

NCCN Clinical Practice Guidelines in Oncology™

Merkel Cell Carcinoma

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Clinical Trials: The NCCN believes that the best management for any cancer patient 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](http://nccn.org/clinical_trials/physician.html)

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

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

These guidelines are a statement of evidence and consensus of the authors regarding their views of currently accepted approaches to treatment. Any clinician seeking to apply or consult these 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 makes no representations nor warranties of any kind whatsoever regarding their content, use, or application and disclaims any responsibility for their application or use in any way. These guidelines are copyrighted by National Comprehensive Cancer Network. All rights reserved. These guidelines and the illustrations herein may not be reproduced in any form without the express written permission of NCCN. ©2008.

Summary of the Guidelines updates

Summary of changes in the 1.2009 version of the Merkel Cell Carcinoma guidelines from the 1.2008 version include:

(MCC-1)

- Footnote b: Changed to, “Imaging may be indicated *to evaluate for the possibility of a skin metastasis from a noncutaneous primary neuroendocrine carcinoma*, especially...”

(MCC-2)

- Clinical N0: A new pathway for “Head and neck cases” was added.
- After SLN Positive: Previously the Guidelines stated “Consider any of the following therapies or combinations of: Node dissection, Adjuvant radiation therapy, Adjuvant chemotherapy.” The guidelines now state “Node dissection *and/or* radiation therapy; *May consider* adjuvant chemotherapy”. (ALSO for MCC-3)
- After SLN Negative; Radiation therapy recommendation: Footnote regarding radiation therapy to primary site was removed.

(MCC-3)

- Footnote m: “...extent of lymph node and visceral organ involvement” was changed to “...extent of lymph node *and/or* visceral...”

(MCC-4)

- After “Multidisciplinary tumor board consultation”: The phrase “Clinical trial” was removed.

(MCC-A): Principles of Radiation Therapy

- “Principles of Radiation Therapy” is a new page that provides specific recommendations for merkel cell carcinoma radiation therapy throughout the guidelines.

(MCC-B): Principles of Excision

- Footnote “1” regarding the uses of the mohs technique is new to the page.

(MCC-C): Chemotherapy Agents

- Entire page revised and now contains chemotherapy recommendations for Local disease, Regional disease, and Disseminated disease.

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CLINICAL PRESENTATION

PRELIMINARY WORKUP

DIAGNOSIS

ADDITIONAL WORKUP

CLINICAL FINDINGS

Suspicious lesion
• H&P
• Complete skin and regional lymph node examination

Biopsy
• H&E
• Immunopanel^a

Merkel cell carcinoma

• Imaging^b studies as clinically indicated
• Consider multidisciplinary tumor board consultation

Clinical N0

Clinical N+

Clinical M1

[See Primary and Adjuvant Treatment \(MCC-2\)](#)

[See Primary and Adjuvant Treatment \(MCC-3\)](#)

