

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines[™])

Merkel Cell Carcinoma

Version 1.2012

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Merkel Cell Carcinoma

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

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Continue

[NCCN Guidelines Panel Disclosures](#)



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NCCN Guidelines™ Version 1.2012 Table of Contents

Merkel Cell Carcinoma

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

[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 Radiation Therapy \(MCC-A\)](#)

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

[Chemotherapy Agents \(MCC-C\)](#)

[Staging \(ST-1\)](#)

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](#)

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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Updates in Version 1.2012 of the NCCN Merkel Cell Carcinoma Guidelines from Version 2.2011 include:

[MCC-5](#)

Follow-up:

- Follow-up visits for physical exam including complete skin and complete lymph node exam changed from “every 1-3 mo for year 1; every 3-6 mo fo year 2; annually thereafter” to “every 3-6 mo for 2 years; then every 6-12 mo thereafter”.

[MCC-A](#)---Principles of Radiation Therapy

- The following statement was added, “Palliation: A less protracted fractionation schedule may be used in the palliative setting, such as 30 Gy in 10 fractions.”
- Footnote “4”: The following statement was removed, “RT may be omitted after axillary/groin LN dissection for microscopic disease”.

[MCC-B](#)---Principles of Excision

Reconstruction:

- Second bullet: Changed to, “ It is recommended that any reconstruction involving extensive undermining or tissue movement be delayed until negative histological margins are verified.”
- Footnote 3 regarding CCPDMA that states, “Usually performed as a meticulous, comprehensive en face permanent section examination of all surgical margins,” is new to the algorithm.



