National Comprehensive Cancer Network®

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Merkel Cell Carcinoma

Version 1.2027 — October 8, 2026

NCCN recognizes the importance of clinical trials and encourages participation when applicable and available. Trials should be designed to maximize inclusiveness and broad representative enrollment.

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NCCN Merkel Cell Carcinoma Panel Members
Summary of the Guidelines Updates

Clinical Presentation, Preliminary Workup, Diagnosis, Additional Workup, Clinical Findings, and Treatment (MCC-1)
Primary and Additional Treatment of Clinical N0 Disease: Local MCC Only, Surgically Resectable (MCC-2)
Primary and Additional Treatment of Clinical N0 Disease: Locally Advanced MCC When Curative Surgery and Adjuvant RT are Not Feasible (MCC-3)
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Abbreviations (ABBR-1)

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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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Updates in Version 1.2027 of the NCCN Guidelines for Merkel Cell Carcinoma include:

MCC-1
- Additional Workup, last bullet revised: *In patients <50 y, ~~C~~*consider genetic counseling to evaluate for germline ~~mutations~~ *pathogenic/likely pathogenic (P/LP) variants* in cancer ~~associated~~ *susceptible* genes ~~in patients <50 y~~
- Footnote f revised: ~~Mutations~~ *Germline P/LP variants* in known cancer ~~associated~~ *susceptible* genes that may be heritable have been reported in approximately 20% of patients with MCC ~~under~~ <50 years of age. . .

MCC-2
- Additional Treatment:
  - Top pathway, bullets revised:
    - ◊ First bullet: RT to the nodal basin *(preferred)*
    - ◊ Second bullet: *Consider* node dissection *in rare clinical circumstances*
  - Following Clear margins, ≥1 adverse risk factors, option revised: *Consider* ~~A~~adjuvant RT

MCC-2A
- Footnotes revised:
  - Footnote k: Adverse risk factors for local *and/or regional* recurrence include: *close or pathologically positive margins,* lymphovascular invasion (LVI), immunosuppression, primary tumor >1 cm, ~~close or pathologically positive margins,~~ positive SLNB, or head/neck site.
  - Footnote m: Imaging via whole-body FDG-PET/CT (preferred at initial workup) or CT with contrast of chest, abdomen, pelvis, and neck if primary on head/neck (and MRI of the brain with and without contrast if clinical suspicion of brain metastases or direct extension*; Caillot R, et al. Eur J Cancer 2025;227:115637*). (Also page MCC-4)
  - Footnote p: . . . 2) the risk of false-negative SLNB is high due to aberrant LN drainage and presence of multiple SLN basins (such as in head/neck or midline trunk MCC) *(Wang SY, et al. JAMA Otolaryngol Head Neck Surg 2026;152:313-322)*; or 3) patient presents with profound immunosuppression.
  - Footnote q: Ma KL, et al. Ann Surg Oncol 2023;30:4345-4355*; Lee JS, et al. Ann Surg Oncol 2019;26:386-394; Perez MC, et al. Ann Surg Oncol 2019;26:379-385.*

MCC-3
- Primary treatment, top option revised: Neoadjuvant nivolumab may be considered in ~~patients who are surgical candidates~~ *those likely to become eligible for surgery*
- Additional Treatment following Progression on neoadjuvant nivolumab, option removed: Discuss RT or surgery for local control versus systemic therapy

MCC-4
- Management of the Primary Tumor, bullets revised:
  - *If surgically resectable, see* MCC-2 *or*
  - *If curative surgery and curative RT are not feasible, see* MCC-3
- Additional Treatment, new bullet added: Consider neoadjuvant nivolumab

MCC-6
- Footnote w revised: Risk factors for *local and/or regional* recurrence include *close or pathologically positive margins,* immunosuppression, advancing age, advancing stage of disease (stage II–IV), non-SLN metastases, MCPyV negative status, as well as additional factors as determined by the treating physicians. . .

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UPDATES

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Updates in Version 1.2027 of the NCCN Guidelines for Merkel Cell Carcinoma include:

MCC-B 2 of 6
- General Treatment Information - Primary MCC Tumor Site, first bullet revised: Wide margins (5 cm *where anatomically feasible*), *with reduced margins (2–3 cm) for head and neck tumors* ~~should be used around the primary site, when clinically feasible with consideration given to anatomic constraints (margins may need to be diminished around~~ *where* critical *normal* structures [~~eg, eye, mouth]~~) *may be adjacent to the clinical target*.
- Primary Tumor/RT Dosing table:
  - Adjuvant RT, bullet revised: Patients with ≥1 ~~or more~~ risk factors for local *and/or regional* recurrence should be considered for adjuvant RT. Risk factors include: *close or pathologically positive margins,* LVI, immunosuppression, primary tumor >1 cm, ~~close or pathologically positive margins,~~ positive SLNB, or head/neck site.
  - Definitive RT to Clinically Evident Tumor, Hypofractionation, RT Dosing revised: 3 Gy x 15~~–17~~ fractions

MCC-B 3 of 6
- Footnote b revised: In patients at higher risk (eg, immunosuppression), avoid ~~hypofractionated~~ *low biologically effective dose* RT *regimens* where there are limited data. (Also page MCC-B 5 of 6)

MCC-B 4 of 6
- Regional Nodes/RT Dosing table:
  - Definitive RT for Clinically Evident Nodal Disease, Hypofractionation, RT Dosing revised: . . .3 Gy x 15~~–17~~ fractions, 6–7 Gy x 5 fractions, 2 ~~treatments~~ *fractions* per week

MCC-B 6 of 6
- Reference 9 revised: ~~Veness M. Hypofractionated radiotherapy in older patients with non-melanoma skin cancer: Less is better. Australas J Dermatol 2018;59:124-127.~~ *Zaorsky NG, Lee CT, Zhang E, et al. Hypofractionated radiation therapy for basal and squamous cell skin cancer: A meta-analysis. Radiother Oncol 2017;125:13-20.*
- New references added:
  - Cook MM, Schaub SK, Goff PH, et al. Postoperative, Single-fraction radiation therapy in Merkel cell carcinoma of the head and neck. Adv Radiat Oncol 2020;5:1248-1254.
  - Huynh ET, Ch'en PY, Hippe DS, et al. One dose of adjuvant 8 Gray postoperative radiotherapy for Merkel cell carcinoma excised with narrow margins: Low toxicity and comparable efficacy to conventional radiotherapy [published online ahead of print, July 20, 2026]. J Am Acad Dermatol. doi:10.1016/j.jaad.2026.07.041.
  - Iyer JG, Parvathaneni U, Gooley T, et al. Single-fraction radiation therapy in patients with metastatic Merkel cell carcinoma. Cancer Med 2015;4:1161-1170.

MCC-D 2 of 6
- Local Disease N0 *(if curative surgery and curative RT not feasible)* table:
  - Bullet removed: For primary disease, adjuvant systemic therapy is not recommended outside of a clinical trial.
  - Row removed: Primary resectable disease
- Footnote removed: When available and clinically appropriate, enrollment in a clinical trial is recommended. (Also page MCC-D 5 of 7)

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Updates in Version 1.2027 of the NCCN Guidelines for Merkel Cell Carcinoma include:

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- Regional Disease N+ table:
  - Primary regional *N*+ (if curative surgery and curative RT not feasible), Recurrent regional ~~disease~~ N+ (if curative surgery and curative RT not feasible), and In-transit ~~disease~~ column:
    - Useful in Certain Circumstances:
      - First bullet revised: If anti-PD-L1 or anti-PD-1 therapy is contraindicated ~~or disease has progressed on anti-PD-L1 or anti-PD-1 monotherapy,~~ may consider:
        - Carboplatin (recurrent regional disease only)
        - Carboplatin/Etoposide (recurrent regional disease only)
        - Cisplatin (recurrent regional disease only)
        - Cisplatin/Etoposide (recurrent regional disease only)
        - CAV (Cyclophosphamide/Doxorubicin [or Epirubicin]/Vincristine)
        - Topotecan
      - New bullet added: If disease has progressed or is refractory on anti-PD-L1 or anti-PD-1 monotherapy, may consider:
        - Ipilimumab
        - Octreotide long-acting release (LAR) (somatostatin analog therapy if somatostatin receptor testing is positive)
        - Pazopanib
        - T-VEC (intralesional Talimogene Laherparepvec) for palliation of injectable sites

MCC-D 4 of 6

- Disseminated Disease M1 table*:*
  - Useful in Certain Circumstances:
    - First bullet revised: If anti-PD-L1 or anti-PD-1 therapy is contraindicated ~~or disease has progressed on anti-PD-L1 or anti-PD-1 monotherapy,~~ may consider:
      - Carboplatin
      - Carboplatin/Etoposide
      - Cisplatin
      - Cisplatin/Etoposide
      - CAV
      - Topotecan
    - New bullet added: If disease has progressed or is refractory on anti-PD-L1 or anti-PD-1 monotherapy, may consider:
      - Ipilimumab
      - Octreotide LAR (somatostatin analog therapy if somatostatin receptor testing is positive) (category 2B)
      - Pazopanib (category 2B)
      - T-VEC for palliation of injectable sites (category 2B)

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Updates in Version 1.2027 of the NCCN Guidelines for Merkel Cell Carcinoma include:

MCC-D 5 of 6

- Footnotes revised:
  - Footnote d: 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.~~
  - Footnote g: In the Stage IV setting, ~~next generation sequencing (NGS)~~ *multigene panel testing (MGPT)* of the tumor sometimes reveals relevant and actionable therapeutic targets.

MCC-D 6 of 6

- Reference 4 revised: Grignani G, Rutkowski P, Lebbe C, et al. ~~545~~ *Final results of POD1UM-201,* a phase 2 study of retifanlimab*, a humanized anti–PD-1 antibody,* in patients with advanced or metastatic Merkel cell carcinoma (MCC). ~~(POD1UM-201) .~~ J ~~Immunother Cancer 2021~~ *Clin Oncol 2025*;~~9:A574-A575~~ *43:16_suppl, 9536-9536*.

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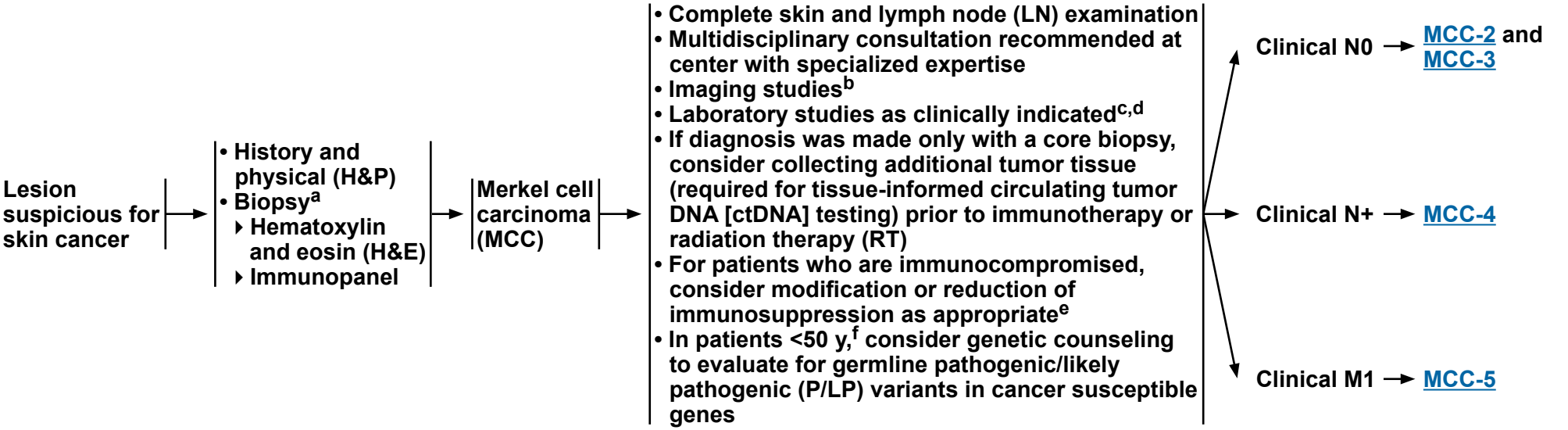

[a] Principles of Pathology (MCC-A).