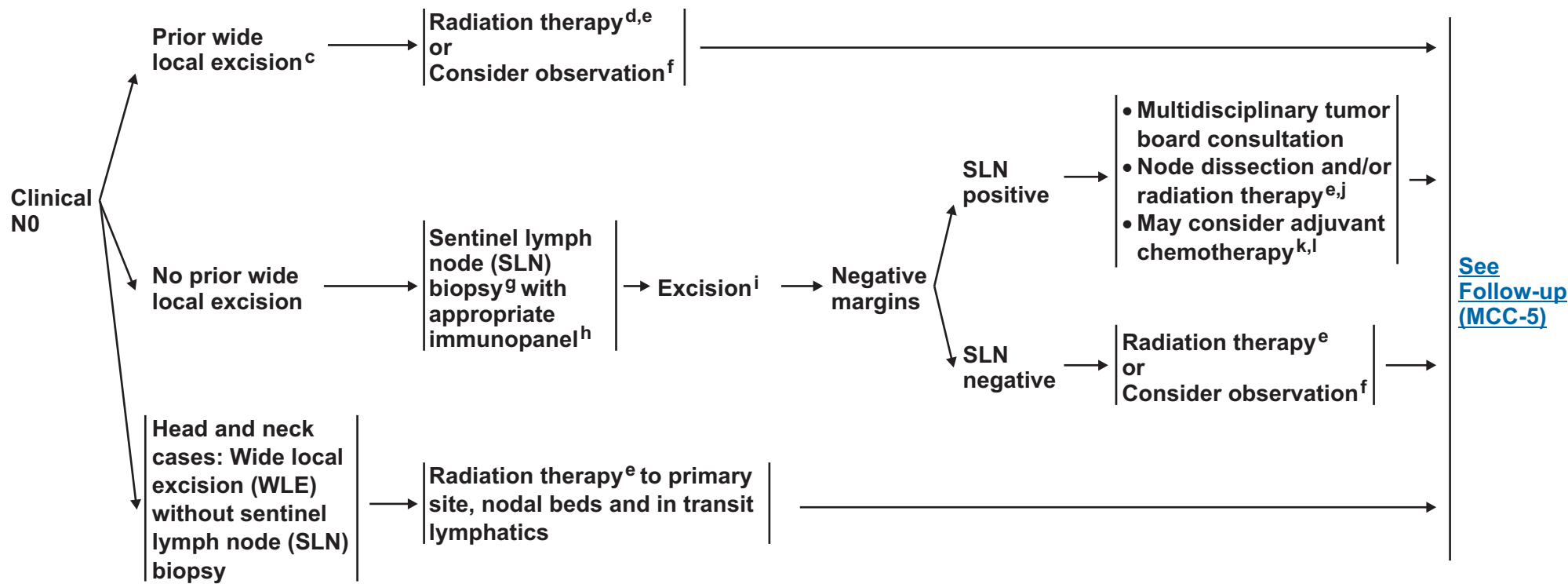
[See Treatment \(MCC-4\)](#)

^aAn appropriate immunopanel should preferably include CK-20 and thyroid transcription factor-1 (TTF-1).

^bImaging (CT, MR, or PET) may be indicated 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



^cAfter wide local excision, sentinel lymph node biopsy may be considered in selected patients, although accuracy of results may be compromised, especially in non-extremity regions.

^dRadiation therapy to primary site, in transit lymphatics (when feasible), and/or draining nodal basins.

^e[See Principles of Radiation Therapy \(MCC-A\)](#).

^fConsider observation with small tumors, widely excised with no other adverse risk factors.

^gThe preferred treatment sequence is for the sentinel lymph node biopsy to precede the excision.

^hAn appropriate immunopanel for SLN examination should preferably include CK-20, and pancytokeratins (AE1/AE3).

ⁱ[See Principles of Excision \(MCC-B\)](#).

^jFor 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).

