National Comprehensive Cancer Network®

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Merkel Cell Carcinoma

Version 1.2017 — October 3, 2016

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NCCN Guidelines Version 1.2017 Panel Members
Merkel Cell Carcinoma

NCCN Guidelines Index
Table of Contents
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Continue

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NCCN Guidelines Version 1.2017 Table of Contents
Merkel Cell Carcinoma

Merkel Cell Carcinoma

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

To find clinical trials online at NCCN Member Institutions, click here: nccn.org/clinical_trials/physician.html.

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

See NCCN Categories of Evidence and Consensus.

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NCCN Guidelines Version 1.2017 Updates
Merkel Cell Carcinoma

NCCN Guidelines Index
Table of Contents
Discussion

Updates in Version 1.2017 of the NCCN Guidelines for Merkel Cell Carcinoma from Version 1.2016 include:

Global Changes

- **Title, algorithm, and all references to "Principles of Chemotherapy (MCC-D)" were amended: "Principles of ~~Chemotherapy~~ *Systemic Therapy* (MCC-D)"**

Merkel Cell Carcinoma

MCC-1

- **Footnote "c" was amended: "~~Imaging (CT, MR, or PET/CT)~~ *Brain MRI with contrast and neck/chest/abdomen/pelvis CT with contrast or FDG-PET* 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 *with contrast* may be used. Imaging may also be useful to evaluate for the possibility of a skin metastasis from a noncutaneous primary neuroendocrine carcinoma (eg, small cell lung cancer), especially in cases where CK-20 is negative."**
- **Footnote "d" was added: *"Imaging is encouraged whenever metastatic or unresectable disease is suspected based on H&P findings. The most reliable staging tool to identify sub-clinical nodal disease is sentinel lymph node biopsy (SLNB)."***

MCC-2

- **For management of the draining nodal basin, "SLN positive" was amended: "~~Consider~~ *B*aseline imaging if studies not already performed"**
- **Footnote "i" was amended: "~~Imaging (CT, MR, or PET/CT)~~ *Brain MRI with contrast and neck/chest/abdomen/pelvis CT with contrast or FDG-PET* 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 *with contrast* may be used." (Also for MCC-5)**
- **Footnote "l" was amended: "Consider RT when there is a potential for anatomic [eg, previous history of surgery including WLE (wide local excision)], operator, or histologic failure (eg, failure to perform appropriate immunohistochemistry on SLNs) that may lead to a false-negative SLNB. Consider RT *in cases of* ~~for~~ profound immunosuppression."**

MCC-3

- **Footnote "m" was amended: "~~Imaging (CT, MR, or PET/CT)~~ *Brain MRI with contrast and neck/chest/abdomen/pelvis CT with contrast or FDG-PET* 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 *with contrast* may be used."**

MCC-4

- **Treatment Of Clinical M1 Disease options were amended:**
  - **"Best Supportive care (See Guidelines for NCCN Palliative Care)" was moved to the bottom of the list.**
  - **Amended the 1st bullet in list of therapies to consider: "~~Chemotherapy~~ *Systemic therapy*"**

MCC-5

- **1st sub-bullet for physical exam schedule under follow-up visits was amended: "Every 3–6 mo for ~~2~~ *3* years*"***

MCC-A Principles of Pathology

- **Amended the 5th sub-bullet in the list of additional clinically revelant factors to report: "Presence of *a* second malignancy *within the pathologic specimen itself* (ie, concurrent squamous cell carcinoma [SCC])"**