[b] Imaging is encouraged for staging of most cases of MCC, because occult metastatic disease resulting 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). Several studies indicate whole-body fluorodeoxyglucose (FDG)-PET with fused axial imaging is more sensitive for detecting occult metastatic disease at baseline; however, CT with contrast of chest/abdomen/pelvis and neck if primary tumor on head/neck (and MRI of the brain with and without contrast if clinical suspicion of brain metastases) is an acceptable alternative. 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 and/or TTF-1 is positive. 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).

[c] Quantitation of serum Merkel cell polyomavirus (MCPyV) oncoprotein antibodies may be considered as part of initial workup; patients who test seronegative have a higher risk of recurrence; in patients who test seropositive, 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. For surveillance, this test is often obtained every 3 months. Miller D, et al. Cancer 2024;130:2670-2682; Paulson KG, et al. Cancer 2017;123:1464-1474.

[d] ctDNA can assess disease burden in both virus-positive and virus-negative MCC and typically becomes positive prior to or at the time of a clinically evident recurrence. For surveillance, this test is often obtained every 3 months. Akaike T, et al. J Clin Oncol 2024;42:3151-3161.

[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 patients who are immunocompromised are at high risk for recurrence, more frequent follow-up may be indicated.

[f] Germline P/LP variants in known cancer susceptible genes that may be heritable have been reported in approximately 20% of patients with MCC <50 years of age. Mohsin N, et al. JAMA Dermatol 2024;160:172-178.

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

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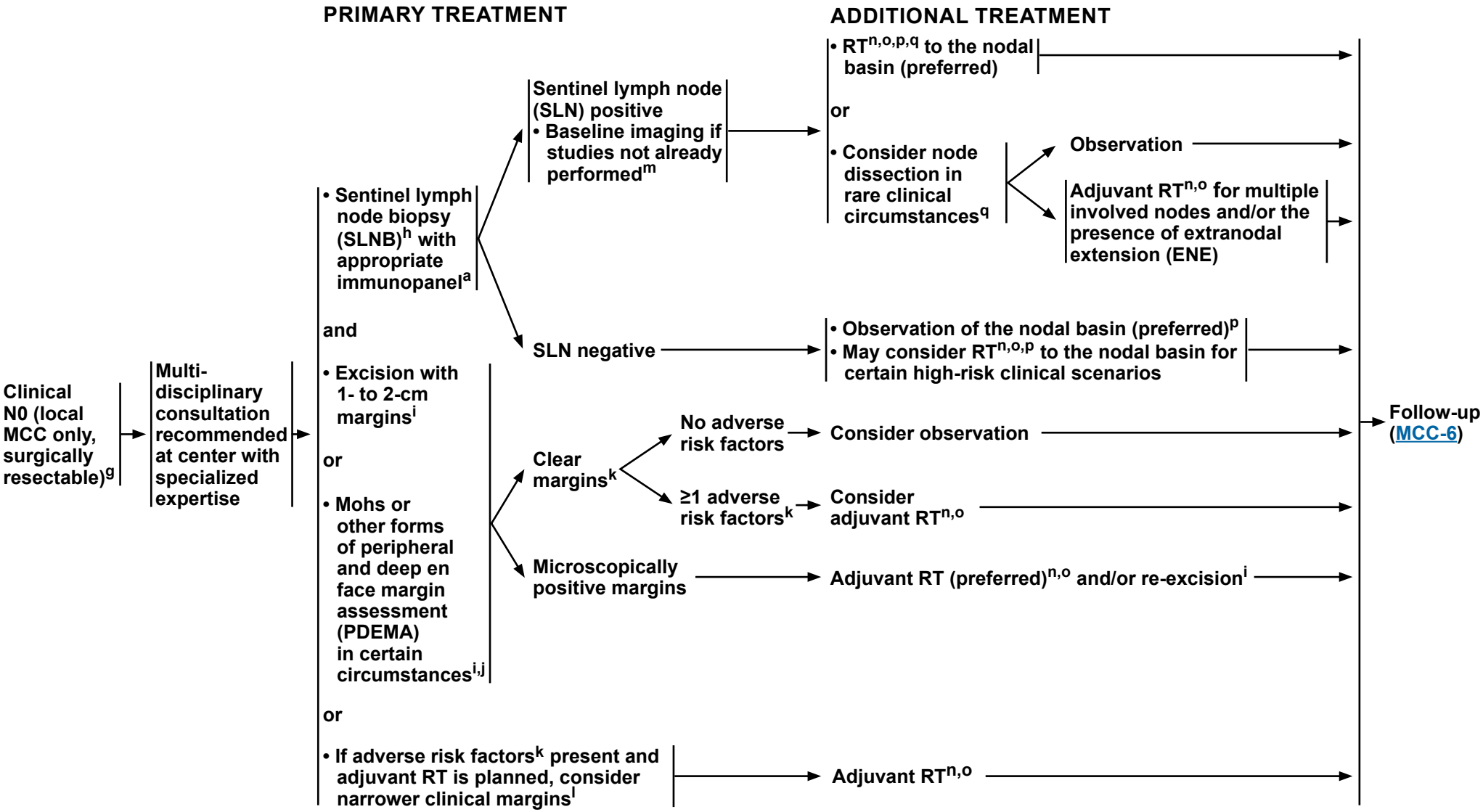
CLINICAL N0 DISEASE, LOCAL MCC ONLY, SURGICALLY RESECTABLE



Footnotes on MCC-2A

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FOOTNOTES

[a] Principles of Pathology (MCC-A).
[g] Criteria for "local MCC only" are disease limited to the primary tumor, with no evidence of in-transit, nodal, or distant disease.
[h] SLNB is an important staging tool. This procedure and subsequent treatment impact regional control for patients with positive SLNs. It is recommended, regardless of surgical approach, that every effort is made to coordinate surgical management such that SLNB is performed prior to or at the time of definitive excision. See MCC-C.
[i] Surgical margins should be balanced with morbidity of surgery, with surgical goal of primary tissue closure to avoid undue delay to adjuvant RT. (If needed, adjuvant RT should be performed as soon as wound healing permits, as delay has been associated with worse outcomes). See Principles of Surgery (MCC-C).
[j] Mohs or other forms of PDEMA may be appropriate. See NCCN Guidelines for Squamous Cell Skin Cancer - Principles of PDEMA Technique for description of PDEMA.
[k] Adverse risk factors for local and/or regional recurrence include: close or pathologically positive margins, lymphovascular invasion (LVI), immunosuppression, primary tumor >1 cm, positive SLNB, or head/neck site.
[l] With the goal of clear or microscopically positive margins versus grossly positive margins.
[m] Imaging via whole-body FDG-PET/CT (preferred at initial workup) or CT with contrast of chest, abdomen, pelvis, and neck if primary on head/neck (and MRI of the brain with and without contrast if clinical suspicion of brain metastases or direct extension; Caillot R, et al. Eur J Cancer 2025;227:115637).
[n] Principles of Radiation Therapy (MCC-B).
[o] Appropriateness of RT should be determined together with a radiation oncologist.
[p] Consider empiric RT to the nodal basin when: 1) the accuracy or reliability of SLNB may have been compromised (eg, prior surgery, extensive chronic lymphocytic leukemia [CLL] within the nodes, history of prior LN excision); 2) the risk of false-negative SLNB is high due to aberrant LN drainage and presence of multiple SLN basins (such as in head/neck or midline trunk MCC) (Wang SY, et al. JAMA Otolaryngol Head Neck Surg 2026;152:313-322); or 3) patient presents with profound immunosuppression.
[q] Ma KL, et al. Ann Surg Oncol 2023;30:4345-4355; Lee JS, et al. Ann Surg Oncol 2019;26:386-394; Perez MC, et al. Ann Surg Oncol 2019;26:379-385.

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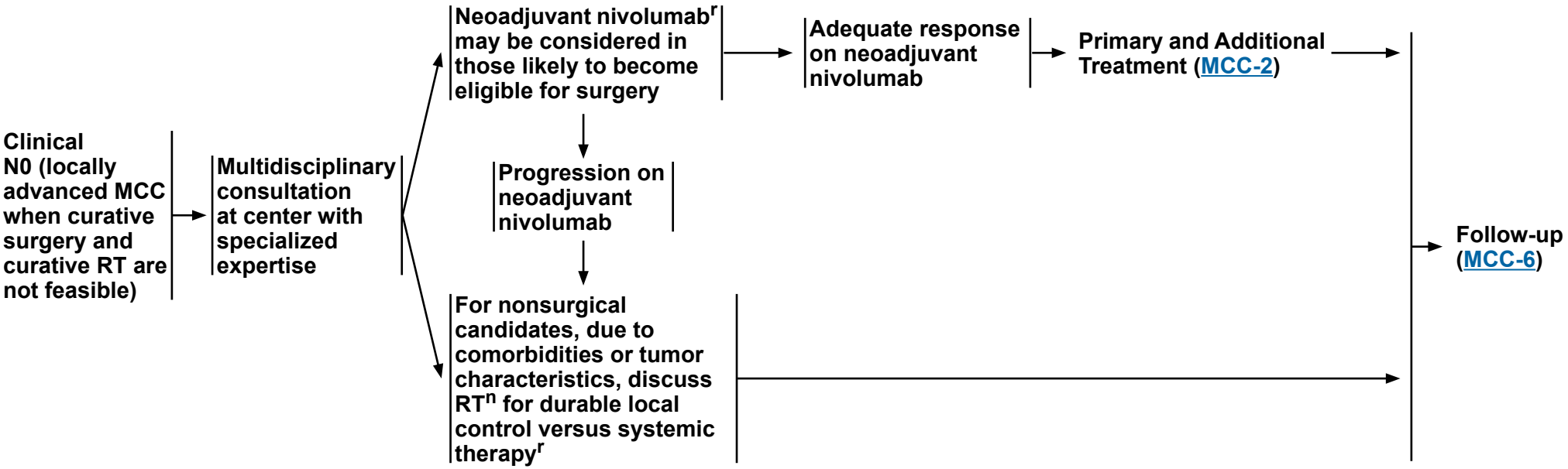
CLINICAL N0 DISEASE, LOCALLY ADVANCED MCC

PRIMARY TREATMENT

ADDITIONAL TREATMENT



[n] Principles of Radiation Therapy (MCC-B).
[r] Principles of Systemic Therapy (MCC-D).

