

## NCCN

# Merkel Cell Carcinoma, Version 1.2014

## Clinical Practice Guidelines in Oncology

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### Overview

Merkel cell carcinoma (MCC) is a rare, aggressive cutaneous tumor that combines the local recurrence rates of infiltrative nonmelanoma skin cancer along with the regional and distant metastatic rates of thick melanoma.<sup>1</sup> 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.<sup>2-4</sup> MCC has a high mortality rate

### Abstract

Merkel cell carcinoma is a rare, aggressive cutaneous tumor that combines the local recurrence rates of infiltrative nonmelanoma skin cancer with the regional and distant metastatic rates of thick melanoma. The NCCN Guidelines for Merkel Cell Carcinoma provide recommendations on the diagnosis and management of this aggressive disease based on clinical evidence and expert consensus. This version includes revisions regarding the use of PET/CT imaging and the addition of a new section on the principles of pathology to provide guidance on the analysis, interpretation, and reporting of pathology results. (*J Natl Compr Canc Netw* 2014;12:410-424)

### 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.

Clinical trials: NCCN believes that the best management for any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

### Please Note

The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) are a statement of consensus of the authors regarding their views of currently accepted approaches to treatment. Any clinician seeking to apply or consult the NCCN Guidelines® is expected to use independent medical judgment in the context of individual clinical circumstances to determine any patient's care or treatment. The National Comprehensive Cancer Network® (NCCN®) makes no representation or warranties of any kind regarding their content, use, or application and disclaims any responsibility for their applications or use in any way. [The full NCCN Guidelines for Merkel Cell Carcinoma are not printed in this issue of JNCCN but can be accessed online at NCCN.org.](#)

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### Disclosures for the NCCN Merkel Cell Carcinoma Panel

At the beginning of each NCCN Guidelines panel meeting, panel members review all potential conflicts of interest. NCCN, in keeping with its commitment to public transparency, publishes these disclosures for panel members, staff, and NCCN itself.

Individual disclosures for the NCCN Merkel Cell Carcinoma Panel members can be found on page 424. (The most recent version of these guidelines and accompanying disclosures are available on the NCCN Web site at [NCCN.org](http://NCCN.org).)

These guidelines are also available on the Internet. For the latest update, visit [NCCN.org](http://NCCN.org).

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that exceeds that of melanoma. The overall 5-year survival rates range from 30% to 64%.<sup>5-7</sup>

A history of extensive sun exposure is a major risk factor for MCC. Older whites ( $\geq 65$  years of age) are at higher risk for MCC, which tends to occur on sun-exposed skin.<sup>8</sup> MCC is disproportionately more common in individuals with immunosuppression, such as those with organ transplants, lymphoproliferative malignancies (eg, chronic lymphocytic leukemia), or HIV infections.<sup>1</sup>

In 2008, Feng et al<sup>9</sup> identified a novel polyomavirus in MCC tumor tissues. This Merkel cell polyomavirus (MCV) is detected in 43% to 100% of patient samples.<sup>10</sup> The role of MCV in the pathogenesis of MCC is under active investigation.<sup>11</sup>

The NCCN Non-Melanoma Skin Cancer Panel has developed guidelines outlining treatment of MCC to supplement the basal and squamous cell skin cancer guidelines (see NCCN Guidelines for Basal and Squamous Cell Skin Cancers, available online at NCCN.org).<sup>12</sup> 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, because the primary tumor lacks distinguishing

Text cont. on page 419.