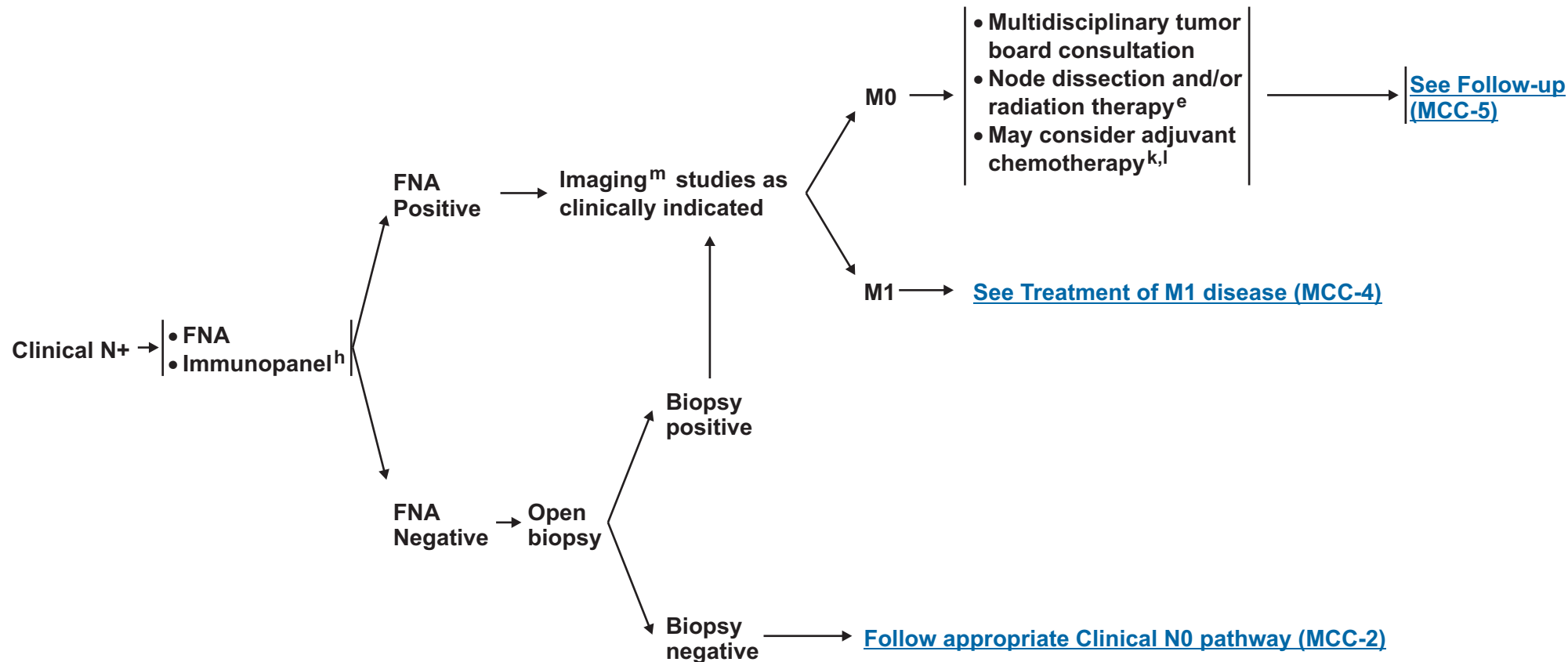
^k[See Chemotherapy Agents \(MCC-C\)](#).

^lAvailable retrospective studies do not suggest prolonged survival benefit for adjuvant chemotherapy.

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PRIMARY AND ADJUVANT TREATMENT: CLINICAL N+ DISEASE



^eSee Principles of Radiation Therapy (MCC-A).

^hAn appropriate immunopanel for LN examination should preferably include CK-20 and pancytokeratins (AE1/AE3).

^kSee Chemotherapy Agents (MCC-C).

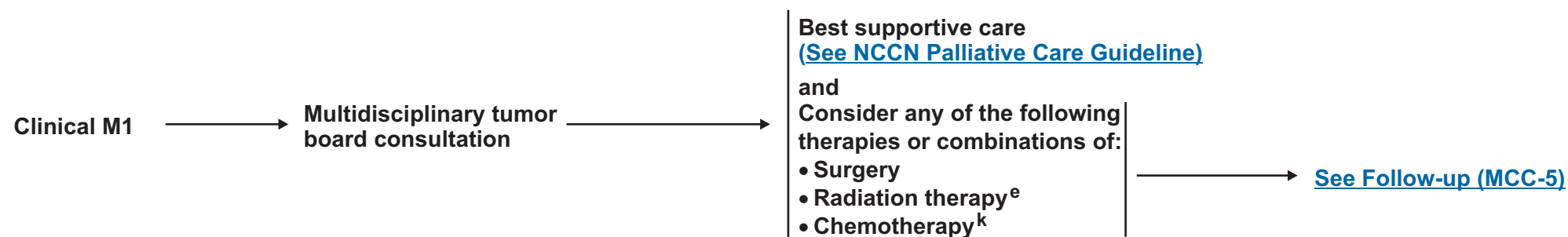
^lAvailable retrospective studies do not suggest prolonged survival benefit for adjuvant chemotherapy.

