

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Merkel Cell Carcinoma

Version 1.2014

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Merkel Cell Carcinoma

[NCCN Guidelines Index](#)
[Merkel Cell Carcinoma TOC](#)
[Discussion](#)

Christopher K. Bichakjian, MD/Chair ☐
University of Michigan
Comprehensive Cancer Center

Thomas Olencki, DO/Vice-Chair †
The Ohio State University Comprehensive
Cancer Center - James Cancer Hospital
and Solove Research Institute

Murad Alam, MD ☐ ¶ §
Robert H. Lurie Comprehensive Cancer
Center of Northwestern University

James Andersen, MD ¶
City of Hope
Comprehensive Cancer Center

Daniel Berg, MD ☐
Fred Hutchinson Cancer Research
Center/Seattle Cancer Care Alliance

Glen Bowen, MD ☐
Huntsman Cancer Institute
at the University of Utah

Richard T. Cheney, MD ≠
Roswell Park Cancer Institute

Gregory A. Daniels, MD, PhD
UC San Diego Moores Cancer Center

L. Frank Glass, MD ☐ ≠
Moffitt Cancer Center

Roy C. Grekin, MD ☐ ¶
UCSF Helen Diller Family
Comprehensive Cancer Center

Kenneth Grossman, MD, PhD †
Huntsman Cancer Institute at
the University of Utah

Alan L. Ho, MD, PhD †
Memorial Sloan-Kettering Cancer Center

Karl D. Lewis, MD
University of Colorado Cancer Center

Daniel D. Lydiatt, DDS, MD ¶ §
Fred & Pamela Buffett Cancer Center at
The Nebraska Medical Center

William H. Morrison, MD §
The University of Texas
MD Anderson Cancer Center

Kishwer S. Nehal, MD ☐ ¶
Memorial Sloan-Kettering Cancer Center

Kelly C. Nelson, MD ≠
Duke Cancer Institute

Paul Nghiem, MD, PhD ☐
Fred Hutchinson Cancer Research Center/
Seattle Cancer Care Alliance

Clifford S. Perlis, MD, MBe ☐ ¶
Fox Chase Cancer Center

Ashok R. Shaha, MD ¶ §
Memorial Sloan-Kettering Cancer Center

Wade Thorstad, MD §
Siteman Cancer Center at Barnes-Jewish
Hospital and Washington University
School of Medicine

Malika Tuli, MD ☐
St. Jude Children's Research Hospital/
University of Tennessee Cancer Institute

Marshall M. Urist, MD ¶
University of Alabama at Birmingham
Comprehensive Cancer Center

Timothy S. Wang, MD ☐
The Sidney Kimmel Comprehensive
Cancer Center at Johns Hopkins

Andrew E. Werchinskiak, MD ☐
Dana-Farber/Brigham and Women's
Cancer Center

Sandra L. Wong, MD, MS ¶
University of Michigan
Comprehensive Cancer Center

John A. Zic, MD ☐
Vanderbilt-Ingram Cancer Center

NCCN
Lauren Gallagher, RPh, PhD
Maria Ho, PhD
Karin G. Hoffmann, RN, CCM
Nicole McMillian, MS

☐ Dermatology
¶ Surgery/Surgical oncology
§ Otolaryngology
≠ Pathology/Dermatopathology
† Medical oncology
§ Radiotherapy/Radiation oncology
‡ Hematology/Hematology oncology
* Writing Committee Member

Continue

[NCCN Guidelines Panel Disclosures](#)

[NCCN Merkel Cell Carcinoma Panel Members](#)
[Summary of the Guidelines Updates](#)

Merkel Cell Carcinoma

- [Clinical Presentation, Preliminary Workup, and Clinical Findings \(MCC-1\)](#)
- [Primary Treatment of Clinical N0 \(MCC-2\)](#)
- [Primary Treatment of Clinical N+ \(MCC-3\)](#)
- [Treatment of Clinical M1 \(MCC-4\)](#)
- [Follow-up and Recurrence \(MCC-5\)](#)
- [Principles of Pathology MCC-A](#)
- [Principles of Radiation Therapy \(MCC-B\)](#)
- [Principles of Excision \(MCC-C\)](#)
- [Principles of Chemotherapy \(MCC-D\)](#)
- [Staging \(ST-1\)](#)

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NCCN Categories of Evidence and Consensus: All recommendations are Category 2A unless otherwise specified.

See [NCCN Categories of Evidence and Consensus](#).

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NCCN Guidelines Version 1.2014 Updates

Merkel Cell Carcinoma

Summary of the changes in 1.2014 of the NCCN Merkel Cell Carcinoma Guidelines from Version 2.2013 include:

Global Change

“Principles of Pathology” (MCC-A) is a new page that provides specific recommendations for analysis, interpretation, and reporting of pathology results.

MCC-1

- *H & P, Complete skin and lymph node examination*, removed from CLINICAL PRESENTATION and added to PRELIMINARY WORKUP.
- Removed footnote. "Synoptic reporting is preferred and should include Breslow thickness and the presence or absence of lymphovascular invasion (LVI). For complete synoptic reporting, see the College of American Pathologist (CAP) Guidelines. (Rao P, Balzer BL, Lemos BD, et al. Protocol for the examination of specimens from patients with merkel cell carcinoma of the skin. Arch Pathol Lab Med 2010;134:341-344)."
- Removed footnote. "An appropriate immunopanel should preferably include CK-20 and thyroid transcription factor-1 (TTF-1)."
- Footnote "b" modified to: "Imaging (CT, MR, 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 in cases where CK-20 is negative."

MCC-2

- "SLN positive":
 - ▶ "*Clinical trial preferred, if available*", added as a treatment option.
 - ▶ Fourth bullet removed: May consider adjuvant chemotherapy
- Removed footnote: "An appropriate immunopanel for SLN examination should preferably include CK-20, and pancytokeratins (AE1/AE3). [See Principles of Pathology \(MCC-A\)](#)."
- Removed footnote: "For lymph nodes that are positive only by immunohistochemical methods but not H&E, consider RT as the sole therapy to the draining nodal basin (s)."
- Removed footnote: [See Principles of Chemotherapy \(MCC-D\)](#).
- Removed footnote: "Available retrospective studies do not suggest prolonged survival benefit for adjuvant chemotherapy."
- Footnote "h" modified to: "Consider observation of the primary site, ~~in site~~, in cases where the primary tumor is small *and* widely excised with no other adverse risk factors such as LVI or immune suppressions."

MCC-3

- Footnote "i" modified to: "Imaging (CT, MR, 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.*"

MCC-4

- Footnote "l" added: "*Under highly selective circumstances, in the context of multidisciplinary consultation, resection of oligometastasis can be considered.*"
- Footnote "m" added: [See Principles of Excision \(MCC-C\)](#).

MCC-5

- Footnote "n" added: "*Imaging (CT, MR, 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 MR may be used.*"

MCC-B Principles of Radiation Therapy

- Fourth bullet modified: "*Expeditious* initiation of adjuvant radiation therapy ~~after within 4 weeks of~~ surgery is preferred as a delay has been associated with worse outcomes."

MCC-C Principles of Excision

- Under Surgical Approaches fourth bullet removed: "*Under highly selective circumstances, in the context of multidisciplinary consultation, resection of oligometastasis can be considered.*"
- Under "Reconstruction," third bullet modified to: "If adjuvant radiation therapy is planned, *extensive tissue movement should be minimized and closure should be chosen to allow expeditious initiation of radiation therapy.*"
- Footnote removed: "Initiation of adjuvant radiation therapy within 4 weeks of surgery is preferred."

MCC-D

- Modified title to *Principles of Chemotherapy*.



NCCN Guidelines Version 1.2014

Merkel Cell Carcinoma

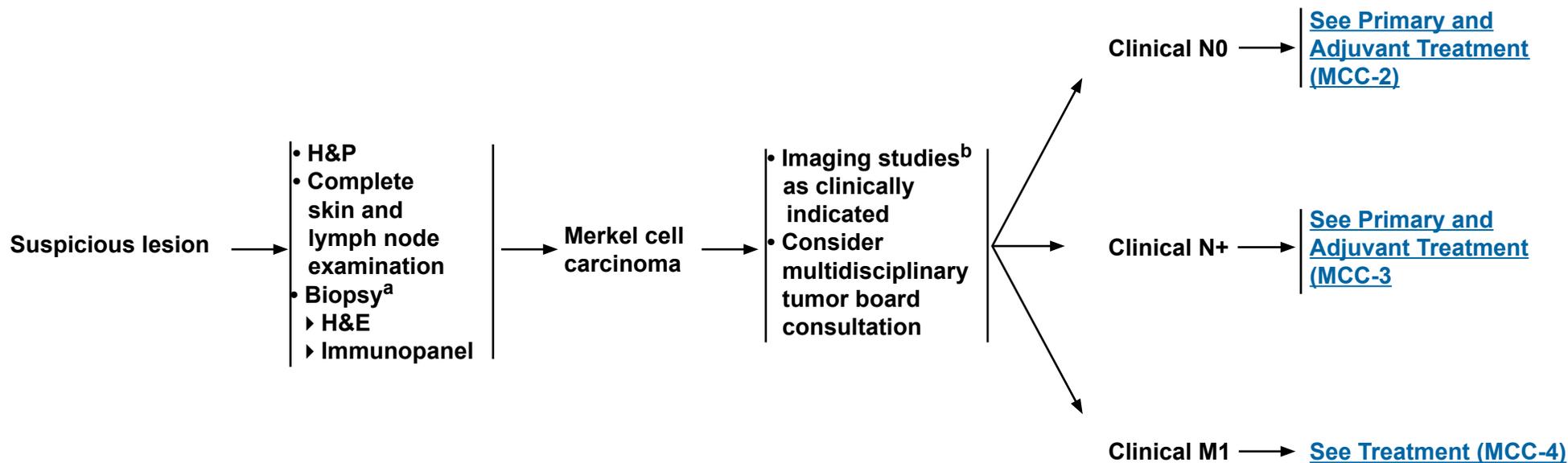
CLINICAL PRESENTATION

PRELIMINARY WORKUP

DIAGNOSIS

ADDITIONAL WORKUP

CLINICAL FINDINGS



^a[Principles of Pathology \(MCC-A\)](#).

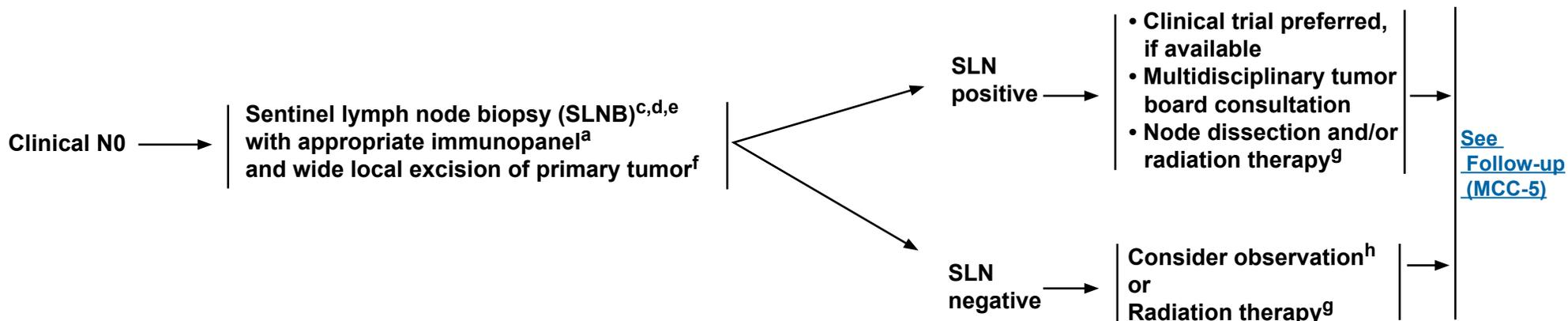
^bImaging (CT, MR, or PET-CT) may be useful to identify and quantify regional and distant metastases. Some studies indicate that PET-CT may be preferred in some clinical circumstances. If PET-CT is not available CT or MRI may be used. Imaging may also be useful to evaluate for the possibility of a skin metastasis from a noncutaneous primary neuroendocrine carcinoma (eg, small cell lung cancer), especially in cases where CK-20 is negative.

