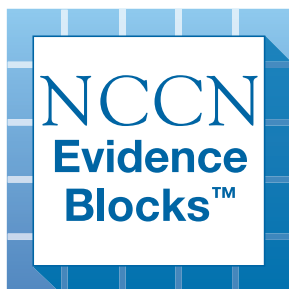# NCCN

National Comprehensive Cancer Network®

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Merkel Cell Carcinoma

NCCN Evidence Blocks™

Version 2.2022 — April 21, 2022

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Find an NCCN Member Institution: https://www.nccn.org/home/member-institutions.

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

See NCCN Categories of Evidence and Consensus.

NCCN Categories of Preference: All recommendations are considered appropriate.

See NCCN Categories of Preference.

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NCCN EVIDENCE BLOCKS CATEGORIES AND DEFINITIONS
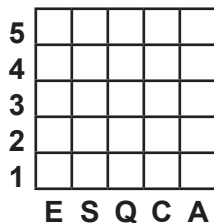
E = Efficacy of Regimen/Agent
S = Safety of Regimen/Agent
Q = Quality of Evidence
C = Consistency of Evidence
A = Affordability of Regimen/Agent

Example Evidence Block
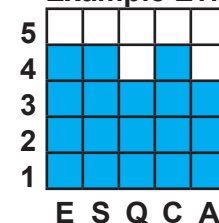
E = 4
S = 4
Q = 3
C = 4
A = 3

Efficacy of Regimen/Agent

5	**Highly effective:** Cure likely and often provides long-term survival advantage
4	**Very effective:** Cure unlikely but sometimes provides long-term survival advantage
3	**Moderately effective:** Modest impact on survival, but often provides control of disease
2	**Minimally effective:** No, or unknown impact on survival, but sometimes provides control of disease
1	**Palliative:** Provides symptomatic benefit only

Safety of Regimen/Agent

5	**Usually no meaningful toxicity:** Uncommon or minimal toxicities; no interference with activities of daily living (ADLs)
4	**Occasionally toxic:** Rare significant toxicities or low-grade toxicities only; little interference with ADLs
3	**Mildly toxic:** Mild toxicity that interferes with ADLs
2	**Moderately toxic:** Significant toxicities often occur but life threatening/fatal toxicity is uncommon; interference with ADLs is frequent
1	**Highly toxic:** Significant toxicities or life threatening/fatal toxicity occurs often; interference with ADLs is usual and severe

Note: For significant chronic or long-term toxicities, score decreased by 1
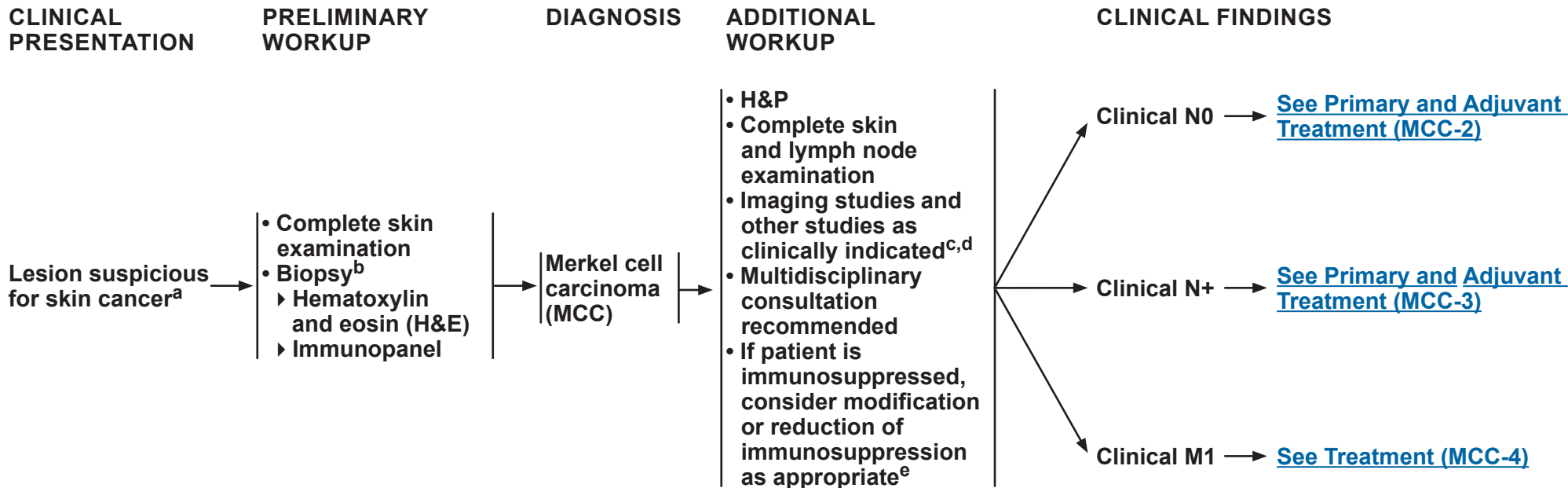
Quality of Evidence

5	**High quality:** Multiple well-designed randomized trials and/or meta-analyses
4	**Good quality:** One or more well-designed randomized trials
3	**Average quality:** Low quality randomized trial(s) or well-designed non-randomized trial(s)
2	**Low quality:** Case reports or extensive clinical experience
1	**Poor quality:** Little or no evidence

Consistency of Evidence

5	**Highly consistent:** Multiple trials with similar outcomes
4	**Mainly consistent:** Multiple trials with some variability in outcome
3	**May be consistent:** Few trials or only trials with few patients, whether randomized or not, with some variability in outcome
2	**Inconsistent:** Meaningful differences in direction of outcome between quality trials
1	**Anecdotal evidence only:** Evidence in humans based upon anecdotal experience

Affordability of Regimen/Agent (includes drug cost, supportive care, infusions, toxicity monitoring, management of toxicity)

5	**Very inexpensive**
4	**Inexpensive**
3	**Moderately expensive**
2	**Expensive**
1	**Very expensive**

EB-1

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CLINICAL PRESENTATION	PRELIMINARY WORKUP	DIAGNOSIS	ADDITIONAL WORKUP	CLINICAL FINDINGS

Lesion suspicious for skin cancer[a]	• Complete skin examination
	• Biopsy[b]
	  ‣ Hematoxylin and eosin (H&E)
	  ‣ Immunopanel
		Merkel cell carcinoma (MCC)	• H&P
			• Complete skin and lymph node examination
			• Imaging studies and other studies as clinically indicated[c,d]
			• Multidisciplinary consultation recommended
			• If patient is immunosuppressed, consider modification or reduction of immunosuppression as appropriate[e]
				Clinical N0 → See Primary and Adjuvant Treatment (MCC-2)
				
				Clinical N+ → See Primary and Adjuvant Treatment (MCC-3)
				
				Clinical M1 → See Treatment (MCC-4)

[a] For more information, see American Academy of Dermatology Association: https://www.aad.org/public/diseases/skin-cancer/merkel-cell-carcinoma.
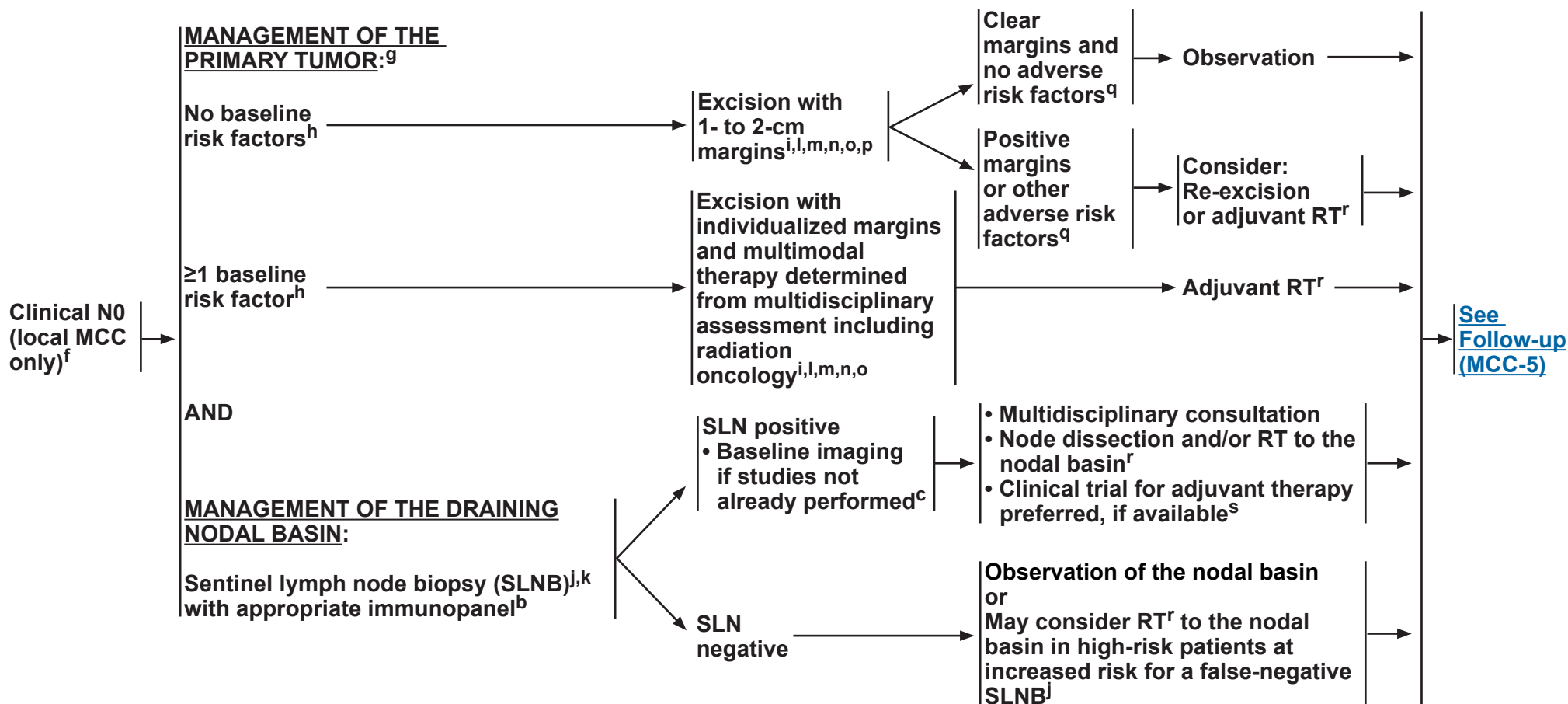
[b] See Principles of Pathology (MCC-A).

[c] Imaging is encouraged in most cases of MCC. Imaging is indicated whenever metastatic or unresectable disease is suspected based on H&P findings. Occult metastatic disease that resulted in upstaging has been detected in 12%–20% of patients presenting without suspicious H&P findings (Singh N, et al. J Am Acad Dermatol 2021;84:330-339). Whole-body PET with fused axial imaging (CT or MR) or chest/abdomen/pelvis CT with contrast, with neck CT if primary tumor on head/neck or brain MRI if clinical suspicion, may be useful to identify and quantify regional and distant metastases. Several studies indicate whole-body PET with fused axial imaging is more sensitive for detecting occult metastatic disease at baseline. 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 CK20 is negative. The most reliable staging tool to identify subclinical nodal disease is sentinel lymph node biopsy (SLNB) (George A, et al. Nucl Med Commun 2014;35:282-290; Hawryluk EB, et al. J Am Acad Dermatol 2013;68:592-599; Siva S, et al. J Nucl Med 2013;54:1223-1229).

[d] Quantitation of serum Merkel cell polyomavirus (MCPyV) oncoprotein antibodies may be considered as part of initial workup; seronegative patients may have a higher risk of recurrence; in seropositive patients, a rising titer may be an early indicator of recurrence; baseline testing should be performed within 3 months of treatment, because titers are expected to decrease significantly after clinically evident disease is eliminated.

[e] As immunosuppression in MCC is a risk factor for poor outcomes, immunosuppressive treatments should be minimized as clinically feasible in consultation with the relevant managing physician. As immunosuppressed patients are at high risk for recurrence, more frequent follow-up may be indicated.

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PRIMARY AND ADJUVANT TREATMENT OF CLINICAL N0 DISEASE

Clinical N0 (local MCC only)[f]

MANAGEMENT OF THE PRIMARY TUMOR:[g]

No baseline risk factors[h] → **Excision with 1- to 2-cm margins[i,l,m,n,o,p]**

- **Clear margins and no adverse risk factors[q]** → **Observation** →
- **Positive margins or other adverse risk factors[q]** → **Consider: Re-excision or adjuvant RT[r]** →

≥1 baseline risk factor[h] → **Excision with individualized margins and multimodal therapy determined from multidisciplinary assessment including radiation oncology[i,l,m,n,o]** → **Adjuvant RT[r]** →

AND

MANAGEMENT OF THE DRAINING NODAL BASIN:

Sentinel lymph node biopsy (SLNB)[j,k] with appropriate immunopanel[b]

- **SLN positive**
  - **Baseline imaging if studies not already performed[c]** →
    - **Multidisciplinary consultation**
    - **Node dissection and/or RT to the nodal basin[r]**
    - **Clinical trial for adjuvant therapy preferred, if available[s]** →
- **SLN negative** → **Observation of the nodal basin or May consider RT[r] to the nodal basin in high-risk patients at increased risk for a false-negative SLNB[j]** →

→ **See Follow-up (MCC-5)**

See Footnotes on MCC-2A

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FOOTNOTES

b See Principles of Pathology (MCC-A).

c Imaging is encouraged in most cases of MCC. Imaging is indicated whenever metastatic or unresectable disease is suspected based on H&P findings. Occult metastatic disease that resulted in upstaging has been detected in 12%–20% of patients presenting without suspicious H&P findings (Singh N, et al. J Am Acad Dermatol 2021;84:330-339). Whole-body PET with fused axial imaging (CT or MR) or chest/abdomen/pelvis CT with contrast, with neck CT if primary tumor on head/neck or brain MRI if clinical suspicion, may be useful to identify and quantify regional and distant metastases. Several studies indicate whole-body PET with fused axial imaging is more sensitive for detecting occult metastatic disease at baseline. 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 CK20 is negative. The most reliable staging tool to identify subclinical nodal disease is SLNB. (George A, et al. Nucl Med Commun 2014;35:282-290; Hawryluk EB, et al. J Am Acad Dermatol 2013;68:592-599; Siva S, et al. J Nucl Med 2013;54:1223-1229).

f Criteria for "Local MCC only" are disease limited to the primary tumor, with no evidence of in-transit, nodal, or distant disease.

g Tarabadkar E, et al. J Am Acad Dermatol 2021;84:340-347.

h Baseline risk factors: larger primary tumor (>1 cm); chronic T-cell immunosuppression, HIV, CLL, solid organ transplant; head/neck primary site; lymphovascular invasion present.

i 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).

j Consider empiric radiation therapy (RT) to the nodal basin when: 1) the accuracy of SLNB may have been subject to anatomic compromise (lymphoma involved nodes, or history of remote lymph node excision); 2) when the risk of false-negative SLNB is high due to aberrant lymph node drainage and presence of multiple SLN basins (such as in head & neck or midline trunk MCC); or 3) when identified by lymphoscintigraphy in cases of profound immunosuppression (ie, solid organ transplant recipients). See Principles of Radiation Therapy (MCC-B).

k SLNB is an important staging tool. This procedure and subsequent treatment impacts regional control for patients with positive SLNs, but the impact of SLNB on overall survival is unclear.

l SLNB is typically performed at this time.

m Narrow excision margins minimize morbidity and microscopically positive margins are acceptable when followed by adjuvant RT to the primary site.

n Mohs or other forms of peripheral and deep en face margin assessment (PDEMA), using margins similar to wide local excision (WLE), may be appropriate. See NCCN Guidelines for Squamous Cell Skin Cancer - Principles of PDEMA Technique for description of PDEMA.

o Surgical margins should be balanced with morbidity of surgery. If appropriate, avoid undue delay in proceeding to RT. See Principles of Excision (MCC-C).

p Goal should be primary tissue closure to allow for initiation of adjuvant RT (if needed) within 3–4 weeks.

q Post-excision adverse risk factors include positive or narrowly clear margins, or lymphovascular invasion or positive SLNB.

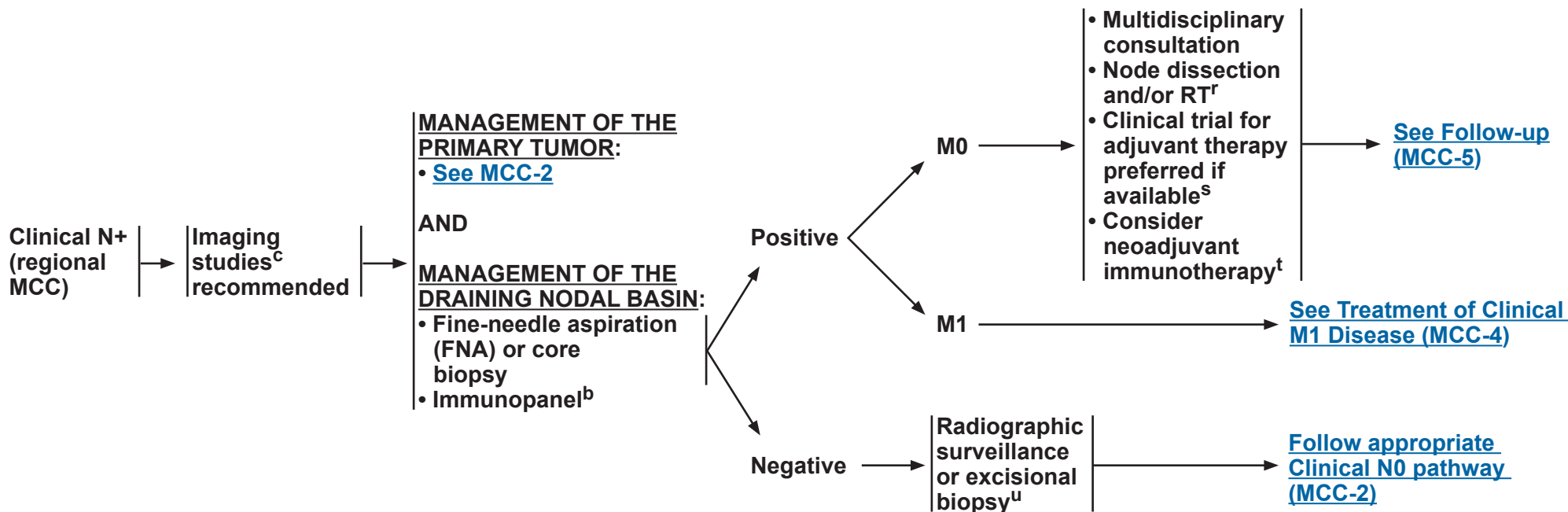r See Principles of Radiation Therapy (MCC-B).

s Adjuvant chemotherapy may be considered in select clinical circumstances; however, available retrospective studies do not suggest survival benefit for adjuvant chemotherapy. No data are available to support the adjuvant use of immunotherapy outside of a clinical trial. See Principles of Systemic Therapy (MCC-D).
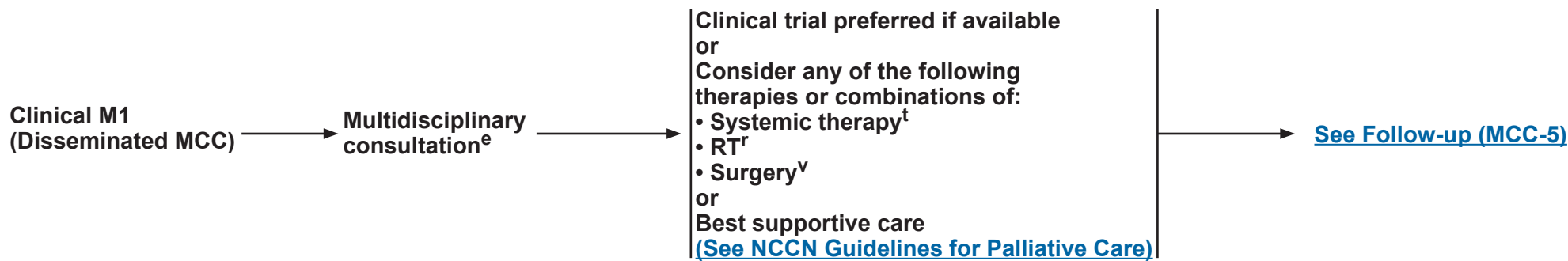
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PRIMARY AND ADJUVANT TREATMENT OF CLINICAL N+ DISEASE

Clinical N+ (regional MCC) → Imaging studies[c] recommended →

MANAGEMENT OF THE PRIMARY TUMOR:
• See MCC-2

AND

MANAGEMENT OF THE DRAINING NODAL BASIN:
• Fine-needle aspiration (FNA) or core biopsy
• Immunopanel[b]

Positive →

M0 →
• Multidisciplinary consultation
• Node dissection and/or RT[r]
• Clinical trial for adjuvant therapy preferred if available[s]
• Consider neoadjuvant immunotherapy[t]
→ See Follow-up (MCC-5)

M1 → See Treatment of Clinical M1 Disease (MCC-4)

Negative → Radiographic surveillance or excisional biopsy[u] → Follow appropriate Clinical N0 pathway (MCC-2)

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[b] See Principles of Pathology (MCC-A).

[c] Imaging is encouraged in most cases of MCC. Imaging is indicated whenever metastatic or unresectable disease is suspected based on H&P findings. Occult metastatic disease that resulted in upstaging has been detected in 12%–20% of patients presenting without suspicious H&P findings (Singh N, et al. J Am Acad Dermatol 2021;84:330-339). Whole-body PET with fused axial imaging (CT or MR) or chest/abdomen/pelvis CT with contrast, with neck CT if primary tumor on head/neck or brain MRI if clinical suspicion, may be useful to identify and quantify regional and distant metastases. Several studies indicate whole-body PET with fused axial imaging is more sensitive for detecting occult metastatic disease at baseline. 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 CK20 is negative. The most reliable staging tool to identify subclinical nodal disease is SLNB. (George A, et al. Nucl Med Commun 2014;35:282-290; Hawryluk EB, et al. J Am Acad Dermatol 2013;68:592-599; Siva S, et al. J Nucl Med 2013;54:1223-1229).

