National Comprehensive Cancer Network®

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Merkel Cell Carcinoma

Version 1.2023 — April 10, 2023

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Merkel Cell Carcinoma

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Þ Internal medicine
† Medical oncology
ζ Otolaryngology
≠ Pathology/Dermatopathology
§ Radiotherapy/Radiation oncology
Ÿ Reconstructive surgery
¶ Surgery/Surgical oncology
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Clinical Trials: NCCN believes that the best management for any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

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

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

See NCCN Categories of Evidence and Consensus.

NCCN Categories of Preference: All recommendations are considered appropriate.

See NCCN Categories of Preference.

Updates in Version 1.2023 of the NCCN Guidelines for Merkel Cell Carcinoma from Version 2.2022 include:

MCC-1
- Preliminary Workup:
  - Bullet removed: Complete skin examination.
  - New bullet added: H&P.
- Additional Workup, bullet removed: H&P.
- Clinical Findings:
  - Following Clinical N0, option revised: Primary and ~~Adjuvant~~ *Additional* Treatment.
  - Following Clinical N+, options revised: Primary and ~~Adjuvant~~ *Additional* Treatment*: Management of Primary Tumor (MCC-2), Management of the Draining Nodal Basin (MCC-3)*
- Footnote removed: For more information, see American Academy of Dermatology Association: https://www.aad.org/public/diseases/skin-cancer/merkel-cell-carcinoma.
- Footnote b revised: Imaging is encouraged ~~in~~ *for staging of* most cases of MCC~~. Imaging is indicated whenever metastatic or unresectable disease is suspected based on H&P findings as. O~~occult metastatic disease ~~that resulted~~ 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). ~~Whole-body PET with fused axial imaging (CT or MR) or chest/abdomen/pelvis CT with contrast, with neck CT if primary tumor on head/neck or brain MRI if clinical suspicion, may be useful to identify and quantify regional and distant metastases.~~ Several studies indicate whole-body PET with fused axial imaging is more sensitive for detecting occult metastatic disease at baseline; *however, CT with contrast of chest/abdomen/pelvis (and neck/brain if clinical suspicion) 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. 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). (Also pages, MCC-2A, MCC-3, and MCC-5)

MCC-2
- Significant changes made to this section.

MCC-2A
- Footnotes updated.

MCC-3
- Header removed: Primary and Adjuvant Treatment of Clinical N+ Disease.
- Headers added to page: Clinical N+ Disease, Workup, Primary Treatment, Clinical Findings, Additional Treatment, Follow-up.
- Additional Treatment:
  - Following M0:
    - ◊ Second bullet revised: Node dissection ~~and/or~~ + RT *(preferred)*
    - ◊ New bullet added: Node dissection or RT
  - Following M1, option revised: Treatment of ~~Clinical~~ M1 Disease (MCC-4).
- New footnote j added: Appropriateness of RT should be performed by a radiation oncologist. (Also pages MCC-4 and MCC-5)
- Footnote o revised: An ~~open~~ *excisional* biopsy may be considered to confirm a negative initial FNA or core ~~lymph node~~ LN biopsy if clinical suspicion remains high.

Continued

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Updates in Version 1.2023 of the NCCN Guidelines for Merkel Cell Carcinoma from Version 2.2022 include:

MCC-4
- Headers added: Metastatic M1 Disease, Follow-up
- Header revised: Treatment of ~~Clinical~~ M1 Disease.
- First option revised: ~~Clinical~~ M1 ~~(~~Disseminated MCC~~)~~.

MCC-5
- Follow-up, second bullet, first sub-bullet revised: ~~Consider~~ *Recommend* routine imaging *surveillance* for patients at high-risk.
- Treatment, following Disseminated, option revised: ~~Clinical~~ *Treatment of* M1 *Disease* (MCC-4).

MCC-A
- Bullets revised:
  - Fifth bullet: . . . 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]*, chromogranin, CD56, or neuron-specific enolase [NSE]), and/or Merkel cell polyomavirus *MCPyV)* T antigen (CM2B4) stains may be employed.
  - Sixth bullet: SLNB evaluation for metastatic MCC requires ~~complete~~ microscopic evaluation of the *entire* SLN(s). Before determining SLNB negativity,
  - multiple levels (recommend at least 2) including H&E and at least one immunohistochemistry stain should be used to help evaluate for
  - metastatic disease. SLNB reporting should also include the number of ~~lymph nodes~~ LN(s) involved, size of largest metastatic deposit (mm),
  - and the presence/absence of *ECE*.
- Bullet removed: For equivocal lesions, consider additional immunostaining with neuroendocrine markers such as chromogranin, synaptophysin, CD56, NSE, and neurofilament.
- Reference 1 added: 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.

MCC-B 1 of 2
- General Treatment Information - Primary MCC Tumor Site:
  - Treatment Information, sub-bullet revised: Bolus is used to achieve adequate skin dose. Wide margins (5 cm) should be used~~, if possible,~~ around the primary site, *when clinically feasible with consideration given to anatomic constraints...*
  - General Dosing Prescription, second sub-bullet: In the palliative setting, a wide range of fractionation schedules may be used, including less protracted fractionation schedules such as 30 Gy in 10 fractions, 20 Gy in 4 or 5 fractions, or 8 Gy in 1 fraction. *These schedules are under a clinical trial for curative intent.*
- Table heading revised: ~~Dose Recommendations~~ *RT Dosing.* (Also page MCC-B 2 of 2).

MCC-B (2 of 2)
- Table heading added: Node Dissection Status.

Continued

Updates in Version 1.2023 of the NCCN Guidelines for Merkel Cell Carcinoma from Version 2.2022 include:

MCC-D (1 of 3)

- Local Disease N0, Recurrent locally advanced, new bullet added: Other recommended regimen.
  - New sub-bullet added: Retifanlimab-dlwr if patient is not amenable to surgery or RT.
- Regional Disease N+:
  - Third bullet revised: ~~Options u~~Useful in certain circumstances *as clinical judgment dictates.*
  - Fourth bullet revised: ~~For r~~*R*ecurrent regional disease~~,~~*:* ~~consider pembrolizumab. If curative surgery and curative RT are not feasible.~~
    - New sub-bullets added:
      - Consider pembrolizumab if curative surgery and curative RT are not feasible.
      - Other recommended regimen.
        - New tertiary bullet added: Retifanlimab-dlwr if patient is not amenable to surgery or RT.
- Footnote a revised: When available and clinically appropriate, enrollment in a clinical trial is recommended. ~~The literature is not directive regarding the specific chemotherapeutic agent(s) offering superior outcomes, but the literature does provide evidence that MCC is chemosensitive, although the responses are not durable, and the agents listed above have been used with some success.~~ (also page MCC-D 2 of 3).
- References moved to new page MCC-D (3 of 3):
  - Nghiem P, Bhatia S, Lipson EJ, et. al. Durable tumor regression and overall survival in patients with advanced Merkel cell carcinoma receiving pembrolizumab as firstline therapy. J Clin Oncol 2019;37:693-702.
  - Topalian SL, Bhatia S, Amin A, et al. Neoadjuvant nivolumab for patients with resectable Merkel cell carcinoma in the CheckMate 358 Trial. J Clin Oncol 2020;38:2476-2487.

MCC-D (2 of 3)

- Disseminated Disease M1:
  - First bullet, