# Merkel Cell Carcinoma

## NCCN Evidence Blocks™

### Panel Members

<table>
<thead>
<tr>
<th>University/Institution</th>
<th>Panel Members</th>
</tr>
</thead>
<tbody>
<tr>
<td>University of Michigan</td>
<td>Christopher K. Bichakjian, MD/Chair ᵃ</td>
</tr>
<tr>
<td>Comprehensive Cancer Center</td>
<td>Anita Engh, PhD</td>
</tr>
<tr>
<td>Karin G. Hoffmann, RN, CCM</td>
<td></td>
</tr>
<tr>
<td>The Ohio State University Comprehensive Cancer Center - James Cancer Hospital and Solove Research Institute</td>
<td>Thomas Olencki, DO/Vice-Chair †</td>
</tr>
<tr>
<td>University of Tennessee Health Science Center</td>
<td>Kris Fisher, MD ᵃ ≠</td>
</tr>
<tr>
<td>Case Comprehensive Cancer Center/University Hospitals Seidman Cancer Center and Cleveland Clinic Taussig Cancer Institute</td>
<td>Brian Gastman, MD Ŷ</td>
</tr>
<tr>
<td>Mayo Clinic Cancer Center</td>
<td>Roy C. Grekin, MD ᵃ ¶</td>
</tr>
<tr>
<td>UCSF Helen Diller Family Comprehensive Cancer Center</td>
<td>Paul Nghiem, MD ᵃ</td>
</tr>
<tr>
<td>Dana-Farber/Brigham and Women’s Cancer Center</td>
<td>Fred Hutchinson Research Center/Seattle Cancer Care Alliance</td>
</tr>
<tr>
<td>Memorial Sloan Kettering Cancer Center</td>
<td>Igor Puzanov, MD ↓</td>
</tr>
<tr>
<td>Roswell Park Cancer Institute</td>
<td>Chrysalynie D. Schmults, MD ᵃ ¶</td>
</tr>
<tr>
<td>Memorial Sloan Kettering Cancer Center</td>
<td>Ashok R. Shaha, MD ↓ ᵃ ¶</td>
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<tr>
<td>Memorial Sloan Kettering Cancer Center</td>
<td>Valencia Thomas, MD ᵃ</td>
</tr>
<tr>
<td>MD Anderson Cancer Center</td>
<td>Yaohui G. Xu, MD, PhD ᵃ</td>
</tr>
<tr>
<td>University of Wisconsin Carbone Cancer Center</td>
<td>John A. Zic, MD ᵃ</td>
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<tr>
<td>Vanderbilt-Ingram Cancer Center</td>
<td>John A. Zic, MD ᵃ</td>
</tr>
</tbody>
</table>

**Disclosures**

- ᵃ Dermatology
- ᵇ Diagnostic/Interventional radiology
- † Surgery/Surgical oncology
- ¶ Otolaryngology
- ≠ Pathology/Dermatopathology
- ↑ Medical oncology
- ᵃ Internal medicine
- § Radiotherapy/Radiation oncology
- Ŷ Reconstructive surgery
- ¶ Hematology/Hematology oncology
- * Discussion Section Writing Committee

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Merkel Cell Carcinoma

NCCN Evidence Blocks™

Clinical Trials: NCCN believes that the best management for any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged. To find clinical trials online at NCCN Member Institutions, click here: nccn.org/clinical_trials/physician.html.

NCCN Categories of Evidence and Consensus: All recommendations are category 2A unless otherwise indicated. See NCCN Categories of Evidence and Consensus.

NCCN Merkel Cell Carcinoma Panel Members

NCCN Evidence Blocks Definitions (EB-1)

Merkel Cell Carcinoma

Clinical Presentation, Preliminary Workup, Diagnosis, Additional Workup, and Clinical Findings (MCC-1)
Primary and Adjuvant Treatment of Clinical N0 Disease (MCC-2)
Primary and Adjuvant Treatment of Clinical N+ Disease (MCC-3)
Treatment of Clinical M1 Disease (MCC-4)
Follow-up and Recurrence (MCC-5)
Principles of Pathology (MCC-A)
Principles of Radiation Therapy (MCC-B)
Principles of Excision (MCC-C)
Principles of Systemic Therapy (MCC-D)
Staging (ST-1)

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### Efficacy of Regimen/Agent

<table>
<thead>
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<th>Score</th>
<th>Description</th>
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<tr>
<td>5</td>
<td>Highly effective: Cure likely and often provides long-term survival advantage</td>
</tr>
<tr>
<td>4</td>
<td>Very effective: Cure unlikely but sometimes provides long-term survival advantage</td>
</tr>
<tr>
<td>3</td>
<td>Moderately effective: Modest impact on survival, but often provides control of disease</td>
</tr>
<tr>
<td>2</td>
<td>Minimally effective: No, or unknown impact on survival, but sometimes provides control of disease</td>
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<td>1</td>
<td>Palliative: Provides symptomatic benefit only</td>
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### Safety of Regimen/Agent

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<th>Score</th>
<th>Description</th>
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<tr>
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<td>Usually no meaningful toxicity: Uncommon or minimal toxicities; no interference with activities of daily living (ADLs)</td>
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<td>4</td>
<td>Occasionally toxic: Rare significant toxicities or low-grade toxicities only; little interference with ADLs</td>
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<tr>
<td>3</td>
<td>Mildly toxic: Mild toxicity that interferes with ADLs</td>
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<td>2</td>
<td>Moderately toxic: Significant toxicities often occur but life threatening/fatal toxicity is uncommon; interference with ADLs is frequent</td>
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<tr>
<td>1</td>
<td>Highly toxic: Significant toxicities or life threatening/fatal toxicity occurs often; interference with ADLs is usual and severe</td>
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### Quality of Evidence