[r] See Principles of Radiation Therapy (MCC-B).

[s] Adjuvant chemotherapy may be considered in select clinical circumstances; however, available retrospective studies do not suggest survival benefit for adjuvant chemotherapy. No data are available to support the adjuvant use of immunotherapy outside of a clinical trial. See Principles of Systemic Therapy (MCC-D).

[t] See Principles of Systemic Therapy (MCC-D).

[u] An open biopsy may be considered to confirm a negative initial FNA or core lymph node biopsy if clinical suspicion remains high.

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TREATMENT OF CLINICAL M1 DISEASE

Clinical M1
(Disseminated MCC) → Multidisciplinary consultation[e] →

Clinical trial preferred if available
or
Consider any of the following therapies or combinations of:
• Systemic therapy[t]
• RT[r]
• Surgery[v]
or
Best supportive care
(See NCCN Guidelines for Palliative Care)

→ See Follow-up (MCC-5)

[e] As immunosuppression in MCC is a risk factor for poor outcomes, immunosuppressive treatments should be minimized as clinically feasible in consultation with the relevant managing physician. As immunosuppressed patients are at high risk for recurrence, more frequent follow-up may be indicated.
[r] See Principles of Radiation Therapy (MCC-B).
[t] See Principles of Systemic Therapy (MCC-D).
[v] Under highly selective circumstances, in the context of multidisciplinary consultation, resection of limited metastases can be considered.

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FOLLOW-UP **RECURRENCE** **TREATMENT**

Follow-up visits:[e]
- **Physical exam including complete skin and complete lymph node exam**
  ‣ **Every 3–6 mo for 3 years**
  ‣ **Every 6–12 mo thereafter**
- **Imaging and other studies as clinically indicated**[c,d,v]
  ‣ **Consider routine imaging for high-risk patients**[w]
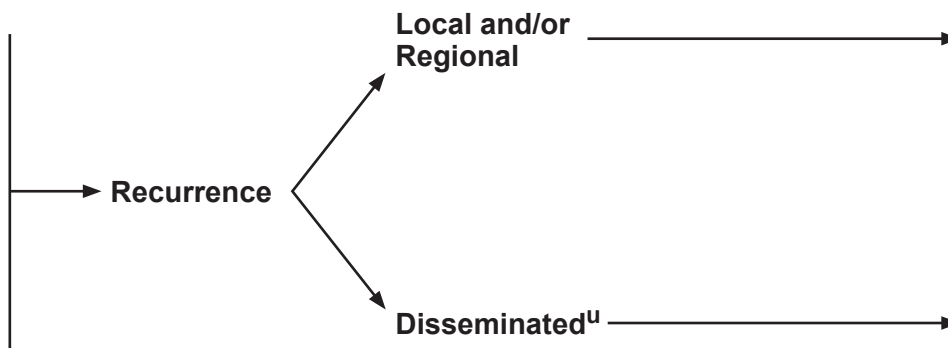
Recurrence

Local and/or Regional →

Clinical trial preferred if available
or
Consider any of the following therapies or combinations of:
- **Systemic therapy**[t]
- **RT**[r]
- **Surgery**[v]
or
Best supportive care
(See NCCN Guidelines for Palliative Care)

Disseminated[u] → **See Clinical M1 (MCC-4)**

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[d] Quantitation of serum MCPyV oncoprotein antibodies may be considered as part of initial workup; seronegative patients may have a higher risk of recurrence; in seropositive patients, a rising titer may be an early indicator of recurrence; baseline testing should be performed within 3 months of treatment, because titers are expected to decrease significantly after clinically evident disease is eliminated.

[e] As immunosuppression in MCC is a risk factor for poor outcomes, immunosuppressive treatments should be minimized as clinically feasible in consultation with the relevant managing physician. As immunosuppressed patients are at high risk for recurrence, more frequent follow-up may be indicated.

[r] See Principles of Radiation Therapy (MCC-B).

[t] See Principles of Systemic Therapy (MCC-D).

[u] Under highly selective circumstances, in the context of multidisciplinary consultation, resection of limited metastases can be considered.

[v] Surveillance imaging is typically via diagnostic CT of chest/abdomen/pelvis with oral and IV contrast; neck CT is often included if primary lesion was on head/neck.

[w] Patients at high risk of recurrence include those who are immunosuppressed and patients who have positive non-SLN metastases.

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PRINCIPLES OF PATHOLOGY

- **Pathologists should be experienced in distinguishing MCC from cutaneous simulants and metastatic tumors.**

- **Synoptic reporting is preferred.**

- **Minimal elements to be reported include largest tumor diameter (cm), peripheral and deep margin status, lymphovascular invasion (LVI), 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)**

  ▸ **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])**

- **Immunohistochemistry should be used for confirmation on all newly diagnosed MCC to exclude possible mimickers such as metastatic small cell carcinoma. Staining with CK20 (membranous and/or paranuclear dot-like) and negativity for thyroid transcription factor-1 (TTF-1) are usually sufficient. If an atypical staining pattern is present, AE1/3 keratin (dot-like), or at least one neuroendocrine marker (such as synaptophysin, neurofilament, chromogranin, CD56, or neuron-specific enolase [NSE]), and/or Merkel cell polyomavirus T antigen (CM2B4) stains may be employed.**

- **For equivocal lesions, consider additional immunostaining with neuroendocrine markers such as chromogranin, synaptophysin, CD56, NSE, and neurofilament.**

- **SLNB evaluation for metastatic MCC requires complete microscopic evaluation of the SLN(s). Before determining SLNB negativity, multiple levels (recommend at least 2) including H&E and at least one immunohistochemistry stain should be used to help evaluate for metastatic disease. SLNB reporting should also include the number of lymph nodes involved, size of largest metastatic deposit (mm), and the presence/absence of extracapsular extension.**

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MCC-A

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PRINCIPLES OF RADIATION THERAPY

General Principles

- Expeditious initiation of adjuvant radiation therapy (RT) after surgery is preferred as soon as wound healing permits, as delay has been associated with worse outcomes.
- There is limited evidence supporting dosing recommendations for MCC. Dose ranges provided are based on clinical practice at NCCN Member Institutions and clinical evidence from studies of other types of skin cancer.

General Treatment Information–Primary MCC Tumor Site

- Treatment Information
  ‣ 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.
- General Dosing Prescription
  ‣ All doses are at 2 Gy/day standard fractionation.
  ‣ In the palliative setting, a wide range of fractionation schedules may be used, including less protracted fractionation schedules such as 30 Gy in 10 fractions, 20 Gy in 4 or 5 fractions, or 8 Gy in 1 fraction.

Following Resection of Primary MCC	Dose Recommendations
Adjuvant RT	
Negative resection margins	**50–56 Gy**
Microscopically positive resection margins	**56–60 Gy**
Grossly positive resection margins and further resection not possible	**60–66 Gy**
No Previous Resection of Primary MCC	**Dose Recommendations**
Unresectable	**60–66 Gy**
Surgery refused by patient	**60–66 Gy**
Surgery would result in significant morbidity	**60–66 Gy**

Note: For more information regarding the categories and definitions used for the NCCN Evidence Blocks™, see page EB-1.
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.

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PRINCIPLES OF RADIATION THERAPY

General Treatment Information–Draining Nodal Basin

- **Treatment Information**
  ‣ **Irradiation of in-transit lymphatics is recommended only when the primary site is in close proximity to the nodal bed.**
- **General Dosing Prescription**
  ‣ **All doses are at 2 Gy/day standard fractionation.**
  ‣ **In the palliative setting, a wide range of fractionation schedules may be used, including less protracted fractionation schedules such as 30 Gy in 10 fractions, 20 Gy in 4 or 5 fractions, or 8 Gy in 1 fraction.**

	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 routinely indicated[3]	**Observation**
SLN positive[4]	**50–56 Gy**
After LN dissection with multiple involved nodes and/or extracapsular extension[5]	**50–60 Gy**

[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 empiric RT to the nodal basin when: 1) the accuracy of SLNB may have been subject to anatomic compromise (lymphoma involved nodes, or history of remote lymph node excision); 2) when the risk of false-negative SLNB is high due to aberrant lymph node drainage and presence of multiple SLN basins (such as in head & neck or midline trunk MCC); or 3) when identified by lymphoscintigraphy in cases of profound immunosuppression (ie, solid organ transplant recipients).
[4] 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.
[5] 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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PRINCIPLES OF EXCISION

Goals:
- **Obtain histologically negative margins when clinically feasible.**
- **Surgical margins should be balanced with morbidity of surgery.**

Surgical Approaches:
- **It is recommended, regardless of the surgical approach, that every effort be made to coordinate surgical management such that SLNB is performed at the time of definitive excision.[1] Excision options include:**
  - **If adjuvant RT is planned, narrow excision margins are likely sufficient. (See MCC-2)**
  - **If adjuvant RT may not be indicated (See MCC-2), perform wide excision with 1- to 2-cm margins to investing fascia of muscle or pericranium when clinically feasible and consistent with reconstruction and radiation goals listed below.**
  - **Techniques for more exhaustive histologic margin assessment may be considered (Mohs or other forms of PDEMA),[2] provided they do not interfere with SLNB when indicated.**
  - **If SLNB is not performed concurrently, it is recommended that SLNB is performed prior to definitive excision with exhaustive histologic margin assessment (ie, Mohs).**

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.**
- **Since RT is often indicated postoperatively, closure should be chosen to allow for expeditious initiation of RT (eg, primary closure, avoiding extensive tissue movement).**

[1] SLNB is an important staging tool. This procedure and subsequent treatment impacts regional control for patients with positive SLNs, but the impact of SLNB on overall survival is unclear.

[2] When Mohs is being performed and the preoperative biopsy is considered insufficient for providing all the staging information required to properly treat the tumor, submission of the central specimen for vertical paraffin-embedded permanent sections or documentation of staging parameters in Mohs report is recommended.

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PRINCIPLES OF SYSTEMIC THERAPY[1]

Local Disease N0:
- For primary disease, adjuvant chemotherapy is not recommended.
- Recurrent locally advanced
  ▸ Consider pembrolizumab[2,3] if curative surgery and curative RT are not feasible.[4]

Regional Disease N+:
- Clinical trial (preferred)
- For regional disease, adjuvant chemotherapy is 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 judgment dictates. No data are available to support the adjuvant use of immunotherapy outside of a clinical trial.
- Options useful in certain circumstances:
  ▸ Neoadjuvant nivolumab[3,5]
  ▸ Cisplatin ± etoposide
  ▸ Carboplatin ± etoposide
- For recurrent regional disease, consider pembrolizumab[2,3] if curative surgery and curative RT are not feasible.[4]

Disseminated Disease M1:
- Clinical trial (preferred)
- Preferred interventions:
  ▸ Avelumab[2,3]
  ▸ Pembrolizumab[2,3,4]
  ▸ Nivolumab[2,3]
- Useful in certain circumstances as clinical judgment dictates for patients with contraindications to checkpoint immunotherapy:
  ▸ Cisplatin ± etoposide
  ▸ Carboplatin ± etoposide
  ▸ Topotecan
  ▸ Cyclophosphamide, doxorubicin (or epirubicin), and vincristine (CAV)

See Evidence Blocks on MCC-D (EB-1)

[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 MCC is chemosensitive, although the responses are not durable, and the agents listed above have been used with some success.