^mImaging (CT, MR, or PET) may be indicated to evaluate extent of lymph node and/or visceral organ involvement.

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TREATMENT: CLINICAL M1 DISEASE

^eSee Principles of Radiation Therapy (MCC-A).^kSee Chemotherapy Agents (MCC-C).

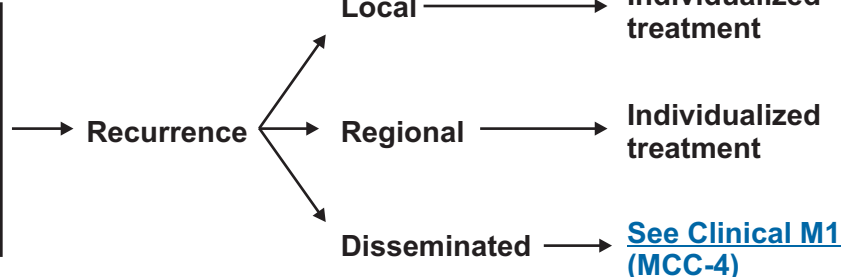
Note: All recommendations are category 2A unless otherwise indicated.

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FOLLOW-UP

RECURRENCE

- Every 1-3 mo for year 1
- Every 3-6 mo for year 2
- Annually thereafter
 - › Physical exam including complete skin and regional lymph node exam
 - › Imaging studies as clinically indicated



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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 adenopathy: head and neck | 60-66 Gy |
| ‣ Clinically evident adenopathy: axilla or groin ¹ | -- ¹ |

• After SLNB without LN Dissection

- | | |
|--|--------------------------------------|
| ‣ Negative SLN biopsy: axilla or groin | Radiation not indicated ² |
| ‣ Negative SLN biopsy: head and neck, if at risk for false negative biopsy | 46-50 Gy ² |
| ‣ Microscopic N+ on SLNB: axilla or groin | 50 Gy ³ |
| ‣ Microscopic N+ on SLNB: head and neck | 50-56 Gy |

• After LN Dissection

- | | |
|--|-----------------------|
| ‣ Lymph node dissection: axilla or groin | 50-54 Gy ⁴ |
| ‣ Lymph node dissection: head and neck | 50-60 Gy |

- 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, consider irradiating nodal beds for subclinical disease. Irradiation of in transit lymphatics is usually 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.

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

²Consider 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.

³Microscopic 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.

⁴RT may be omitted after axillary/groin LN dissection for microscopic disease. Postoperative radiation is indicated for multiple involved nodes and/or presence of more than focal extracapsular extension.

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PRINCIPLES OF EXCISION

Goal:

- Clear surgical margins when clinically feasible.

Varied Approaches:

- 1-2 cm margins to investing fascia of muscle or pericranium with clear pathologic margins, when clinically feasible.
- Mohs technique¹
- Modified Mohs = Mohs technique with additional final margin for permanent section assessment.
- CCPDMA= Complete circumferential and peripheral deep-margin assessment.

Reconstruction:

- Immediate reconstruction in most cases.
- It is preferable to delay reconstruction involving extensive undermining or flaps until negative surgical margins are assessed and certified pathologically clear.
- When primary closure is not possible, consider split-thickness skin grafting (STSG) to monitor for recurrence.

¹Mohs technique is used primarily in MCC to insure complete removal and clear margins, and secondarily for its tissue sparing capabilities.

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CHEMOTHERAPY AGENTS¹**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 alone or combined with etoposide
- Carboplatin alone or combined with etoposide

Disseminated disease:

- Cisplatin plus etoposide
- Carboplatin plus etoposide
- Cyclophosphamide, doxorubicin (or epirubicin) and vincristine
- Topotecan has been used

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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Discussion

NCCN Categories of Evidence and Consensus

Category 1: The recommendation is based on high-level evidence (e.g. randomized controlled trials) and there is uniform NCCN consensus.

Category 2A: The recommendation is based on lower-level evidence and there is uniform NCCN consensus.