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<tr>
<td>5</td>
<td>High quality: Multiple well-designed randomized trials and/or meta-analyses</td>
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<tr>
<td>4</td>
<td>Good quality: One or more well-designed randomized trials</td>
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<tr>
<td>3</td>
<td>Average quality: Low quality randomized trial(s) or well-designed non-randomized trial(s)</td>
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<td>2</td>
<td>Low quality: Case reports or extensive clinical experience</td>
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<tr>
<td>1</td>
<td>Poor quality: Little or no evidence</td>
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### Consistency of Evidence

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<th>Description</th>
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<td>5</td>
<td>Highly consistent: Multiple trials with similar outcomes</td>
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<tr>
<td>4</td>
<td>Mainly consistent: Multiple trials with some variability in outcome</td>
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<tr>
<td>3</td>
<td>May be consistent: Few trials or only trials with few patients, whether randomized or not, with some variability in outcome</td>
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<tr>
<td>2</td>
<td>Inconsistent: Meaningful differences in direction of outcome between quality trials</td>
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<td>1</td>
<td>Anecdotal evidence only: Evidence in humans based upon anecdotal experience</td>
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### Affordability of Regimen/Agent (includes drug cost, supportive care, infusions, toxicity monitoring, management of toxicity)

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<th>Score</th>
<th>Description</th>
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<td>5</td>
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<tr>
<td>4</td>
<td>Inexpensive</td>
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<td>3</td>
<td>Moderately expensive</td>
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<tr>
<td>2</td>
<td>Expensive</td>
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<tr>
<td>1</td>
<td>Very expensive</td>
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<tr>
<td>CLINICAL PRESENTATION</td>
<td>PRELIMINARY WORKUP</td>
</tr>
<tr>
<td>-----------------------</td>
<td>-------------------</td>
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<tr>
<td>Suspicious lesion</td>
<td>• H&amp;P</td>
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<tr>
<td></td>
<td>• Complete skin and lymph node examination&lt;br&gt;• Biopsy&lt;br&gt;› Hematoxylin and eosin (H&amp;E)&lt;br&gt;› Immunopanel</td>
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<td></td>
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*a Quantitation of MCPyV oncoprotein antibodies may be considered as part of initial workup; sero-negative patients may have a higher risk of recurrence; in sero-positive patients, a rising titer may be an early indicator of recurrence.

*b See Principles of Pathology (MCC-A).

*c Brain MRI with contrast and neck/chest/abdomen/pelvis CT with contrast or whole body FDG PET/CT may be useful to identify and quantify regional and distant metastases. Some studies indicate that whole body FDG PET/CT may be preferred in some clinical circumstances. If whole body FDG PET/CT is not available, CT or MRI with contrast may be used. Imaging may also be useful to evaluate for the possibility of a skin metastasis from a noncutaneous primary neuroendocrine carcinoma (eg, small cell lung cancer), especially in cases where CK-20 is negative.

*d Imaging is encouraged whenever metastatic or unresectable disease is suspected based on H&P findings. The most reliable staging tool to identify sub-clinical nodal disease is sentinel lymph node biopsy (SLNB).

Note: For more information regarding the categories and definitions used for the NCCN Evidence Blocks™, see page EB-1. All recommendations are category 2A unless otherwise indicated. Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.
### Primary and Adjuvant Treatment of Clinical N0 Disease

**Management of the Primary Tumor:**
- **Wide excision**\(^{e,f}\)

**Management of the Draining Nodal Basin:**
- **Sentinel lymph node biopsy (SLNB)**\(^{g,h}\) with appropriate immunopanel\(^b\)

**Adjuvant radiation therapy to the primary tumor site**\(^j\) or **Consider observation of the primary tumor site**\(^k\)

#### SLN positive
- **Baseline imaging** if studies not already performed\(^d\)

#### SLN negative
- **Observation of the nodal basin** or **Consider radiation therapy**\(^j\) to the nodal basin in high-risk patients\(^g,l\)

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\(^b\) See Principles of Pathology (MCC-A).

\(^e\) See Principles of Excision (MCC-C). In selected cases in which complete surgical excision is not possible, surgery is refused by the patient, or surgery would result in significant morbidity, radiation monotherapy may be considered (See Principles of Radiation Therapy [MCC-B]).

\(^f\) Surgical margins should be balanced with morbidity of surgery. If appropriate, avoid undue delay in proceeding to RT (See Principles of Excision MCC-C).

\(^g\) In the head and neck region, risk of false-negative SLNBs is higher due to aberrant lymph node drainage and frequent presence of multiple SLN basins. If SLNB is not performed or is unsuccessful, consider irradiating nodal beds for subclinical disease (See Principles of Radiation Therapy MCC-B).

\(^h\) SLNB is an important staging tool for regional control, but the impact of SLNB on overall survival is unclear.

\(^i\) Brain MRI with contrast and neck/ chest/ abdomen/ pelvis CT with contrast or whole body FDG PET/ CT may be useful to identify and quantify regional and distant metastases. Some studies indicate that whole body FDG PET/ CT may be preferred in some clinical circumstances. If whole body FDG PET/ CT is not available, CT or MRI with contrast may be used.

\(^j\) See Principles of Radiation Therapy (MCC-B).

\(^k\) Consider observation of the primary site in cases where the primary tumor is small (eg, <1 cm) and widely excised with no other adverse risk factors such as LVI (lymphovascular invasion) or immunosuppression.

\(^l\) Consider RT when there is a potential for anatomic [eg, previous history of surgery including WLE (wide local excision)], operator, or histologic failure (eg, failure to perform appropriate immunohistochemistry on SLNs) that may lead to a false-negative SLNB. Consider RT in cases of profound immunosuppression.