[2] Data from non-randomized trials in patients with MCC demonstrate that rates of durable response are improved with PD-1/PD-L1 blockade compared with cytotoxic therapy. The safety profiles for checkpoint immunotherapies are significantly different from cytotoxic therapies. Consult prescribing information for recommendations on detection and management of immune-related adverse events associated with checkpoint immunotherapies. Clinician and patient education is critical for safe administration of checkpoint immunotherapies.

[3] See NCCN Guidelines for Management of Immunotherapy-Related Toxicities.

[4] Nghiem P, Bhatia S, Lipson EJ, et. al. Durable tumor regression and overall survival in patients with advanced Merkel cell carcinoma receiving pembrolizumab as first-line therapy. J Clin Oncol 2019;37:693-702.

[5] Topalian SL, Bhatia S, Amin A, et al. Neoadjuvant nivolumab for patients with resectable Merkel cell carcinoma in the CheckMate 358 Trial. J Clin Oncol 2020;38:2476-2487.

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5		E = Efficacy of Regimen/Agent
4		S = Safety of Regimen/Agent
3		Q = Quality of Evidence
2		C = Consistency of Evidence
1		A = Affordability of Regimen/Agent
	E S Q C A	

SYSTEMIC THERAPY

	Therapy for Recurrent Locally Advanced Disease	Therapy for Recurrent Regional Disease
Pembrolizumab	🔲	🔲

	Neoadjuvant/adjuvant Therapy for Regional Disease	Therapy for Disseminated Disease
Preferred Interventions		
Avelumab	—	🔲
Nivolumab	—	🔲
Pembrolizumab	—	🔲
Useful in Certain Circumstances		
Nivolumab	🔲	—
Cisplatin	🔲	🔲
Cisplatin/etoposide	🔲	🔲
Carboplatin	🔲	🔲
Carboplatin/etoposide	🔲	🔲
Topotecan	—	🔲
CAV with cyclophosphamide, doxorubicin, and vincristine	—	🔲
CAV with cyclophosphamide, epirubicin, and vincristine	—	🔲

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American Joint Committee on Cancer (AJCC)
TNM Staging Classification for Merkel Cell Carcinoma
(8th ed., 2017)

Table 1. **Definitions for T, N, M**

T	**Primary Tumor**
TX	Primary tumor cannot be assessed (e.g., curetted)
T0	No evidence of primary tumor
Tis	*In situ* primary tumor
T1	Maximum clinical tumor diameter ≤2 cm
T2	Maximum clinical tumor diameter >2 but ≤5 cm
T3	Maximum clinical tumor diameter >5 cm
T4	Primary tumor invades fascia, muscle, cartilage, or bone

Clinical (N)

N	**Regional Lymph Nodes**
NX	Regional lymph nodes cannot be clinically assessed (e.g., previously removed for another reason, or because of body habitus)
N0	No regional lymph node metastasis detected on clinical and/or radiologic examination
N1	Metastasis in regional lymph node(s)
N2	In-transit metastasis (discontinuous from primary tumor; located between primary tumor and draining regional nodal basin, or distal to the primary tumor) *without* lymph node metastasis
N3	In-transit metastasis (discontinuous from primary tumor; located between primary tumor and draining regional nodal basin, or distal to the primary tumor) *with* lymph node metastasis

Pathological (pN)

pN	**Regional Lymph Nodes**
pNX	Regional lymph nodes cannot be assessed (e.g., previously removed for another reason or *not* removed for pathological evaluation)
pN0	No regional lymph node metastasis detected on pathological evaluation
pN1	Metastasis in regional lymph node(s)
pN1a(sn)	Clinically occult regional lymph node metastasis identified only by sentinel lymph node biopsy
pN1a	Clinically occult regional lymph node metastasis following lymph node dissection
pN1b	Clinically and/or radiologically detected regional lymph node metastasis, microscopically confirmed
pN2	In-transit metastasis (discontinuous from primary tumor; located between primary tumor and draining regional nodal basin, or distal to the primary tumor) *without* lymph node metastasis
pN3	In-transit metastasis (discontinuous from primary tumor; located between primary tumor and draining regional nodal basin, or distal to the primary tumor) *with* lymph node metastasis

Clinical (M)

M	**Distant Metastasis**
M0	No distant metastasis detected on clinical and/or radiologic examination
M1	Distant metastasis detected on clinical and/or radiologic examination
M1a	Metastasis to distant skin, distant subcutaneous tissue, or distant lymph node(s)
M1b	Metastasis to lung
M1c	Metastasis to all other visceral sites

Pathological (M)

M	**Distant Metastasis**
M0	No distant metastasis detected on clinical and/or radiologic examination
pM1	Distant metastasis microscopically confirmed
pM1a	Metastasis to distant skin, distant subcutaneous tissue, or distant lymph node(s), microscopically confirmed
pM1b	Metastasis to lung, microscopically confirmed
pM1c	Metastasis to all other distant sites, microscopically confirmed

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American Joint Committee on Cancer (AJCC)
AJCC Prognostic Stage Groups for Merkel Cell Carcinoma
(8th ed., 2017)

Table 2. AJCC Prognostic Groups

Clinical (cTNM)

	T	N	M
Stage 0	Tis	N0	M0
Stage I	T1	N0	M0
Stage IIA	T2-T3	N0	M0
Stage IIB	T4	N0	M0
Stage III	T0-T4	N1-3	M0
Stage IV	T0-T4	Any N	M1

Pathological (pTNM)

	T	N	M
Stage 0	Tis	N0	M0
Stage I	T1	N0	M0
Stage IIA	T2-T3	N0	M0
Stage IIB	T4	N0	M0
Stage IIIA	T1-T4	N1a(sn) or N1a	M0
	T0	N1b	M0
Stage IIIB	T1-T4	N1b-3	M0
Stage IV	T0-T4	Any N	M1

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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 indicated.

NCCN Categories of Preference	
Preferred intervention	Interventions that are based on superior efficacy, safety, and evidence; and, when appropriate, affordability.
Other recommended intervention	Other interventions that may be somewhat less efficacious, more toxic, or based on less mature data; or significantly less affordable for similar outcomes.
Useful in certain circumstances	Other interventions that may be used for selected patient populations (defined with recommendation).

All recommendations are considered appropriate.

Discussion

This discussion corresponds to the NCCN Guidelines for Merkel Cell Carcinoma. Last updated: January 31st, 2022.

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Overview

Merkel cell carcinoma (MCC) is a rare cutaneous neuroendocrine neoplasia with approximately 2,488 cases per year in the United States.[1] Despite this, MCC is one of the most aggressive skin cancers, and its incidence is dramatically increasing.[1-6] As MCC tumors are frequently misdiagnosed,[7-9] part of the apparent increase in incidence may be due to the discovery of biomarkers that improve detection of the disease.[10,11] MCC can grow rapidly and metastasize early, with 63% of primary lesions having grown rapidly in the 3 months prior to diagnosis.[7] Large meta-analyses have shown that at least half of patients with MCC develop lymph node metastases and nearly one third develop distant metastases.[12-19] Several studies document the development of locoregional recurrence in up to half of all cases of MCC.[8,18-22] MCC has a high mortality rate exceeding melanoma. The 5-year relative or MCC-specific survival rates range from 41% to 77%, depending on stage at presentation.[2,8,12,14,16,17,19,21-26]

Literature Search Criteria and Guidelines Update Methodology

Prior to the update of this version of the NCCN Guidelines for Merkel Cell Carcinoma, an electronic search of the PubMed database was performed to obtain key literature using the following search term: Merkel cell carcinoma. The PubMed database was chosen as it remains the most widely used resource for medical literature and indexes peer-reviewed biomedical literature.[27]

The search results were narrowed by selecting studies in humans published in English. Results were confined to the following article types: Clinical Trial; Guideline; Meta-Analysis; Randomized Controlled Trial; Systematic Reviews; and Validation Studies.

The data from key PubMed articles as well as articles from additional sources deemed as relevant to these guidelines and discussed by the panel have been included in this version of the Discussion section (eg, e-publications ahead of print, meeting abstracts). Recommendations for which high-level evidence is lacking are based on the panel's review of lower-level evidence and expert opinion.

The complete details of the Development and Update of the NCCN Guidelines are available at www.NCCN.org.

Risk Factors for MCC

Sun exposure is believed to be a major risk factor for MCC, based on increased incidence in geographic areas with higher UV (ultraviolet) indices,[12,28,29] the tendency to occur on skin areas that are exposed to the sun,[7,8,12,18,19,28,30] and the frequency of MCCs comingled or adjacent to other skin lesions caused by UV exposure.[9,31-33] MCC incidence increases with age and is more likely to occur in Caucasians compared with other ethnicities.[2,7,8,12-15,17,23,28,34-36] MCC is disproportionally more common in immunosuppressed individuals, such as those with organ transplants, lymphoproliferative malignancies (such as chronic lymphocytic leukemia [CLL]), or HIV infections.[7,28,37-43] Several studies have reported that MCC-specific survival is worse for those with immunosuppression,[8,35,42,44-50] although other studies have found no correlation.[51-53] Lastly, Merkel cell polyomavirus (MCPyV), a recently discovered polyomavirus in MCC tumor tissues,[54] is detected in 43% to 100% of tumors.[55-58] MCPyV negative-tumors tend to occur more often on the head, neck, or trunk, and have been associated with increased recurrence[58] and decreased MCC-specific survival and overall survival (OS) in some studies[59-62] but not others.[63,64] Recent genetic analyses have also found a much higher mutational burden in MCPyV-negative tumors, and that only the MCPyV-negative group are enriched for cytosine to thymine (C to T) mutations indicative of UV damage.[65-67]

Diagnosis and Workup

Initial workup of a suspicious lesion starts with a complete skin examination and biopsy of the primary tumor. Initial diagnosis of MCC in the primary lesion by hematoxylin and eosin (H&E) staining should be confirmed by performing immunohistochemistry (IHC) staining. An appropriate immunopanel should include cytokeratin 20 (CK20) and thyroid transcription factor 1 (TTF-1). Other IHC neuroendocrine markers such as synaptophysin, neurofilament protein, chromogranin A, CD56, or neuron-specific endolase (NSE) may be used to exclude other diagnostic considerations.

The goals of histologic evaluation of primary MCC tumors are: 1) to accurately diagnose and distinguish the tumor from cutaneous simulants and metastatic tumors; 2) to provide complete pathologic tumor characteristics for staging according to recommended AJCC and CAP guidelines; and 3) to standardize pathologic data collection to further understand the critical biologic features that impact MCC behavior and prognosis. In accordance with the AJCC, the NCCN Panel agrees that synoptic reporting is preferred. At a minimum, the pathology report should include tumor size, peripheral and deep margin status, lymphovascular invasion (LVI), and extracutaneous extension to the bone, muscle fascia, or cartilage, as these features may prove to have prognostic value. The NCCN Panel strongly encourages reporting of the following additional primary tumor features: tumor depth (Breslow, in mm), tumor-infiltrating lymphocytes (TILs) (not identified, brisk, or non-brisk), tumor growth pattern (nodular or infiltrative), and the presence of a second malignancy such as concurrent SCC within the pathologic specimen itself.

