tumor). Each tumor should be assessed independently of the others. Variability in histologic features should be considered with adequate sampling performed to either assure or exclude histologic variability. With regard to the T

score, for staging purposes, the pT score is established based on the primary tumor reaching the highest T classification (by size for pT1 – pT3; or by invasion into extracutaneous tissue for pT4).

ypTMN: If multimodality therapy (i.e., neoadjuvant chemotherapy, radiation therapy, or both chemotherapy and radiation therapy) has been utilized the T score will be modified with the prefix "y". The "y" categorization is not an estimate of tumor prior to multimodality therapy (i.e., before initiation of neoadjuvant therapy). Rather, the extent of tumor actually present at the time of examination must be disclosed. If neoadjuvant therapy renders macroscopic examination of tumor involvement inconclusive, dissection methods should be considered, which allow for mapping of the treated area, emphasizing the areas of potential deepest invasion.

rTNM: The "r" prefix indicates a recurrent tumor when staged after a documented disease-free interval.

aTNM: The "a" prefix designates the stage determined at autopsy.

Residual Tumor (R)

The absence or presence of residual tumor at the primary tumor site after treatment is denoted by the symbol R. The R categories for the primary tumor site are as follows:

R	R Definition
RX	Presence of residual tumor cannot be assessed
R0	No residual tumor
R1	Microscopic residual tumor
R2	Macroscopic residual tumor at the primary cancer site or regional nodal sites

- **Margins:**

  - The distance of tumor from closest **peripheral** and **deep** margin should be reported in mm for all specimens including small incisional biopsies. If the specimen is oriented, the anatomic location of the closest margins should be stated, and sections submitted demonstrating these areas. If a re-excision and no remaining tumor is identified macroscopically, the distance of prior surgery sequelae to the closest peripheral and deep margins should be reported, and sections submitted demonstrating these areas.

LYMPH NODES ("N" of TNM)

- **Lymph Nodes:**

Definition of Regional Lymph Node Pathological (pN)

pN Category	pN Criteria
pNX	Regional lymph nodes cannot be assessed (e.g., 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, microscopically confirmed*
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.*

If lymph nodes are identified:

- Specify the number of lymph nodes and sentinel lymph nodes examined.
- Provide a range in size of greatest dimension.
- Indicate the presence or absence of tumor involvement (correlating with macrometastases).
    - Specify the size of the largest metastatic deposit in mm.
- State if extranodal extension is macroscopically apparent and the location of the lymph nodes, if applicable.
- Submit all lymph nodes found.
- Smaller lymph nodes can be submitted in toto.
- Larger lymph nodes are bivalved and entirely submitted.
- If possible, submit lymph node sections so that the long axis of the lymph node is demonstrated.

METASTASIS ("M" of TNM)

- **Metastasis:**

When applicable, indicate whether distant metastasis is identified and specify the site.

Definition of Distant Metastasis
Pathological (M) (required only if confirmed pathologically)

pM Category	pM Criteria
M0	No distant metastasis detected on clinical and/or radiologic examination
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

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

Merkel cell carcinoma can metastasize to almost any organ site. Metastases occur most commonly to distant skin, followed by the lung, liver, bone, and central nervous system.

REFERENCE REVIEW:

1. Amin MB, Edge SB, Green FL, Byrd DR, et al. (Eds.) *AJCC Cancer Staging Manual,* 8th ed. New York; NY: Springer; 2017.

2. Rao P, Balzer BL, Lemos BD, et al. Protocol for the Examination of Specimens from Patients with Merkel Cell Carcinoma of the Skin. *CAP Cancer Protocol 3.0.1.1.* 2012.

3. Lester S. *Manual of Surgical Pathology*, 3rd ed. Philadelphia, PA: Elsevier Saunders; 2010.

4. Smoller BR, Bichakjian C, Brown JA, et al. Protocol for the Examination of Specimens from Patients with Merkel Cell Carcinoma of the Skin. *CAP Cancer Protocol Merkel Cell 4.0.0.1*. 2017.