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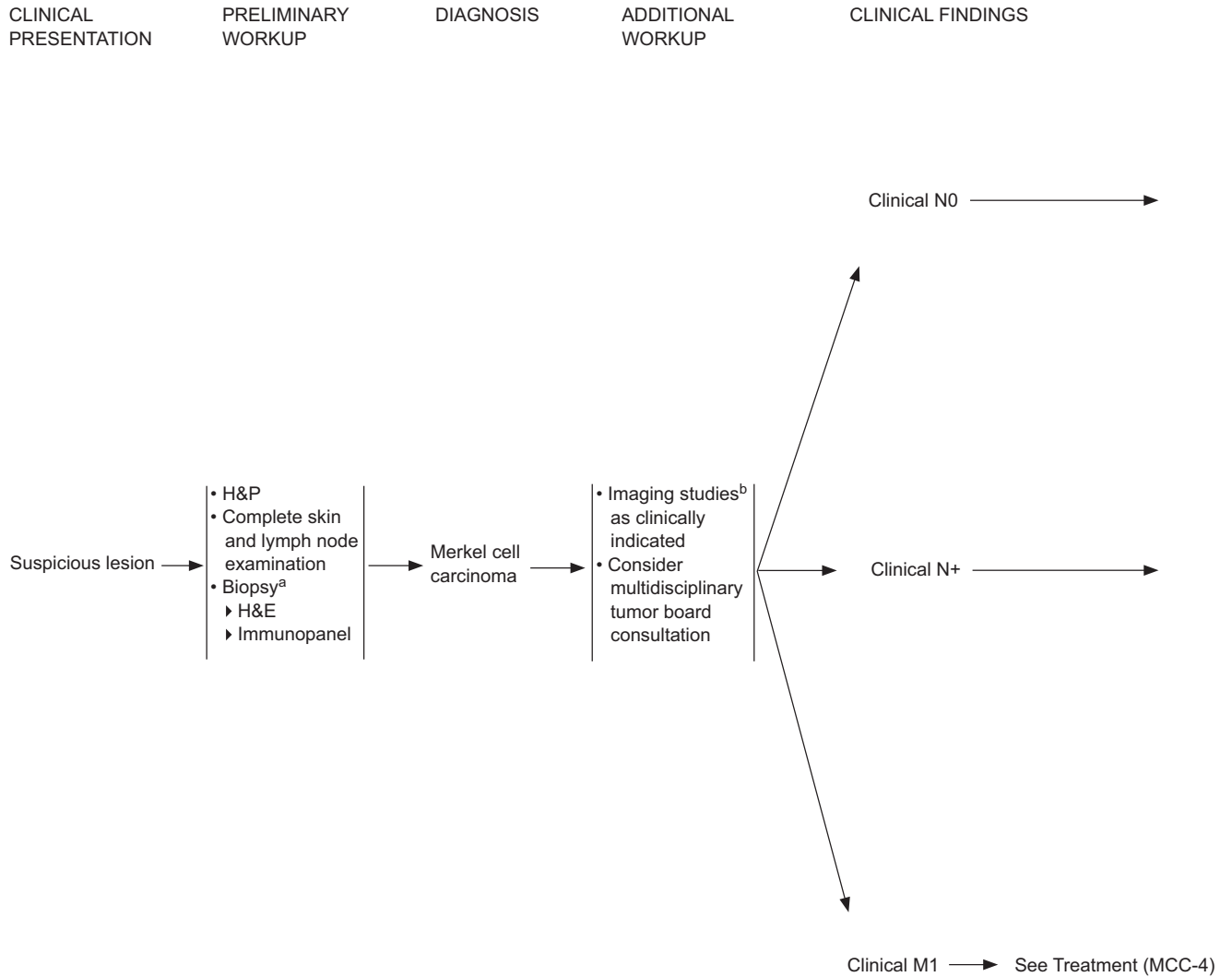
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Specialties:  $\otimes$ Dermatology;  $\uparrow$ Surgery/Surgical Oncology;  
 $\zeta$ Otolaryngology;  $\neq$ Pathology/Dermatopathology;  $\dagger$ Medical  
Oncology;  $\S$ Radiotherapy/Radiation Oncology;  $\#$ Hema-  
tology/Hematology Oncology



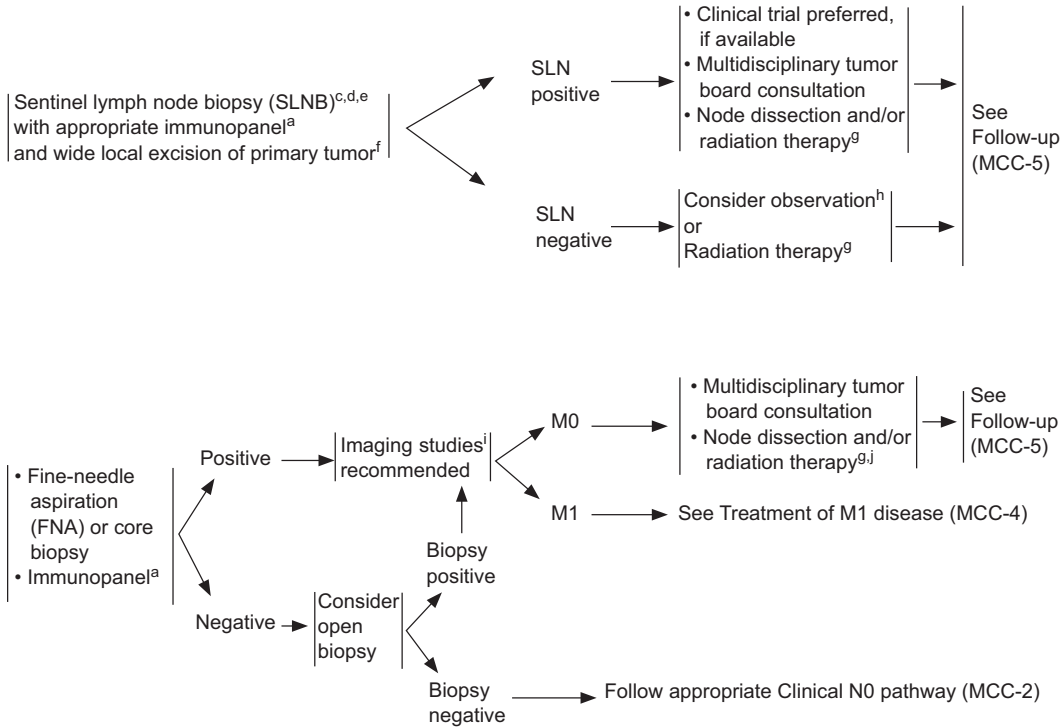
<sup>a</sup>See Principles of Pathology (MCC-A).

<sup>b</sup>Imaging (CT, MRI, or PET/CT) may be useful to identify and quantify regional and distant metastases. Some studies indicate that PET/CT may be preferred in some clinical circumstances. If PET/CT is not available CT or MRI 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 when CK20 is negative.

MCC-1

Merkel Cell Carcinoma, Version 1.2014

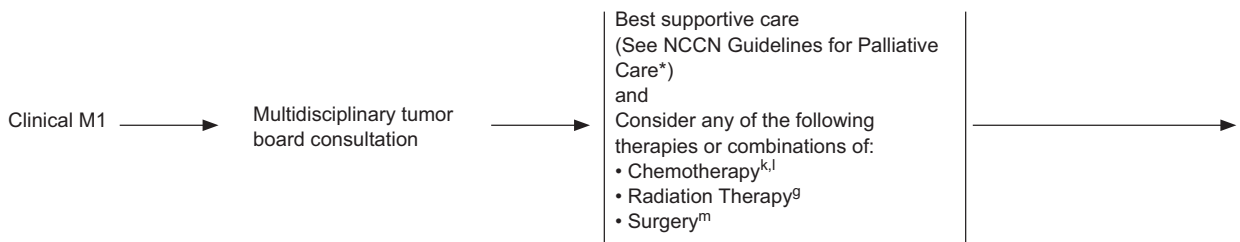
PRIMARY AND ADJUVANT TREATMENT



<sup>a</sup>See Principles of Pathology (MCC-A).  
<sup>c</sup>The preferred treatment sequence is for the SLNB to precede the excision. After wide local excision, SLNB may be considered in selected patients, although accuracy of results may be compromised.  
<sup>d</sup>In the head and neck region, risk of false-negative SLNBs is higher because of 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 MCC-B).  
<sup>e</sup>SLNB is an important staging tool for regional control, but the impact of SLNB on overall survival is unclear.  
<sup>f</sup>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]).  
<sup>g</sup>See Principles of Radiation Therapy (MCC-B).  
<sup>h</sup>Consider observation of the primary site, in cases where the primary tumor is small and widely excised with no other adverse risk factors, such as LVI or immune suppression.  
<sup>i</sup>Imaging (CT, MRI, or PET/CT) may be indicated to evaluate extent of lymph node and/or visceral organ involvement. Some studies indicate that PET/CT may be preferred in some clinical circumstances. If PET/CT is not available CT or MRI may be used.  
<sup>j</sup>Adjuvant chemotherapy may be considered in select clinical circumstances; however, available retrospective studies do not suggest prolonged survival benefit for adjuvant chemotherapy. (See Principles of Chemotherapy [MCC-D]).

MCC-2, MCC-3

TREATMENT: CLINICAL M1 DISEASE



\*To view the most recent version of these guidelines, visit [NCCN.org](http://NCCN.org).

<sup>9</sup>See Principles of Radiation Therapy (MCC-B).

<sup>k</sup>See Principles of Chemotherapy (MCC-D).

<sup>l</sup>Under highly selective circumstances, in the context of multidisciplinary consultation, resection of oligometastasis can be considered.

<sup>m</sup>See Principles of Excision (MCC-C).

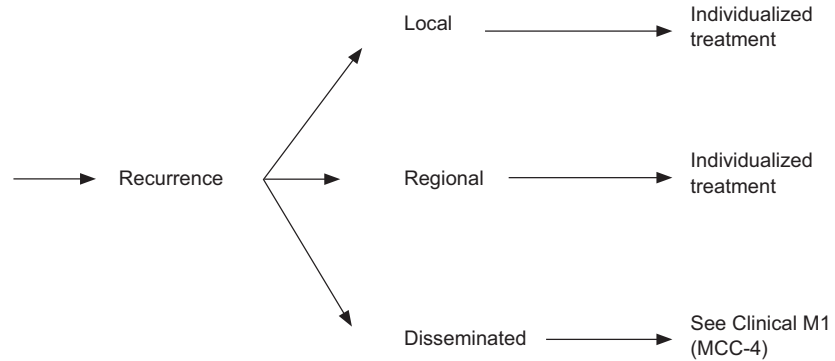
MCC-4

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FOLLOW-UP

RECURRENCE

- Follow-up visits:
- Physical exam including complete skin and complete lymph node exam
    - ▶ every 3-6 mo for 2 y
    - ▶ every 6-12 mo thereafter
  - Imaging studies as clinically indicated<sup>n</sup>
    - ▶ Consider routine imaging for high-risk patients



<sup>n</sup>Imaging (CT, MRI, or PET/CT) may be useful to identify and quantify regional and distant metastases. Some studies indicate that PET/CT may be preferred in some clinical circumstances. If PET/CT is not available CT or MRI may be used.

MCC-5

#### 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 AJCC and CAP recommendations):
  - ▶ Depth (Breslow, in mm)
  - ▶ Mitotic index (#/mm<sup>2</sup> preferred, #/HPF, or MIB-1 index)
  - ▶ Tumor-infiltrating lymphocytes (not identified, brisk, non-brisk)
  - ▶ Tumor growth pattern (nodular or infiltrative)
  - ▶ Presence of second malignancy (ie, concurrent squamous cell cancer [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 positive with a perinuclear “dot-like” pattern. CK7 and TTF-1 (positive in >80% of small cell lung cancers) are negative.
- For equivocal lesions, consider additional immunostaining with neuroendocrine markers 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 hematoxylin and eosin sections are negative, as well as tumor burden (% of node), location of tumor (subcapsular sinus, parenchyma), and the presence/absence of extracapsular extension.