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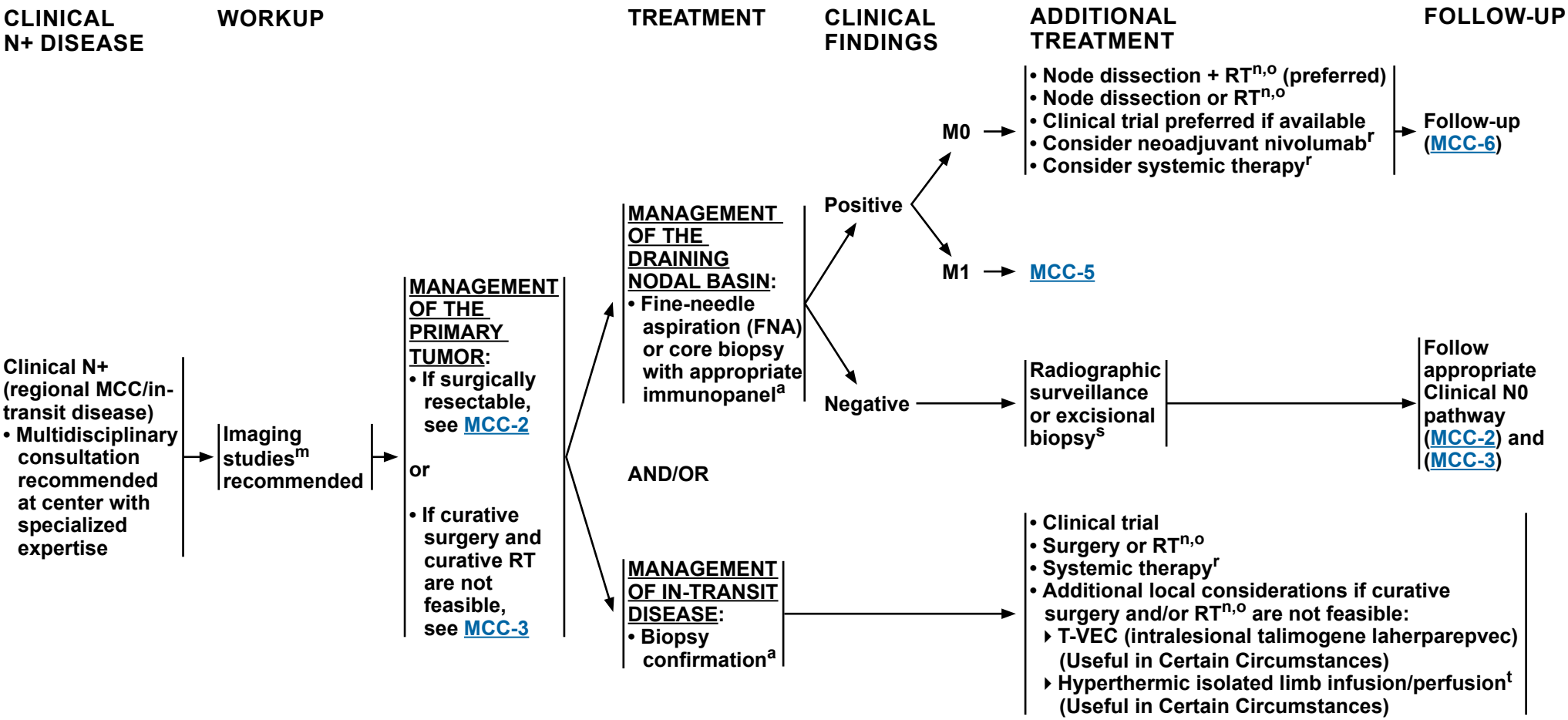

[a] Principles of Pathology (MCC-A).
[m] Imaging via whole-body FDG-PET/CT (preferred at initial workup) or CT with contrast of chest, abdomen, pelvis, and neck if primary on head/neck (and MRI of the brain with and without contrast if clinical suspicion of brain metastases or direct extension; Caillot R, et al. Eur J Cancer 2025;227:115637).
[n] Principles of Radiation Therapy (MCC-B).
[o] Appropriateness of RT should be determined together with a radiation oncologist.
[r] Principles of Systemic Therapy (MCC-D).
[s] An excisional biopsy may be considered to confirm a negative initial FNA or core LN biopsy if clinical suspicion remains high.
[t] Thiels CA, et al. J Surg Oncol 2016;114:187-192.

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[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 patients who are immunocompromised are at high risk for recurrence, more frequent follow-up may be indicated.
[n] Principles of Radiation Therapy (MCC-B).
[o] Appropriateness of RT should be determined together with a radiation oncologist.
[r] Principles of Systemic Therapy (MCC-D).
[u] Under highly selective circumstances, in the context of multidisciplinary consultation, resection of limited metastases can be considered.

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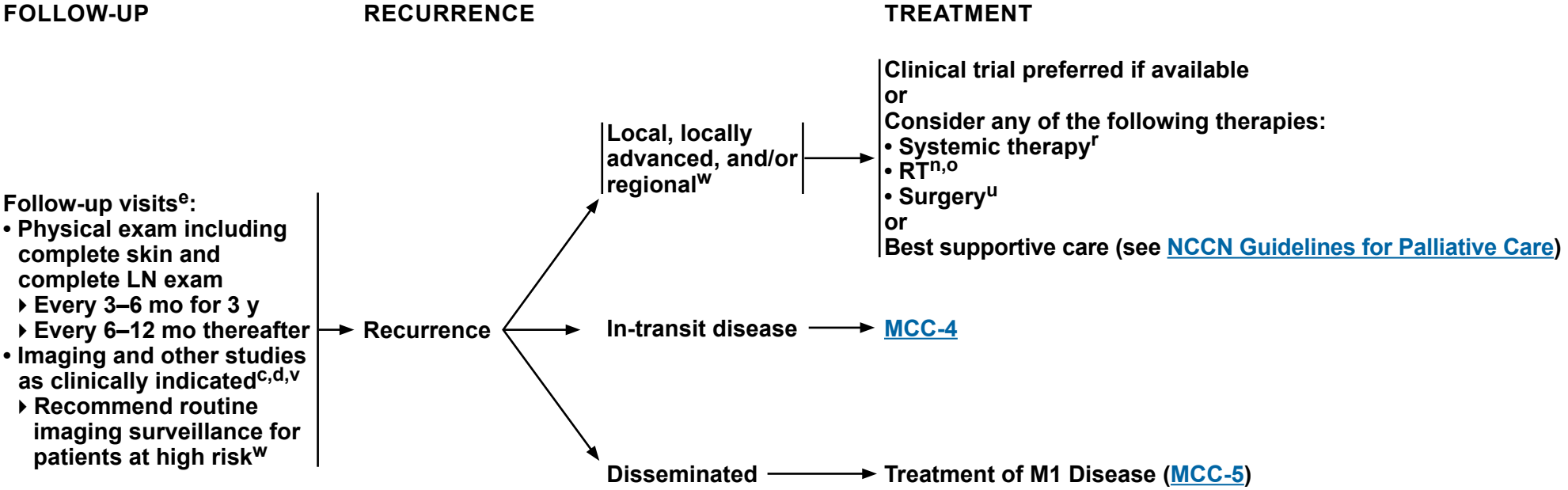

[c] Quantitation of serum MCPyV oncoprotein antibodies may be considered as part of initial workup; patients who test seronegative have a higher risk of recurrence; in patients who test seropositive, a rising titer may be an early indicator of recurrence; baseline testing should be performed within 3 months of treatment because titers are expected to decrease significantly after clinically evident disease is eliminated. For surveillance, this test is often obtained every 3 months. Miller D, et al. Cancer 2024;130:2670-2682; Paulson KG, et al. Cancer 2017;123:1464-1474.

[d] ctDNA can assess disease burden in both virus-positive and virus-negative MCC and typically becomes positive prior to or at the time of a clinically evident recurrence. For surveillance, this test is often obtained every 3 months. Akaike T, et al. J Clin Oncol 2024;42:3151-3161.

[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 patients who are immunocompromised are at high risk for recurrence, more frequent follow-up may be indicated.

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

[o] Appropriateness of RT should be determined together with a radiation oncologist.

[r] 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. Whole-body FDG-PET/CT may be indicated to evaluate for in-transit metastases if the primary lesion is on the extremity.

[w] Risk factors for local and/or regional recurrence include close or pathologically positive margins, immunosuppression, advancing age, advancing stage of disease (stage II–IV), non-SLN metastases, MCPyV negative status, as well as additional factors as determined by the treating physicians. McEvoy AM, et al. J Am Acad Dermatol 2024;90:569-576.

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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):
  - Thickness (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 (IHC) 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, INSM1 [insulinoma-associated protein 1],[1] Chromogranin A, CD56, or neuron-specific enolase [NSE]), and/or MCPyV T antigen (CM2B4) stains may be used.
- SLNB evaluation for metastatic MCC requires microscopic evaluation of the entire SLN(s). Before determining SLNB negativity, multiple levels (recommend at least 2) including H&E and at least one IHC stain should be used to help evaluate for metastatic disease. SLNB reporting should also include the number of LN(s) involved, size of largest metastatic deposit (mm), and the presence/absence of ENE.

[1] Lilo MT, Chen Y, LeBlanc RE. INSM1 is more sensitive and interpretable than conventional immunohistochemical stains used to diagnose Merkel cell carcinoma. Am J Surg Pathol 2018;42:1541-1548.

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PRINCIPLES OF RADIATION THERAPY

General Principles[1,2]

- Expeditious initiation of adjuvant RT after surgery is preferred as soon as wound healing permits, as delay >7 to 8 weeks has been associated with worse outcomes.[3]
- 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.
- Recommendations for external beam RT (EBRT) apply to both photons and electrons.
  - Image-guided RT (IGRT) is considered best practice when treating with intensity-modulated RT (IMRT), proton beam radiotherapy, or three-dimensional (3D) conformal radiation. The use of IGRT for other types of radiotherapy to treat skin cancer is considered unnecessary.
- Application of bolus over the primary tumor should be considered to ensure full dose to the surface. Use of surface dosimeters should be considered to verify delivered dose.
- Radiation treatments should be given by a practicing radiation oncologist with radiation physics support to meet established quality assurance and dosimetric constraints.

Primary Tumor and Palliative RT Dosing Table on MCC-C (2 of 6)

Regional Nodes and Palliative RT Dosing Table on MCC-C (4 of 6)

References on MCC-B 6 of 6

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PRINCIPLES OF RADIATION THERAPY
PRIMARY TUMOR SITE

General Treatment Information–Primary MCC Tumor Site

- Wide margins (5 cm where anatomically feasible), with reduced margins (2–3 cm) for head and neck tumors where critical normal structures may be adjacent to the clinical target.
- If electron beam is used, an energy and prescription isodose should be chosen that will deliver adequate dose to the lateral and deep margins.

Primary Tumor	RT Dosing
Adjuvant RT • Patients with ≥1 risk factors for local and/or regional recurrence should be considered for adjuvant RT. Risk factors include: close or pathologically positive margins, LVI, immunosuppression, primary tumor >1 cm, positive SLNB, or head/neck site.	
• **Conventional fractionation[a,4] (1.8–2 Gy/fraction)** ▸ Negative resection margins ▸ Microscopically positive resection margins ▸ Grossly positive resection margins and further resection not possible	 50–56 Gy 56–60 Gy 60 Gy
• **Hypofractionation[b,c]**	2.2–2.5 Gy x 20 fractions 3–3.5 Gy x 10 fractions 8 Gy x 1 fraction[d,5,6,7]
Definitive RT to Clinically Evident Tumor	
• **Conventional fractionation[a,4] (1.8–2 Gy/fraction)** ▸ Unresectable ▸ Surgery refused by patient ▸ Surgery would result in significant morbidity	 56–60 Gy
• **Hypofractionation[b]**	2.5 Gy x 20 fractions 3 Gy x 15 fractions[4] 4 Gy x 10 fractions 6–7 Gy x 5 fractions[e] (non-consecutive days) 8 Gy x 3 fractions[e] (non-consecutive days)
Palliative Regimens	
• **Hypofractionation[b]**	3 Gy x 10 fractions 4 Gy x 5 fractions 8 Gy x 1–3 fractions[e,f,8]

Footnotes on MCC-B 3 of 6

References on MCC-B 6 of 6

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PRINCIPLES OF RADIATION THERAPY
FOOTNOTES

[a] In subsets of patients at high risk, such as with chronic or profound immune suppression, an RT dose up to 66 Gy may be considered.
[b] In patients at higher risk (eg, immunosuppression), avoid low biologically effective dose RT regimens where there are limited data.
[c] Consider dose painting higher dose/fraction to a subvolume incorporating areas of concerning margins.
[d] May consider a single postoperative fraction of RT (8 Gy) if patient is not a candidate for conventional fractionated radiation due to multiple comorbidities or if surgical margins are negative and risk factors are minimal.
[e] Caution using multiple fractions >5 Gy/fraction when targets involve cartilage or bone.
[f] Durable palliation is likely to be higher with 8 Gy x 3 fractions.

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PRINCIPLES OF RADIATION THERAPY
DRAINING NODAL BASIN

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.
  - Consider empiric RT to the nodal basin when:
    - ◊ The accuracy or reliability of SLNB may have been compromised (eg, prior surgery, extensive chronic lymphocytic leukemia [CLL] within the nodes, history of prior LN excision).
    - ◊ The risk of false-negative SLNB is high due to aberrant LN drainage and presence of multiple SLN basins (such as in head/neck or midline trunk MCC).
    - ◊ Patient presents with profound immunosuppression.

