MERKEL CELL CARCINOMA

Effective Date: March 2019
The recommendations contained in this guideline are a consensus of the Alberta Provincial Cutaneous Tumour Team and are a synthesis of currently accepted approaches to management, derived from a review of relevant scientific literature. Clinicians applying these guidelines should, in consultation with the patient, use independent medical judgment in the context of individual clinical circumstances to direct care.

All cancer drugs described in the guidelines are funded in accordance with the Outpatient Cancer Drug Benefit Program, at no charge, to eligible residents of Alberta, unless otherwise explicitly stated. For a complete list of funded drugs, specific indications, and approved prescribers, please refer to the Outpatient Cancer Drug Benefit Program Master List.

Participation of members of the Alberta Provincial Cutaneous Tumour Team in the development of this guideline has been voluntary and the authors have not been remunerated for their contributions. There was no direct industry involvement in the development or dissemination of this guideline. CancerControl Alberta recognizes that although industry support of research, education and other areas is necessary in order to advance patient care, such support may lead to potential conflicts of interest. Some members of the Alberta Provincial Cutaneous Tumour Team are involved in research funded by industry or have other such potential conflicts of interest. However the developers of this guideline are satisfied it was developed in an unbiased manner.
BACKGROUND

Merkel cell carcinoma (MCC) is a rare neuroendocrine tumour that accounts for a small proportion of cutaneous malignancies. MCC typically presents as a fleshy nodule with a red or blue discoloration and the majority occur in the head and neck region. Patients are generally older (mean patient age 75 years), often immunocompromised, fair-skinned women. Ultraviolet radiation may be an etiological factor in MCC as most tumours are located on sun-exposed areas of the skin. Heath developed the AEIOU mnemonic for clinical features associated with Merkel cell carcinoma. In his study, 89% of patients presented with 3 or more of the AEIOU clinical features (asymptomatic, expanding rapidly, immune suppressed, older than 50 years of age, UV exposed site). There is mounting evidence that the tumour is due to reactivation of a latent viral infection, as polyomavirus particles are present in the majority of cases (i.e., up to 80%).

Merkel cell carcinoma is an aggressive tumour associated with a high rate of recurrence and carries a poor prognosis. The overall 5-year survival rates range from 30 to 64%. The local recurrence rate is 26-44% after primary treatment. As many as 30% of patients have regional lymph node involvement at the time of diagnosis with a 55% rate of regional lymph node relapse after treatment and a 34-49% rate of distant metastasis. There have been reports of patients with spontaneous resolution of MCC. Almost all patients with visceral metastasis (stage IV) eventually die of the disease. Given the relative rarity of the tumour, no large multicentre randomized trials have been conducted to assess staging, treatment modality, recurrence rate, and overall survival. Therefore, there is little evidence to guide practice for MCC. The purpose of this guideline is to provide recommendations on the management of MCC in Alberta. Whenever possible recommendations are evidence-based and when insufficient evidence exists provincial consensus has been used to guide practice.

GUIDELINE QUESTIONS

- What is the widely accepted staging classification for Merkel cell carcinoma (MCC)?
- What is the most appropriate treatment for MCC Stage I-IV?
- What are the management strategies for recurrence of MCC?
- How should a patient with MCC be followed?

DEVELOPMENT AND REVISION HISTORY

This guideline was reviewed and endorsed by the Alberta Cutaneous Tumour Team. Members of the Alberta Cutaneous Tumour Team include surgeons, dermatologists, dermatopathologists, medical oncologists, radiation oncologists, nurses, and researchers. Evidence was selected and reviewed by a working group comprised of members from the Alberta Cutaneous Tumour Team and a Knowledge Management Specialist from the Guideline Resource Unit. A detailed description of the methodology followed during the guideline development process can be found in the Guideline Resource Unit Handbook.