For patients with biopsy-confirmed MCC, additional workup may include complete history and physical examination including that of the skin and lymph nodes, and imaging studies as clinically indicated. Imaging is encouraged in most cases of MCC and is indicated whenever metastatic or unresectable disease is suspected based on history and physical (H&P) findings (eg, enlarged or tender lymph nodes). It should be noted that occult metastatic disease that resulted in upstaging has been detected in 12% to 20% of patients presenting without suspicious H&P findings.[68] Several studies indicate that whole-body PET with fused axial imaging is more sensitive for detecting occult metastatic disease at baseline.[68] Recommended imaging modalities include brain MRI with contrast if clinical suspicion, chest/abdomen/pelvis CT with contrast with neck CT for primary tumor on the head/neck, or whole-body FDG PET/CT, which might be preferred for primary tumor on an extremity. CT or MRI with contrast may be used if whole-body FDG PET/CT is not available. The use of brain MRI varies among NCCN Panel Members. Some panel members reserve this test for cases that have an indication of brain metastases or in which widespread systemic disease has been detected.[69] 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 [SCLC]), especially in cases where CK20 is negative. It must be noted that the most reliable staging tool to identify subclinical nodal disease is a sentinel lymph node biopsy (SLNB).

Multidisciplinary consultation is recommended. As immunosuppression in MCC is a risk factor for poor outcomes,[8,35,42,44-49,52] immunosuppressive treatments should be minimized as clinically feasible in consultation with the relevant managing physician. As immunosuppressed patients are at high risk for recurrence,[46,49,50,70] more frequent follow-up may be indicated.

Characteristics and Differential Diagnosis

MCC is rarely clinically suspected at presentation because the primary tumor lacks distinguishing features and is often asymptomatic. In a study of 195 patients with pathologically confirmed MCC, 88% of MCC tumors were asymptomatic and correct clinical diagnosis was rare (only 1%).[7] Based on clinical impression, 56% of MCC tumors were initially presumed

to be benign cysts/lesions.[7] Other studies confirm that MCCs are frequently clinically misdiagnosed as benign lesions or non-melanoma skin cancers (NMSCs) or other rare malignant skin tumors.[8,9,71] Misdiagnosis is even more prevalent among MCC tumors that are admixed or adjacent to other skin tumors.[9,72]

MCC tumors visualized by H&E typically contain small round cells with sparse cytoplasm, abundant mitoses, and dense core granules in the cytoplasm.[63,73-76] MCC is similar to a variety of other widely recognized small round cell tumors, including metastatic visceral neuroendocrine carcinomas (eg, neuroblastoma, rhabdomyosarcoma, metastatic carcinoid, SCLC, lymphomas, osteosarcoma).[77-82] The most difficult differentiation is often between primary MCC and metastatic SCLC.

IHC has proved useful for distinguishing MCC from other small round cell tumors. In one early study, MCC was correctly diagnosed by light microscopy in 60% of cases, but IHC or electron microscopy was needed to diagnose the remaining cases.[83] CK20 and TTF-1 often provide the greatest sensitivity and specificity to exclude SCLC. CK20 is positive in 75% to 100% of primary MCC tumors and rarely positive in SCLC. TTF-1 is never positive in MCC, but is often positive in SCLC (>80%) and other primary pulmonary tumors.[10,11,73,81,84-87] Neuroendocrine markers such as chromogranin, synaptophysin, CD56, NSE, and neurofilament are found in most MCC tumors.[31,73,76,81,82,88-96] Although the specificity of each of these for MCC is not high, when used together they can help identify MCC tumors that are CK20 negative or have other features that make them difficult to diagnose (eg, tumors with squamous components or epidermotropism).[97-103]

Several groups have explored the significance of antibodies to MCPyV in patients with MCC.[104-106] In one prospective validation study that included 219 patients with newly diagnosed MCC, patients who were oncoprotein antibody seronegative at diagnosis had a significantly higher risk of

recurrence, suggesting that they may benefit from more intensive surveillance.[58] For seropositive patients, the oncoprotein antibody test may be a useful component of ongoing surveillance because a rising titer can be an early indicator of recurrence.[58]

Pathology Report

The AJCC strongly encourages synoptic reporting for MCC primary tumor specimens, including but not limited to the parameters needed for determining T-stage.[107] The College of American Pathologists (CAP) also provides a complete synoptic report protocol for cutaneous MCC.[108,109]

Tumor Size (Diameter)

In addition to the analyses of National Cancer Database (NCDB) data that support T-staging criteria for the AJCC staging guidelines,[14,16] many studies have analyzed the relationship between tumor diameter and various outcomes—including lymph node involvement, ability of treatment to achieve local control, probability of distant metastasis, disease-specific survival (DSS), and OS. Results from smaller studies (N < 400) are variable[8,21,22,35,45,51,110] but analyses of large databases have all found primary tumor size to be significantly associated with nodal involvement, DSS, and OS.[15,17,52,111-113] It is important to note that even in these studies, the risk of microscopic lymph node involvement is non-negligible even among patients in the smallest tumor size category.[17,52,112,114,115]

Peripheral and Deep Margin Status

Results vary between studies analyzing the prognostic value of margin status, with some studies showing correlations with local control, OS, or disease-specific death (DSD),[21,24,25,45,113] but others finding no significant associations with outcome.[23,116-120] The largest study looking at margin status in 6,901 MCC cases in the NCDB showed that margin status was significantly associated with survival for patients with stage I, stage II, or stage III MCC.[113] One study of 179 cases found that margin status was

correlated with local recurrence in patients who were treated with surgery alone, but was far less predictive among patients who received adjuvant radiation therapy (RT).[25]

Lymphovascular Invasion
Several studies with large sample sizes have found LVI to be predictive of SLN positivity, recurrence, OS, and DSS.[24,93,114,119,121-123] A large (N = 500) review of a prospective database supported that LVI in the primary tumor was highly correlated with DSD. Specifically, <1% versus 35% of those who died of MCC were LVI-negative and LVI-positive, respectively.[24]

Extracutaneous Extension
The 8th edition of the AJCC Cancer Staging Manual includes primary tumor invasion of fascia, muscle, cartilage, or bone as the definition of stage T4 for MCC.[16] This is supported by results from several studies.[14,92,111,121] For example, an analysis of a large database (SEER, N = 2104) found that tumor extension beyond the dermis was an independent prognostic factor for DSS.[111] Another analysis of approximately 5000 MCC cases from the NCDB found that tumor diameter was reasonably predictive of relative survival among patients with small primary tumors, but resulted in poor separation among patients with larger primary tumors (>2 cm).[14]

Tumor Thickness
Multiple institutions have published studies showing correlation between tumor thickness or Breslow depth and SLN positivity, DFS, DSS, and OS.[52,115,121,124,125] The statistical significance of these correlations varies, perhaps because primary tumor thickness may be correlated with primary tumor size.[52] Per the AJCC staging guidelines, tumor thickness should be measured as for Breslow thickness in cutaneous melanoma—as the microscopic distance from the granular layer of the overlying epidermis to the deepest point of tumor invasion—and recorded in mm.[107,109]

Tumor Infiltrating Lymphocytes
Several studies have found that the presence of TILs in MCC tumors was associated with improved survival outcomes.[121,125-131] Notably, a recent retrospective cohort study (N = 2182) established that subdivision of TIL status into non-brisk and brisk was associated with incrementally improved OS compared with no TILs.[126] The prognostic value of TILs seems to depend on the type of immune cells present; however, it is not clear which type of TILs has prognostic value.[128-130] The CAP protocol for MCC defines TILs as lymphocytes present at the interface of the tumor and stroma, without specifying any molecular markers.[109] The categories for TILs are based on the presence and distribution of lymphocytes in the tumor sample.[109] TILs "not identified" includes samples in which lymphocytes are present but do not infiltrate the tumor. "Nonbrisk" is to be used when lymphocyte infiltration is focal or not present across the entire base of the vertical growth phase, and "brisk" is to be used when lymphocytes diffusely infiltrate the entire base of the dermal tumor or the entire invasive component of the tumor.[109]

Tumor Growth Pattern
A variety of terms have been used to describe the distinct growth patterns observed in MCC tumors.[73,76,92,102,115,121,132-134] In general, growth pattern seems to be prognostic if tumors are grouped into one of two categories: 1) "nodular" (or "circumscribed," "solid," "organoid," "polypoid," or "multinodular"); or 2) "infiltrative" (or "diffuse" or "trabecular").[115,121] Per the CAP protocol, nodular pattern is defined as tumors with a relatively well-circumscribed interface with the surrounding tissue, typically composed of one or multiple nodules.[109] Infiltrative pattern is defined as tumors without a well-circumscribed interface, composed of single cells, rows, or trabeculae—strands of cells infiltrating through dermal collagen or deeper soft tissue.[109] Retrospective studies using these categories have found the infiltrative growth pattern to be associated with higher risk of SLN positivity

or poor outcomes,[92,115,121] possibly due to the difficulty in fully excising tumors that are poorly circumscribed.

Presence of Secondary Malignancy

Patients diagnosed with MCC are at higher risk of developing a second cancer, including SCC; BCC; melanoma; CLL; non-Hodgkin lymphomas (NHLs); lung, breast, and kidney cancers; and vice versa.[8,24,26,39,83,119,131,132,134-141] Currently, there appears to be more data showing no significant association between secondary malignancies and the likelihood of MCC SLN positivity, lymph node metastasis, locoregional control (LRC), or survival.[24,114,119] In addition, there are numerous reports of other skin lesions or malignancies found within or adjacent to MCC tumors, most commonly SCC, followed by BCC, melanoma, actinic keratoses, and Bowen disease.[9,31-33,63,98-101,103,125,133,142-145] It is not known whether the "combined" phenotype is associated with poor outcomes, as there are little comparative data available. One small retrospective study found that patients with the combined tumors were more likely to have had prior NMSCs, nonhematologic extracutaneous cancers, and immunosuppression/pro-inflammatory comorbidities, and tend to have more metastasis, treatment failures, and death from disease.[9]

Imaging

The utility of imaging as part of baseline staging for MCC is an issue of debate in the literature. A number of retrospective analyses have reported data on detection and appearance of MCC tumors using various imaging methods, including conventional x-ray,[74,83,146] CT,[83,146-150] ultrasound,[83,146,149] MRI,[74,146,149,151] scintigraphy,[152-154] and PET or PET/CT.[149,151,155-168] For CT and FDG PET or FDG PET/CT, there are reports showing detection of MCC primary tumors, lymph node metastases, and distant metastases in a wide range of anatomic locations. Though the reported sensitivity and specificity of MRI were lower than CT and FDG PET/CT,[151] it is still the best imaging tool available for rare cases

of MCC brain metastases.[169-171] A number of studies have attempted to determine the utility of specific imaging methodologies for detecting MCC tumors, either in terms of the sensitivity, specificity, and positive/negative predictive value, or in terms of making an impact on disease restaging or management. However, many studies are limited by small sample size (N < 30) and did not consistently use pathologic confirmation as a standard of reference for determining positive and negative predictive values.