Regional Nodes	RT Dosing
Adjuvant RT	
• **Conventional fractionation[a] (1.8–2 Gy/day)** ▸ SLNB without LN dissection ◊ SLN negative — RT not routinely indicated ◊ SLN positive ▸ After LN dissection with multiple involved nodes and/or ENE[g]	 Observation 50–56 Gy 50–60 Gy
• **Hypofractionation[b,c,h]**	2.2–2.5 Gy x 20 fractions 3–3.5 Gy x 10 fractions 8 Gy x 2 fractions[e]
Definitive RT for Clinically Evident Nodal Disease	
• **Conventional fractionation[a] (1.8–2 Gy/day)** ▸ No SLNB or LN dissection ◊ Clinically evident lymphadenopathy ◊ Clinically node negative, but at risk for subclinical disease	 60 Gy[i] 46–50 Gy
• **Hypofractionation[b,h]**	2.5 Gy x 20 fractions 3 Gy x 15 fractions[4] 6–7 Gy x 5 fractions, 2 fractions per week[j,9]
Palliative Regimens	
• **Hypofractionation[b,h]**	3 Gy x 10 fractions 4 Gy x 5 fractions 8 Gy x 1–3 fractions[e,f]

Footnotes on MCC-B 5 of 6
References on MCC-B 6 of 6

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PRINCIPLES OF RADIATION THERAPY
FOOTNOTES

[a] In subsets of patients at high risk, such as with chronic or profound immune suppression, an RT dose up to 66 Gy may be considered.
[b] In patients at higher risk (eg, immunosuppression), avoid low biologically effective dose RT regimens where there are limited data.
[c] Consider dose-painting higher dose/fraction to a subvolume incorporating areas of concerning margins.
[e] Caution using multiple fractions >5 Gy/fraction when targets involve cartilage or bone.
[f] Durable palliation is likely to be higher with 8 Gy x 3 fractions.
[g] Adjuvant RT following LN dissection is more likely indicated for multiple involved nodes, the presence of ENE, or larger nodal size (eg, >1 cm).[10]
[h] Use caution for patients with existing lymphedema or at high risk for lymphedema (ie, high BMI, groin nodal basin, individual who currently smokes).
[i] LN dissection is the recommended initial therapy for clinically evident adenopathy, followed by postoperative RT if indicated.
[j] Generally reserved for patients who are older or unable to come for protracted course.

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PRINCIPLES OF RADIATION THERAPY
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PRINCIPLES OF SURGERY

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 prior to or at the time of definitive excision.[a] Excision options include:
  - If adjuvant RT is planned, narrow excision margins are likely sufficient (MCC-2).
  - If adjuvant RT may not be indicated (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),[b] provided they do not interfere with SLNB. If SLNB is not performed concurrently, it is recommended that SLNB is performed prior to definitive excision.

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).

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

Local Disease N0 (MCC-D 2 of 6)

Regional Disease N+ (MCC-D 3 of 6)

Disseminated Disease M1 (MCC-D 4 of 6)

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PRINCIPLES OF SYSTEMIC THERAPY[a]

Local Disease N0 (if curative surgery and curative RT not feasible)	
Primary Locally Advanced N0	**Preferred** • Avelumab[1,2] • Pembrolizumab[3] **Other Recommended** • Retifanlimab-dlwr[4] **Useful in Certain Circumstances** • Neoadjuvant Nivolumab[b,5]
Recurrent Locally Advanced N0	**Preferred** • Pembrolizumab[c,3] • Retifanlimab-dlwr[4] **Other Recommended** • Avelumab[1,2]

[a] Data from non-randomized trials in patients with MCC demonstrate that rates of durable response are improved with programmed cell death protein 1 (PD-1)/programmed death ligand 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. See NCCN Guidelines for Management of Immune Checkpoint Inhibitor-Related Toxicities.

[b] Nivolumab and hyaluronidase-nvhy subcutaneous injection may be substituted for IV nivolumab. Nivolumab and hyaluronidase-nvhy has different dosing and administration instructions compared to IV nivolumab.

[c] Pembrolizumab and berahyaluronidase alfa-pmph subcutaneous injection may be substituted for IV pembrolizumab. Pembrolizumab and berahyaluronidase alfa-pmph has different dosing and administration instructions compared to IV pembrolizumab.

References on MCC-D 6 of 6

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PRINCIPLES OF SYSTEMIC THERAPY[a]

Regional Disease N+[d]	
Primary Regional N+ (resectable)	**Useful in Certain Circumstances** • Neoadjuvant Nivolumab[b,5]
Primary Regional N+ (if curative surgery and curative RT not feasible) **Recurrent Regional N+ (if curative surgery and curative RT not feasible)** **In-Transit**	**Preferred** • Clinical trial • Avelumab[6-8] • Nivolumab[b,5,9] • Pembrolizumab[c,3] • Retifanlimab-dlwr[4] **Other Recommended** • Ipilimumab + Nivolumab[e,f,10-12] **Useful in Certain Circumstances** • If anti-PD-L1 or anti-PD-1 therapy is contraindicated may consider: ▸ Carboplatin (recurrent regional disease only)[13] ▸ Carboplatin/Etoposide (recurrent regional disease only)[13] ▸ Cisplatin (recurrent regional disease only)[14,15] ▸ Cisplatin/Etoposide (recurrent regional disease only)[14,15] ▸ CAV (Cyclophosphamide/Doxorubicin [or Epirubicin]/Vincristine)[15,16] ▸ Topotecan[17] • If disease has progressed or is refractory on anti-PD-L1 or anti-PD-1 monotherapy, may consider: ▸ Ipilimumab[18] ▸ Octreotide long-acting release (LAR) (somatostatin analog therapy if somatostatin receptor testing[19] is positive) ▸ Pazopanib[20] ▸ T-VEC (intralesional Talimogene Laherparepvec)[21] for palliation of injectable sites

Footnotes on MCC-D 5 of 6
References on MCC-D 6 of 6

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PRINCIPLES OF SYSTEMIC THERAPY[a]

Disseminated Disease M1

Preferred
- Clinical trial
- Avelumab[6-8]
- Nivolumab[b,5,9]
- Pembrolizumab[c,3]
- Retifanlimab-dlwr[4]

Other Recommended
- Ipilimumab + Nivolumab[e,f,10-12]

Useful in Certain Circumstances[g]
- If anti-PD-L1 or anti-PD-1 therapy is contraindicated may consider:
  - Carboplatin[13]
  - Carboplatin/Etoposide[13]
  - Cisplatin[14,15]
  - Cisplatin/Etoposide[14,15]
  - CAV[15,16]
  - Topotecan[17]
- If disease has progressed or is refractory on anti-PD-L1 or anti-PD-1 monotherapy, may consider:
  - Ipilimumab[18]
  - Octreotide LAR (somatostatin analog therapy if somatostatin receptor testing[19] is positive) (category 2B)
  - Pazopanib[20] (category 2B)
  - T-VEC[21] for palliation of injectable sites (category 2B)

Footnotes on MCC-D 5 of 6
References on MCC-D 6 of 6

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FOOTNOTES

[a] 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. See NCCN Guidelines for Management of Immune Checkpoint Inhibitor-Related Toxicities.

[b] Nivolumab and hyaluronidase-nvhy subcutaneous injection may be substituted for IV nivolumab. Nivolumab and hyaluronidase-nvhy has different dosing and administration instructions compared to IV nivolumab.

[c] Pembrolizumab and berahyaluronidase alfa-pmph subcutaneous injection may be substituted for IV pembrolizumab. Pembrolizumab and berahyaluronidase alfa-pmph has different dosing and administration instructions compared to IV pembrolizumab.

[d] 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.

[e] Nivolumab and hyaluronidase-nvhy is not approved for concurrent use with IV Ipilimumab; however, for nivolumab monotherapy, nivolumab and hyaluronidase-nvhy subcutaneous injection may be substituted for IV nivolumab. Nivolumab and hyaluronidase-nvhy has different dosing and administration instructions compared to IV nivolumab.

[f] Ipilimumab + nivolumab is particularly indicated for disease that is refractory to PD-1 therapy.[22]

[g] In the stage IV setting, multigene panel testing (MGPT) of the tumor sometimes reveals relevant and actionable therapeutic targets.[23]

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References on MCC-D 6 of 6

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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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Continued

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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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ABBREVIATIONS

3D	three-dimensional
CAP	College of American Pathologists
CLL	chronic lymphocytic leukemia
ctDNA	circulating tumor DNA
EBRT	external beam radiation therapy
ENE	extranodal extension
FDG	fluorodeoxyglucose
FNA	fine-needle aspiration
H&E	hematoxylin and eosin
H&P	history and physical
IGRT	image-guided radiation therapy
IHC	immunohistochemistry
IMRT	intensity-modulated radiation therapy
LAR	long-acting release
LN	lymph node
LVI	lymphovascular invasion
MCC	Merkel cell carcinoma
MCPyV	Merkel cell polyomavirus
NSE	neuron-specific enolase
PD-1	programmed cell death protein 1
PDEMA	peripheral and deep en face margin assessment
PD-L1	programmed death ligand 1
P/LP	pathogenic/likely pathogenic
SCC	squamous cell carcinoma
SLN	sentinel lymph node
SLNB	sentinel lymph node biopsy
TTF-1	thyroid transcription factor-1

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NCCN Guidelines Version 1.2027
Merkel Cell Carcinoma

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NCCN Categories of Evidence and Consensus	
Category 1	Based upon high-level evidence (≥1 randomized phase 3 trials or high-quality, robust meta-analyses), there is uniform NCCN consensus (≥85% support of the Panel) that the intervention is appropriate.
Category 2A	Based upon lower-level evidence, there is uniform NCCN consensus (≥85% support of the Panel) that the intervention is appropriate.
Category 2B	Based upon lower-level evidence, there is NCCN consensus (≥50%, but <85% support of the Panel) 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	Interventions that are based on superior efficacy, safety, and evidence; and, when appropriate, affordability.
Other recommended	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.

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Discussion

- The Discussion on the following pages describes the data and clinical information that support the recommendations in the algorithm.
- The presence of a "Discussion update in progress" watermark indicates that the section is being updated. The date of the last update is shown on MS-2.

Guidelines Update Methodology

- For complete details, refer to Development and Update of Guidelines.
- Prior to the update of the NCCN Guidelines, an electronic search of the PubMed database (https://pubmed.ncbi.nlm.nih.gov) using relevant search terms was performed to obtain key literature in the field published since the previous Guidelines update. The PubMed database was chosen because it remains the most widely used resource for medical literature and indexes peer-reviewed biomedical literature. The search results were narrowed by selecting studies in humans published in English. Results were confined to select article types including, but not limited to: Clinical Trial; Randomized Controlled Trial; Meta-Analysis; Systematic Review; and Validation Study. The data from key PubMed articles as well as articles from additional sources deemed as relevant to these Guidelines as discussed by the Panel during the Guidelines update have been included in the Discussion section. Recommendations for which high-level evidence is lacking are based on the Panel's review of lower-level evidence and expert opinion.
- NCCN Guidelines strive to use language that is person-first, non-stigmatizing, and inclusive and representative of all individuals to whom the Guideline recommendations may apply. Therefore, NCCN Guidelines incorporate organ-specific, non-gendered recommendations and respectful terminology that avoids harmful or disparaging stereotypes. NCCN's Guidance on Inclusive Language can be found at https://www.nccn.org/business-policy/policy-and-advocacy-program/advancing-cancer-equity.
- Refer to the NCCN Chemotherapy Order Templates (NCCN Templates®) Systemic Therapy Regimen Naming Methods: Appendix I for information about systemic therapy regimen naming methods used within the Guidelines algorithm.

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Discussion

This discussion corresponds to the NCCN Guidelines for Merkel Cell Carcinoma. Last updated: October 24, 2025.