This guideline was originally developed in May 2008. This guideline was revised in November 2009, May 2010, March 2011, July 2015 and most recently in February 2019.
SEARCH STRATEGY

The MEDLINE, CINAHL, Cochrane, ASCO abstracts and proceedings, and PubMed databases were searched for practice guidelines, systematic reviews, and clinical trials relevant to the topic. In addition, individual guideline organizations were searched for relevant practice guidelines. Search terms included ‘Merkel cell carcinoma’ and ‘skin or cutaneous’. Non-English publications were excluded, as well as publications that included less than ten patients with Merkel cell carcinoma. The original search included publications from the year 1966 and onward with subsequent updates covering publications from the date of the last search through the date on which the update was conducted. The latest update searched MEDLINE and PubMed databases (January 2015 through December 2018) and retrieved 261 articles. A total of 12 relevant articles were identified. In addition, four clinical practice guidelines were identified from European Dermatology Forum and European Association of Dermato-Oncology, Fred Hutchinson Cancer Research Center, the National Comprehensive Cancer Network and the National Institute for Health and Care Excellence.

TARGET POPULATION

The recommendations outlined in this guideline apply to adults over the age of 18 years with Merkel cell carcinoma of the skin. Different principles may apply to patients with other cutaneous malignancies (i.e., melanoma, basal cell carcinoma, etc.) and those with Merkel cell carcinoma of non-cutaneous origin or who present with metastatic Merkel cell carcinoma from an unknown primary. Different principles may apply to pediatric patients as well.

RECOMMENDATIONS

Merkel cell carcinoma is an uncommon cancer and there is a lack of strong evidence to guide practice. Recommendations included are based on available evidence (e.g., poor quality evidence such as case series) and Provincial Tumour Team consensus. Treatment should be individualized based on patients and disease factors.

1. Staging and Work-up

- Patients should be staged using the 8th Edition American Joint Committee on Cancer staging system for MCC, see Appendix A18,19.
- History, physical examination, and relevant investigation should guide further treatment.
- Imaging where clinical evidence suggests metastases. FDG-PET/CT scan is preferred, body CT is an alternative if the former is not available.

2. Summary of Treatment Options

The treatment of choice for MCC is surgical resection. The tumour is both radiosensitive and chemosensitive, raising the possibility of other strategies in treating this condition. As such patients would benefit from management in multidisciplinary settings.
Surgery

- Wide local excision (i.e., intra-operative margins of 2 cm if possible, with the final goal being histologically clear pathological margins) is recommended whenever possible.
- Mohs micrographic surgery is appropriate as a tissue-sparing technique when the tumour is in a sensitive area such as head and neck area and there are concerns of functional impairment from too radical an excision, provided the tumour is de-bulked first and submitted for pathological review using permanent sections. Evaluation of re-excision specimens should include a comment to the extent of clear margins.
- Sentinel lymph node biopsy (protocol below) should be performed simultaneously with excision if possible.
- Standard requirements to be included in the pathology report have been defined by the College of American Pathologists and can be found in the Appendix B.
- The need for complete lymph node dissection should be at the discretion of the surgeon based on comorbidity factors, age, and whether there is a high probability of persistent disease.

Radiation

- Local radiation therapy can be considered in patients who are deemed to be poor operative candidates, who refuse surgery, or who have metastatic disease. In those patients without distant metastatic disease, they are offered primary radiotherapy to a high dose (55-66 Gy to the primary site and the draining regional lymphatics, delivered in 2-2.5 Gy/ day fractions). Concurrent chemotherapy using cisplatin or carboplatin plus etoposide will be considered in these cases.
- In patients with metastatic disease and uncontrolled primary disease, patients will be offered palliative radiotherapy to achieve local control.
- Adjuvant radiation therapy to the primary site and to the regional lymph node basin should be considered, especially when high risk features are present, including T2 disease, surgical margins less than 0.5cm, lymphvascular invasion, or perineural invasion. All Mohs surgery patients should be consulted for discussion about radiotherapy, since margin status is usually unclear. Adjuvant treatment will be delivered to primary with or without nodes to a dose of 50-55Gy in 2-2.5Gy fractions. In cases with gross margin involvement, a boost will be considered.
- As an alternative to adjuvant radiation therapy, observation following surgery could be considered in select patients (i.e., small primary, widely excised, no risk factors).
- Other than on the face, wide margins of 5 cm around the primary site should be used, because of risk of satellite development.