MCC-B Principles of Radiation Therapy

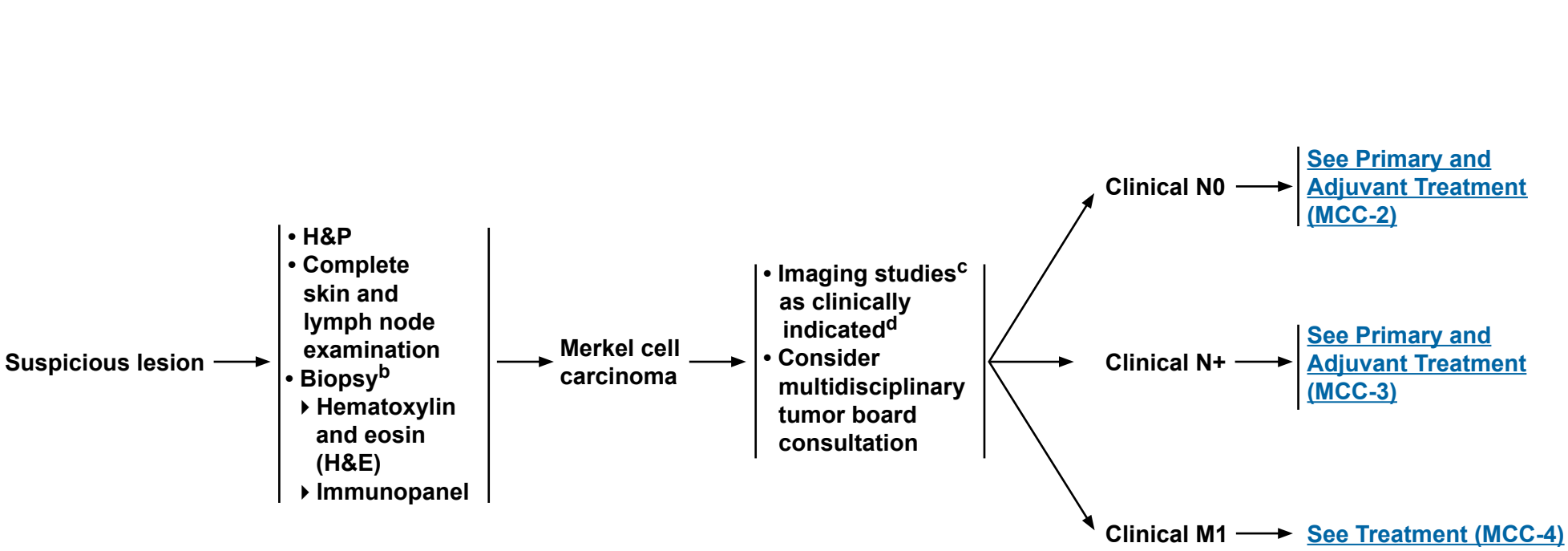
- **Primary Tumor Site**
  - **Description of clinical setting statement was amended: "~~Previous~~ *Following* resection of primary MCC"**
  - **Bullet "2" was amended: "All doses are at 2 Gy/d standard fractionation. Bolus is used to achieve adequate skin dose. Wide margins (5 cm) should be used, if possible, around the primary site. If electron beam is used, an energy and prescription isodose should be chosen that will deliver adequate *dose to the* lateral and deep margins."**

MCC-C Principles of Excision

- **For "Surgical Approaches" the 2nd sub-bullet was amended: "Techniques for more exhaustive histologic margin assessment may be considered (Mohs *micrographic surgery* ~~technique~~, modified Mohs *micrographic surgery*, CCPDMA), provided they do not interfere with SLNB when indicated."**
- **Footnote "2" was amended: "If Mohs *micrographic* surgery is used, a debulked specimen of the central portion of the tumor should be sent for permanent vertical section microstaging."**
- **Footnote "3" was amended: "Modified Mohs = Mohs ~~technique~~ *micrographic surgery* with additional permanent section final margin assessment; CCPDMA = complete circumferential and peripheral deep margin assessment."**