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Overview

Merkel cell carcinoma (MCC) is a rare cutaneous neuroendocrine neoplasia with approximately 2488 individuals affected per year in the United States.[1] Despite this, MCC is one of the most aggressive skin cancers, and its incidence is dramatically increasing.[1-4] Changes in environmental risk factors, an aging population, as well as improved recognition and diagnosis of MCC lead to an increase in disease incidence.[4] In addition, utilization of biomarkers distinguish MCC from metastatic small cell lung cancer (SCLC).[5,6]

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. [8-15] Several studies document the development of locoregional recurrence in up to half of all instances of MCC.[14-20] 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.[2,10,13,18-23] Given the risk of locoregional recurrence and metastasis, consensus recommendation is to include multidisciplinary consultation when caring for patients with MCC.

Guidelines Update Methodology

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

Literature Search Criteria and Guidelines Update Methodology

Prior to the update of this version of the NCCN Clinical Practice Guidelines (NCCN Guidelines®) for Merkel Cell Carcinoma, an electronic search of the PubMed database was performed to obtain key literature using the search term: Merkel cell carcinoma. The PubMed database was chosen because it remains the most widely used resource for medical literature and indexes peer-reviewed biomedical literature.[24]

The search results were narrowed by selecting studies in humans published in English. Results were confined to the following article types: Clinical Trial, Phase 2; Clinical Trial, Phase 3; Clinical Trial, Phase 4; Guideline; Meta-Analysis; Practice Guideline; 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 as discussed by the Panel during the Guidelines update have been included in this version of the Discussion section. Recommendations for which high-level evidence is lacking are based on the Panel's review of lower-level evidence and expert opinion.

Sensitive/Inclusive Language

NCCN Guidelines strive to use language that advances the goals of equity, inclusion, and representation.[25] NCCN Guidelines endeavor to use language that is person-first; not stigmatizing; anti-racist, anti-classist, anti-misogynist, anti-ageist, anti-ableist, and anti-weight biased; and inclusive of individuals of all sexual orientations and gender identities. NCCN Guidelines incorporate non-gendered language, instead focusing on organ-specific recommendations. This language is both more accurate and more inclusive and can help fully address the needs of individuals of all sexual orientations

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and gender identities. NCCN Guidelines will continue to use the terms men, women, female, and male when citing statistics, recommendations, or data from organizations or sources that do not use inclusive terms. Most studies do not report how sex and gender data are collected and use these terms interchangeably or inconsistently. If sources do not differentiate gender from sex assigned at birth or organs present, the information is presumed to predominantly represent cisgender individuals. NCCN encourages researchers to collect more specific data in future studies and organizations to use more inclusive and accurate language in their future analyses.

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, the tendency to occur on skin areas that are exposed to the sun, and the frequency of MCCs comingled or adjacent to other skin lesions caused by UV exposure.[26-32] MCC incidence increases with age and is more likely to occur in white individuals compared with people from other ethnicities.[4,7,8,13,19] MCC is disproportionally more common in immunosuppressed individuals, such as those with organ transplants, lymphoproliferative malignancies (such as chronic lymphocytic leukemia [CLL]), or human immunodeficiency virus (HIV) infections.[7,33-39] Several studies have reported that MCC-specific survival is worse for those with immunosuppression,[19,38,40-47] although other studies have found no correlation.[48-50] Lastly, Merkel cell polyomavirus (MCPyV), a polyomavirus in MCC tumor tissues, is detected in 43% to 100% of tumors.[51-56] MCPyV negative-tumors tend to occur more often on the head, neck, or trunk, and have been associated with increased recurrence[55] and decreased MCC-specific survival and overall survival (OS) in some studies[57-60] but not others.[61,62] 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.[63-65]

Preliminary Workup and Diagnosis

Initial workup of a suspicious lesion starts with a complete history and physical (H&P) 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, insulinoma-associated protein 1 (INSM1), chromogranin A, CD56, or neuron-specific enolase (NSE) may be used to exclude other diagnostic considerations.

The goals of histologic evaluation of primary MCC tumors are to: 1) accurately diagnose and distinguish the tumor from cutaneous simulants and metastatic tumors; 2) provide complete pathologic tumor characteristics for staging according to recommended American Joint Committee on Cancer (AJCC) and College of American Pathologists (CAP) guidelines; and 3) 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

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non-brisk), tumor growth pattern (nodular or infiltrative), and the presence of a second malignancy such as concurrent squamous cell carcinoma (SCC) within the pathologic specimen itself.

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.[66] The CAP also provides a complete synoptic report protocol for cutaneous MCC.[67]

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),[17,21,22,42,68] but others finding no significant associations with outcome.[69-74] The largest study investigating margin status in 6901 patients with MCC in the National Cancer Database (NCDB) showed that margin status was significantly associated with survival for MCC with stage I, stage II, or stage III.[68] One study of 179 patients found that margin status was correlated with local recurrence in MCC treated with surgery alone, but was far less predictive among patients who received adjuvant radiation therapy (RT).[21]

Lymphovascular Invasion

Several studies with large sample sizes have found LVI to be predictive of sentinel lymph node (SLN) positivity, recurrence, OS, and DSS.[22,72,75-78] 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.[22]

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.[12,66] This is supported by results from several studies.[10,76,79,80] 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.[79] Another analysis of approximately 5000 patients with MCC 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).[10]

Tumor Size and Tumor Thickness

In addition to the analyses of NCDB data that support T-staging criteria for the AJCC staging guidelines,[10,12] many studies have analyzed the relationship between tumor thickness 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[17-19,41,42,48,81] but analyses of large databases have all found primary tumor size to be significantly associated with nodal involvement, DSS, and OS.[11,13,49,68,79,82] 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.[13,49,77,82,83]

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Multiple institutions have published studies showing correlation between tumor thickness or Breslow depth and SLN positivity, disease-free survival (DFS), DSS, and OS.[49,76,83-85] The statistical significance of these correlations varies, perhaps because primary tumor thickness may be correlated with primary tumor size.[49] 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.[66,67]

Tumor Infiltrating Lymphocytes

Several studies have found that the presence of TILs in MCC tumors was associated with improved survival outcomes.[76,85-91] Notably, a 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.[86] 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.[88-90] The CAP protocol for MCC defines TILs as lymphocytes present at the interface of the tumor and stroma, without specifying any molecular markers.[67] The categories for TILs are based on the presence and distribution of lymphocytes in the tumor sample. TILs "not identified" includes samples in which lymphocytes are present but do not infiltrate the tumor. "Nonbrisk" should be used when lymphocyte infiltration is focal or not present across the entire base of the vertical growth phase, and "brisk" should be used when lymphocytes diffusely infiltrate the entire base of the dermal tumor or the entire invasive component of the tumor.[67]

Tumor Growth Pattern

A variety of terms have been used to describe the distinct growth patterns observed in MCC tumors.[76,80,83,92-96] 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").[76,83] 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.[67] 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. Retrospective studies using these categories have found the infiltrative growth pattern to be associated with higher risk of SLN positivity or poor outcomes,[76,80,83] 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; basal cell carcinoma (BCC); melanoma; CLL; non-Hodgkin lymphomas (NHLs); lung, breast, and kidney cancers; and vice versa.[19,23,35,91,94,97-104] 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.[22,72,77] 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.[29-32,61,85,92,105-113] 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 non-melanoma skin cancers (NMSCs), nonhematologic extracutaneous cancers, and immunosuppression/pro-inflammatory comorbidities, and tend to have more metastasis, disease progression, and death from disease.[32]

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Additional Workup

For patients with biopsy-confirmed MCC, additional workup along with a multidisciplinary consultation at a center with specialized expertise may include complete skin and lymph node examination, imaging studies, and laboratory studies as clinically indicated including MCPyV and MCC circulating tumor (ctDNA) testing. If diagnosis was made with a core biopsy, consider collecting additional tumor tissue needed for tumor-informed ctDNA testing prior to immunotherapy or RT, as the original core biopsy sample may be insufficient. As immunosuppression in MCC is a risk factor for poor outcomes,[19,38,40-46,49,114] immunosuppressive treatments should be minimized as clinically feasible in consultation with the relevant treating physician. The risk for disease recurrence is higher in patients with immunosuppression[43,46,47,114,115]; therefore, more frequent follow-up may be indicated. Additionally in patients <50 years of age diagnosed with MCC, genetic counseling should be considered to evaluate for germline mutations in cancer-associated genes as they have been reported in about 20% of patients in this age group.[116]

Laboratory Testing

Several groups have explored the significance of antibodies to MCPyV in patients with MCC.[56,117-119] 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.[55] For patients who were seropositive, the oncoprotein antibody test every 3 months may be a useful component of ongoing surveillance because a rising titer can be an early indicator of recurrence.

In MCC, ctDNA is a promising minimally invasive tool for early stage multi-cancer screening and tumor development monitoring via detection of cell-free DNA fragments.[120] Disease burden in both virus-positive and virus-negative MCC can be evaluated by ctDNA testing and surveillance is commonly obtained every 3 months.[121] The ctDNA results typically become positive prior to or at the time of a clinically evident recurrence.[122] The use of ctDNA in MCC has shown high disease sensitivity and prognostic accuracy for early detection of MCC recurrence. Based on NCCN Panel expertise, it is recommended that additional tissue be harvested if a core biopsy is performed as there may be insufficient tissue remaining for a tissue-informed ctDNA test. This would negate the usefulness of ctDNA testing for continued surveillance of disease burden. Unlike traditional ctDNA testing, tissue-informed ctDNA has higher sensitivity as it utilizes a patients' tumor tissue as a baseline to indicate specific somatic mutations for assay personalization.[123] However, there are no current recommendations for treatment options following a positive ctDNA result; therefore, additional studies are required to utilize ctDNA surveillance effectively for patient care.

Imaging Studies

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,[102,124,125] CT,[102,125-129] ultrasound,[102,125,128] MRI,[124,125,128,130] scintigraphy,[131-133] and PET or PET/CT.[128,130,134-147] 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,[130] it is still the best imaging tool available for rare cases of MCC brain metastases.[148-150] A number of studies

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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.

Imaging is encouraged for staging of most MCC because occult metastatic disease that resulted in upstaging has been detected in 12% to 20% of patients presenting without suspicious H&P findings.[151] This study by Singh et al indicates that whole-body PET with fused axial imaging is more sensitive for detecting occult metastatic disease at baseline.[151] Acceptable alternative imaging modalities include 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 indicated to evaluate for in-transit metastasis for a 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 patients that have an indication of brain metastases, such as clinical symptoms, or in which widespread systemic disease has been detected.[152] Imaging may also be useful to evaluate for the possibility of a skin metastasis from a noncutaneous primary neuroendocrine carcinoma (eg, SCLC), especially in cases where CK20 is negative and/or TTF-1 is positive. It must be noted that the most reliable staging tool to identify subclinical nodal disease is sentinel lymph node biopsy (SLNB).