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PRIMARY AND ADJUVANT TREATMENT: CLINICAL N0 DISEASE



^a[See Principles of Pathology \(MCC-A\).](#)

^cThe preferred treatment sequence is for the sentinel lymph node biopsy to precede the excision. After wide local excision, sentinel lymph node biopsy may be considered in selected patients, although accuracy of results may be compromised.

^dIn the head and neck region, risk of false negative sentinel lymph node biopsy is higher, due to aberrant lymph node drainage and frequent presence of multiple sentinel lymph node basins. If SLNB is not performed or unsuccessful, consider irradiating nodal beds for subclinical disease [\(See MCC-B\)](#).

^eSentinel lymph node biopsy is an important staging tool for regional control, but the impact of SLNB on overall survival is unclear.

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

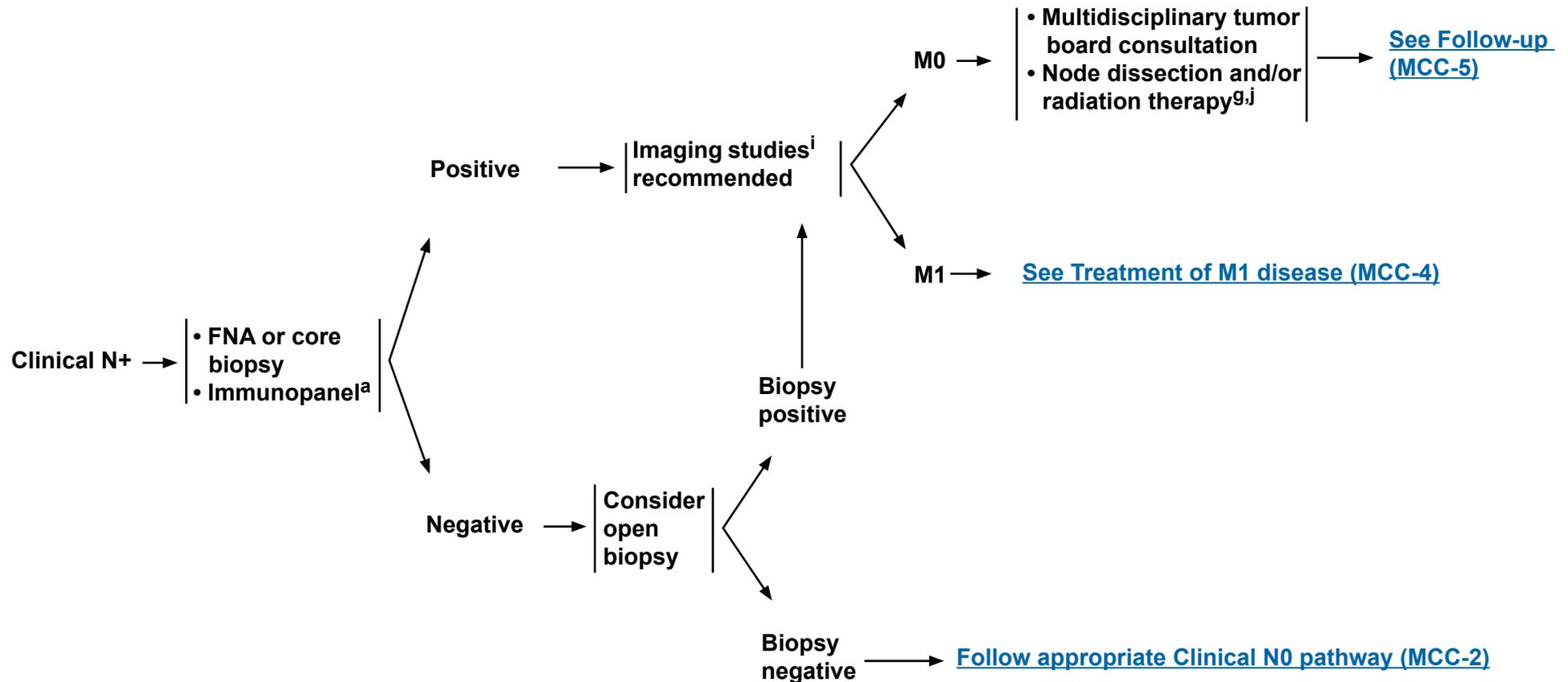
^g[See Principles of Radiation Therapy \(MCC-B\)](#).