MCC-A

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PRINCIPLES OF RADIATION THERAPYDose recommendations for radiation therapy:

- Primary Site:
  - ▶ Negative resection margins 50-56 Gy
  - ▶ Microscopic (+) resection margins 56-60 Gy
  - ▶ Gross (+) resection margins or unresectable 60-66 Gy
- Nodal Bed:
  - ▶ No SLNB or LN dissection
    - ◊ Clinically (-) but at risk for subclinical disease 46-50 Gy
    - ◊ Clinically evident lymphadenopathy 60-66 Gy<sup>1,2</sup>
  - ▶ After SLNB Without LN Dissection
    - ◊ Negative SLN biopsy: axilla or groin Radiation not indicated<sup>3</sup>
    - ◊ Negative SLN biopsy: head and neck, if at risk for false-negative biopsy 46-50 Gy<sup>3</sup>
    - ◊ Microscopic N+ on SLNB: axilla or groin 50 Gy<sup>4</sup>
    - ◊ Microscopic N+ on SLNB: head and neck 50-56 Gy<sup>4</sup>
  - ▶ After LN Dissection
    - ◊ Lymph node dissection: axilla or groin 50-54 Gy<sup>5</sup>
    - ◊ Lymph node dissection: head and neck 50-60 Gy
- Expedient initiation of adjuvant radiation 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 isodose line (eg, 90%) should be used that will deliver adequate lateral and deep margins.
- Extremity and torso MCC: after negative SLNB and wide local excision (WLE), in most instances, radiation therapy is given to the primary site only. SLNB dictates the need for regional irradiation. If SLNB is negative, then regional nodal basins can be observed. If SLNB is not performed or is unsuccessful, consider irradiating nodal beds for subclinical disease. Irradiation of in-transit lymphatics is often not feasible unless the primary site is in close proximity to the nodal bed.
- Head and neck MCC: risk of false-negative SLNB is higher, due to aberrant lymph node drainage and frequent presence of multiple sentinel node basins. The radiation field to treat the primary site is often overlying the draining lymph node beds. Treatment options for clinically node-negative MCC of the head and neck include:
  - ▶ Perform SLNB and WLE. If SLNB is negative, options are to irradiate the primary site ± nodal beds and in-transit lymphatics or observe;
  - OR
  - ▶ Perform WLE without performing SLNB and irradiate the primary tumor site, in-transit lymphatics, and regional nodal sites.
- Palliation: a less protracted fractionation schedule may be used in the palliative setting, such as 30 Gy in 10 fractions.

<sup>1</sup>Lymph node dissection is the recommended initial therapy for clinically evident adenopathy in the axilla or groin, followed by postoperative radiation if indicated.

<sup>2</sup>Shrinking field technique.

<sup>3</sup>Consider RT when there is a potential for anatomic (eg, previous history of surgery including WLE), operator, or histologic failure (eg, failure to perform appropriate immunohistochemistry on SLNs) that may lead to a false-negative SLNB.

<sup>4</sup>Microscopic N+ is defined as single node involvement that is neither palpable clinically nor abnormal by imaging criteria that microscopically consists of small metastatic foci without extracapsular extension.

<sup>5</sup>Postoperative irradiation is indicated for multiple involved nodes extracapsular extension.

MCC-B



#### PRINCIPLES OF EXCISION

##### Goal:

- To obtain histologically negative margins when clinically feasible.
- Although clear surgical margins are desirable, they should not be pursued with extensive surgery that would significantly delay adjuvant RT, if RT is indicated for treatment.

##### Surgical Approaches:

- It is recommended, regardless of the surgical approach, that every effort be made to coordinate surgical management such that SLNB is performed before definitive excision.<sup>1</sup> Excision options include:
  - ▶ Wide excision with 1- to 2-cm margins to investing fascia of muscle or pericranium when clinically feasible.
  - ▶ When tissue sparing is of critical importance, techniques for more exhaustive histologic margin assessment may be considered (Mohs technique, modified Mohs, CCPDMA).<sup>2,3</sup>

##### Reconstruction:

- Immediate reconstruction in most cases.
- It is recommended that any reconstruction involving extensive undermining or tissue movement be delayed until negative histologic margins are verified.
- 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.