Computed Tomography

Only a few studies have evaluated the independent utility of CT for detection of MCC tumors.[102,125-130] 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.[127] 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 was unable to detect micrometastases as well as larger lymph node metastases, including single node positivity in six patients and multiple positive nodes in five patients.[130]

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.[128,130,134-147] 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.[140] In the only prospective study to date, FDG-PET/CT had a sensitivity of 95% and a specificity of 88%, respectively.[147] Small retrospective studies indicate that FDG-PET/CT might not be useful in detecting lymph node metastasis (compared with SLNB),[144] as well as primary tumor site in patients with unknown primary MCC.[145] 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 treatment in 6% to 37% of patients.[135-139,141-143,146,147] Most of the changes in staging and disease management were due to discovery of more extensive lymph node involvement, distant metastatic

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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%).[130] Furthermore, in some studies, FDG-PET/CT detected positive lymph nodes and distant metastases that were not detectable by CT scans.[137,138,147] In a 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).[151]

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 NMSCs or other rare malignant skin tumors.[19,32,153] Misdiagnosis is even more prevalent among MCC tumors that are admixed or adjacent to other skin tumors.[32,154]

MCC tumors visualized by H&E typically contain small round cells with sparse cytoplasm, abundant mitoses, and dense core granules in the cytoplasm.[61,93,95,124,155] 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).[156-161] 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 patients, but IHC or electron microscopy was needed to diagnose the remaining patients.[102] 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.[5,6,93,160,162-165] Neuroendocrine markers such as INSM1, chromogranin, synaptophysin, CD56, NSE, and neurofilament are found in most MCC tumors.[29,75,80,93,95,160,161,166-173] The NCCN Panel recommends that these markers be considered for additional immunostaining. 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).[96,108-110,112,113,174]

Staging and Treatment of the Primary Tumor

Surgery is the primary treatment modality for most MCC and 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 9387 patients with MCC from the NCDB with a median follow-up of 28.2 months.[12] The NCCN staging of MCC largely parallels the AJCC guidelines and divides presentation into surgically resectable local, locally

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advanced (curative surgery and RT not feasible), regional/in-transit, and disseminated disease.[66] Clinical exam, imaging, laboratory studies, a multidisciplinary consultation, immunosuppression assessment, and potentially a genetics consultation are used to make an initial determination of the clinical N-stage and M-stage. Clinical staging 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,[12,41,175-178] and these findings are reflected in the AJCC staging system.[66] However, the NCCN recommendations for pathologic evaluation of nodal status and management of the nodal basin are the same for both groups of patients. Prior to the start of primary treatment, the NCCN Panel recommends that patients receive a multidisciplinary consultation at a center with specialized expertise.

Sentinel Lymph Node Biopsy

SLNB is an important staging tool for identifying subclinical nodal metastases, which is valuable for accurate staging in addition to impacting subsequent treatment decisions.[19,50,83] Given the benefits of performing SLNB, every effort should be made to perform sentinel lymph node biopsy prior to or at the time of primary tumor excision. This is particularly important in the cases of head and neck MCC given the concern that resection and reconstruction prior to performing a SLNB may impact the accuracy of subsequent nodal basin mapping.[179]

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%.[19,46,49,94,127,180,181] As discussed in the elements of pathology report, a number of primary tumor characteristics have been proposed to be predictive of SLN positivity, including primary tumor diameter, thickness, LVI, and TILs.[49,77,83,91,182] Some studies showed significant association between SLN negativity and lower risk of recurrence and improved DSS or OS,[46,49,50,78,127,182-185] while others did not.[77,181,186] 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%.[46,50,180] Some studies have reported complicated drainage patterns for MCCs occurring in the head and neck.[187-189] Besides, multiple SLNs have been identified in some patients, suggesting that the inability to identify all relevant SLNs may contribute to the relatively high rates of false-negative SLNBs.[46,50,180]

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%).[184] 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 lymph node dissection (LND) had lower risk of all-cause mortality, and that SLNB plus LND was also associated with improved MCC-specific mortality.[41] There is insufficient information to ascertain whether these associations are due to the SLNB procedure itself or due to subsequent disease 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,[19,42] except for one report of significantly longer OS.[190]

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SLNB Pathology

IHC analysis has been shown to be effective in detecting MCC lymph node metastases not detected by H&E.[138,191-193] IHC with CK20 has been included as part of routine screening in multiple studies.[50,144,190,191,194] 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, MCPyV, and synaptophysin.[50,77,83,144,190,192,194]

Fine-Needle Aspiration

Several retrospective studies have reported that fine-needle aspiration (FNA) biopsy is an accurate method for diagnosing MCC lesions, including primary tumors and nodal and distant metastases.[195-198] One small study compared FNA results with subsequent LND results, and found that the FNA procedure identified all patients with lymph node (LN) metastases that were >6 mm, but did not consistently identify smaller foci.[196] 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 MCCs were positive for CK20, AE1/AE3, synaptophysin, NSE, and CD56.[195,197,198] Chromogranin staining was present in a smaller proportion of patient samples (36%).[197,198] Markers for melanoma (ie, S100, HMB45, Melan A, CD45) or lymphoma (leukocyte common antigen) were nearly always negative.[195,197,198]

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 nonsurgical primary treatment.[42,199] 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.[19,21,42,48,190,200-209] Whereas there are a number of retrospective studies that found that negative margin status was associated with improved local recurrence and survival,[21,22,42,68,203,205,210-212] other analyses did not consistently find such associations.[17,71-74,137,213-217] There is evidence that margin status has an impact on survival regardless of adjuvant RT receipt.[212] Among cases with stage I/II disease treated with surgery only, recurrence rates and OS were better for negative versus positive margins.[205] 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.[179,218]

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.[203,204,206] In many studies, Mohs and wide local excision (WLE) resulted in similar rates of recurrence and survival.[19,201,204,205,208] 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.[207] Among those treated with WLE, 2-cm and 3-cm clinical margins resulted in incomplete excision in 50% and 0% of patients, respectively.[219] For patients with histologically clear margins, retrospective data suggest a trend toward reduced risk of

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recurrence for patients with histologic margins >1 cm versus <1 cm.[21,190,220] However, those who received adjuvant RT and had margins <1 cm had similar OS to those who did not receive adjuvant RT and had margins >1 cm.[220] There are data supporting excision margins >2 cm as being significantly associated with higher OS,[220,221] while some studies contend that increasing histologic margin size beyond 1 cm is not associated with additional clinical benefit.[69,190,200]

In addition to Mohs, other forms of peripheral and deep en face margin assessment (PDEMA) are appropriate surgical approaches in certain circumstances. PDEMA, or complete margin assessment, is a term used for a subset of surgical techniques for high-quality histologic visualization and interpretation of the margin surface or surgically excised tissue. Mohs micrographic surgery is the most common utilized PDEMA technique. PDEMA is a team procedure that requires the participation of physicians from multiple disciplines while Mohs physicians serve as both surgeon and pathologist, requiring highly specialized training. Efforts have been extended to generate consensus recommendations to offer Mohs surgeons guidance and promote standardization to make data aggregate from multicenter clinical trials.[222]

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Radiation Therapy for Primary Tumor Site

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.[223,224] There are a large number of retrospective studies that include very small samples of patients (N < 10) who received definitive RT instead of surgery.[17,22,42,71,153,175,214,215,217,225-233] Patients whose disease 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.[42,199] 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; $P < .001$).[199] However, the patient population where MCC was 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%; $P < .0001$).[13] Retrospective studies of MCC treated with definitive RT to their primary and/or nodal MCC reported in-field recurrence rates of <25%, with median time to in-field recurrence ranging from 4 to 6.3 months.[21,234-239] 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%; $P = .02$).[232]

The NCCN Panel generally recommends that RT be initiated as soon as wound healing permits as delays >7 to 8 weeks have been associated with poorer outcomes.[240,241] Due to the limited data available for MCC, the Panel's recommendations for RT dosing are based on clinical practice at their institutions and clinical evidence from studies of various skin cancers. These recommendations are separated into adjuvant, definitive, and palliative RT with dosing for conventional fractionation and hypofractionation.[242] Hypofractionation consists of a higher dose of radiation per fraction leading to overall

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fewer fractions and a shorter time frame for treatment. While hypofractionation is useful for certain patients, it should be avoided in patients with higher risk disease as there is limited data available. Additionally, when treating MCC with intensity-modulated RT (IMRT), proton beam RT, or 3D conformal RT, it is considered best practice to use image-guided RT (IGRT). IGRT for other types of radiation techniques used to treat MCC is considered unnecessary. The NCCN Panel also recommends that a practicing radiation oncologist with radiation physics support utilizes a bolus over the primary tumor and a surface dosimeter to confirm the dose delivered to the site of treatment.

For RT to the primary tumor site, when clinically feasible due to anatomic constraints, wide margins (5 cm) should be used. These margins may need to be diminished due to closeness to critical structures such as the eye or mouth. Consideration should also be given, if using an electron beam, to ensure delivery of an adequate dose to the lateral and deep margins during selection of energy and prescription isodose. Generally, patients with ≥1 risk factors for local recurrence are considered for adjuvant RT. Included in these risk factors are LVI, immunosuppression, primary tumor >1 cm, close or pathologically positive margins, positive SLNB, or primary tumor site on head or neck.

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Clinical N0: Local MCC Only, Surgically Resectable

The disease management plan for primary MCC tumors that are surgically resectable is dictated by the state of the surgical margins and the presence of adverse 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.[19,22,38,40-47,49,72,75-78,114,243] These are risk factors of particular concern because they are highly associated with poor outcomes. Mohs micrographic surgery (Mohs) and PDEMA are methods for surgical excision of the primary tumor, using margins similar to WLE (See NCCN Guidelines for Squamous Cell Skin Cancer – Principles of PDEMA Technique, available at www.NCCN.org). These alternative methods ensure complete tumor removal and clear margins, while sparing surrounding healthy tissue. Regardless of the surgical technique used, the goal should be primary tissue closure to avoid any undue delay in proceeding with RT and allow for initiation of adjuvant RT.[241] Prior to the start of primary treatment, it is recommended that patients receive a multidisciplinary consultation at a center with specialized expertise.

Primary treatment for patients that are deemed surgically resectable include excision with 1 to 2 cm margins,[241] or in certain circumstances Mohs or others forms of PDEMA, as well as SLNB with an appropriate immunopanel. Because of the high historic risk of local recurrence in MCC, there is emphasis on a complete extirpation of tumor at the time of initial resection to achieve histologically clear surgical margins when clinically feasible.[68,179,244] If clear margins are achieved, observation is recommended if there are no adverse risk factors; however, if one or more adverse risk factors are detected, adjuvant radiation therapy is recommended as an additional treatment.[241] In the case of microscopically positive margins, adjuvant RT is preferred along with or over re-excision. If adjuvant RT is planned and there are any adverse risk factors present, narrower clinical margins should be considered with the goal of obtaining clear or microscopically positive margins and minimize morbidity.[241] Surgical margins should be balanced with morbidity of surgery.

In addition to surgical resection, primary treatment also includes SLNB with an appropriate immunopanel. The preferred additional treatment for patients with negative SLN is continued observation of the nodal basin. RT to the nodal basin may be considered in certain high-risk scenarios, such as a

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compromised SLNB result, high probability of false-negative SLN due to aberrant lymph node drainage or multiple SLN basins, or profound immunosuppression. Appropriateness of RT should be determined together with a radiation oncologist. If the SLNB is positive, baseline imaging should be performed, if not previously performed. Imaging may include whole-body FDG-PET/CT, which is preferred at initial workup or CT with contrast of chest, abdomen, pelvis, and neck if the primary tumor is on the head/neck. Additionally, MRI of the brain with and without contrast is recommended if there is clinical suspicion of brain metastases or direct extension. Following imaging, additional treatments include RT to the nodal basin or node dissection.[245] If node dissection is performed, the patient can be observed for disease progression or subsequent adjuvant RT can be applied for multiple involved nodes and/or the presence of extranodal extension (ENE).

Clinical N0: Locally Advanced MCC When Curative Surgery and Adjuvant RT Are not Feasible

A multidisciplinary consultation at a specialized center is recommended for locally advanced Merkel cell carcinoma (laMCC) patients for whom curative surgery and curative RT is not feasible prior to deciding on a primary treatment path. After a multidisciplinary discussion, the favored treatment option includes neoadjuvant immunotherapy with an anti- programmed cell death protein 1 (PD-1) agent *(see Systemic Therapy for Merkel Cell Carcinoma)* for patients who are surgical candidates. If adequate treatment response is observed, patients become eligible for the primary and additional treatment options for patients with surgically resectable local MCC. On the other hand, if there is disease progression while being treated with neoadjuvant nivolumab, the treating physician should discuss options of RT or surgery for local control versus additional systemic therapies. Patients that are considered nonsurgical candidates due to comorbidities or tumor characteristics, also require a discussion regarding the advantages and disadvantages of treatment with RT for durable local control versus systemic therapy.

Nodal Staging and Treatment of Regional Disease

Management of the Primary Tumor for Regional Disease

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 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[246]). The primary tumor can be treated as clinical N0 and follow the resectable local MCC or laMCC pathways including SLNB after initial recommended imaging studies to evaluate the extent of lymph node and/or visceral organ involvement. Subsequently, there are separate recommendations for the management of the draining nodal basin and in-transit disease; however, these treatment options can both be considered for appropriate patients. As with other stages, whenever possible a multidisciplinary consultation at the specialized center is recommended to determine the optimal treatment selection.