Category 2B: The recommendation is based on lower-level evidence and there is nonuniform NCCN consensus (but no major disagreement).

Category 3: The recommendation is based on any level of evidence but reflects major disagreement.

All recommendations are category 2A unless otherwise noted.

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.¹⁻¹⁶ Several large reviews document the development of local recurrence in 25-30% of all cases of MCC, regional disease in 52-59% of all cases, and distant metastatic disease in 34-36% of cases.^{1,16,17} MCC has a mortality rate that exceeds that of melanoma.¹⁸ The overall 5-year survival rates range from 30-64%.^{3,19} A history of extensive sun exposure is a risk factor for MCC. Older white men (65 years or older) are at higher risk for MCC, which tends to occur on the areas of the skin that are exposed to sun.²⁰

NCCN Non-Melanoma Skin Cancer Panel has developed guidelines outlining treatment of MCC to supplement the squamous cell and basal cell skin cancer guidelines ([NCCN Basal Cell and Squamous Cell Skin](#)

[Cancers Guidelines](#)).²¹ MCC is a rare tumor; therefore, no prospective, statistically significant data are available to verify the validity of any prognostic features or treatment outcomes. The panel relied on trends that are documented in smaller, individual studies and in meta-analyses as well as their own collective experiences.

Diagnosis and Workup

Initial workup of a suspicious lesion starts with a complete examination of skin and regional lymph nodes followed by biopsy ([MCC-1](#)). The primary goal in biopsy of a MCC is to confirm the diagnosis. Rarely does MCC present clinically as a classic lesion where MCC is expected to be the main diagnosis. The histologic diagnosis may 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.

Initial diagnosis of MCC in the primary lesion by hematoxylin and eosin staining (H&E) 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).²²⁻²⁴ CK-20 is a very sensitive marker for MCC, since it is positive in 89-100% of tumors. TTF-1 is expressed in 83-100% of SCLC but it is consistently absent in MCC. Other immunohistochemical markers including chromogranin A, synaptophysin, neurofilament protein, neuron specific enolase, leukocyte common antigen (CD45), S-100 protein, and pancytokeratin (panCK) may be used in addition to CK-20 and TTF-1 to exclude other diagnostic considerations.⁵ In addition to the above mentioned markers, a majority of primary and metastatic MCCs also express KIT receptor tyrosine kinase (CD117).²⁵

Additional workup of a patient with MCC includes imaging studies as clinically indicated, which parallels most suggested approaches to such patients in the biomedical literature.^{5,6,13} Imaging (x-ray, CT, MRI or PET scan) may be indicated to evaluate for the possibility of a skin metastasis from a non-cutaneous carcinoma (eg. small cell carcinoma of the lung), especially in cases where CK-20 is negative. One diagnostic test to consider is a radiolabeled scan using a somatostatin analogue.^{5,6}

Treatment is primarily dependent on accurate histopathologic interpretation and on microstaging of the primary lesion. Thus, excisional biopsy of the entire lesion with narrow clear surgical margins is preferred, whenever possible, to obtain the most accurate diagnostic and microstaging information. Then, definitive excision with or without sentinel lymph node biopsy (SLNB) can best be performed. IHC analysis has been shown to be effective in detecting more lymph node metastases in patients with MCC.^{3,26} 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.^{27,28} An appropriate immunopanel for SLNB should include CK-20 and pancytokeratins. Performing a wide local excision initially, especially in the head, neck and trunk regions may potentially interfere with the accuracy of subsequent SLNB.

Staging

In a biomedical literature, the most consistently reported adverse prognostic feature is tumor stage followed by tumor size.^{1,2,6,8,10,11,13,14,16} The NCCN staging of MCC parallels the American Joint Committee on Cancer (AJCC) guidelines and divides presentation into local, regional, and disseminated disease.²⁹ An MCC web site from Seattle Cancer Care Alliance also has a useful staging table (www.merkelcell.org).