#### PRINCIPLES OF CHEMOTHERAPY<sup>4</sup>

##### Local Disease:

- Adjuvant chemotherapy not recommended unless clinical judgment dictates otherwise.

##### Regional Disease:

- Adjuvant chemotherapy not routinely recommended as adequate trials to evaluate usefulness have not been done, but could be used on a case-by-case basis if clinical judgment dictates.
- Cisplatin ± etoposide
- Carboplatin ± etoposide

##### Disseminated Disease:

As clinical judgment indicates:

- Cisplatin ± etoposide
- Carboplatin ± etoposide
- Topotecan
- Cyclophosphamide, doxorubicin (or epirubicin), and vincristine (CAV)

<sup>1</sup>SLNB is an important staging tool and may contribute to regional control; the impact of SLNB on overall survival is unclear.

<sup>2</sup>If Mohs surgery is used, a debulked specimen of the central portion of the tumor should be sent for permanent vertical section microstaging.

<sup>3</sup>Modified Mohs = Mohs technique with additional permanent section final margin assessment; CCPDMA = complete circumferential and peripheral deep margin assessment.

<sup>4</sup>When 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.

MCC-C, MCC-D

Cont. from page 411.

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 lung cancer.

### Pathology Report

The Principles of Pathology in the algorithm (see MCC-A, page 416) outlines 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.<sup>13</sup> 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 biologic features that influence MCC behavior and prognosis. At 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, an emerging body of literature 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 regarding survival or sentinel lymph node positivity in MCC.<sup>14–18</sup> Therefore, including these features in pathology report is recommended whenever possible.

Initial diagnosis of MCC in the primary lesion by hematoxylin-eosin (H&E) staining should be further confirmed with immunohistochemical (IHC) staining. An appropriate immunopanel should preferably include cytokeratin 20 (CK20) and thyroid transcription factor-1 (TTF-1), which often provide the greatest sensitivity and specificity for excluding small cell lung cancer.<sup>19–21</sup> CK20 is a very sensitive marker for MCC, with positive results in 89% to 100% of cases. TTF-1 is expressed in 83% to 100% of small cell lung cancer cases, but it is consistently absent in MCC. Other IHC markers, including chromogranin A, synaptophysin,

neurofilament protein, neuron-specific enolase, and CD56, may be used in addition to CK20 and TTF-1 to exclude other diagnostic considerations.<sup>22</sup>

### Imaging

Additional workup of a patient with MCC may include imaging studies.<sup>23</sup> In asymptomatic patients with primary MCC, sentinel lymph node biopsy (SLNB) is considered the most sensitive staging test for the detection of nodal metastases.<sup>15,16,18</sup> Imaging may be useful for identifying distant metastases, as clinically indicated, because of 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 in 22% of cases.<sup>24</sup> PET also altered the radiation technique or dose recommended in another 15% of cases. Similar results were reported in another review of 97 cases, 16% of which were upstaged after baseline PET/CT scans.<sup>25</sup> In addition, PET/CT frequently identified bone metastases that were not detected with CT. According to a meta-analysis of 6 studies, the sensitivity and specificity of PET/CT are 90% and 98%, respectively.<sup>26</sup>

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 lung cancer), especially when CK20 is negative.

### Staging

In the biomedical literature, the most consistently reported adverse prognostic feature is tumor stage followed by tumor size.<sup>2,4,27–33</sup> The staging of MCC in these guidelines parallels that of the AJCC guidelines and divides presentation into local, regional, and disseminated disease.<sup>34</sup> 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.<sup>7</sup> An MCC Web site from Seattle Cancer Care Alliance also has a useful staging table (available at [www.merkelcell.org](http://www.merkelcell.org)).

### Treatment

After workup, treatment primarily depends on accurate histopathologic interpretation and microstag-

ing of the primary lesion. A multidisciplinary panel is recommended to ensure high-quality coordinated care for patients diagnosed with this rare and challenging disease.<sup>35</sup>

Surgery is the primary treatment modality for MCC. However, individual clinicians and NCCN Member Institutions show some variability regarding the management of patients with MCC because of the absence of prospective clinical trials. Therefore, these guidelines are suitably broad to reflect all of the approaches offered by participating NCCN Member Institutions.