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**Clinical Trials:** NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.
**Clinical N+**
- Fine-needle aspiration (FNA) or core biopsy
- Immunopanel

**Positive**
- Imaging studies recommended

**M0**
- Multidisciplinary tumor board consultation
- Node dissection and/or radiation therapy

**M1**
- See Treatment of Clinical M1 Disease (MCC-4)

**Negative**
- Consider open biopsy

**Biopsy positive**
- See Follow-up (MCC-5)

**Biopsy negative**
- Follow appropriate Clinical N0 pathway (MCC-2)

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bSee Principles of Pathology (MCC-A).
mBrain MRI with contrast and neck/chest/abdomen/pelvis CT with contrast or whole body FDG PET/CT to evaluate extent of lymph node and/or visceral organ involvement. Some studies indicate that whole body FDG PET/CT may be preferred in some clinical circumstances. If whole body FDG PET/CT is not available, CT or MRI with contrast may be used.

jSee Principles of Radiation Therapy (MCC-B).

Adjuvant chemotherapy may be considered in select clinical circumstances; however, available retrospective studies do not suggest survival benefit for adjuvant chemotherapy. (See Principles of Systemic Therapy [MCC-D]).

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TREATMENT OF CLINICAL M1 DISEASE

Clinical M1 → Multidisciplinary tumor board consultation → Clinical trial preferred if available or Consider any of the following therapies or combinations of:
- Systemic therapy
- Radiation therapy
- Surgery
or Best supportive care (See Guidelines for NCCN Palliative Care)

See Follow-up (MCC-5)

\[\text{\textsuperscript{1}}\text{See Principles of Radiation Therapy (MCC-B)}. \]
\[\text{\textsuperscript{2}}\text{See Principles of Systemic Therapy (MCC-D)}. \]
\[\text{\textsuperscript{3}}\text{Under highly selective circumstances, in the context of multidisciplinary consultation, resection of oligometastasis can be considered.} \]
\[\text{\textsuperscript{4}}\text{See Principles of Excision (MCC-C)}. \]

\textbf{Note: For more information regarding the categories and definitions used for the NCCN Evidence Blocks\textsuperscript{TM}}, see page EB-1.

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Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.
FOLLOW-UP

Follow-up visits:
- Physical exam including complete skin and complete lymph node exam
  - Every 3–6 mo for 3 years
  - Every 6–12 mo thereafter
- Imaging studies as clinically indicated
- Consider routine imaging for high-risk patients

RECURRENCE

Individualized treatment

Local

Regional

Disseminated

Individualized treatment

See Clinical M1 (MCC-4)

Quantitation of MCPyV oncoprotein antibodies may be considered as part of initial workup; sero-negative patients may have a higher risk of recurrence; in sero-positive patients, a rising titer may be an early indicator of recurrence.

Brain MRI with contrast and neck/chest/abdomen/pelvis CT with contrast or whole body FDG PET/CT may be useful to identify and quantify regional and distant metastases. Some studies indicate that whole body FDG PET/CT may be preferred in some clinical circumstances. If whole body FDG PET/CT is not available, CT or MRI with contrast may be used.

As immunosuppressed patients are at high risk for recurrence, more frequent follow-up may be indicated. Immunosuppressive treatments should be minimized as clinically feasible.

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**PRINCIPLES OF PATHOLOGY**

- Pathologist should be experienced in distinguishing MCC from cutaneous simulants and metastatic tumors.

- Synoptic reporting is preferred.

- Minimal elements to be reported include tumor size (cm), peripheral and deep margin status, lymphovascular invasion, and extracutaneous extension (ie, bone, muscle, fascia, cartilage).

- Strongly encourage reporting of these additional clinically relevant factors (compatible with the American Joint Committee on Cancer [AJCC] and the College Of American Pathologists [CAP] recommendations):
  - Depth (Breslow, in mm)
  - Mitotic index (#/mm² preferred, #/HPF [High-power fields], or MIB-1 index)
  - Tumor-infiltrating lymphocytes (not identified, brisk, non-brisk)
  - Tumor growth pattern (nodular or infiltrative)
  - Presence of a second malignancy within the pathologic specimen itself (ie, concurrent squamous cell carcinoma [SCC])

- An appropriate immunopanel should preferably include CK20 and thyroid transcription factor-1 (TTF-1). Immunohistochemistry for CK20 and most low-molecular-weight cytokeratin markers is typically positive with a paranuclear “dot-like” pattern. CK7 and TTF-1 (positive in >80% of small cell lung cancers) are typically negative.

- For equivocal lesions, consider additional immunostaining with neuroendocrine markers such as chromogranin, synaptophysin, CD56, neuron-specific enolase (NSE), and neurofilament.

- SLNB evaluation should preferably include an appropriate immunopanel (ie, CK20 and pancytokeratins [AE1/AE3]) based on the immunostaining pattern of the primary tumor, particularly if H&E sections are negative, as well as tumor burden (% of node), tumor location (eg, subcapsular sinus, parenchyma), and the presence/absence of extracapsular extension.
**PRINCIPLES OF RADIATION THERAPY**

**PRIMARY TUMOR SITE**

- Consider observation of primary site when primary tumor is small (≤1 cm), widely excised, and without other risk factors such as lymphovascular invasion or immunosuppression

- Negative resection margins → 50–56 Gy

- Microscopically positive resection margins → 56–60 Gy

- Grossly positive resection margins and further resection not possible → 60–66 Gy

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- Expeditious initiation of adjuvant therapy after surgery is preferred as delay has been associated with worse outcomes.