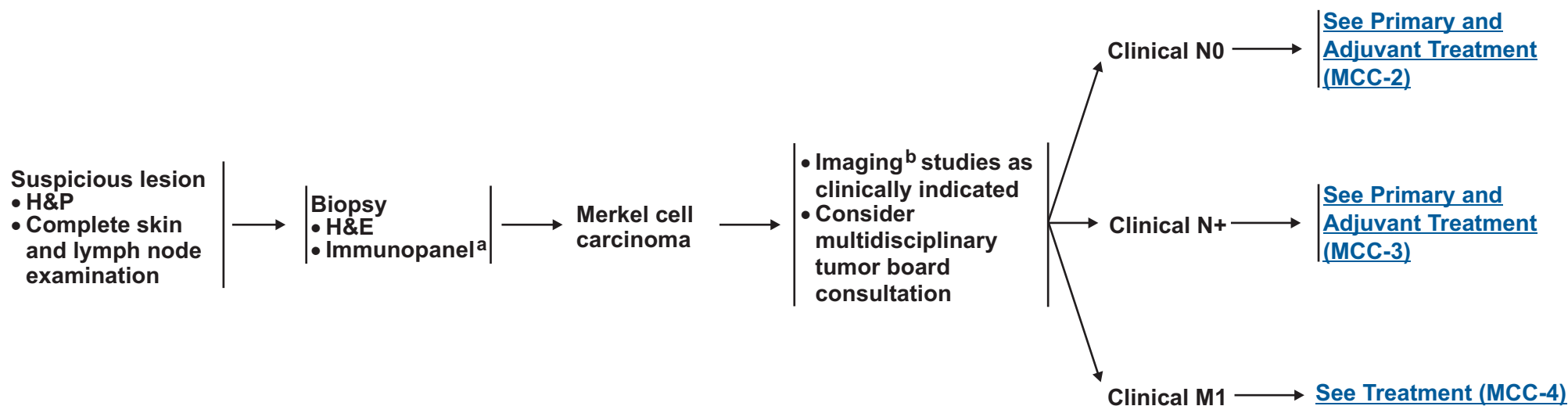
CLINICAL PRESENTATION

PRELIMINARY WORKUP

DIAGNOSIS

ADDITIONAL WORKUP

CLINICAL FINDINGS



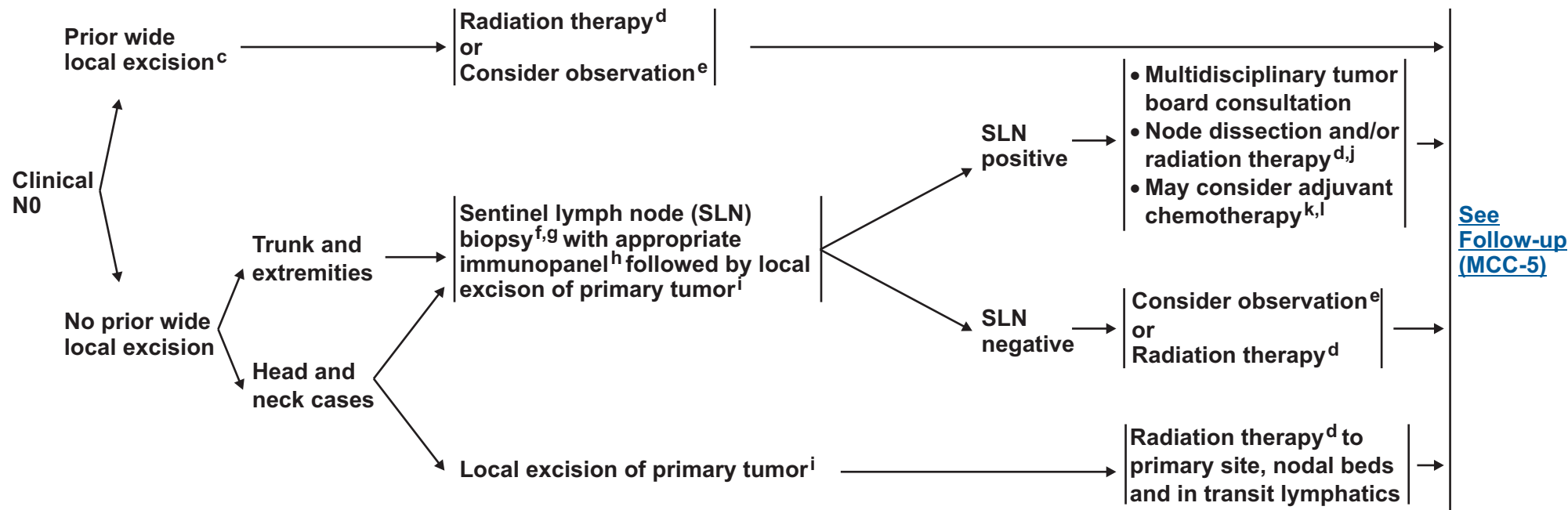
^aAn appropriate immunopanel should preferably include CK-20 and thyroid transcription factor-1 (TTF-1).

^bImaging (CT, MR, or PET-CT) may be useful to identify and quantify regional and distant metastases. 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



^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.

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

^eConsider observation of the tumor bed, in cases where the primary tumor is small, widely excised with no other adverse risk factors.

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

⁹In 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.

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

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

^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 \(MCC-C\)](#).

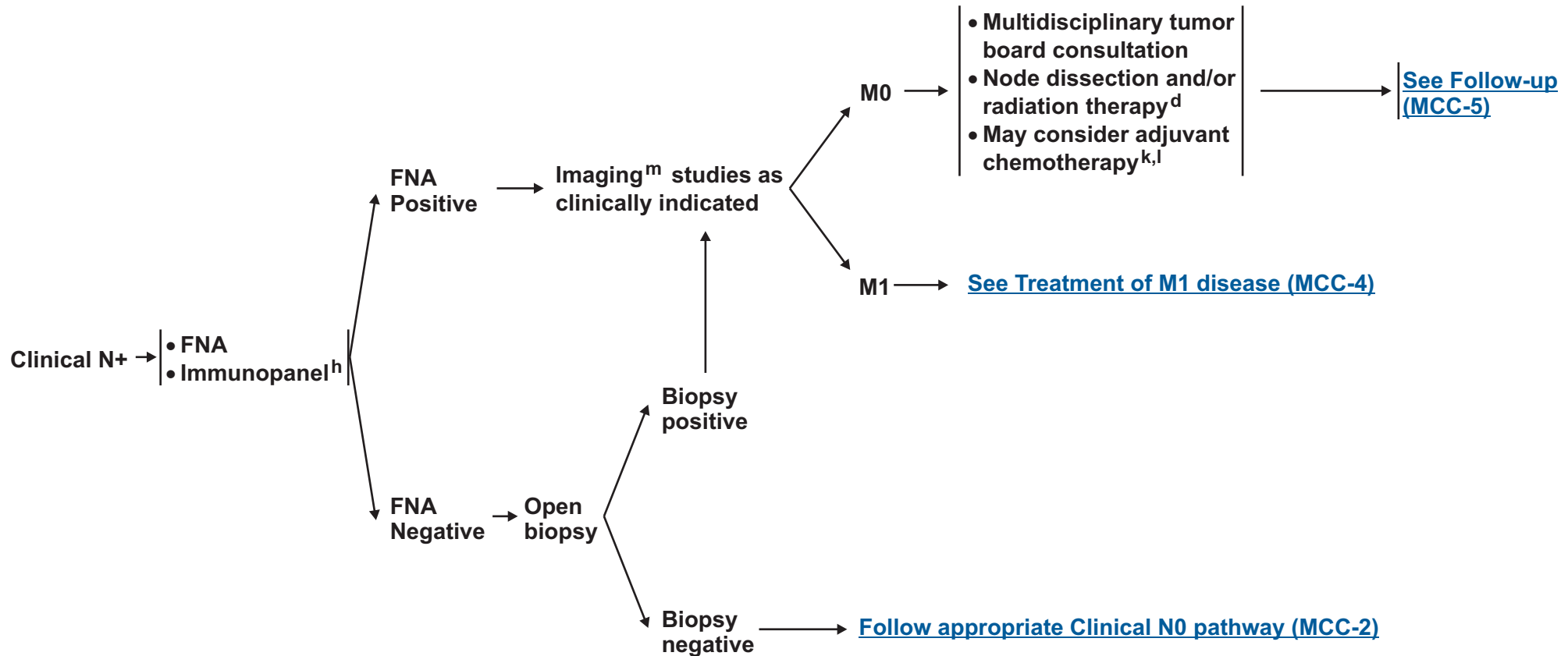
^lAvailable retrospective studies do not suggest prolonged survival benefit for adjuvant chemotherapy.

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

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PRIMARY AND ADJUVANT TREATMENT: CLINICAL N+ DISEASE



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

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

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

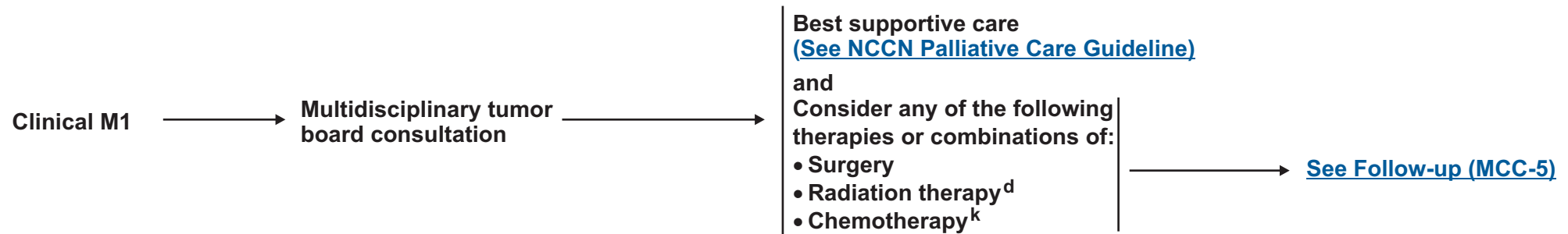
^lAvailable retrospective studies do not suggest prolonged survival benefit for adjuvant chemotherapy.

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

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

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TREATMENT: CLINICAL M1 DISEASE



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

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

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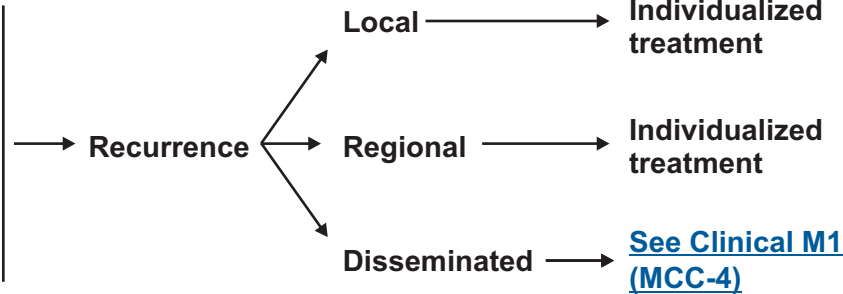


FOLLOW-UP

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 indicated



Note: All recommendations are category 2A unless otherwise 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 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

- 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 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. 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.

²Shrinking field technique. ⁵Postoperative irradiation is indicated for multiple involved nodes or extracapsular extension.

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.

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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 technique^{1,2}
- Modified Mohs = Mohs technique with additional final margin for permanent section assessment.
- CCPDMA= Complete circumferential and peripheral deep-margin assessment.³

Reconstruction:

- Immediate reconstruction in most cases.
- It is recommended that any reconstruction involving extensive undermining or tissue movement be delayed until negative histological margins are verified.
- When primary closure is not possible, consider split-thickness skin grafting (STSG) to monitor for recurrence.

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

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

³ Usually performed as a meticulous, comprehensive en face permanent section examination of all surgical margins.

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.



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 ± 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.