### Surgery

Surgery is the mainstay of primary treatment for clinically localized (NO, M0) MCC.<sup>36</sup> Because of the historic high risk of local recurrence in MCC, the panel's tenets for surgical excision emphasize complete extirpation of tumor at initial resection to achieve clear surgical margins when clinically feasible. However, this should not be pursued to the degree that it significantly delays any planned adjuvant radiation therapy (RT). An analysis of 3 pooled prospective trials in patients receiving adjuvant RT for high-risk MCC found that preradiation margin status had no impact on time to locoregional failure.<sup>37</sup>

Wide local excision with 1- to 2-cm margins to the investing fascial layer remains the standard surgical technique.<sup>36</sup> Mohs surgery, modified Mohs surgery, or complete circumferential peripheral and deep-margin assessment (CCPDMA) may be considered if tissue sparing is critical, such as for facial MCC.<sup>38,39</sup> Mohs micrographic surgery is superior to conventional surgical excision in high-risk basal and squamous cell carcinomas. In MCC, it may be used to ensure complete tumor removal and clear margins, while secondarily sparing surrounding healthy tissue.<sup>40</sup> 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 before definitive surgery, because surgery may alter lymphatic drainage. SLNB is usually performed intraoperatively during wide local excision.

**Reconstruction:** Reconstruction is usually performed immediately after surgery. Because histologic margins may be obscured by extensive undermining or tissue movement, verification of clear margins should pre-

cede any major reconstruction. Efforts should also be made to minimize delay to adjuvant radiation, such as through primary closure. If postoperative radiation is planned, significant tissue movement should be avoided because it may obscure the target area.

### SLNB

SLNB is very important in the staging and treatment of MCC, although its reported effect on overall survival has been mixed in literature.<sup>41</sup> One review of 161 patients with MCC found that SLNB allowed identification of micrometastases in one-third of patients with early-stage disease.<sup>42</sup> 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 panel believes that identifying patients with positive microscopic nodal disease and then performing full lymph node dissections or RT maximizes the care of regional disease in this patient population. However, it should be noted that SLNB may be less reliable in the head and neck region than in the trunk and extremities. The complex and variable drainage pattern of the area can lead to false-negative results.<sup>43</sup> 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.<sup>6,44</sup> CK20 immunostaining in the pathologic assessment of sentinel lymph nodes removed from patients with MCC is a valuable diagnostic adjunct, because it allows accurate identification of micrometastases.<sup>45,46</sup> Other elements to be detailed are the tumor burden of each node, location, and presence or absence of extracapsular extension.

### Radiation Therapy

Although reports in the literature on the benefits of RT have been mixed, recent studies provide increasing support for the use of postoperative radiation in MCC to minimize locoregional recurrence.<sup>47</sup> 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.<sup>48</sup> Jouary et al<sup>49</sup> conducted the only randomized trial to date in

MCC. Patients with stage I disease treated with wide excision and RT to the tumor bed were randomized to undergo adjuvant regional RT or observation. The trial was closed prematurely because of a decline in recruitment attributed to the advent of sentinel node dissection. Analysis of 83 cases showed no overall survival improvement with adjuvant radiation, but a significant decrease in risk of regional recurrence was found compared with the observation group (0% vs 16.7%). A large retrospective analysis of 1187 cases from the SEER database showed longer overall survival in patients who received adjuvant RT after surgery compared with those who did not (median survival, 63 vs 45 months;  $P=.0002$ ).<sup>50</sup> Improvement was most pronounced for patients with tumors larger than 2 cm (median survival, 50 vs 21 months;  $P=.0003$ ).