Computed Tomography

Only a few studies have evaluated the independent utility of CT for detection of MCC tumors.[83,146-151] According to Gupta et al, the calculated sensitivity and specificity of baseline CT imaging for detection of lymph node metastases were 20% and 87%, respectively. Conversely, for the detection of distant metastases, the sensitivity and specificity were 100% and 48%, respectively. For both nodal and distant spread of MCC, true positives oftentimes had disease that were clinically evident at presentation.[148] A separate study came to similar conclusions, reporting that the low sensitivity and high specificity of CT scans were 47% and 97%, respectively, in detecting nodal disease. In this study, CT imaging not only failed to detect micrometastases, but also larger lymph node metastases, including single node positivity in 6 patients and multiple positive nodes in 5 patients.[151]

FDG PET/CT

Compared with CT imaging, there are many more studies with larger sample sizes on the utility of FDG PET/CT for detecting MCC tumors.[149,151,155-168] Overall, FDG PET/CT has high sensitivity and specificity when compared with subsequent pathologic, clinical, or imaging results, with calculated values of 90% and 98%, respectively, according to a meta-analysis.[161] In the only prospective study to date, FDG PET/CT had a sensitivity of 95% and a specificity of 88%, respectively.[168] Small retrospective studies indicate that FDG PET/CT might not be useful in

detecting lymph node metastasis (compared with SLNB),[165] as well as primary tumor site in patients with unknown primary MCC.[166] A number of studies reported that results from FDG PET/CT scans at initial presentation impacted baseline staging in 6% to 39% of patients and changed management in 6% to 37% of patients.[156-160,162-164,167,168] Most of the changes in staging and disease management were due to discovery of more extensive lymph node involvement, distant metastatic disease, or previously undetected secondary cancers, suggesting that FDG PET imaging may be more useful in patients with clinically advanced disease at presentation.

Some evidence suggests that FDG PET/CT may be more useful than CT in detecting nodal and distant MCC. In a retrospective analysis, in which CT and FDG PET results were compared to SLNB results, the calculated sensitivity of FDG PET was notably better than that for CT (83% vs. 47%).[151] Furthermore, in some studies, FDG PET/CT detected positive lymph nodes and distant metastases that were not detectable by CT scans.[158,159,168] In a recent large retrospective study, patients who underwent PET/CT had disease upstaged more often than those with CT alone (16.8% vs. 6.9%; *P* = .0006).[68]

Staging and Treatment of the Primary Tumor

Surgery is the primary treatment modality for MCC, and it is needed for accurate pathological staging of both the primary lesion and regional disease. The current AJCC staging system (8th edition) is based on an updated analysis of 9,387 cases of MCC from the NCDB with a median follow-up of 28.2 months.[16] The NCCN staging of MCC parallels the AJCC guidelines and divides presentation into local, regional, and disseminated disease.[107] Clinical exam and initial imaging studies (if indicated) are used to make an initial determination of the clinical N-stage and M-stage, which determines the recommended approach for evaluating pathologic nodal status. There is evidence that among patients with clinically apparent nodal disease at presentation, those with unknown primary have a better outcome than those with synchronous known primary,[16,35,172-175] and these findings are reflected in the AJCC staging system.[107] However, the NCCN recommendations for pathologic evaluation of nodal status and management of the nodal basin are the same for both groups of patients.

The management plan for primary MCC tumors is dictated by the presence of baseline risk factors, which include larger primary tumor size (>1 cm), chronic T-cell immunosuppression, HIV, CLL, solid organ transplant, head/neck primary site, and LVI. LVI[24,93,114,119,121-123] and immunosuppression[8,35,42,44-50,52] are risk factors of particular concern because they are highly associated with poor outcomes. For patients with no baseline risk factor, wide local excision (WLE) with 1- to 2-cm margins is recommended. If clear margins are achieved and there is no adverse risk factor, observation is recommended. In the case of positive margins and presence of other adverse risk factors, re-excision or adjuvant RT is recommended. Post-excision adverse risk factors include positive or narrowly clear margins, LVI, or positive SLNB. For patients with 1 or more baseline risk factors, excision with individualized margins and multimodal therapy determined by multidisciplinary assessment including radiation oncology is recommended. After which, adjuvant RT may be initiated.

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 histologically clear surgical margins when clinically feasible. To minimize morbidity, narrow excision margins resulting in possible microscopically positive margins are acceptable when followed by adjuvant RT to the primary site. Surgical margins should be balanced with morbidity of surgery. Alternative methods for complete removal of the primary tumor include Mohs micrographic surgery (Mohs) and peripheral and deep en face margin assessment (PDEMA), using margins similar to WLE (See NCCN Guidelines for Squamous Cell Skin Cancer – Principles of PDEMA Technique). These alternative methods ensure complete tumor removal and clear margins, while sparing surrounding healthy tissue. Regardless of the surgical technique employed, the goal should be primary tissue closure to avoid any undue delay in proceeding to RT and allow for initiation of adjuvant RT, if needed, within 3 to 4 weeks. In selected cases in which 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* in the algorithm). In all cases, surgical management should be coordinated so that SLNB is performed prior to or at the same time as definitive surgery.

Surgery for Primary Tumor

Given the potential for rapid growth, surgery has been the most common approach used to treat primary MCC tumors and has been shown to produce superior outcomes compared to non-surgical primary treatment.[45,176] Outcomes for a variety of surgical approaches to remove MCC primary tumors have been reported in the literature, including biopsy approaches, either with or without subsequent re-excision to obtain clear margins, standard excision, local amputation, and Mohs or other approaches with integrated complete margin assessment.[8,25,45,51,177-187] Whereas there are a number of retrospective studies that found that

negative margin status was associated with improved local recurrence and survival,[24,25,45,113,181,183,188-190] other analyses did not consistently find such associations.[21,23,118-120,158,191-195] There is evidence that margin status has an impact on survival regardless of adjuvant RT receipt.[190] Among patients with stage I/II disease treated with surgery only, recurrence rates and OS were better for negative versus positive margins.[183] On the other hand, for high-risk local and regional MCC, margin status did not seem to have an impact on recurrence in those who received adjuvant RT.[196,197]

Mohs is a useful technique for margin control in MCC and has been associated with improved outcomes compared with standard excision for primary MCC lesions.[181,182,184] In many studies, Mohs and WLE resulted in similar rates of recurrence and survival.[8,178,182,183,186] There is much debate about the size of surgical excision margins needed to achieve histologically clear margins. Among patients treated with Mohs, the mean margin needed to achieve histologic clearance was 16.7 mm, and 2-cm and 3-cm surgical margins would have resulted in incomplete histologic clearance in 25% and 12% of patients, respectively.[185] Among those treated with WLE, 2-cm and 3-cm clinical margins resulted in incomplete excision in 50% and 0% of patients, respectively.[198] For patients with histologically clear margins, retrospective data suggest a trend toward reduced risk of recurrence for patients with histologic margins greater than 1 cm versus less than 1 cm.[25,179,199] However, those who received adjuvant RT and had margins less than 1 cm had similar OS to those who did not receive adjuvant RT and had margins greater than 1 cm.[199] There are data supporting excision margins greater than 2 cm as being significantly associated with higher OS,[199,200] while some studies contend that increasing histologic margin size beyond 1 cm is not associated with additional clinical benefit.[116,177,179]

Definitive Radiation Therapy for Locoregional Disease

Historically, surgery has been the mainstay of treatment for local and regional MCC; as a result, data on the efficacy of definitive RT are extremely limited. There are a large number of retrospective studies that include very small samples of patients (N < 10) who received definitive RT instead of surgery.[21,24,45,71,118,172,192,193,195,201-209] As mentioned previously, patients who received nonsurgical initial treatment, most often definite RT or RT in conjunction with chemotherapy, tended to have poorer outcomes than those initially treated with surgery.[45,176] The largest study (N > 2000) comparing outcomes between definitive RT and surgery showed improved OS with surgery (± adjuvant RT) versus definitive RT, both among patients with stage I/II disease (median OS, 76 vs. 25 months; *P* < .001) and among those with stage III disease (median OS, 30 vs. 15 months; *P* < .001).[176] However, the patient population treated with surgery was more likely to have factors associated with improved outcomes such as smaller primary tumor size, tumor in the upper extremity, shorter time to diagnosis, treatment at an academic hospital, and no chemotherapy.

For those with local or locoregional MCC who are poor surgical candidates or refuse surgery, however, initial treatment that includes definitive RT likely provides good outcomes. One study using SEER data found that among patients who did not receive surgery (N = 746), those who received RT had better OS and DSS than those who did not (DSS at 5 years: 73% vs. 54%; *P* < .0001).[17] Retrospective studies of patients treated with definitive RT to their primary and/or nodal MCC reported in-field recurrence rates of less than 25%, with median time to in-field recurrence ranging from 4 to 6.3 months.[25,210-215] One meta-analysis of 264 patients with locoregional MCC treated with definitive RT reported that cumulative in-field recurrence rate was 12% per site, and that in-field recurrence was significantly more likely at regional versus primary irradiated sites (16% vs. 7.6%, *P* = .02).[208]

Nodal Staging and Treatment of Regional Disease

SLNB is considered the most reliable staging tool for identifying subclinical nodal extension. SLNB is recommended for all patients with clinically node-negative disease who are fit for surgery. The NCCN Panel believes that by identifying patients with positive microscopic nodal disease and then performing full lymph node dissections (LNDs) and/or RT, the care of regional disease in this patient population is maximized. SLNB should be performed prior to surgical removal of the primary tumor, with special care taken in the head and neck region where drainage patterns are often complex and can lead to unreliable SLNB results (risk of false negative results[216]).

IHC analysis should be included in the SLNB evaluation in addition to H&E sections to reduce risk of false negative results. CK20 immunostaining should be included in the pathologic assessment to facilitate accurate identification of micrometastases. An appropriate immunopanel may also include pancytokeratins (AE1/AE3), depending on the immunostaining pattern of the primary tumor. Some NCCN Member Institutions routinely use both CK20 and pancytokeratin stains to evaluate SLN samples to ensure detection of MCC metastases, because results from these two markers are not always consistent. The pathology report should also include the number of lymph nodes involved, size of largest metastatic deposit (mm), and the presence or absence of extracapsular extension (ECE).

Patients with negative SLNB results should continue observation of the nodal basin. Empiric RT to the nodal basin in high-risk patients is recommended when: 1) the accuracy of SLNB may have been subject to anatomic compromise (lymphoma involved nodes, history of remote lymph node excision); 2) when the risk of false-negative SLNB is high due to aberrant lymph node drainage and presence of multiple SLN basins (such as in head & neck or midline trunk MCC); or 3) when identified by

lymphoscintigraphy in cases of profound immunosuppression (ie, solid organ transplant recipients).

Patients with positive SLNB results should receive baseline imaging, if not already performed, to screen for and quantify regional and distant metastases. If the tumor burden in the sentinel node is low, the risk of distant disease may also be low. However, it is important to confirm staging, and baseline scans are useful for comparison in the event of a suspected recurrence.

A clinical N+ diagnosis (palpable lymph nodes) should be confirmed by using fine-needle aspiration (FNA) or core biopsy of the draining nodal basin with an appropriate immunopanel. An open biopsy may be considered to confirm a negative initial FNA or core lymph node biopsy if clinical suspicion remains high. If negative results are confirmed, the patient should be managed as clinical N0 and follow the clinical N0 pathway including sentinel lymph node biopsy. If initial or subsequent lymph node biopsy results are positive, imaging studies are recommended if not already performed to evaluate the extent of lymph node and/or visceral organ involvement. If a distant metastasis is detected, management should follow the M1 pathway. In case of no detected distant metastases, multidisciplinary consultation and node dissection and/or RT is recommended. Enrollment in a clinical trial for adjuvant therapy is preferred, if available. Neoadjuvant immunotherapy can be considered.