- All doses are at 2 Gy/d standard fractionation. Bolus is used to achieve adequate skin dose. Wide margins (5 cm) should be used, if possible, around the primary site. If electron beam is used, an energy and prescription isodose should be chosen that will deliver adequate dose to the lateral and deep margins.

- Palliation: A less protracted fractionation schedule may be used in the palliative setting, such as 30 Gy in 10 fractions.

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### PRINCIPLES OF RADIATION THERAPY

#### DRAINING NODAL BASIN

<table>
<thead>
<tr>
<th>Condition</th>
<th>DOSE RECOMMENDATIONS</th>
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<tbody>
<tr>
<td>No SLNB or LN dissection</td>
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</tr>
<tr>
<td>Clinically evident lymphadenopathy</td>
<td>60–66 Gy&lt;sup&gt;1,2&lt;/sup&gt;</td>
</tr>
<tr>
<td>Clinically node negative, but at risk for subclinical disease</td>
<td>46–50 Gy</td>
</tr>
<tr>
<td>SLNB without LN dissection</td>
<td></td>
</tr>
<tr>
<td>SLN negative</td>
<td>RT not indicated, unless at risk for false-negative SLNB&lt;sup&gt;3,4&lt;/sup&gt;</td>
</tr>
<tr>
<td>SLN positive&lt;sup&gt;5&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>After LN dissection with multiple involved nodes and/or extracapsular extension&lt;sup&gt;6&lt;/sup&gt;</td>
<td>50–60 Gy</td>
</tr>
<tr>
<td></td>
<td>50–60 Gy</td>
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</table>

1. Lymph node dissection is the recommended initial therapy for clinically evident adenopathy, followed by postoperative RT if indicated.
2. Shrinking field technique.
3. Consider RT when there is a potential for anatomic (e.g., previous WLE), operator, or histologic failure (e.g., failure to perform appropriate immunohistochemistry on SLNs) that may lead to a false-negative SLNB.
4. In the head and neck region, risk of false-negative SLNB is higher due to aberrant lymphatic drainage and frequent presence of multiple SLN basins. If SLNB is unsuccessful, consider irradiating draining nodal basin for subclinical disease.
5. Microscopic nodal disease (SLN positive) is defined as nodal involvement that is neither clinically palpable nor abnormal by imaging criteria, and microscopically consists of small metastatic foci without extracapsular extension.
6. Adjuvant RT following lymph node dissection is only indicated for multiple involved nodes and/or the presence of extracapsular extension. Adjuvant RT following LN dissection is generally not indicated for patients with low tumor burden on SLNB or with a single macroscopic clinically detected lymph node without extracapsular extension.

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PRINCIPLES OF EXCISION

Goals:
• To obtain histologically negative margins when clinically feasible.
• Surgical margins should be balanced with morbidity of surgery. If appropriate, avoid undue delay in proceeding to radiation therapy.

Surgical Approaches:
• It is recommended, regardless of the surgical approach, that every effort be made to coordinate surgical management such that SLNB is performed prior to definitive excision.\(^1\) Excision options include:
  › Wide excision with 1- to 2-cm margins to investing fascia of muscle or pericranium when clinically feasible.
  › Techniques for more exhaustive histologic margin assessment may be considered (Mohs micrographic surgery, modified Mohs micrographic surgery, CCPDMA),\(^2,3\) provided they do not interfere with SLNB when indicated.

Reconstruction:
• It is recommended that any reconstruction involving extensive undermining or tissue movement be delayed until negative histologic margins are verified and SLNB is performed if indicated.
• If adjuvant radiation therapy is planned, extensive tissue movement should be minimized and closure should be chosen to allow for expeditious initiation of radiation therapy.

\(^1\)SLNB is an important staging tool and may contribute to regional control; the impact of SLNB on overall survival is unclear.
\(^2\)If Mohs micrographic surgery is used, a debulked specimen of the central portion of the tumor should be sent for permanent vertical section microstaging.
\(^3\)Modified Mohs = Mohs micrographic surgery with additional permanent section final margin assessment; CCPDMA = complete circumferential and peripheral deep margin assessment.

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All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.
PRINCIPLES OF SYSTEMIC THERAPY

Local Disease:
• Adjuvant chemotherapy not recommended

Regional Disease:
• Clinical trial (preferred)
• Adjuvant chemotherapy not routinely recommended as survival benefit has not been demonstrated in available retrospective studies, but could be used on a case-by-case basis if clinical judgement dictates
  › Cisplatin ± etoposide
  › Carboplatin ± etoposide

Disseminated Disease:
• Clinical trial (preferred)
• Avelumab2
• Pembrolizumab2
• Nivolumab2
• As clinical judgment dictates for patients with contraindications to checkpoint immunotherapy:
  › Cisplatin ± etoposide
  › Carboplatin ± etoposide
  › Topotecan
  › (CAV): Cyclophosphamide, doxorubicin (or epirubicin), and vincristine

See Evidence Blocks on MCC-D (EB-1)

1When available and clinically appropriate, enrollment in a clinical trial is recommended. The literature is not directive regarding the specific chemotherapeutic agent(s) offering superior outcomes, but the literature does provide evidence that Merkel cell carcinoma is chemosensitive, although the responses are not durable, and the agents listed above have been used with some success.