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

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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

Used with the permission of the American Joint Committee on Cancer (AJCC), Chicago, Illinois. The original and primary source for this information is the AJCC Cancer Staging Manual, Seventh Edition (2010) published by Springer Science and Business Media LLC (SBM). (For complete information and data supporting the staging tables, visit www.springer.com.) Any citation or quotation of this material must be credited to the AJCC as its primary source. The inclusion of this information herein does not authorize any reuse or further distribution without the expressed, written permission of Springer SBM, on behalf of the AJCC.

[Continue](#)



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.

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 25-30% of all cases of MCC, regional disease in 52-59% of all cases, and distant metastatic disease in 34-36% of cases.²⁻⁴ MCC has a high mortality rate that exceeds that of melanoma. The overall 5-year survival rates range from 30-64%.^{5,6} MCC is more common in immunosuppressed individuals, such as those with HIV infections or organ transplants.¹ A history of extensive sun exposure is also 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.⁷ In 2008, Feng et al⁸ identified a novel polyomavirus in MCC tumor tissues. This Merkel cell polyomavirus (MCV) is detected in

43% to 100% of patient samples.⁹ The role of MCV in the pathogenesis of MCC is under active investigation.¹⁰

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](#)).¹¹ 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 lymph nodes followed by biopsy. 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).¹²⁻¹⁴ 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.¹⁵

The prognostic value of histopathologic features of the primary tumor remains uncertain. However, there is an emerging body of literature which suggests that lymphovascular invasion, tumor thickness, mitotic rate, tumor growth pattern, and tumor-infiltrating lymphocytes (particularly intra-tumoral CD8+ lymphocytes) may provide relevant prognostic information with regard to survival and/or sentinel lymph node positivity in MCC.¹⁶⁻¹⁹ It is therefore suggested that these features be included in the pathology report whenever possible.^{20, 21}

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.^{15, 22, 23} Imaging (CT, MRI or PET/CT 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. Imaging may also be useful in identifying distant metastases. In a retrospective review, PET/CT resulted in a change of management for 9 out of 18 patients, all with late stage disease.²⁴

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.^{6, 25} 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.^{26, 27} 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 the biomedical literature, the most consistently reported adverse prognostic feature is tumor stage followed by tumor size.^{2, 4, 22, 23, 28-32} The NCCN staging of MCC parallels the American Joint Committee on Cancer (AJCC) guidelines and divides presentation into local, regional, and disseminated disease.²¹ The AJCC staging system is based on an analysis of 5,823 cases from the National Cancer Data Base with a median follow-up of 64 months.³³ 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. 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 circumferential and peripheral deep-margin margin assessment (CCPDMA), and Mohs or modified Mohs surgery.³⁴ 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.³⁵ If Mohs was used, the panel emphasized that a specimen from the central portion of the tumor should be sent for permanent section microstaging.

SLNB

SLNB is very important in the staging and treatment of MCC.³⁶ Studies suggest that elective lymph node dissection decreases regional recurrence rates and improves survival.^{28, 29} Most studies that examine the use of SLNB in MCC suggest a positive benefit but have only short-term follow-up.³⁷⁻⁴⁰ 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.⁵ 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. Adjuvant chemotherapy may be considered if appropriate. Patients with negative sentinel lymph nodes may consider observation

or undergo postoperative radiation. The NCCN Panel believes that by identifying patients with positive microscopic nodal disease and then performing full lymph node dissections and/or radiation therapy, the care of regional disease in this patient population is maximized. However, it should be noted that compared to the trunk and extremities, SLNB is less reliable in the head and neck region and is therefore not mandatory. The complex and variable drainage pattern of the area can lead to false negativity.⁴¹ Finally, as with melanoma, it is always best to perform the SLNB before definitive local excision to maximize accuracy.

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.⁴² 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.⁴³ The panel included radiation as a treatment option for all stages of MCC. Radiation is acceptable as primary therapy in select cases when complete excision is not feasible or refused by the patient. An Australian retrospective review of 43 patients reported an in-field tumor control rate of 75% using radiation alone.⁴⁴ Radiation may also be useful in the palliative setting. Specifications on radiation dosing, as well as for different MCC sites (head and neck versus extremity and torso), are detailed in the algorithm.



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. 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.^{45, 46} Data are insufficient to assess whether chemotherapeutic regimens improve either relapse-free or overall survival in MCC patients with distant metastatic disease.⁴⁷⁻⁵⁰ If it is used, the panel recommends cisplatin or carboplatin with or without etoposide.⁵¹ 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.⁴⁹ 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.

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. 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 parallel the recommendations in the 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 3-6 months for the first two years, then every 6-12 months 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.^{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.



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