Chemotherapy

- Adjuvant chemotherapy is not recommended unless administered to debulk disease with radiotherapy.
- Chemotherapy can be used on a case-by-case basis for regional or disseminated disease:
  - Cisplatin ± etoposide (regional or disseminated)
  - Carboplatin ± etoposide (regional or disseminated)
  - Topotecan (disseminated)

Immunotherapy

- Recommended option for disseminated disease: avelumab, pembrolizumab, nivolumab.
- Avelumab dose: 10 mg/kg every 2 weeks by intravenous infusion over 60 minutes.
3. **Summary of Clinical Scenarios:**

**A. Clinical Node-Negative**
- Sentinel lymph node biopsy recommended prior to surgical removal of the primary tumour.
- Wide local excision with clear margins.
- Postoperative radiation therapy of the primary site or observation (limited to small primary lesions <1 cm, that have been widely excised and no adverse risk factors).
- Positive sentinel lymph node biopsy:
  - Recommended multidisciplinary tumour board consultation, baseline imagine, participation in clinical trial, and lymph node dissection and/or radiation therapy to the nodal basin.
  - Adjuvant radiation therapy after lymph node dissection for patients with multiple nodes and/or presence of extracapsular extension.
- Negative sentinel lymph node biopsy:
  - Observation of nodal basin.

**B. Clinical Node-Positive**
- Confirm diagnosis by fine-needle aspiration or core biopsy with appropriate immunopanel.
- Recommend imaging with FDG PET/CT where possible.
- If no distant metastasis, recommend multidisciplinary tumour board consultation and lymph node dissection with radiation therapy (dose of 50-60 Gy if extracapsular extension is detected or multiple nodes involved).
- Lymph node dissection is the preferred approach for first line treatment.
- Open biopsy to confirm initial negative biopsy may be considered.

**C. Metastatic**
- Multidisciplinary tumour board consultation to consider: immunotherapy preferred or combination of chemotherapy, radiation therapy or surgery as palliative care.
- Full imaging work up.
- Management should be individually tailored.
- Clinical trial is preferred.

4. **Follow-up**

- Physical exam including complete skin exam and regional lymph node exam.
- Imaging performed at the discretion of treating physician (FDG-PET/CT, MRI, neck/ chest/ abdomen/ pelvis CT).
- Frequency:
  - Year 1-2: every 4 months
  - Years 3-5: every 6 months
5. Management of Recurrences

- Local or regional recurrences: individualize treatment.
- Disseminated recurrence: patients should be monitored closely for recurrence of locoregional or distant disease. Lymph node or distant metastatic disease has a uniformly grave prognosis; however, there may be a role for chemotherapy in prolonging survival.
- Given the complex issues in dealing with this aggressive tumour, patients are best served by being cared for in a tertiary care setting with a multidisciplinary approach.


Lymph node deposits of metastatic MCC may be difficult to identify on routine hematoxylin and eosin (H&E)-stained sections. As for melanoma and breast carcinoma, the use of immunohistochemistry has been shown to increase the sensitivity of identifying occult lymph node metastases. Based on recommendations from the College of American Pathologists and discussions with M.D. Anderson Cancer Center, the following protocol is suggested:

- Bisect sentinel lymph node.
- If initial H&E section is negative, then cut 200 µm into block and repeat H&E stain.
- Perform anti-keratin immunohistochemistry, preferably using an antibody cocktail, including antibody against low-molecular weight keratin (e.g. Cam 5.2).
- If any concerns regarding non-epithelial keratin staining, anti-cytokeratin 20 immunohistochemistry can be performed.

The number, size, and intra-nodal location of any metastatic deposits of MCC should be documented in the final pathology report (see Appendix B).

DISCUSSION

Presentation and Work-Up

MCC is rarely suspected at the time of initial presentation. Heath developed the AEIOU mnemonic for clinical features associated with Merkel cell carcinoma. In his study 89% of patients presented with 3 or more of the AEIOU clinical features (asymptomatic, expanding rapidly, immune suppressed, older than 50 years of age, UV exposed site). It generally presents as cutaneous disease only, however, some patients present with evidence of regional or distant metastasis. The most common location of metastasis are the draining lymph node basin (27-60%), distant skin (9-30%), lung (10-23%), central nervous system (18%), bone (10-15%), and liver (30%). Other reported areas of distant metastasis include testis, pancreas, heart, bone marrow, pleura, parotid, gastrointestinal tract, prostate and bladder. The clinical differential diagnosis for MCC includes basal cell carcinoma, squamous cell carcinoma, cyst, pyogenic granuloma, amelanotic malignant melanoma, lymphoma cutis, and lipoma.