MCC-D Principles of Systemic Therapy

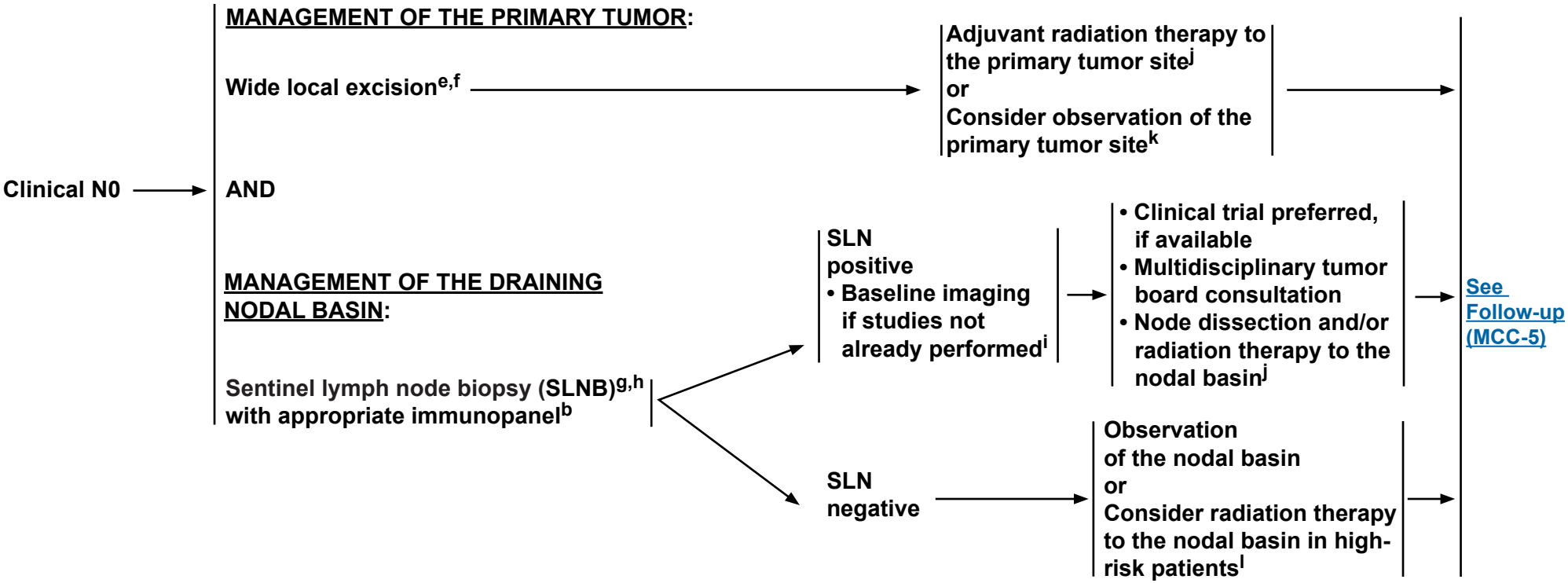
- **1st bullet under "Regional Disease" was amended: "Adjuvant chemotherapy not routinely recommended as ~~adequate trials to evaluate usefulness have not been done~~ *survival benefit has not been demonstrated in available retrospective studies*, but could be used on a case-by-case basis if clinical judgment dictates"**
- **1st bullet under "Disseminated Disease" was added: *"Clinical trial (preferred)"***
- **5th bullet under "As clinical judgement indicates" was added: *"Pembrolizumab"***
- **Footnote "2' was added: *"Preliminary data from non-randomized trials in patients with MCC demonstrate that response rates for pembrolizumab are similar to those previously reported for chemotherapy."***



[a]The value of baseline MCPyV (Merkel cell polyomavirus) serology for prognostic significance and to track disease recurrence is being evaluated.
[b]See Principles of Pathology (MCC-A).
[c]Brain MRI with contrast and neck/chest/abdomen/pelvis CT with contrast or FDG-PET 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 with contrast may be used. Imaging may also be useful to evaluate for the possibility of a skin metastasis from a noncutaneous primary neuroendocrine carcinoma (eg, small cell lung cancer), especially in cases where CK-20 is negative.
[d]Imaging is encouraged whenever metastatic or unresectable disease is suspected based on H&P findings. The most reliable staging tool to identify sub-clinical nodal disease is sentinel lymph node biopsy (SLNB).