Management of the Draining Nodal Basin

A clinical N+ diagnosis (palpable lymph nodes) should be confirmed by using FNA or core biopsy of the draining nodal basin with an appropriate immunopanel. An excisional biopsy may be considered to confirm a negative initial FNA or core lymph node biopsy if clinical suspicion remains high.

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Alternatively, patients with negative results can also continue radiographic surveillance. If initial or subsequent lymph node biopsy results are positive and distant metastasis is detected, disease management should follow the M1 pathway. In case of no detected distant metastases, node dissection and RT (preferred), node dissection or RT, clinical trial, and consideration for systemic therapy are recommended treatment options. The node dissection and RT treatment option is preferred and enrollment in a clinical trial for adjuvant therapy is preferred, if available.

IHC analysis should be included in the SLNB evaluation in addition to H&E sections to reduce the 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 ENE.

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.

Adjuvant systemic therapy should be considered for certain patients with regional disease as part of a multidisciplinary consultation. For patients with primary or recurrent regional MCC where curative surgery and curative RT is not feasible, adjuvant systemic therapy similar to the options available to individuals with disseminated disease is considered and treatment in the context of a clinical trial is preferred, when available.

Management of In-transit Disease

The AJCC 8th edition staging system defines MCC in-transit lesions as discontinuous from primary tumor, located between the primary tumor and the draining regional nodal basin or distal to the primary tumor site.[12,66] The in-transit disease pathway delineates alternative treatment options when compared to regionally nodal positive MCC. For management of in-transit disease, diagnosis confirmation with biopsy is recommended. Following confirmation, treatment options for in-transit disease include clinical trials, surgery, radiation treatment, as well as systemic therapy, and additional local considerations if curative surgery and/or RT are not feasible. Systemic therapy options for in-transit disease were expanded to mimic the regimens previously only available for primary or recurrent regional N+ and metastatic disease. The additional considerations include T-VEC (intralesional talimogene laherparepvec) and hyperthermic isolated limb infusion/perfusion, which are considered regimens useful in certain circumstances. These treatment options are discussed in the *Systemic Therapy for Merkel Cell Carcinoma* section within this discussion. While the Panel has made these general treatment recommendations for in-transit disease, it is important to note that due to the lack of high quality peer-reviewed primary literature, these recommendations are based on expert opinion.[247-250] This lack of large studies has led to individualized treatment decisions with the input of a multidisciplinary team at a high-volume treatment center.

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Surgery Versus Radiation Therapy for Regional Disease

Since the presence of MCC in the lymph nodes is associated with poorer prognosis,[12,18,79,185,203,251] 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, 11.8–28.5 months; $P = .034$), as did RT to the nodal basin (median, 11.3–46.2 months; $P = .01$).[213] 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%; $P < .01$).[127]

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.[21,68,77,175,199,225,230,252,253] 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; $P < .001$).[199] In contrast, Bhatia et al found no significant difference in OS for surgery alone compared with RT alone or surgery plus RT.[68] Furthermore, while some studies suggest that nodal surgery may improve outcomes,[48,252-254] a few found that patients who received nodal RT alone fared better,[18,21] and others found no clear trends according to nodal treatment.[18,77,175,225,230,255] Perez et al and Lee et al, retrospectively, evaluated outcomes for MCC 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.[256,257]

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,[12,22,49,72] increasing number of nodes involved,[13,17,68,79,82,181,215,228,239,258,259] and the presence of ECE[84,181,228]). These findings suggest that the aggressiveness of nodal treatment should perhaps be commensurate with the extent of nodal disease. 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.[260]

Postoperative Radiation for Locoregional Disease

Many studies have found that postoperative RT is associated with lower recurrence and/or improved survival compared with surgery alone.[21,68,179,201,217,243,261-265] 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.[17,19,46,72,266-268] 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 MCCs, 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.

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Overall, studies reporting results specifically for patients with stage I/II disease agree that adjuvant RT to the primary tumor significantly reduced locoregional recurrence,[15,207,264,269-271] while many also reported improvements in survival.[68,204,205,217,263,269] Kang et al examined 42 patients with 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%; $P < .001$).[269] Of note, three large studies using NCDB data (N > 1000 patients with stage I/II MCC) concluded that surgery plus RT or conformal RT (CRT) led to significantly better survival results compared to surgery alone.[68,204,205] Even though benefit has been noted for low-risk stage I MCC,[264,270] local MCC with high-risk features might have the most to gain from adjuvant RT.[21,243,262,267,272] Particularly, a study of 1858 patients with stage I/II MCC 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 ($P = .478$).[263]

Regarding the clinical benefit of adjuvant RT for patients with node-positive versus node-negative MCC, results vary widely between studies.[17,21,46,48,50,68,69,72,73,127,217,243,256,266,273-275] Some studies showed that postoperative RT was associated with improved survival in patients with stage I/II disease, but not for stage III disease.[68,217] 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 patients with negative nodes.[243] In other studies, nodal RT in patients with positive SLNB significantly reduced 3-year relapse-free survival rate (51% vs. 0%; $P < .01$),[127] as well as 3-year regional control (95% vs. 66.7%; $P = .008$).[276] A large study using NCDB data (N = 447) of patients with SLNB-positive MCC reported that compared with completion lymph node dissection (CLND), observation, or RT alone, CLND and adjuvant RT were associated with better OS.[275] Several studies pointed out that the utility of adjuvant RT might be extended to patients with negative nodes.[21,50,69,73,273,276] Of note, tumor-bed irradiation was significantly associated with prolonged DFS ($P = .006$) and OS ($P = .014$) in patients with negative SLNB.[50] In another study, RT to regional nodes was associated with improved regional control, irrespective of clinical status ($P = .01$).[73] Overall, studies have both supported[21] and refuted[266] the effectiveness of nodal RT in reducing nodal relapse in node-negative patients.

As with primary tumor site, draining nodal basin is separated into adjuvant, definitive, and palliative RT with dosing for conventional fractionation and hypofractionation.[242] Unless noted, Panel's recommendations for RT dosing are based on clinical practice at their institutions and clinical evidence from studies of various skin cancers. While hypofractionation is useful for certain patients, it should be avoided in patients with higher risk disease as there is limited data available. Irradiation of in-transit lymphatics is recommended only when the primary site is in close proximity to the nodal bed. Empiric RT to the nodal basin can be considered in patients with certain high-risk clinical scenarios: 1) the accuracy or reliability of SLNB may have been compromised (eg, prior surgery, extensive CLL within the nodes, history of prior LN excision); 2) the risk of false-negative SLNB is high due to aberrant lymph node drainage and presence of multiple SLN basins (such as in head and neck or midline trunk MCC); or 3) patients present with profound immunosuppression.

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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.[16,72,101,102,138,277-279] 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) at a center with specialized expertise. Comprehensive imaging is recommended for all patients with any clinically detected and pathologically proven regional or distant metastases. In general, the treatment of 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 (see *Systemic Therapy for Merkel Cell Carcinoma* section). 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 patient-specific circumstances, palliative care alone may be the most appropriate option for some patients (See NCCN Guidelines for Palliative Care, available at www.NCCN.org).

Systemic Therapy for Merkel Cell Carcinoma

Immunotherapy

Results from clinical trials, case, retrospective, and prospective studies support the use of avelumab, ipilimumab, ipilimumab/nivolumab, nivolumab, pembrolizumab, retifanlimab-dlwr, and local therapy talimogene laherparepvec (T-VEC) for the treatment of certain patients with local, regional, or disseminated disease. Although there are no randomized comparative trials comparing immune checkpoint inhibitors (ICIs) and chemotherapy, ICIs provide response rates similar to those previously reported for chemotherapy and may provide greater durability of response.

Avelumab

Two retrospective multi-institutional studies assessed treatment outcomes for avelumab in MCC. Advanced stage (IIIB/IV) avelumab-treated MCC was studied in 90 patients in six U.S. academic medical centers.[280] A median follow-up of 20.8 months (95% CI, 19.1–24.2) and median duration of treatment of 13.5 months (95% CI, 6.4–30.6) were achieved. Patients treated with avelumab had a 73% (95% CI, 64–83) objective response rate (ORR), 24.4 month (95% CI, 8.31–not estimable [NE]) median progression-free survival (PFS), and 30.7 month (95% CI, 11.2–NE) median OS.[280]

SPEAR-Merkel was an additional retrospective observational study of metastatic MCC (mMCC) and laMCC response to first-line avelumab treatment that included selected patients treated by the US Oncology Network from 2017 to 2019.[281] For mMCC (N = 19) median OS was 20.2 months (95% CI, 10.0–not reached [NR]), PFS was 10 months (95% CI, 2.8–NR), and 63.2% (95% CI, 38.4%–83.7%) response rate. Median OS and PFS were not reached in the laMCC (N = 9) group; however, a response rate of 66.7% (95% CI, 29.9–92.5) was recorded.[281]

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The JAVELIN Merkel 200 trial, is an open-label multicenter prospective clinical trial testing avelumab in patients with histologically confirmed and measurable stage IV distant MCC.[282-288] The cohort of patients in Part A of the trial had mMCC, which progressed after more than 1 prior line of chemotherapy (N = 88), with a median follow-up of 65.1 months (range, 60.8–74.1 months), median OS was 12.6 months (95% CI, 7.5–17.1), and with a 5-year OS rate of 26% (95% CI, 17–36).[285] The Part B cohort was treated with avelumab as first-line therapy (N = 116), the median follow-up was 21.2 months (range, 14.9–36.6), the ORR was 39.7% (95% CI, 30.7–49.2), median PFS was 4.1 months (95% CI, 1.4–6.1), and median OS was 20.3 months (95% CI, 12.4–NE).[287] A 2022 update to the part B cohort reported a median follow-up of 54.3 months (range, 48.0–69.7) as well as a 4-year OS rate of 38% (95% CI, 29–47), where programmed death ligand 1 (PD-L1) positive tumor median OS was 38.7 months (N = 21; 95% CI, 11.3–NE) and 16.1 months (N = 87; 95% CI, 9.6–42) for PD-L1 negative tumors.[288]

Ipilimumab ± Nivolumab

Ipilimumab, a cytotoxic T lymphocyte antigen-4 (CTLA-4) targeted antibody, has been evaluated as a monotherapy as well as in combination with nivolumab, an anti- PD-1 inhibitor.[121] A small retrospective study (N = 5) conducted in Germany, where systemic therapy in 2021 was limited to avelumab, treated avelumab-refractory disease with combination ipilimumab plus nivolumab.[289] Combination therapy was tolerated well with no grade 2 or 3 treatment-related adverse events (TRAEs). Patients with refractory disease experienced a high response rate and durable response in this and other studies.[289,290]

In a randomized, open label, phase II trial, two cohorts of combined nivolumab plus ipilimumab with or without stereotactic body radiotherapy (SBRT), cohort A and B respectively, were evaluated for ORR.[291] Of the 50 patients enrolled in the trial, 24 had not previously taken ICIs. Overall patients had a median follow-up of 14.6 months. All of the patients with no ICI exposure (N = 22; 95% CI, 82–100) had an objective response, including a complete response in nine patients (41%; 95% CI, 21–63). Of the 26 patients with previous ICI exposure, eight (31%; 95% CI, 15–52) had an objective response and four (15%; 95% CI, 5–36) had a complete response. No significant differences in ORR were observed between both cohorts of patients with or without SBRT (*P* = 0.26). These results indicate that the addition of SBRT did not improve the efficacy of ipilimumab plus nivolumab. Grade 3 or 4 TRAEs were observed in 10 (40%) cohort A and 8 (32%) of cohort B patients.