The panel included radiation as a treatment option for all stages of MCC. However, because of the lack of prospective trials with clearly defined patient cohorts and treatment protocols (eg, surgical margins before 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, because delay may lead to negative outcomes. Radiation may also be useful in the palliative setting. Specifications on radiation dosing, and for different MCC sites (head and neck vs extremity and torso), are detailed in Principles of Radiation Therapy in the algorithm (see MCC-B, page 417).

### Chemotherapy

Literature on chemotherapeutic options for MCC is sparse.<sup>51</sup> Most NCCN Member Institutions only use chemotherapy with or without surgery and/or RT for stage IV distant metastatic disease (M1). A few 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 a prolonged survival benefit for adjuvant chemotherapy.<sup>52,53</sup> Data are insufficient to assess whether chemotherapeutic regimens improve either relapse-free or overall survival in patients with MCC with distant metastatic disease.<sup>5,54-58</sup>

If chemotherapy is used, the panel recommends cisplatin or carboplatin with or without etoposide.<sup>5,59</sup>

Topotecan has also been used in some instances (eg, older patients). Cyclophosphamide in combination with doxorubicin and vincristine (CAV) was a commonly administered regimen, but it is associated with significant toxicity.<sup>56</sup> Clinicians should exercise independent medical judgment in choosing the chemotherapeutic regimen. Although the 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:** Excisional biopsy of the entire lesion with narrow clear surgical margins is preferred, whenever possible, to obtain the most accurate diagnostic and microstaging information. SLNB is offered to patients with clinical N0 disease for accurate nodal staging. As in melanoma, performing the SLNB before definitive local excision to maximize accuracy in MCC is best. In clinical practice, SLNB is typically performed concurrent with definitive wide local excision.

After surgery, patients may consider observation of the primary site or undergo postoperative RT. Observation should be limited to patients with small primary lesions that have been widely excised and who present with no adverse risk factors, such as lymphovascular invasion or immunosuppression.<sup>60</sup> 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. Clinical trial participation is preferred when available. Most patients undergo completion lymph node dissection and/or RT.

**Clinical Node-Positive Disease:** A clinical N+ diagnosis should be confirmed using 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 with or without RT. 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 result. 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. 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 panel encourages participation in clinical trials when available.

### Follow-Up and Recurrence

The panel's recommendations for close clinical follow-up of patients with MCC immediately after diagnosis and treatment parallel 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 2 years, then every 6 to 12 months thereafter. The recommended frequency of follow-up visits is purposely broad to 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 approximately 8 months, with 90% of the recurrences occurring within 24 months.<sup>5,6,30</sup> Self-examination of the skin is useful for patients with MCC, because these patients are likely at greater risk for other nonmelanoma skin cancers. Imaging studies should be performed as clinically indicated. For patients at high risk, routine imaging should be considered. PET/CT scans may be useful to identify and quantify metastases, especially bone involvement.<sup>25</sup>

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

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Individual Disclosures for the NCCN Merkel Cell Carcinoma Panel					
Panel Member	Clinical Research Support/Data Safety Monitoring Board	Advisory Boards, Speakers Bureau, Expert Witness, or Consultant	Patent, Equity, or Royalty	Other	Date Completed
Murad Alam, MD, MSCI	None	Amway	None	Allergan; Medicus; and Optmed	11/27/13
James S. Andersen, MD	Allergan	None	None	None	11/23/12
Daniel Berg, MD	None	None	None	None	12/3/13
Christopher K. Bichakjian, MD	None	None	None	None	8/1/13
Glen M. Bowen, MD	None	None	None	None	5/31/13
Richard T. Cheney, MD	None	None	None	None	1/17/14
Gregory A. Daniels, MD, PhD	Amgen Inc.; Bristol-Myers Squibb Company; and Genentech, Inc.	Prometheus	None	None	6/12/13
L. Frank Glass, MD	None	None	None	None	2/9/12
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Kenneth Grossmann, MD, PhD	Novartis Pharmaceuticals Corporation	Bristol-Myers Squibb Company; Prometheus; Roche Genentech; and Roche Laboratories, Inc.	None	None	3/11/13
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The NCCN guidelines staff have no conflicts to disclose.