^hConsider 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.

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PRIMARY AND ADJUVANT TREATMENT: CLINICAL N+ DISEASE



^aSee Principles of Pathology (MCC-A).

^gSee Principles of Radiation Therapy (MCC-B).

ⁱImaging (CT, MR, 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.

^jAdjuvant 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]).

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TREATMENT: CLINICAL M1 DISEASE



^lUnder highly selected circumstances, in the context of multidisciplinary consultation, resection of oligometastasis can be considered.

^k[See Principles of Chemotherapy \(MCC-D\)](#).

^g[See Principles of Radiation Therapy \(MCC-B\)](#).

^m[See Principles of Excision \(MCC-C\)](#).

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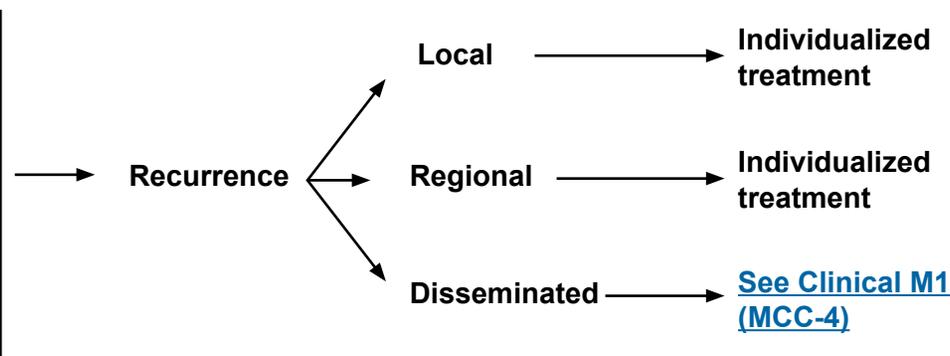


FOLLOW-UP

RECURRENCE

Follow-up visits:

- Physical exam including complete skin and complete lymph node exam
 - ▶ every 3-6 mo for 2 years
 - ▶ every 6-12 mo thereafter
- Imaging studies as clinically indicatedⁿ
 - ▶ Consider routine imaging for high-risk patients



ⁿImaging (CT, MR, 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 MR may be used.

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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 (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 (#/mm² preferred, #/HPF, or MIB-1 index)**
 - ▶ **Tumor infiltrating lymphocytes (not identified, brisk, non-brisk)**
 - ▶ **Tumor growth pattern (Nodular or infiltrative)**
 - ▶ **Presence of second malignancy (i.e., concurrent SCC)**
- **An appropriate immunopanel should preferably include CK-20 and thyroid transcription factor-1 (TTF-1). Immunohistochemistry for CK20 and most low molecular weight cytokeratin markers is positive with a paranuclear “dot-like” pattern. CK7 and thyroid transcription factor-1 (TTF-1) (positive in >80% small cell lung cancer) are negative.**
- **For equivocal lesions, consider additional immunostaining with neuroendocrine markers chromogranin, synaptophysin, CD56, neuron specific enolase (NSE), and neurofilament.**
- **Sentinel lymph node biopsy evaluation should preferably include an appropriate immunopanel (i.e. CK-20 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), location of tumor (subcapsular sinus, parenchyma) and the presence/absence of extracapsular extension.**

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NCCN Guidelines Version 1.2014

Merkel Cell Carcinoma

PRINCIPLES OF RADIATION THERAPY

Dose 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^{1,2}

• After SLNB without LN Dissection

- ▶ Negative SLN biopsy: axilla or groin Radiation not indicated³
- ▶ Negative SLN biopsy: head and neck, if at risk for false negative biopsy 46-50 Gy³
- ▶ Microscopic N+ on SLNB: axilla or groin 50 Gy⁴
- ▶ Microscopic N+ on SLNB: head and neck 50-56 Gy⁴

• After LN Dissection

- ▶ Lymph node dissection: axilla or groin 50-54 Gy⁵
- ▶ 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 at 2 Gy/day 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 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 sentinel node biopsy 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.

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

²Shrinking field technique.

³Consider 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.

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

⁵Postoperative irradiation is indicated for multiple involved nodes or extracapsular extension.

Note: All recommendations are category 2A unless otherwise indicated.

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

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 sentinel lymph node biopsy is performed prior to definitive excision.¹ Excision options include:
- Wide excision with 1-2 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).^{2,3}

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.

¹Sentinel lymph node biopsy is an important staging tool and may contribute to regional control; the impact of sentinel lymph node biopsy on overall survival is unclear.

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

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

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PRINCIPLES OF CHEMOTHERAPY ¹

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)**

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.

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Staging

Table 1

American Joint Committee on Cancer (AJCC) TNM Staging Classification for Merkel Cell Carcinoma (7th ed., 2010)

Primary Tumor (T)

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

Regional Lymph Nodes (N)

- NX** Regional lymph nodes cannot be assessed
- N0** No regional lymph node metastasis
- cN0** Nodes negative by clinical exam* (no pathologic node exam performed)
- pN0** Nodes negative by pathologic exam
- N1** Metastasis in regional lymph node(s)
- N1a** Micrometastasis**
- N1b** Macrometastasis***
- N2** In transit metastasis****

* Clinical detection of nodal disease may be via inspection, palpation, and/or imaging.

** Micrometastases are diagnosed after sentinel or elective lymphadenectomy.

*** Macrometastases are defined as clinically detectable nodal metastases confirmed by therapeutic lymphadenectomy or needle biopsy.

**** 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.

Distant Metastasis (M)

- M0** No distant metastases
- M1** Metastasis beyond regional lymph nodes
- M1a** Metastasis to skin, subcutaneous tissues or distant lymph nodes
- M1b** Metastasis to lung
- M1c** Metastasis to all other visceral sites

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NCCN Guidelines Version 1.2014 Staging Merkel Cell Carcinoma

Staging

Table 1 (continued)

American Joint Committee on Cancer (AJCC)

TNM Staging Classification for Merkel Cell Carcinoma (7th ed., 2010)

ANATOMIC STAGE/PROGNOSTIC GROUPS

Patients with primary Merkel cell carcinoma with no evidence of regional or distant metastases (either clinically or pathologically) are divided into two stages: Stage I for primary tumors ≤ 2 cm in size and Stage II for primary tumors >2 cm in size. Stages I and II are further divided into A and B substages based on method of nodal evaluation. Patients who have pathologically proven node negative disease (by microscopic evaluation of their draining lymph nodes) have improved survival (substaged as A) compared to those who are only evaluated clinically (substaged as B). Stage II has an additional substage (IIC) for tumors with extracutaneous invasion (T4) and negative node status regardless of whether the negative node status was established microscopically or clinically. Stage III is also divided into A and B categories for patients with microscopically positive and clinically occult nodes (IIIA) and macroscopic nodes (IIIB). There are no subgroups of Stage IV Merkel cell carcinoma.