Treatment

Surgery is the primary treatment modality for MCC. There was tremendous variability among individual clinicians and NCCN institutions regarding the use of following treatment options:

- SLNB or elective lymph node dissection for clinically normal regional lymph node basin(s);
- Postoperative radiation therapy for the primary tumor, draining lymphatics, and/or regional lymph node basins; and
- Adjuvant chemotherapy for local or regional disease.

Therefore, the MCC guidelines are suitably broad to reflect all the approaches taken by participating NCCN institutions.

Excision

Local wide excision is the recommended primary treatment for clinically localized (N0) disease ([MCC-B](#)). 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. Surgical techniques include excision with wide margins to the investing fascia layer with complete peripheral margin examination and Mohs or modified Mohs surgery.³⁰ Mohs micrographic surgery is superior to conventional surgical excision in basal cell carcinoma and squamous cell carcinoma. In MCC, it is primarily used to ensure complete tumor removal and clear margins, while secondarily sparing surrounding healthy tissue.³¹

Sentinel Lymph Node Biopsy

Sentinel lymph node biopsy is very important in the staging and treatment of MCC.³² Studies suggest that elective lymph node dissection decreases regional recurrence rates and improves survival.^{2,8} Most studies that examine the use of SLNB in MCC suggest

a positive benefit but have only short-term follow-up.³³⁻³⁶ One review found that pathologic nodal staging was associated with improved survival and decreased nodal recurrence. Evidence suggests the incidence of a positive sentinel lymph node is independent of primary tumor size.¹⁹ Essentially all participating NCCN institutions use the SLNB technique routinely for MCC, as they do for melanoma. SLNB is offered to patients who are otherwise healthy for staging purposes; a positive sentinel lymph node is followed-up with a completion lymph node dissection and/or radiation therapy if appropriate. The NCCN Panel believes that by identifying patients with positive microscopic nodal disease and then performing full lymph node dissections, the care of regional disease in this patient population is maximized. Finally, as with melanoma, it is always best to perform the SLNB before definitive local excision.

Radiation Therapy

Although the literature on the benefits of radiation therapy has been mixed, recent studies are providing increasing support of 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.³⁷ In a review of 82 cases diagnosed between 1992 and 2004, administration of radiotherapy to the primary site or regional lymph nodes was associated with a prolonged time to recurrence and survival.³⁸ The panel included radiation as a treatment option for all stages of MCC. Specifications on radiation dosing, as well as for different MCC sites (head and neck versus extremity and torso), are detailed on [MCC-A](#).

Chemotherapy

Most NCCN institutions only use chemotherapy with or without surgery and/or radiation therapy for stage IV, distant metastatic disease (M1). A

few member institutions suggest considering adjuvant chemotherapy for selected cases of regional (N+) disease. Available data from retrospective studies do not suggest prolonged survival benefit for adjuvant chemotherapy.^{39,40} Data are insufficient to assess whether chemotherapeutic regimens improve either relapse-free or overall survival in MCC patients with distant metastatic disease.⁴¹⁻⁴⁴ If it is used, the panel recommends etoposide in combination with cisplatin or carboplatin, or cyclophosphamide in combination with doxorubicin and vincristine ([MCC-C](#)). Topotecan has also been used in some instances (eg. older patients).

Metastatic Disease

The panel recommends multidisciplinary tumor board consultation for patients with metastatic disease to consider any or a combination of radiation, surgery, and chemotherapy ([MCC-4](#)). Full imaging workups are recommended for all patients with clinically proven regional or metastatic disease. In general, the case of patients with distant metastasis must be individually tailored.

Follow-up

Finally, the NCCN panel's recommendations for close clinical follow-up of MCC patients immediately after diagnosis and treatment ([MCC-5](#)) parallel the recommendations in the biomedical literature. The schedule is the same regardless of whether patients are N0, N+, or clinical M1. The physical examination should include a complete skin and regional lymph node examination, every 1-3 months for the first year, every 3-6 months in the second year and annually thereafter. The panel's recommendations also reflect the facts that the median time to recurrence in patients with MCC is about 8 months, with 90% of the recurrences occurring within 24 months.^{3,10,19} 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.

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