The work-up for MCC includes physical examination, biopsy, and imaging. The primary skin lesion is generally asymptomatic. Patients with disseminated disease may have constitutional symptoms (e.g. fatigue), localizing signs (e.g. hemoptysis, neurologic defect, adenopathy secondary to metastasis), or both. MCC most commonly presents as a blue or red solitary, dome-shaped nodule or firm plaque. Lesions are most often smaller than 2 cm in greatest dimension, but may exceed 15 cm in diameter.
Lesions on the head and neck typically are smaller than lesions in other locations\textsuperscript{5}. The most common locations for MCC include the head and neck region and the extremities; however, any mucosal or cutaneous site may be affected. The surface is often shiny with telangiectasias. Ulceration is uncommon.

Biopsy includes hematoxylin and eosin staining, as well as immunohistochemistry (i.e. CK-20, CK-7, and/or thyroid transcription factor-1). For diagnostic imaging FDG-PET/CT scans are indicated to detect distant metastases. A meta-analysis of six studies reported the sensitivity and specificity of FDG-PET/CT as 90\% and 98\%, respectively\textsuperscript{26}. A prospective study found similar results with 56 scans of patients with MCC and that FDG-PET/CT imaging lead to a change in patient management in approximately a third of patients\textsuperscript{27}. The following additional tests may also be indicated: sentinel lymph node biopsy (SLNB) to determine the presence or absence of lymph node disease (e.g. all blue stained nodes and nodes with radioactive counts exceeding 10\% of the ex vivo count of the hottest lymph node), and additional studies as clinically indicated (i.e. CT scan of chest/abdomen).

**Treatment**

MCC is an uncommon skin cancer in the larger group of small cell neuroendocrine tumours and therefore there is limited evidence to guide practice for MCC. While the most common neuroendocrine tumour, small cell lung cancer, has a variety of treatment modalities including hypo- or hyper-fractionated radiation therapy with concurrent chemotherapy, chemotherapy alone, prophylactic whole brain radiotherapy, and consolidative radiation for responders to chemotherapy, it is not clear what the optimal treatment modalities, combination, sequencing, and techniques are for MCC.

Primary therapy for MCC consists of surgery, including wide local excision with intra-operative margins of 2 cm when possible (at least 1 cm margin)\textsuperscript{3}, to achieve histologically clear pathological margins whenever possible. Mohs micrographic surgery can be considered as a tissue-sparing technique when the tumour is located in an area such as the head and neck where extensive surgery may lead to functional impairment or greatly affect cosmesis\textsuperscript{28,29}. Nodal assessment with SLNB should be performed simultaneously with excision if possible, as information gained from the biopsy predicts the need for further treatment\textsuperscript{30}. A SEER analysis of 1193 patients with stage I-II MCC showed that five-year MCC-specific survival was increased in patients who underwent SLNB as compared to those who didn’t (79.2\% vs. 73.8\%; p=0.004)\textsuperscript{31}. A meta-analysis, of seven studies and found SLNB significantly predicted better disease free survival for clinically node negative patients than nodal observation (HR 1.61, 95\% CI 1.05-2.46)\textsuperscript{32}. Completion lymph node dissection or radiation therapy or both should be given to the nodal basin if the SLNB is positive\textsuperscript{33}. A review of a prospective database of 364 patients with stage I-III MCC who underwent complete resection with or without adjuvant local radiation therapy (23\%), lymph node radiation therapy (23\%), and chemotherapy (15\%) found that among 108 recurrences, the majority (80\%) occurred in patients who had clinically involved lymph nodes or patients who did not undergo pathologic lymph node evaluation\textsuperscript{30}.