2Preliminary data from non-randomized trials in patients with MCC demonstrate that rates of durable response are improved with PD-1/PD-L1 blockade compared with cytotoxic therapy. The safety profiles for checkpoint immunotherapies are significantly different from cytotoxic therapies. Consult prescribing information for recommendations on detection and management of immune-related adverse events associated with checkpoint immunotherapies. Clinician and patient education is critical for safe administration of checkpoint immunotherapies.
# Systemic Therapy for Advanced Disease

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<th>Adjuvant Therapy for Regional Disease*</th>
<th>Therapy for Disseminated Disease</th>
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<tr>
<td>Avelumab</td>
<td>![Efficacy] ![Safety] ![Quality] ![Consistency] ![Affordability]</td>
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<tr>
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<td>![Efficacy] ![Safety] ![Quality] ![Consistency] ![Affordability]</td>
</tr>
<tr>
<td>Cisplatin</td>
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<tr>
<td>Cisplatin + etoposide</td>
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<tr>
<td>Carboplatin</td>
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<tr>
<td>Carboplatin + etoposide</td>
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<td>Topotecan</td>
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<tr>
<td>CAV with cyclophosphamide, doxorubicin, and vincristine</td>
<td>![Efficacy] ![Safety] ![Quality] ![Consistency] ![Affordability]</td>
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<tr>
<td>CAV with cyclophosphamide, epirubicin, and vincristine</td>
<td>![Efficacy] ![Safety] ![Quality] ![Consistency] ![Affordability]</td>
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*After node dissection and/or radiation therapy
# Merkel Cell Carcinoma

## Staging

### American Joint Committee on Cancer (AJCC)

#### TNM Staging Classification for Merkel Cell Carcinoma (8th ed., 2016)

### Primary Tumor (T)

<table>
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<th>Code</th>
<th>Description</th>
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<td>Primary tumor cannot be assessed (e.g., curetted)</td>
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<tr>
<td>T0</td>
<td>No evidence of primary tumor</td>
</tr>
<tr>
<td>Tis</td>
<td>In situ primary tumor</td>
</tr>
<tr>
<td>T1</td>
<td>Maximum clinical tumor diameter ≤2 cm</td>
</tr>
<tr>
<td>T2</td>
<td>Maximum clinical tumor diameter &gt;2 but ≤5 cm</td>
</tr>
<tr>
<td>T3</td>
<td>Maximum clinical tumor diameter &gt;5 cm</td>
</tr>
<tr>
<td>T4</td>
<td>Primary tumor invades fascia, muscle, cartilage, or bone</td>
</tr>
</tbody>
</table>

### Regional Lymph Nodes (N)

#### Clinical (N)

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>NX</td>
<td>Regional lymph nodes cannot be clinically assessed (e.g., previously removed for another reason, or because of body habitus)</td>
</tr>
<tr>
<td>N0</td>
<td>No regional lymph node metastasis detected on clinical and/or radiologic examination</td>
</tr>
<tr>
<td>N1</td>
<td>Metastasis in regional lymph node(s)</td>
</tr>
<tr>
<td>N2</td>
<td>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</td>
</tr>
<tr>
<td>N3</td>
<td>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</td>
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</table>

#### Pathological (pN)

<table>
<thead>
<tr>
<th>Code</th>
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</thead>
<tbody>
<tr>
<td>pNX</td>
<td>Regional lymph nodes cannot be assessed (e.g., previously removed for another reason or not removed for pathological evaluation)</td>
</tr>
<tr>
<td>pN0</td>
<td>No regional lymph node metastasis detected on pathological evaluation</td>
</tr>
<tr>
<td>pN1</td>
<td>Metastasis in regional lymph node(s)</td>
</tr>
<tr>
<td>pN1a (sn)</td>
<td>Clinically occult regional lymph node metastasis identified only by sentinel lymph node biopsy</td>
</tr>
<tr>
<td>pN1a</td>
<td>Clinically occult regional lymph node metastasis following lymph node dissection</td>
</tr>
<tr>
<td>pN1b</td>
<td>Clinically and/or radiologically detected regional lymph node metastasis microscopically confirmed</td>
</tr>
<tr>
<td>pN2</td>
<td>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</td>
</tr>
<tr>
<td>pN3</td>
<td>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</td>
</tr>
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### Distant Metastasis (M)

#### Clinical (M)

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<thead>
<tr>
<th>Code</th>
<th>Description</th>
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<tbody>
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<td>No distant metastasis detected on clinical and/or radiologic examination</td>
</tr>
<tr>
<td>M1</td>
<td>Distant metastasis detected on clinical and/or radiologic examination</td>
</tr>
<tr>
<td>M1a</td>
<td>Metastasis to distant skin, distant subcutaneous tissue, or distant lymph node(s)</td>
</tr>
<tr>
<td>M1b</td>
<td>Metastasis to lung</td>
</tr>
<tr>
<td>M1c</td>
<td>Metastasis to all other visceral sites</td>
</tr>
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</table>

#### Pathological (M)

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>M0</td>
<td>No distant metastasis detected on clinical and/or radiologic examination</td>
</tr>
<tr>
<td>pM1</td>
<td>Distant metastasis microscopically confirmed</td>
</tr>
<tr>
<td>pM1a</td>
<td>Metastasis to distant skin, distant subcutaneous tissue, or distant lymph node(s), microscopically confirmed</td>
</tr>
<tr>
<td>pM1b</td>
<td>Metastasis to lung, microscopically confirmed</td>
</tr>
<tr>
<td>pM1c</td>
<td>Metastasis to all other distant sites, microscopically confirmed</td>
</tr>
</tbody>
</table>

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Staging continued

American Joint Committee on Cancer (AJCC)
TNM Staging Classification for Merkel Cell Carcinoma
(8th ed., 2016)

AJCC Prognostic Stage Groups

Clinical (cTNM)

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<tr>
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<td>M0</td>
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</tr>
<tr>
<td>T2–3</td>
<td>N0</td>
<td>M0</td>
<td>IIA</td>
</tr>
<tr>
<td>T4</td>
<td>N0</td>
<td>M0</td>
<td>IIB</td>
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<td>N1–3</td>
<td>M0</td>
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</tr>
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<td>M1</td>
<td>IV</td>
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Pathological (pTNM)