Adjuvant systemic therapy is not routinely recommended because no survival benefit has been reported. Most NCCN Member Institutions only use systemic therapy for stage IV, distant metastatic disease (M1), with or without surgery and/or RT. A few NCCN Member Institutions suggest considering adjuvant systemic therapy for select cases of clinical (macroscopic) regional (N1b or N2) disease. However, available retrospective studies do not suggest that adjuvant chemotherapy provides survival benefit, and most institutions only use adjuvant chemotherapy for

MCC in select cases. For select patients for whom adjuvant systemic therapy is considered, treatment in the context of a clinical trial is preferred, when available. Although not routinely recommended for adjuvant treatment of regional disease, if used in select cases the panel recommends cisplatin or carboplatin with or without etoposide, or neoadjuvant nivolumab. For recurrent regional disease, pembrolizumab can be considered if curative surgery and curative RT are not feasible.

Sentinel Lymph Node Biopsy

Large retrospective analyses (N > 100) or meta-analyses of SLNB in patients with clinically node-negative, localized MCC have reported rates of SLN positivity ranging from 30% to 40%.[8,49,52,134,148,217,218] As discussed in the elements of pathology report, there are a number of primary tumor characteristics that have been proposed to be predictive of SLN positivity, including primary tumor diameter, thickness, LVI, and TILs.[52,114,115,131,219] Some studies showed significant association between SLN negativity and lower risk of recurrence and improved DSS or OS,[49,52,53,122,148,219-222] while others did not.[114,218,223] Reported rates of regional relapse in patients with negative SLNB results range from 5% to 12%, with corresponding false-negative rates between 17% and 21%.[49,53,217] Some studies have reported complicated drainage patterns for MCCs occurring in the head and neck.[224-226] Besides, multiple SLNs have been identified in some patients, suggesting that failure to identify all relevant SLNs may contribute to the relatively high rates of false-negative SLNBs.[49,53,217]

Another issue of debate is whether the SLNB procedure itself offers some protection against recurrence, progression, or death from disease for patients with clinically node-negative disease. One retrospective study of patients with clinical stage I/II MCC found that those who underwent SLNB had improved 5-year DSS compared with those who did not undergo SLNB, although the actual difference was small (79% vs. 74%).[221] Another analysis of a large population database found that compared with patients

who had no pathologic nodal evaluation, those with SLNB alone or SLNB plus LND had lower risk of all-cause mortality, and that SLNB plus LND was also associated with improved MCC-specific mortality.[35] There is insufficient information to ascertain whether these associations are due to the SLNB procedure itself or due to subsequent management choices informed by the results of pathologic nodal evaluation. Other retrospective studies have found that among patients presenting with clinically node-negative MCC, SLNB is not significantly associated with improved LRC or OS,[8,45] except for one report of significantly longer OS.[179]

SLNB Pathology

IHC analysis has been shown to be effective in detecting MCC lymph node metastases not detected by H&E.[159,227-229] IHC with CK20 has been included as part of routine screening in multiple studies.[53,165,179,227,230] Other IHC stains for histologic analysis of SLNs have also been reported such as pancytokeratins (AE1/AE3, CAM5.2), or antibodies sometimes used for differential diagnosis of primary MCC lesions, such as chromogranin A, neurofilament, and synaptophysin.[53,114,115,165,179,228,230]

Fine-Needle Aspiration

Several retrospective studies have reported that FNA biopsy is an accurate method for diagnosing MCC lesions, including primary tumors and nodal and distant metastases.[231-234] One small study compared FNA results with subsequent LND results, and found that the FNA procedure identified all cases of LN metastases that were greater than 6 mm, but did not consistently identify smaller foci.[232] This finding underscores that FNA biopsy is not an appropriate method for detection of clinically occult metastases, but is effective for verifying MCC in palpable nodes. IHC analyses of FNA samples showed that most cases were positive for CK20, AE1/AE3, synaptophysin, NSE, and CD56.[231,233,234] Chromogranin staining was present in a smaller proportion of cases (36%).[233,234] Markers for

melanoma (ie, S100, HMB45, Melan A, CD45) or lymphoma (leukocyte common antigen) were nearly always negative.[231,233,234]

Surgery Versus Radiation Therapy for Regional Disease

Since the presence of MCC in the lymph nodes is associated with poorer prognosis,[16,21,22,45,111,181,191,201,222,235] the clinical instinct is to aggressively treat the nodal basin in patients with pathologically positive lymph node(s). Indeed, a retrospective study of 82 patients with locoregional MCC found that nodal treatment was associated with improved disease control: LND prolonged the time to first recurrence (median of 11.8–28.5 months; P = .034), as did RT to the nodal basin (median of 11.3–46.2 months; P = .01).[191] A meta-analysis that included 39 patients with SLN positivity found that those who received some form of post-SLNB treatment for nodal disease (therapeutic LND [TLND], RT, chemotherapy) had improved 3-year relapse-free survival (51% vs. 0%; P < .01).[148]

Due to lack of prospective data, however, it is unclear whether surgical approaches or RT are more effective as initial treatment for nodal MCC. For studies with at least 20 patients with MCC lymph node involvement, few reported outcomes for specific nodal treatments.[22,25,51,113,114,172,176,201,206,236-238] Wright et al showed that surgery (with or without adjuvant RT) was associated with better OS compared with definitive RT (median 30 vs. 15 months, P < .001).[176] In contrast, Bhatia et al found no significant difference in OS for surgery alone compared with RT alone or surgery plus RT.[113] Furthermore, while some studies suggest that nodal surgery may improve outcomes,[51,236-238] a few found that patients who received nodal RT alone fared better,[22,25] and others found no clear trends according to nodal treatment.[22,114,172,201,206,239] Perez et al. and Lee et al., retrospectively, evaluated outcomes for patients treated with lymph node dissection versus RT for sentinel lymph node biopsy positive disease and found low rates of regional recurrence

for both treatment modalities, suggesting that both treatment modalities may be effective in appropriate patient cohorts.[240,241]

There are very few data to inform the extent of nodal surgery needed for patients with biopsy-proven regional disease. Results from retrospective analyses suggest that MCC prognosis worsens with increasing nodal involvement (clinically detectable nodal involvement versus microscopic nodal involvement,[16,24,52,119] increasing number of nodes involved,[17,21,111-113,193,204,215,218,242,243] and the presence of ECE[124,204,218]). These findings suggest that the aggressiveness of nodal treatment should perhaps be commensurate with the extent of nodal disease. The type of LN surgery may not be very important if patients are also treated with RT. A pooled analysis of several prospective studies found that the margin status of surgically removed lymph nodes was not associated with locoregional recurrence in patients who received RT to the nodal basin.[244] One of these prospective studies also found that among patients with locoregional MCC, all of whom were treated with surgery plus RT (with or without chemotherapy), nodal involvement was not prognostic for DSS or OS.[245]

Postoperative Radiation and Systemic Therapy for Locoregional Disease

Postoperative Radiation

Many studies have found that postoperative RT is associated with lower recurrence and/or improved survival compared with surgery alone.[19,21,25,35,49,51,53,113,116,118-120,123,148,158,178,181-183,190,191,193,195,197,201,204,240,246-265] However, many of these studies reported mixed results, finding that adjuvant RT was significantly associated with improvements in some but not all outcome measures or only in particular subsets of patients. Some studies, on the other hand, found no significant correlations with outcomes.[8,21,49,119,259,263,266] For most of these studies, the results are difficult to interpret because they included a range of MCC stages, a mix of primary and recurrent MCC cases, a variety of surgical procedures prior to

RT, and a mix of patients who received RT to the primary site only, nodal basin only, or both. For studies that included sub-group analysis, the sample sizes were usually too small for meaningful interpretations.

Overall, studies reporting results specifically for patients with stage I/II disease agree that adjuvant RT to the primary tumor significantly reduced the rate and time to locoregional recurrence,[19,185,248,252,262,267] while many also reported improvements in survival.[113,182,183,195,248,251] Kang et al examined 42 cases of stage I/II MCC and determined that those who had RT to their primary site had significantly higher 2-year local recurrence-free survival compared to those who did not receive RT (89% vs. 36%, P < .001).[248] Of note, three large studies using NCDB data (N > 1000 stage I/II patients) concluded that surgery plus RT or conformal RT (CRT) led to significantly better survival results compared to surgery alone.[113,182,183] Even though benefit has been noted for low-risk stage I MCC,[252,262] local MCC with high-risk features might have the most to gain from adjuvant RT.[25,123,247,249,259] Particularly, a recent study of 1,858 stage I/II MCC patients who met indication for RT according to the NCCN recommendation (positive margin, tumor size ≥1 cm, LVI) concluded that 5-year OS advantage was identified for those who received RT when indicated (P < .003). On the other hand, no OS advantage was observed when patients received guideline-discordant RT (P = .478).[251]

Regarding the clinical benefit of adjuvant RT for patients with node-positive versus node-negative MCC, results vary widely between studies.[21,25,49,51,53,113,116,119,120,123,148,195,240,258,263-265] Some studies showed that postoperative RT was associated with improved survival in patients with stage I/II disease, but not for stage III disease.[113,195] In contrast, a retrospective study found that postoperative RT to the primary tumor bed improved LRC and DSS in patients with pathologic or clinically positive nodes, but not in node-negative patients.[123] In other studies, nodal RT in SLNB-positive patients significantly reduced 3-year relapse-free survival

rate (51% vs. 0%; $P < .01$),[148] as well as 3-year regional control (95% vs. 66.7%; $P = .008$).[268] A large study using NCDB data (N = 447) of SLNB-positive MCC patients reported that compared with completion lymph node dissection (CLND), observation, or RT alone, CLND and adjuvant RT were associated with better OS.[265] Several studies pointed out that the utility of adjuvant RT might be extended to node-negative patients.[25,53,116,120,258,268] Specifically, tumor-bed irradiation was significantly associated with prolonged DFS ($P = .006$) and OS ($P = .014$) in SLNB-negative patients.[53] In another study, RT to regional nodes was associated with improved regional control, irrespective of clinical status ($P = .01$).[120] Overall, studies have both supported[25] and refuted[263] the effectiveness of nodal RT in reducing nodal relapse in node-negative patients.

Postoperative Systemic Therapy

High-quality clinical data on adjuvant systemic therapy options are lacking since very few patients receive chemotherapy for MCC. For most of the studies in which some subsets of patients received postoperative chemotherapy, often in combination with adjuvant RT, use of chemotherapy was not associated with reduced risk of recurrence or distant metastasis, or improved survival.[21,35,51,113,120,181,202,245,259,260,269,270] Two studies found that adjuvant chemotherapy was associated with *worse* survival.[21,269] Several studies found that postoperative chemoradiation did not improve outcomes compared with postoperative RT.[51,181,259] Particularly, results from a prospective trial of chemoradiation (carboplatin plus etoposide) in 40 patients with stage I–III disease compared with historical controls (N = 62) treated with postoperative RT did not support the use of adjuvant chemotherapy.[245] A large NCDB study (N = 4,815) found that, relative to surgery alone, postoperative chemoradiation improved OS but postoperative chemotherapy (without RT) had the opposite effect.[181] There was a nonsignificant trend toward improved OS with postoperative chemoradiation compared with postoperative RT alone ($P = .08$). However, this difference was only significant in patients with positive margins ($P = .03$) and primary tumor size ≥3 cm ($P = .02$).[181] These results suggest that although postoperative chemotherapy alone is unlikely to improve outcomes, postoperative chemoradiation may have a role in particularly high-risk cases in which residual disease is present after surgery.