Definitive radiation therapy is a reasonable treatment for unresectable stage I-III MCC. A systemic review of 18 articles assessed the relapse and death rates of 48 stage I/II and 20 stage III MCC patients receiving either local or local-regional irradiation\textsuperscript{34}. This study found that stage I/II patients treated with local irradiation had a relapse rate of 25\% and 4\% of patients died from MCC, and those treated with local-regionial irradiation had a relapse rate of 21\% and 8\% died from MCC. Stage III patients treated with local-regionial irradiation had a 60\% relapse rate and 35\% of patients died from MCC. A similar systemic review of 23 articles found a cumulative post radiation in-field recurrence rate of 11.7\%\textsuperscript{35}. There was no association between radiation dose and recurrence (p=0.197).
Adjuvant radiation therapy to the primary site should be considered for MCC\textsuperscript{36}. An analysis of SEER data from patients with histologically confirmed MCC who underwent surgical resection with or without adjuvant radiation therapy evaluated MCC-specific and overall survival\textsuperscript{37}. This study found that patients who received radiation therapy had improved overall survival (p=0.03) but not MCC-specific survival (p=0.26). A similar retrospective study found that on multivariate analysis, radiation therapy was associated with improved overall survival (HR 0.53, 95% CI 0.31-0.93; p=0.030) and MCC-specific survival (HR 0.42, 95% CI 0.26-0.70; p=0.001)\textsuperscript{38}. Another retrospective study found the opposite to be true; improved cancer-specific survival (65\% vs. 49\%; p=0.03) but not overall survival (56\% vs. 46\%; p=0.20) with adjuvant radiation therapy in 180 patients with mostly localized MCC\textsuperscript{39}. Adjuvant radiation therapy is indicated in patients with nodal disease (i.e., clinically positive or identified by SLNB). Patients who do not undergo SLNB can be considered for adjuvant radiation therapy\textsuperscript{36}. A randomized controlled trial in stage I patients treated by wide local excision and local radiation therapy, plus regional adjuvant radiation therapy or observation found no significant improvement in overall survival (p=0.989) or progression-free survival (p=0.4) with regional radiation therapy. However, the regional recurrence rate was reduced (0\% vs. 16.7\%; p=0.007) with treatment\textsuperscript{40}.

While there is limited evidence to support adjuvant chemotherapy in patients with MCC, adjuvant chemotherapy can be considered in patients with advanced disease including those with a positive SLNB\textsuperscript{41}. Some patients do respond to chemotherapy, but toxicity must be weighed against the benefits. Agents that have been used include cisplatin or carboplatin, etoposide, and topotecan (in older patients)\textsuperscript{42-46}. Metastatic MCC should also be considered for chemotherapy\textsuperscript{47}.

Systemic immunotherapy should be considered as a treatment option for disseminated disease. Phase II of the JAVELIN Merkel 200 trial studied Avelumab in patients with metastatic MCC either as 1\textsuperscript{st} line therapy\textsuperscript{48} or in chemotherapy-refractory MCC\textsuperscript{49-51}. In patients with no prior systemic therapy, after a median follow-up of 5.1 months (range 0.3-11.3 months), the overall response rate was 62.1\%, and 83\% of patients had a duration of response of at least 6 months\textsuperscript{48}. In patients treated with avelumab after progression on chemotherapy, the overall response rate was 33.0\% after a minimum follow up of 12 months. At the time of data cut-off, 72.4\% of responses were ongoing\textsuperscript{51}. A different phase II trial studied patients with advanced MCC treated with pembrolizumab\textsuperscript{52}; after a median follow up of 33 weeks (range 7-53 weeks) the overall response rate was 56\%, with a response duration ranging from 2.2-9.7 months. The ongoing CHECKMATE 358 phase I/II trial is studying nivolumab in patients with resectable MCC\textsuperscript{53}. In patients treated with nivolumab prior to surgery, 80\% had tumour regression and 65\% had a major pathologic response including 8 complete responses.