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

PRIMARY AND ADJUVANT TREATMENT OF CLINICAL N0 DISEASE



[b] See Principles of Pathology (MCC-A).
[e] See Principles of Excision (MCC-C). In selected cases in which complete surgical excision is not possible, surgery is refused by the patient, or surgery would result in significant morbidity, radiation monotherapy may be considered (See Principles of Radiation Therapy [MCC-B]).
[f] Surgical margins should be balanced with morbidity of surgery. If appropriate, avoid undue delay in proceeding to RT. (See Principles of Excision MCC-C)
[g] In the head and neck region, risk of false-negative SLNBs is higher due to aberrant lymph node drainage and frequent presence of multiple SLN basins. If SLNB is not performed or is unsuccessful, consider irradiating nodal beds for subclinical disease (See Principles of Radiation Therapy MCC-B).
[h] SLNB is an important staging tool for regional control, but the impact of SLNB on overall survival is unclear.
[i] Brain MRI with contrast and neck/chest/abdomen/pelvis CT with contrast or FDG-PET 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 with contrast may be used.
[j] See Principles of Radiation Therapy (MCC-B).
[k] Consider observation of the primary site in cases where the primary tumor is small (eg, <1 cm) and widely excised with no other adverse risk factors such as LVI (lymphovascular invasion) or immunosuppression.
[l] Consider RT when there is a potential for anatomic [eg, previous history of surgery including WLE (wide local excision)], operator, or histologic failure (eg, failure to perform appropriate immunohistochemistry on SLNs) that may lead to a false-negative SLNB. Consider RT in cases of profound immunosuppression.

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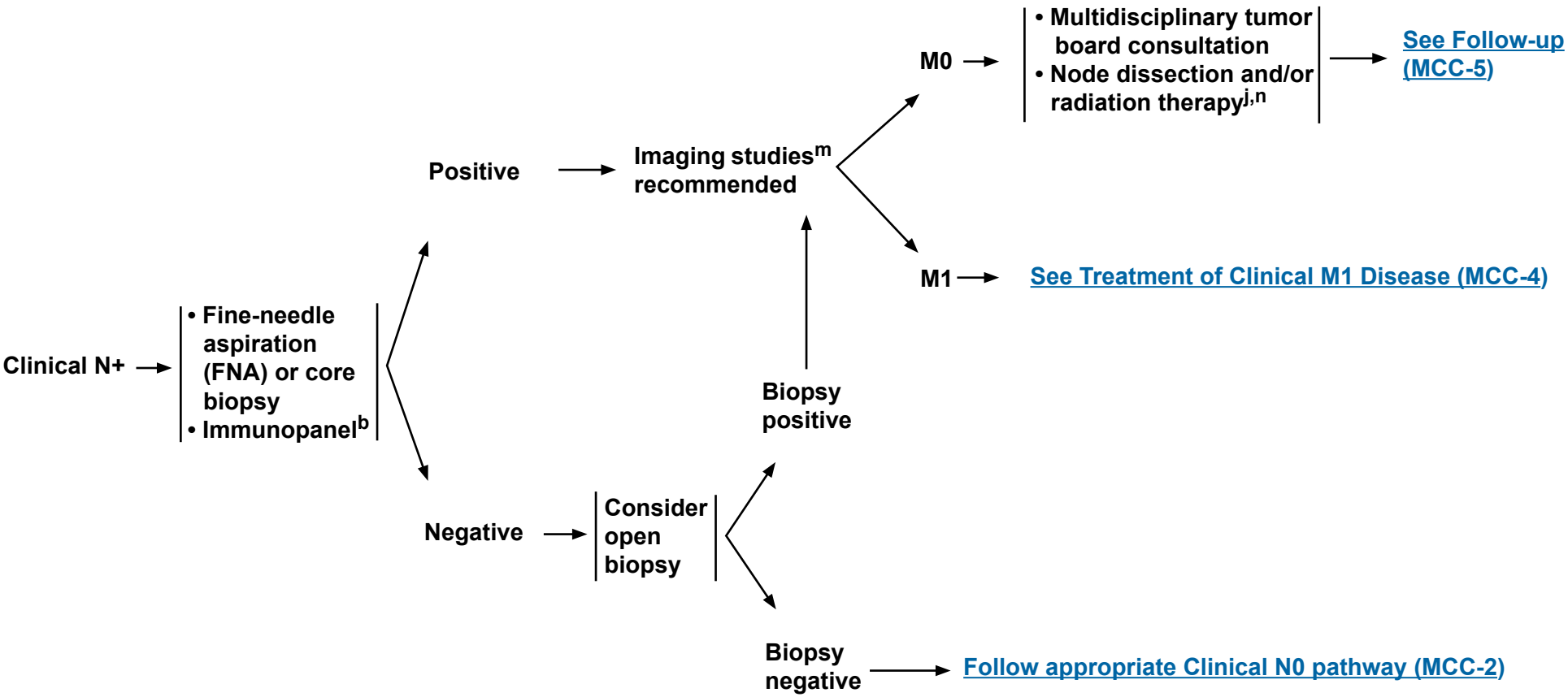
PRIMARY AND ADJUVANT TREATMENT OF CLINICAL N+ DISEASE