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<th>M0</th>
<th>0</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1</td>
<td>N0</td>
<td>M0</td>
<td>1</td>
</tr>
<tr>
<td>T2–3</td>
<td>N0</td>
<td>M0</td>
<td>IIA</td>
</tr>
<tr>
<td>T4</td>
<td>N0</td>
<td>M0</td>
<td>IIB</td>
</tr>
<tr>
<td>T1–4</td>
<td>N1a(sn) or N1a</td>
<td>M0</td>
<td>IIIA</td>
</tr>
<tr>
<td>T0</td>
<td>N1b</td>
<td>M0</td>
<td>IIIB</td>
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<tr>
<td>T1–4</td>
<td>N1b–3</td>
<td>M0</td>
<td>IIIB</td>
</tr>
<tr>
<td>T0–4</td>
<td>Any N</td>
<td>M1</td>
<td>IV</td>
</tr>
</tbody>
</table>

Discussion

This discussion is being updated to correspond with the newly updated algorithm. Last updated 12/16/14

NCCN Categories of Evidence and Consensus

Category 1: Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

Category 2A: Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

Category 2B: Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate.

Category 3: Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate.

All recommendations are category 2A unless otherwise noted.

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Overview

Merkel cell carcinoma (MCC) is a rare, aggressive cutaneous tumor that combines the local recurrence rates of infiltrative non-melanoma skin cancer along with the regional and distant metastatic rates of thick melanoma. Several large reviews document the development of local recurrence in 25% to 30% of all cases of MCC, 52% to 59% of all cases of regional disease, and 34% to 36% of all cases of distant metastatic disease. MCC has a high mortality rate that exceeds that of melanoma. The overall 5-year survival rates range from 30% to 64%.

A history of extensive sun exposure is a major risk factor for MCC. Older Caucasians (65 years or older) are at higher risk for MCC, which tends to occur on the areas of the skin that are exposed to the sun. MCC is disproportionately more common in immunosuppressed individuals, such as those with organ transplants, lymphoproliferative malignancies (such as chronic lymphocytic leukemia), or HIV infections.

In 2008, Feng and colleagues identified a novel polyomavirus in MCC tumor tissues. This Merkel cell polyomavirus (MCV or MCPyV) is detected in 43% to 100% of patient samples. The role of MCV in the pathogenesis of MCC is under active investigation. There is ongoing research on the value of baseline MCV serology to predict outcome and to detect disease recurrence.

The NCCN Non-Melanoma Skin Cancer Panel has developed guidelines outlining treatment of MCC to supplement the squamous cell and basal cell skin cancer guidelines (see NCCN Guidelines for Basal Cell Skin Cancer and NCCN Guidelines for Squamous Cell Skin Cancer). MCC is a rare tumor; therefore, prospective, statistically significant data are lacking to verify the validity of prognostic features or treatment outcomes. The panel relied on trends that are documented in smaller, individual studies, in meta-analyses, and in their own collective experiences.

Diagnosis and Workup

The diagnosis of MCC is rarely clinically suspected, as the primary tumor lacks distinguishing characteristic features. Initial workup of a suspicious lesion starts with a complete examination of the skin and lymph nodes followed by biopsy. The histologic diagnosis may also be challenging because MCC is similar to a variety of other widely recognized small round blue cell tumors. The most difficult differentiation is often between primary MCC and metastatic small cell carcinoma of the lung.

Pathology Report

The Principles of Pathology in the algorithm outlined elements that should be included in a pathology report, preferably in synoptic format. The College of American Pathologists (CAP) provides a complete synoptic report protocol for cutaneous MCC. The goals are to: 1) accurately diagnose the condition and distinguish it from cutaneous simulants and metastatic tumors; 2) provide complete pathologic tumor characteristics for staging according to recommended AJCC and CAP guidelines; and 3) standardize pathologic data collection to further understand the critical biological features that impact MCC behavior and prognosis. At a minimum, the report should include tumor size, peripheral and deep margin status, lymphovascular invasion, and extracutaneous extension to the bone, muscle fascia, or cartilage. The prognostic value of histopathologic features of the primary tumor remains uncertain. However, there is an emerging body of literature that suggests that tumor thickness, mitotic rate, tumor growth pattern, tumor-infiltrating lymphocytes (particularly intratumoral CD8+ lymphocytes),
and the presence of a second malignancy such as concurrent squamous cell carcinoma may provide relevant prognostic information with regards to survival and/or sentinel lymph node positivity in MCC.\textsuperscript{16-20} It is therefore suggested that these features be included in the pathology report whenever possible.

Initial diagnosis of MCC in the primary lesion by hematoxylin and eosin (H&E) staining should be further confirmed by performing immunohistochemical (IHC) staining. An appropriate immunopanel should preferably include cytokeratin 20 (CK-20) and thyroid transcription factor 1 (TTF-1), which often provide the greatest sensitivity and specificity to exclude small cell lung cancer (SCLC).\textsuperscript{21-23} CK-20 is a very sensitive marker for MCC, since it is positive in 89% to 100% of cases. TTF-1 is expressed in 83% to 100% of SCLC but it is consistently absent in MCC. Other IHC markers such as chromogranin A, synaptophysin, neurofilament protein, neuron specific enolase, and CD56 may be used in addition to CK-20 and TTF-1 to exclude other diagnostic considerations.\textsuperscript{24}