Stage 0	Tis	N0	M0
Stage IA	T1	pN0	M0
Stage IB	T1	cN0	M0
Stage IIA	T2/T3	pN0	M0
Stage IIB	T2/T3	cN0	M0
Stage IIC	T4	N0	M0
Stage IIIA	Any T	N1a	M0
Stage IIIB	Any T	N1b/N2	M0
Stage IV	Any T	Any N	M1

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Discussion

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.

Table of Contents

Overview	MS-2
Diagnosis and Workup	MS-2
Pathology Report.....	MS-2
Imaging.....	MS-3
Staging	MS-3
Treatment	MS-3
Surgery.....	MS-4
Sentinel Lymph Node Biopsy.....	MS-4
Radiation Therapy.....	MS-5
Chemotherapy.....	MS-5
NCCN Recommendations.....	MS-5
Follow-up and Recurrence	MS-6
References	MS-7

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.¹ 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.²⁻⁴ MCC has a high mortality rate that exceeds that of melanoma. The overall 5-year survival rates range from 30% to 64%.⁵⁻⁷

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.⁸ MCC is disproportionately more common in immunosuppressed individuals, such as those with organ transplants, lymphoproliferative malignancies (such as chronic lymphocytic leukemia), or HIV infections.¹

In 2008, Feng and colleagues⁹ identified a novel polyomavirus in MCC tumor tissues. This Merkel cell polyomavirus (MCV) is detected in 43% to 100% of patient samples.¹⁰ The role of MCV in the pathogenesis of MCC is under active investigation.¹¹

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 and Squamous Cell Skin Cancers](#)).¹² 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.¹³ 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.¹⁴⁻

¹⁸ 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).¹⁹⁻²¹ 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 including 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.²²

Imaging

Additional workup of a patient with MCC may include imaging studies.²³ In asymptomatic patients with primary MCC, sentinel lymph node biopsy (SLNB) is considered the most sensitive staging test for the detection of nodal metastases.^{15,16,18} 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.²⁴ 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.²⁵ 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.²⁶

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.^{2,4,27-33} The NCCN staging of MCC parallels the AJCC guidelines and divides presentation into local, regional, and disseminated disease.³⁴ 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.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.³⁵

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.³⁶ 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.³⁷

Wide local excision with 1- to 2-cm margins to the investing fascia layer remains the standard surgical technique.³⁶ 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.^{38,39} 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.⁴⁰ 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.⁴¹ One review of 161 patients with MCC found that SLNB identified micrometastases in one-third of early-stage patients.⁴² 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.⁴³ 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.^{6,44} 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.^{45,46} 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.⁴⁷ 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.⁴⁸ Jouary and colleagues⁴⁹ 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; $P = .0002$).⁵⁰ Improvement was most pronounced for patients with tumors larger than 2 cm (median survival 50 months vs. 21 months; $P = .0003$). 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.⁵¹ 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.^{52,53} Data are insufficient to assess whether chemotherapeutic regimens improve either relapse-free or overall survival in MCC patients with distant metastatic disease.^{5,54-58} If it is used, the panel recommends cisplatin or carboplatin with or without etoposide.^{5,59} 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.⁵⁶ 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

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 with melanoma, it is always best to perform the SLNB before definitive local excision to maximize accuracy. In clinical practice, SLNB is typically performed concurrent with the definitive wide local excision.



Following 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 present with no adverse risk factors such as lymphovascular invasion or immunosuppression.⁶⁰

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 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 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. 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 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 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.^{5,6,30} 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.²⁵

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

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