[b] See Principles of Pathology (MCC-A).
[m] Brain MRI with contrast and neck/chest/abdomen/pelvis CT with contrast or FDG-PET 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 with contrast may be used.
[j] See Principles of Radiation Therapy (MCC-B).
[n] Adjuvant chemotherapy may be considered in select clinical circumstances; however, available retrospective studies do not suggest prolonged survival benefit for adjuvant chemotherapy. (See Principles of Systemic Therapy [MCC-D]).

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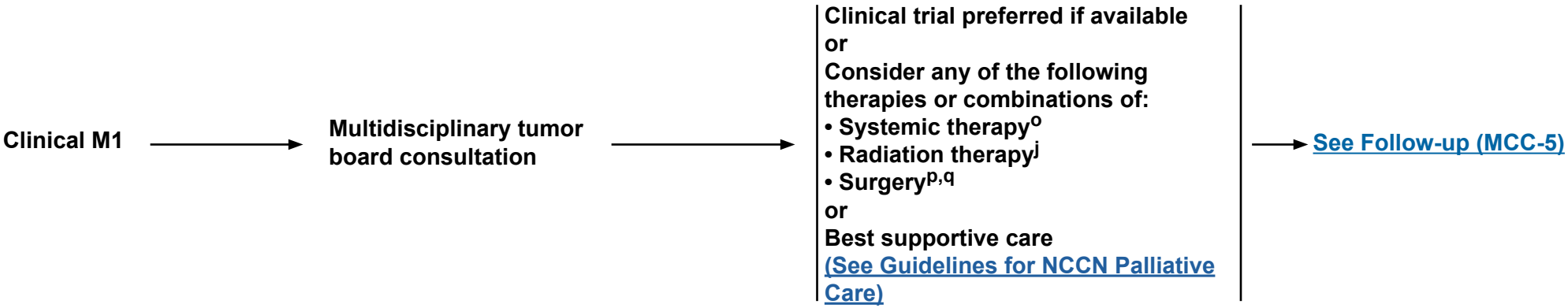
TREATMENT OF CLINICAL M1 DISEASE



[j] See Principles of Radiation Therapy (MCC-B).
[o] See Principles of Systemic Therapy (MCC-D).
[p] Under highly selective circumstances, in the context of multidisciplinary consultation, resection of oligometastasis can be considered.
[q] See Principles of Excision (MCC-C).