**GLOSSARY OF ABBREVIATIONS**

<table>
<thead>
<tr>
<th>Acronym</th>
<th>Description</th>
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<tbody>
<tr>
<td>MCC</td>
<td>Merkel cell carcinoma</td>
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<tr>
<td>MSKCC</td>
<td>The Memorial Sloan-Kettering Cancer Center</td>
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<tr>
<td>SEER</td>
<td>Surveillance, Epidemiology, and End Results Program</td>
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<tr>
<td>SLNB</td>
<td>Sentinel Lymph Node Biopsy</td>
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DISSEMINATION

- Present the guideline at the local and provincial tumour team meetings and weekly rounds.
- Post the guideline on the Alberta Health Services website.
- Send an electronic notification of the new guideline to all members of CancerControl Alberta

MAINTENANCE

A formal review of the guideline will be conducted at the Annual Provincial Meeting in 2021. If critical new evidence is brought forward before that time, however, the guideline working group members will revise and update the document accordingly.

REFERENCES


17. Argiris A. CLINICAL ONCOLOGY, 3RD EDITION. Shock 2005;23(3).


22. Prieto V. Dr. V. prieto, department of pathology, university of texas M.D.; personal communication. 2010 April 4.


APPENDIX A

AJCC (8th Edition) Anatomic Stage/Prognostic Groups for Merkel Cell Carcinoma

Primary Tumor (T)
TX Primary tumor cannot be assessed
T0 No evidence of primary tumor
Tis In situ primary tumor
T1 ≤ 2 cm maximum tumor diameter
T2 > 2 cm but ≤ 5 cm maximum tumor diameter
T3 > 5 cm maximum tumor diameter
T4 Primary tumor invades bone, muscle, fascia, or cartilage

Regional Lymph Nodes (N) Clinical (N)
NX Regional nodes cannot be assessed
N0 No regional node metastasis
N1 Metastasis in regional lymph node(s)
N2 In transit metastasis\(^a\) without lymph node metastasis
N3 In-transit metastasis\(^a\) with lymph node metastasis

Pathological (pN)
pNX Regional lymph nodes cannot be assessed
pN0 No regional lymph node metastasis
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\(^a\) without lymph node metastasis
pN3 In-transit metastasis\(^a\) with lymph node metastasis

Distant Metastasis (M) Clinical (M)
M0 No distant metastasis
M1 Distant metastasis
M1a distant skin, distant subcutaneous tissues, or distant lymph nodes
M1b to lung
M1c to all other visceral sites

Pathological (M)
M0 No distant metastasis
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

\(^a\)In transit metastasis: a tumor distinct from the primary lesion and located either (1) between the primary lesion and the draining regional lymph nodes or (2) distal to the primary lesion.

<table>
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<tr>
<th>Clinical (cTNM)</th>
<th>Pathological (pTNM)</th>
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<tr>
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</tr>
<tr>
<td>T1</td>
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<td>T2-3</td>
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<td>T4</td>
<td>N0</td>
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<td>T0-4</td>
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<td>T0-4</td>
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<tr>
<td>T1-4</td>
<td>N1a(sn) or N1a</td>
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<td>T0</td>
<td>N1b</td>
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<td>T1-4</td>
<td>N1b-3</td>
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<td>T0-4</td>
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APPENDIX B

Reporting Elements for Merkel Cell Carcinoma Following Incisional Biopsy, Excision, Re-Excision, or Lymphadenectomy (College of American Pathologists, 2017)21

Procedure
___ 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: ___ cm
+ Additional dimensions: ___ x ___ cm
___ Cannot be determined (explain):

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

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
___ 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/mm²
  + ___ ≥ 1/mm² (specify number): ______

+ Tumor-Infiltrating Lymphocytes
  + ___ Not identified
  + ___ Present, nonbrisk
  + ___ Present, brisk

+ Tumor Growth Pattern
  + ___ Nodular
  + ___ Infiltrative

+ Presence of Second Malignancy
  + ___ Present (specify type): __________________________
  + ___ Not identified

Regional Lymph Nodes
___ 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

+ Extramodal 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)

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
- 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 ≤ 5cm
- 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 (e.g., previously removed for another reason or NOT removed for pathological evaluation) not examined pathologically
- pN0: No regional lymph nodes 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
- pN1b: Clinically and/or radiologically detected regional lymph node metastasis#
- pN2: In transit metastasis without lymph node metastasis
- pN3: In transit metastasis 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 tissues, or distant lymph nodes 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 (optional)
+Specify: ______________________________
+ Comment(s):

+ 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