**Imaging**

Additional workup of a patient with MCC may include imaging studies.\textsuperscript{25} In asymptomatic patients with primary MCC, sentinel lymph node biopsy (SLNB) is considered the most sensitive staging test for the detection of nodal metastases.\textsuperscript{17,18,20} Imaging may be useful in identifying distant metastases as clinically indicated due to the metastatic potential of this tumor. PET/CT scanning is gaining importance in diagnostic imaging of MCC and may be preferred in some instances. CT or MRI may be used if PET/CT is not available. In a review of 102 patients, PET/CT changed the stage and primary treatment of 22% of patients.\textsuperscript{26} PET also altered the radiation technique or dose for another 15% of patients. Similar results were reported in another review of 97 patients, 16% of whom were upstaged by baseline PET/CT scans.\textsuperscript{27} In addition, PET/CT frequently identified bone metastases that were undetected by CT. According to a meta-analysis of 6 studies, the sensitivity and specificity of PET/CT are 90% and 98%, respectively.\textsuperscript{28} Imaging (CT, MRI, or PET/CT scan) may also be indicated to evaluate for the possibility of a skin metastasis from a noncutaneous carcinoma (eg, small cell carcinoma of the lung), especially in cases where CK-20 is negative.

**Staging**

In the biomedical literature, the most consistently reported adverse prognostic feature is tumor stage followed by tumor size.\textsuperscript{2,4,29-35} The NCCN staging of MCC parallels the AJCC guidelines and divides presentation into local, regional, and disseminated disease.\textsuperscript{36} The AJCC staging system is based on an analysis of 5823 cases from the National Cancer Data Base with a median follow-up of 64 months.\textsuperscript{7} An MCC website from Seattle Cancer Care Alliance also has a useful staging table (www.merkelcell.org).

**Treatment**

After workup, treatment is primarily dependent on accurate histopathologic interpretation and on microstaging of the primary lesion. A multidisciplinary panel is recommended to ensure high-quality coordinated care for patients diagnosed with this rare and challenging disease.\textsuperscript{37} Surgery is the primary treatment modality for MCC. However, there is some variability among individual clinicians and NCCN Member Institutions regarding the management of patients with MCC due to the absence of prospective clinical trials. Therefore, the MCC guidelines are
suitably broad to reflect all the approaches taken by participating NCCN Member Institutions.

**Surgery**

Surgery is the mainstay of primary treatment for clinically localized (N0, M0) MCC. Because of the high historic risk of local recurrence in MCC, the panel’s tenets for surgical excision emphasize complete extirpation of tumor at the time of initial resection to achieve clear surgical margins when clinically feasible. However, this should not be pursued to the degree of significantly delaying any planned adjuvant radiation therapy (RT). An analysis of 3 pooled prospective trials in patients receiving adjuvant RT for high-risk MCC found that pre-radiation margin status had no impact on time to locoregional failure.

Wide local excision with 1- to 2-cm margins to the investing fascia layer remains the standard surgical technique. Mohs surgery, modified Mohs surgery, or complete circumferential peripheral and deep-margin assessment (CCPDM) may be considered if tissue sparing is critical, such as for facial MCC. Mohs micrographic surgery is superior to conventional surgical excision in high-risk basal cell carcinoma and squamous cell carcinoma. In MCC, it may be used to ensure complete tumor removal and clear margins, while secondarily sparing surrounding healthy tissue. If Mohs is used, the panel emphasized that a specimen from the central portion of the tumor should be sent for permanent section microstaging.

In all cases, treatment should be coordinated so that SLNB is performed prior to definitive surgery as surgery may alter lymphatic drainage. SLNB is usually performed intraoperatively during wide local excision.

**Reconstruction**

Reconstruction is usually performed immediately after surgery. As histologic margins may be obscured by extensive undermining or tissue movement, verification of clear margins should precede any major reconstruction. Efforts should also be made to minimize delay to adjuvant radiation, such as by primary closure. If postoperative radiation is planned, significant tissue movement should be avoided as it may obscure the target area.

**Sentinel Lymph Node Biopsy**

SLNB is very important in the staging and treatment of MCC, although its impact on overall survival has been mixed in literature. One review of 161 patients with MCC found that SLNB identified micrometastases in one-third of early-stage patients. Recurrence occurred in 56% of SLNB-positive and 39% of SLNB-negative patients. Essentially all participating NCCN Member Institutions use the SLNB technique routinely for MCC, as they do for melanoma. The NCCN Panel believes that by identifying patients with positive microscopic nodal disease and then performing full lymph node dissections and/or RT, the care of regional disease in this patient population is maximized. However, it should be noted that compared to the trunk and extremities, SLNB may be less reliable in the head and neck region. The complex and variable drainage pattern of the area can lead to false negativity. Performing a wide local excision before SLNB may potentially interfere with the accuracy of subsequent SLNB.

IHC analysis has been shown to be effective in detecting more lymph node metastases in patients with MCC and should be included in the SLNB evaluation in addition to H&E sections. CK-20 immunostaining in the pathologic assessment of sentinel lymph nodes removed from MCC patients is a valuable diagnostic adjunct, as it allows accurate identification of micrometastases. Other elements to be detailed are
the tumor burden of each node, location, and the presence or absence of extracapsular extension.