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FOLLOW-UP[a] **RECURRENCE**

[a]The value of baseline MCPyV serology for prognostic significance and to track disease recurrence is being evaluated.
[i]Brain MRI with contrast and neck/chest/abdomen/pelvis CT with contrast or FDG-PET 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 with contrast may be used.
[r]As immunosuppressed patients are at high risk for recurrence, more frequent follow-up may be indicated. Immunosuppressive treatments should be minimized as clinically feasible.

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PRINCIPLES OF PATHOLOGY

- Pathologist should be experienced in distinguishing MCC from cutaneous simulants and metastatic tumors.
- Synoptic reporting is preferred.
- Minimal elements to be reported include tumor size (cm), peripheral and deep margin status, lymphovascular invasion, and extracutaneous extension (ie, bone, muscle, fascia, cartilage).
- Strongly encourage reporting of these additional clinically relevant factors (compatible with the American Joint Committee on Cancer [AJCC] and the College Of American Pathologists [CAP] recommendations):
  - Depth (Breslow, in mm)
  - Mitotic index (#/mm^2 preferred, #/HPF [High-power fields], or MIB-1 index)
  - Tumor-infiltrating lymphocytes (not identified, brisk, non-brisk)
  - Tumor growth pattern (nodular or infiltrative)
  - Presence of a second malignancy within the pathologic specimen itself (ie, concurrent squamous cell carcinoma [SCC])
- An appropriate immunopanel should preferably include CK20 and thyroid transcription factor-1 (TTF-1). Immunohistochemistry for CK20 and most low-molecular-weight cytokeratin markers is typically positive with a paranuclear “dot-like” pattern. CK7 and TTF-1 (positive in >80% of small cell lung cancers) are typically negative.
- For equivocal lesions, consider additional immunostaining with neuroendocrine markers such as chromogranin, synaptophysin, CD56, neuron-specific enolase (NSE), and neurofilament.
- SLNB evaluation should preferably include an appropriate immunopanel (ie, CK20 and pancytokeratins [AE1/AE3]) based on the immunostaining pattern of the primary tumor, particularly if H&E sections are negative, as well as tumor burden (% of node), tumor location (eg, subcapsular sinus, parenchyma), and the presence/absence of extracapsular extension.