The most common systemic therapy regimen used for adjuvant treatment of regional disease is cisplatin or carboplatin with or without etoposide;[21,51,202,245,259,269] however, information about the agents used was not available from the NCDB analysis that showed that postoperative chemotherapy may provide clinical benefit in certain high-risk patients.[181] The recommendations for immune checkpoint inhibitors (ICIs) pembrolizumab[271-273] and neoadjuvant nivolumab[274] are based on data from two clinical trials, whose results are elaborated in the *Systemic Therapy for Metastatic or Unresectable Disease – Immunotherapy* section.

Treatment of Distant Metastatic Disease

Many retrospective studies have reported the pattern of MCC metastatic spread to distant sites based on large patient databases that include data from various points in the development of the disease.[19,20,83,119,132,146,159,163,167,275-277] Based on these analyses, distant metastatic MCC is most likely to arise in distant lymph nodes or skin, bone/bone marrow, lung/pleura, or liver, followed by the pancreas, adrenal glands, brain, kidneys, subcutaneous tissue, or muscle.

The NCCN Panel recommends multidisciplinary consultation for patients with distant metastatic disease (M1). Comprehensive imaging is recommended for all patients with any clinically detected and pathologically proven regional or distant metastases. In general, the management of patients with distant metastases must be individually tailored. 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. Clinical trials testing therapies shown to be effective against other metastatic cancers (eg, melanoma) should be considered. The multidisciplinary panel may consider treatment with one or more of the following modalities: systemic therapy, RT, and surgery. Systemic therapy and RT will likely be the primary treatment options to consider. Options include avelumab, pembrolizumab, nivolumab (preferred) or cisplatin or carboplatin with or without etoposide, topotecan, cyclophosphamide, doxorubicin (or epirubicin), and vincristine (CAV) (useful in certain circumstances as clinical judgment dictates for patients with contraindications to ICI). Surgery may be beneficial in highly selective circumstances for resection of oligometastases or symptomatic lesions. All patients should receive best supportive care, and depending on the extent of the disease and other case-specific circumstances, palliative care alone may be the most appropriate option for some patients (See NCCN Guidelines for Palliative Care).

Systemic Therapy for Metastatic or Unresectable Disease

Immunotherapy

Results from recent prospective clinical trials support the use of the ICIs avelumab,[278-283] pembrolizumab,[271-273] and nivolumab[284] for the treatment of patients with disseminated MCC. Although there are no randomized comparative trials comparing ICIs and chemotherapy, ICIs provide response rates similar to those previously reported for chemotherapy, and may provide greater durability of response.

The recommendation for avelumab is based on data from the JAVELIN Merkel 200 trial, an open-label multicenter trial testing avelumab in patients with histologically confirmed and measurable stage IV distant MCC.[278-283] For the cohort of patients whose disease had progressed after more than 1 prior line of chemotherapy (N = 88), after a median follow-up of 65.1 months, the median OS was 12.6 months, with the 48- and 60-month OS rates of 30% and 26%, respectively.[281] For the cohort of patients treated with avelumab as first-line therapy (N = 116), after a median follow-up for 21.2 months, the OR was 39.7%, median PFS was 4.1 months, and median OS was 20.3 months.[283,285]

The recommendation for pembrolizumab is supported by data from the phase II, single-arm multicenter trial testing pembrolizumab in patients with distant metastatic or locoregional MCC not amenable to definitive surgery or RT (N = 50).[271-273] After a median follow-up of 31.8 months, the ORR was 58%. The median PFS was 16.8 months and the 3-year PFS was 39.1%. The median OS was not reached and the 3-year OS was 59.4% for all patients and 89.5% for responders.[273]

The recommendation for neoadjuvant nivolumab is supported by data from the Checkmate 358 phase I/II trial that included 39 patients with resectable MCC.[274] Among 36 patients who underwent surgery, 47.2% achieved a pathologic complete response. Among 33 radiographically evaluable

patients who underwent surgery, 54.5% had tumor reductions greater than or equal to 30%.[274]

Based on analyses of the trials described, toxicity profiles in patients with MCC were similar for avelumab, pembrolizumab, and nivolumab, with treatment-related adverse events (AEs) occurring in 68% to 77% of patients, and grade 3 or 4 AEs occurring in 5% to 21%. Immune-related AEs were seen in less than 20% of patients receiving avelumab, and were all grade 1 or 2.[271-274,278-283] The safety profiles for checkpoint immunotherapies are significantly different from cytotoxic therapies, so clinician and patient education is critical for safe administration of checkpoint immunotherapies. For example, patients with well-controlled HIV, although not represented in initial trials, appear to respond to PD1 pathway blockade at a rate (two of three cases in one series) that is similar to patients without immune compromise.[286] It is important to consult the prescribing information for recommendations regarding contraindications to checkpoint immunotherapy as well as the detection and management of immune-related AEs[287-289] (See NCCN Guidelines for Management of Immunotherapy-Related Toxicities).

Chemotherapy
Responses to chemotherapy in patients with MCC have been reported for a variety of regimens, including regimens that contain platinum agents (often in combination with etoposide), cyclophosphamide (often in CAV), cyclophosphamide with methotrexate and 5-fluorouracil (CMF), paclitaxel, nab-paclitaxel, docetaxel, ifosfamide, anthracycline, 5-fluorouracil, topotecan, gemcitabine, and irinotecan.[210,270,275,290-293] In analyses with more than 20 patients, reported overall response rates (ORRs) were usually around 40% to 60%. In several studies the response rate appeared to depend on the number of prior chemotherapy regimens, with reports of response rates up to 70% for first-line chemotherapy, and as low as 9% to 20% in patients who received one or more prior lines of

chemotherapy.[210,270,275,290-295] Reported responses to chemotherapy were fairly short-lived, with a median duration ranging from approximately 2 to 9 months.[210,270,275,291-294] Reported rates of toxic death were between 3% and 10%, with elderly patients being at higher risk.[210,270,275]

Follow-up and Recurrence

As described in *Overview*, recurrence and development of lymph node and distant metastases in MCC are not uncommon.[8,18-22,124,202,255] Based on data from large retrospective analyses (N > 100), the median time to recurrence in patients with MCC is about 8 to 9 months, with 90% of the recurrences occurring within 24 months.[21,22,51,159] Time to local recurrence is generally shorter than for regional recurrence, and time to distant metastasis is longer.[8,20,21,201] Due to the fast-growing nature of the disease, detection of multiple distant metastases at once is not uncommon.[146] As described in *Presence of Secondary Malignancy* above, patients who have had MCC are also at increased risk for a prior, concurrent, or subsequent second primary malignancy.[26,39,135-138]

Multiple retrospective analyses,[73,118,120,215,236,260] data from a phase II study,[245] and a few meta analyses[208,296,297] have shown that recurrence of MCC is associated with poor prognosis. Collectively, these studies support that locoregional recurrence is associated with development of distant metastasis, and that all types of recurrences (local, regional, and distant) may be associated with poorer DSS and OS. A few retrospective studies did not find a significant association between recurrence and outcome measures including survival.[51,192,211,214,215,239]

The NCCN Panel recommends close clinical follow-up for patients with MCC starting immediately after diagnosis and treatment. The physical examination should include a complete skin and complete lymph node examination every 3 to 6 months for the first 3 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 for frequent clinical exams during the first 3 years also reflect the fact that MCC will recur in up to half of patients, and most recurrences occur within the first few years after diagnosis. Education regarding self-examination of the skin is useful for patients with MCC because of their increased risk for other NMSCs.

Imaging studies should be performed as clinically indicated, such as in cases of emergent adenopathy or organomegaly, unexplained changes in liver function tests, or development of new suspicious symptoms. For high-risk patients (eg, stage IIIB or higher, immunosuppression), routine imaging should be considered. Recommended imaging modality options are the same as for the initial clinical workup in patients for whom regional or distant metastases are suspected: brain MRI with contrast if clinically indicated and neck/chest/abdomen/pelvis CT with contrast or whole-body FDG PET/CT. Whole-body FDG PET/CT scans may be useful to identify and quantify metastases, especially bone involvement. If whole-body FDG PET/CT is not available, CT or MRI with contrast may be used. As immunosuppressed patients are at high risk for recurrence, more frequent follow-up may be indicated. To lower the risk of recurrence/progression, immunosuppressive treatments should be minimized as clinically feasible.

As described previously, MCPyV oncoprotein antibody testing performed at initial workup may help guide surveillance.[58,104-106] Patients who are oncoprotein antibody seronegative at diagnosis may be at higher risk of recurrence and may benefit from more intensive surveillance.[58] For patients who are seropositive at baseline, the MCPyV oncoprotein antibody test may be a useful component of ongoing surveillance because a rising titer can be an early indicator of recurrence.[58]

Management of patients who present with local, regional, or disseminated recurrence is similar to those with clinical M1 disease. Systemic therapy, RT, or surgery, or a combination of modalities, are among treatment options for these patients. Clinical trial enrollment is preferred, if available. All patients should receive best supportive care, and depending on the extent of the disease and other case-specific circumstances, palliative

care alone may be the most appropriate option for some patients ([See NCCN Guidelines for Palliative Care](#)).

Imaging Surveillance

Retrospective studies of follow-up imaging results have reported both local and systemic MCC recurrences detected by a variety of techniques, including MRI,[146] CT,[146,147,157] and FDG PET/CT.[149,155-157,159,163,164,167,298] Data on the accuracy of imaging techniques for follow-up surveillance are limited, because very few report whether or not the imaging findings were histologically confirmed.[147,155,156] The yield from different imaging regimens and techniques is also unknown, as most studies did not clarify the frequency of follow-up or whether the patients had no evidence of disease prior to follow-up imaging. One recent retrospective study of 61 stage III MC patients who were clinically asymptomatic and underwent surveillance FDG-PET/CT revealed a recurrence rate of 33%, with a median follow-up period of 4.8 years. The sensitivity, specificity, and accuracy were determined to be 92%, 93%, and 93%, respectively.[298]

Treatment of Recurrence

Although patients with MCC recurrence were included in many studies attempting to determine efficacy of specific treatments for MCC, few studies reported outcomes specifically for patients treated for recurrence.[51,116,120,192,203,208,211,214,215,235,245,246,255,269,297] One retrospective analysis of 55 patients with recurrent MCC identified several factors associated with improved DSS after recurrence: location of primary MCC, type of recurrence, disease-free interval, and whether the patient was disease free after treatment for recurrence.[269] Another retrospective analysis of 70 patients with locoregional MCC recurrence also found that the type of first recurrence and disease-free interval were prognostic for development of subsequent distant recurrence, and that the disease-free interval was prognostic for OS.[235]

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