Ipilimumab with or without nivolumab was studied in a nonrandomized, open label, multicenter phase I/II trial for 68 patients with recurrent or metastatic MCC.[292] Patients were treated with nivolumab (N = 25) or nivolumab plus ipilimumab (N = 43) with an observed ORR and median DOR of 60% and 60.6 months with nivolumab and 58% and 25.9 months with nivolumab plus ipilimumab, respectively. Additionally, the median PFS was 21.3 months for nivolumab and 8.4 months for the combination regimen. The OS for nivolumab and nivolumab plus ipilimumab was 80.7 and 29.8 months, respectively. The TRAE incidence was higher for the combination than the monotherapy (47% vs. 28%).

Nivolumab

Nivolumab in the neoadjuvant setting was studied in the Checkmate 358 phase I/II trial that included 39 patients with resectable MCC stage IIA–IV who had received ≥1 doses of nivolumab.[293] Among 36 patients who underwent surgery, 47.2% (N = 17) achieved a pathologic complete response (pCR). In

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54.5% (N = 18) of 33 radiographically evaluable patients who underwent surgery, 54.5% had tumor reductions of ≥30%. The median follow-up for this cohort was 20.3 months (range, 0.5–39.7); however, median recurrence-free survival and OS were not reached in this study.[293]

In a non-comparative, open label, multicohort phase I/II trial, the efficacy and safety of nivolumab monotherapy was evaluated (N = 25) where an overall follow-up of 26 weeks was observed.[294] Response assessment was completed in 22 patients of which 14 were treatment-naïve and eight had treatment with one to two prior systemic therapies. ORR in patients who were treatment-naïve was 71% (95% CI, 42–92) and 63% (95% CI, 25–92) in the group of patients with previously treated disease. The treatment-naïve group had a higher percentage of patients with a complete response and stable disease than the previously treated group (CR, 21% vs. 0%; SD, 21% vs. 13%). On the other hand, the treatment-naïve group had lower partial response and progressive disease (PR, 50% vs. 63%; SD, 7% vs. 25%). This data supports the addition of nivolumab monotherapy as a systemic therapy option for certain patients with advanced MCC.

Pembrolizumab

A phase II, single-arm multicenter trial tested pembrolizumab in patients with distant metastatic or locoregional MCC not amenable to definitive surgery or RT with no prior MCC systemic therapy treatment (N = 50).[295-297] After a median follow-up of 31.8 months (range, 0.4–56.9), the ORR was 58% (95% CI, 43.2–71.8) with a 30% complete response (N = 15; 95% CI, 17.9–44.6) and 28% partial response (N = 14; 95% CI, 16.2–42.5).[297] For this study, the median PFS was 16.8 months (95% CI, 4.6–43.4) and the 3-year estimated PFS was 39.1%.[297] While the median OS was not reached, and the OS for all participants at 3-years was 59.4% and 89.5% for patients with responsive disease (complete and partial response).[297]

Retifanlimab-dlwr

POD1UM-201 is an open-label, single-arm, multicenter, phase II trial for patients with unresectable laMCC or mMCC.[298] This study tested retifanlimab-dlwr in patients with chemotherapy-naïve or chemotherapy-refractory disease and had no prior therapy with anti-PD-1/L1 regimens. Current data is available for the chemotherapy-naïve group (N = 87) of which the first 65 patients were assessed with an ORR of 46.2% (N = 30) with 12.3% (N = 8) complete response and 33.8% (N = 22) partial response. Additionally, the disease control rate for the group assessed was 53.8% (N = 35).

Talimogene laherparepvec

T-VEC is a modified oncolytic herpes simplex virus that promotes an antitumor response. Treatment with T-VEC as a local therapy was approved by the U.S. Food and Drug Administration (FDA) for treatment of advanced melanoma.[299] In a phase III study, intralesional T-VEC injection had superior durable and overall response rates in patients with advanced melanoma.[300] The clinical benefit of T-VEC in patients with advanced MCC has been presented in case reports or series.[301-303] These patients reported complete response with intralesional T-VEC use with limited toxicities and present a compelling argument in patients with anti-PD-1/L1 refractory MCC or for individuals with contraindications to receiving other immunotherapies

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

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seen in <20% of patients receiving avelumab, and were all grade 1 or 2.[282-287,293,295-297] 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 were not represented in initial trials; however, the infection does appear to respond to PD1 pathway blockade at a rate (two of three patients in one series) that is similar to patients without immune compromise.[304] 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[299] (See NCCN Guidelines for Management of Immune Checkpoint Inhibitor-Related Toxicities, available at www.NCCN.org).

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.[234,277,305-309] In analyses with >20 patients, reported 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.[234,277,305-311] Reported responses to chemotherapy were fairly short-lived, with a median duration ranging from approximately 2 to 9 months.[234,277,306-310] Reported rates of toxic death were between 3% and 10%, with patients who are older being at higher risk.[234,277,306]

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.[41,68,73,203,267,306,312-314] Two studies found that adjuvant chemotherapy was associated with worse survival.[17,313] Several studies found that postoperative chemoradiation did not improve outcomes compared with postoperative RT.[48,203,267] 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.[314] A large NCDB study (N = 4815) found that, relative to surgery alone, postoperative chemoradiation improved OS but postoperative chemotherapy (without RT) had the opposite effect.[203] 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).[203] These results suggest that although postoperative chemotherapy alone is unlikely to improve outcomes, postoperative chemoradiation may have a role in particularly high-risk MCCs 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[17,48,226,267,313,314]; however, information about the agents used was not available from the NCDB analysis that showed that postoperative chemotherapy may provide clinical benefit in certain patients with high-risk disease.[203]

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Alternative Therapies

Hyperthermic Isolated Limb Infusion/Perfusion

While established as a regional therapy in melanoma, hyperthermic isolated limb perfusion (HILP) as a MCC treatment option is not as extensively studied. In a single institution retrospective review of 10 studies over 6 years, an initial group of four patients treated with HILP were identified.[315] All patients experienced complete response, however two of the patients developed early metastatic recurrence and the other two had no evidence of disease at the last 36-month follow-up. An additional group of 12 patients treated with HILP were identified through systemic review. Twelve (86%) of the patients with follow-up had a complete response while one had stable disease and another partial response. Within 6 months, four patients presented with locoregional recurrence and a further six had distant metastases. Despite the development of distant metastases, HILP presents a viable treatment option to achieve complete response.

Octreotide

Octreotide is a somatostatin analog (SSA) used as a treatment option in neuroendocrine tumors (NET), such as MCC, that express the somatostatin receptor (SSTR). In a multicenter phase II study (N = 58), octreotide demonstrated poor tumor regression with a 3% partial response; however, the disease was stabilized for at least 6 months in 47% of patients (N = 27).[316] A retrospective study in patients with mMCC included 39 patients whose MCC expressed SSTR and a subset (N = 19) were treated with an SSA.[317] From the SSA group, only seven had a target lesion from which a response could be evaluated and 43% (N = 3) experienced disease control with a median PFS of 237 days. Of the remaining 12 individuals in the SSA group, 42% (N = 5) also experienced disease control with a median PFS of 429 days. As metastatic MCC commonly expresses SSTRs, octreotide can lead to significant disease control.

Pazopanib

Pazopanib is a tyrosine kinase inhibitor approved for the treatment of advanced renal cell carcinoma and soft tissue sarcoma with prior chemotherapy treatment.[299] It is not currently approved by the FDA for use in MCC; however, it does show promise as a treatment option for certain patients with advanced MCC in case reports and institutional database analyses.[318,319] In a case study (N = 5), patients with mMCC were treated with pazopanib (N = 4) or cabozantinib (N = 1) and one pazopanib recipient had a complete response after 3 months.[319] Four patients experienced a 5 month to 3.5 year disease stabilization. Overall patients did not experience any unusual toxicities. These results support the use of pazopanib in certain patients with disseminated disease.

NCCN Systemic Therapy Recommendations

In-transit Disease

After a multidisciplinary consultation at a center with specialized expertise, systemic therapy may be considered if curative surgery and/or RT are not feasible. The NCCN Panel recommendation is that both T-VEC and HILP can be considered and may be useful in certain circumstances.

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Local Disease

Adjuvant systemic therapy is not recommended outside of a clinical trial for primary resectable disease. However, systemic therapies are recommended for primary and recurrent locally advanced MCC if curative surgery and curative RT are not feasible. The NCCN Panel considers all regimens for local disease as category 2A where there is uniform NCCN consensus that the intervention is appropriate based on lower-level evidence. For primary laMCC, avelumab and pembrolizumab are preferred regimens, retifanlimab-dlwr is classified as other recommended regimen, and neoadjuvant nivolumab as useful in patients who are surgical candidates. For recurrent laMCC, the preferred regimens are pembrolizumab and retifanlimab-dlwr while avelumab is recommended as other recommended regimen.

Regional and Disseminated Disease

Neoadjuvant nivolumab is a NCCN category 2A regimen recommended in certain circumstances for patients with primary regional MCC disease. Primary and recurrent regional disease where curative surgery and curative RT are not feasible along with metastatic disease have four preferred regimens recommended as treatment options. These preferred category 2A regimens are avelumab, nivolumab, pembrolizumab, and retifanlimab-dlwr. Ipilimumab plus nivolumab is also a category 2A regimen, however it is only recommended under certain circumstances.

Other useful in certain circumstances regimens are recommended for consideration if anti-PD-L1 or anti-PD-1 therapy is contraindicated or the disease has progressed on monotherapy regimens. Topotecan, CAV (cyclophosphamide, doxorubicin [or epirubicin], and vincristine), ipilimumab, octreotide long-acting release (LAR), pazopanib, and T-VEC are recommended under these conditions for primary/recurrent regional and disseminated disease. Octreotide LAR, pazopanib, and T-VEC are considered category 2B regimens for disseminated disease, but all other regimens are category 2A for all three settings. Carboplatin or cisplatin with or without etoposide are only recommended regimens for recurrent regional or disseminated disease.

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Follow-up and Recurrence

Recurrence and development of lymph node and distant metastases in MCC are not uncommon.[14-19,84,226,320] 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.[17,18,48,138] Time to local recurrence is generally shorter than for regional recurrence, and time to distant metastasis is longer.[16,17,19,225] Due to the fast-growing nature of the disease, detection of multiple distant metastases at once is not uncommon.[125] 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.[23,35,97-100]

Multiple retrospective analyses,[71,73,93,239,252,312] data from a phase II study,[314] and a few meta-analyses[232,321,322] have shown that recurrence of MCC is associated with poor prognosis. Collectively, these studies support that locoregional recurrence is associated with the 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 found no significant association between recurrence and outcome measures including survival.[48,214,235,238,239,255]

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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 recommendation for frequent clinical exams during the first 3 years also reflects 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 and other 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. As patients with immunosuppression are at higher 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.[55,117-119] Patients who are oncoprotein antibody seronegative at diagnosis may be at higher risk of recurrence and may benefit from more intensive surveillance.[55] 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.[55] Additionally, MCC ctDNA assessment is an option if the treating physician considers it clinically relevant to monitor disease burden with a typical surveillance of every 3 months. [122]

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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,[125] CT,[125,126,136] and FDG-PET/CT.[128,134-136,138,142,143,146,323] 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.[126,134,135] 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 retrospective study of 61 patients with stage III MC 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.[323]

For disease features considered of higher risk (eg, stage IIIB or higher, immunosuppression), routine imaging surveillance 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. Surveillance imaging is typically via diagnostic CT of chest/abdomen/pelvis with oral and IV contrast; neck CT is often included if the primary lesion was on the head/neck. Whole-body FDG-PET/CT may be indicated to evaluate for in-transit metastases if the primary lesion is on the extremity.

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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 MCC treated for recurrence.[48,69,73,214,232,238,239,251,261,313,314] 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.[313] 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.[251]

Management of MCC with local, locally advanced, regional, or disseminated recurrence is similar to 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 patient-specific circumstances, palliative care alone may be the most appropriate option for some patients (See NCCN Guidelines for Palliative Care, available at www.NCCN.org). For recurrence of in-transit disease, the Panel recommends treating the patient as a Clinical N+ in-transit disease where a multidisciplinary consultation at an experienced center is encouraged and clinical trials, surgery, radiation, or certain systemic therapies may be considered as additional treatment.

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