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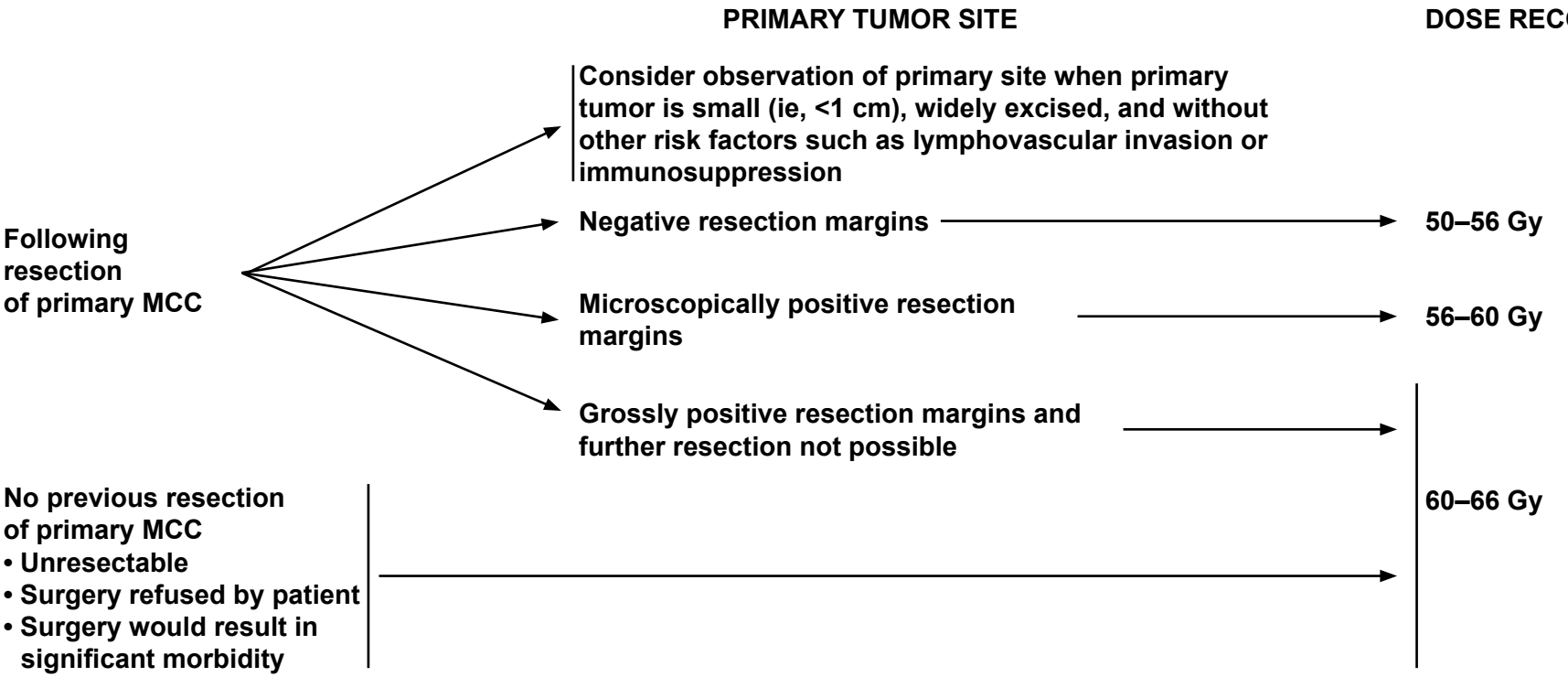
PRINCIPLES OF RADIATION THERAPY



- Expeditious initiation of adjuvant therapy after surgery is preferred as delay has been associated with worse outcomes.
- All doses are at 2 Gy/d standard fractionation. Bolus is used to achieve adequate skin dose. Wide margins (5 cm) should be used, if possible, around the primary site. If electron beam is used, an energy and prescription isodose should be chosen that will deliver adequate dose to the lateral and deep margins.
- Palliation: A less protracted fractionation schedule may be used in the palliative setting, such as 30 Gy in 10 fractions.

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

PRINCIPLES OF RADIATION THERAPY

	DRAINING NODAL BASIN		DOSE RECOMMENDATIONS
No SLNB or LN dissection	Clinically evident lymphadenopathy	→	60–66 Gy[1,2]
	Clinically node negative, but at risk for subclinical disease	→	46–50 Gy
SLNB without LN dissection	SLN negative	→ RT not indicated, unless at risk for false-negative SLNB[3,4] →	Observe
	SLN positive[5]	→	50–56 Gy
After LN dissection with multiple involved nodes and/or extracapsular extension[6]		→	50–60 Gy

- **Expeditious initiation of adjuvant therapy after surgery is preferred as delay has been associated with worse outcomes.**
- **All doses are at 2 Gy/d standard fractionation. A less protracted fractionation schedule may be used in the palliative setting, such as 30 Gy in 10 fractions.**
- **Irradiation of in-transit lymphatics is often not feasible unless the primary site is in close proximity to the nodal bed.**

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

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

PRINCIPLES OF EXCISION

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

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

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

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

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

PRINCIPLES OF SYSTEMIC THERAPY[1]

Local Disease:
- Adjuvant chemotherapy not recommended unless clinical judgement dictates otherwise

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

Disseminated Disease:
- Clinical trial (preferred)

As clinical judgement dictates:
- Cisplatin ± etoposide
- Carboplatin ± etoposide
- Topotecan
- (CAV): Cyclophosphamide, doxorubicin (or epirubicin), and vincristine
- Pembrolizumab[2]

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

[2]Preliminary data from non-randomized trials in patients with MCC demonstrate that response rates for pembrolizumab are similar to those previously reported for chemotherapy.