**Radiation Therapy**

Although the literature on the benefits of RT has been mixed, recent studies are providing increasing support for the use of postoperative radiation in MCC to minimize locoregional recurrence. According to a meta-analysis comparing surgery alone with surgery plus adjuvant radiation, the use of local adjuvant radiation after complete excision lowered the risk of local and regional recurrences. Jouary and colleagues conducted the only randomized trial to date in MCC. Patients with stage I disease treated by wide excision and RT to the tumor bed were randomized to adjuvant regional RT or observation. The trial was closed prematurely due to a drop in recruitment attributed to the advent of sentinel node dissection. Analysis of 83 patients showed no overall survival improvement with adjuvant radiation, but a significant decrease in risk of regional recurrence was found compared to the observation group (0% vs. 16.7%). A large retrospective analysis of 1187 cases from the SEER database demonstrated longer overall survival of patients who received adjuvant RT compared to those who did not after surgery (median survival 63 months vs. 45 months; \( P = .0002 \)). Improvement was most pronounced for patients with tumors larger than 2 cm (median survival 50 months vs. 21 months; \( P = .0003 \)). Another analysis of the SEER database also reported improved overall survival with adjuvant RT, although disease-specific survival was not improved. The panel included radiation as a treatment option for all stages of MCC. However, due to the lack of prospective trials with clearly defined patient cohorts and treatment protocols (eg, surgical margins prior to RT, location of radiation field), the recommendations are suitably broad to reflect all the approaches taken by participating NCCN Member Institutions. Adjuvant radiation is commonly performed within a few weeks after surgery, as delay may lead to negative outcomes. Radiation may also be useful in the palliative setting. Specifications on radiation dosing, as well as for different MCC sites (head and neck vs. extremity and torso), are detailed in the algorithm under *Principles of Radiation Therapy*.

**Chemotherapy**

There is sparse literature on chemotherapeutic options for MCC. Most NCCN Member Institutions only use chemotherapy with or without surgery and/or RT for stage IV, distant metastatic disease (M1). A few NCCN Member Institutions suggest considering adjuvant chemotherapy for select cases of clinical (macroscopic) regional (N1b or N2) disease. The most common regimen used for regional disease is cisplatin or carboplatin with or without etoposide. Available data from retrospective studies do not suggest prolonged survival benefit for adjuvant chemotherapy. Data are insufficient to assess whether chemotherapeutic regimens improve either relapse-free or overall survival in MCC patients with distant metastatic disease. If it is used, the panel recommends cisplatin or carboplatin with or without etoposide. Topotecan has also been used in some instances (eg, older patients). Cyclophosphamide in combination with doxorubicin and vincristine (CAV) used to be a commonly administered regimen, but it is associated with significant toxicity. Clinicians should exercise independent medical judgment in choosing the chemotherapeutic regimen. Although the NCCN Panel recognized that MCC is a rare disease that precludes robust randomized studies, enrollment in clinical trials is encouraged whenever available and appropriate.
NCCN Recommendations

Clinical Node-Negative Disease

Wide local excision of the entire lesion with clear surgical margins is preferred, whenever possible. Surgical margins should be balanced with morbidity of surgery. SLNB is offered to patients with clinical N0 disease for accurate nodal staging.

Following surgery, patients may undergo postoperative RT of the primary site or consider observation. Efforts should be made to avoid delay of adjuvant RT if planned. Observation should be limited to patients with small primary lesions (eg, less than 1 cm) that have been widely excised and present with no adverse risk factors such as lymphovascular invasion or immunosuppression.

Radiation is acceptable as primary therapy in select cases when complete excision is not feasible or refused by the patient.

A positive sentinel lymph node is preferably followed up with a multidisciplinary tumor board consultation. Baseline imaging with CT, MR, or PET/CT should be considered as these may be helpful in detecting regional and distant metastases. PET/CT may be preferred in certain instances. Where available, clinical trial participation is the preferred choice for patients with positive SLNB. Most patients undergo completion lymph node dissection and/or RT to the nodal basin. If SLNB results are negative, observation is appropriate. Patients with profound immunosuppression or who are at high risk may consider RT to the nodal basin. If SLNB is not performed or is unsuccessful, RT to the nodal bed should be considered.

Clinical Node-Positive Disease

A clinical N+ diagnosis should be confirmed by fine-needle aspiration or core biopsy with an appropriate immunopanel.

If initial biopsy results are positive, imaging studies (CT, MRI, or PET/CT) are recommended if not already performed at baseline. If distant metastasis is detected, management should follow the M1 pathway. If no distant metastasis is present, the panel recommends multidisciplinary tumor board consultation and lymph node dissection. RT is recommended following lymph node dissection if extracapsular extension is detected or multiple nodes are involved. Adjuvant chemotherapy may be considered in select cases, although no survival benefit has been reported.

An open biopsy may be considered to confirm a negative initial biopsy. If results remain negative, patients should be managed as clinical N0.

Metastatic Disease

The panel recommends multidisciplinary tumor board consultation for patients with metastatic disease to consider any or a combination of chemotherapy, radiation, and surgery. Full imaging workups are recommended for all patients with clinically proven regional or metastatic disease. In general, the management of patients with distant metastases must be individually tailored. Clinical trial is preferred if available. Chemotherapy and RT will likely be the primary treatment options to consider. Surgery may be beneficial for select patients with oligometastasis. All patients should receive best supportive care. The NCCN Panel encourages participation in clinical trials where available.

Follow-up and Recurrence

The NCCN Panel’s recommendations for close clinical follow-up of MCC patients immediately after diagnosis and treatment parallel the recommendations in the literature. The physical examination should include a complete skin and regional lymph node examination every 3 to 6 months for the first two years, then every 6 to 12 months thereafter. The recommended frequency of follow-up visits is purposely broad to
Merkel Cell Carcinoma

allow for an individualized schedule based on the risk of recurrence, stage of disease, and other factors such as patient anxiety and clinician preference. The panel's recommendations also reflect the fact that the median time to recurrence in patients with MCC is about 8 months, with 90% of the recurrences occurring within 24 months. Self-examination of the skin is useful for patients with MCC, because these patients are likely at greater risk for other non-melanoma skin cancers. Imaging studies should be performed as clinically indicated. For high-risk patients, routine imaging should be considered. PET/CT scans may be useful to identify and quantify metastases, especially bone involvement.

Patients who present with local or regional recurrence should receive individualized treatment. For disseminated recurrence, follow the treatment pathway for metastatic disease.
References