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.

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

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

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+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.

Discussion

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

NCCN Categories of Evidence and Consensus

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

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

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

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

All recommendations are category 2A unless otherwise noted.

Table of Contents

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 disproportionally 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 colleagues[9] identified a novel polyomavirus in MCC tumor tissues. This Merkel cell polyomavirus (MCV or MCPyV) is detected in 43% to 100% of patient samples.[10] The role of MCV in the pathogenesis of MCC is under active investigation.[11] There is ongoing research on the value of baseline MCV serology to predict outcome and to detect disease recurrence.[12,13]

The NCCN Non-Melanoma Skin Cancer Panel has developed guidelines outlining treatment of MCC to supplement the squamous cell and basal cell skin cancer guidelines (see NCCN Guidelines for Basal Cell Skin Cancer and NCCN Guidelines for Squamous Cell Skin Cancer).[14] 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.[15] 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.[16-20] It is therefore suggested that these features be included in the pathology report whenever possible.

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

Imaging

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

Imaging (CT, MRI, or PET/CT scan) may also be indicated to evaluate for the possibility of a skin metastasis from a noncutaneous carcinoma (eg, small cell carcinoma of the lung), especially in cases where CK-20 is negative.

Staging

In the biomedical literature, the most consistently reported adverse prognostic feature is tumor stage followed by tumor size.[2,4,29-35] The NCCN staging of MCC parallels the AJCC guidelines and divides presentation into local, regional, and disseminated disease.[36] The AJCC staging system is based on an analysis of 5823 cases from the National Cancer Data Base with a median follow-up of 64 months.[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.[37]

Surgery is the primary treatment modality for MCC. However, there is some variability among individual clinicians and NCCN Member Institutions regarding the management of patients with MCC due to the absence of prospective clinical trials. Therefore, the MCC guidelines are

suitably broad to reflect all the approaches taken by participating NCCN Member Institutions.

Surgery

Surgery is the mainstay of primary treatment for clinically localized (N0, M0) MCC.[38] 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.[39]

Wide local excision with 1- to 2-cm margins to the investing fascia layer remains the standard surgical technique.[38] 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.[40,41] 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.[42] 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.[43] One review of 161 patients with MCC found that SLNB identified micrometastases in one-third of early-stage patients.[44] 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.[45] 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.[6,46] 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.[47,48] 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.[49] 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.[50] Jouary and colleagues[51] 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).[52] Improvement was most pronounced for patients with tumors larger than 2 cm (median survival 50 months vs. 21 months; P = .0003). Another analysis of the SEER database also reported improved overall survival with adjuvant RT, although disease-specific survival was not improved.[53] 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.[54] 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.[55,56] Data are insufficient to assess whether chemotherapeutic regimens improve either relapse-free or overall survival in MCC patients with distant metastatic disease.[5,57-61] If it is used, the panel recommends cisplatin or carboplatin with or without etoposide.[5,62] 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.[59] Clinicians should exercise independent medical judgment in choosing the chemotherapeutic regimen. Although the NCCN Panel recognized that MCC is a rare disease that precludes robust randomized studies, enrollment in clinical trials is encouraged whenever available and appropriate.

NCCN Recommendations

Clinical Node-Negative Disease

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

Following surgery, patients may undergo postoperative RT of the primary site or consider observation. Efforts should be made to avoid delay of adjuvant RT if planned. Observation should be limited to patients with small primary lesions (eg, less than 1 cm) that have been widely excised and present with no adverse risk factors such as lymphovascular invasion or immunosuppression.[63]

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

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

Clinical Node-Positive Disease

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

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

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

Metastatic Disease

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

Follow-up and Recurrence

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

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.[5,6,32] 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.[27]

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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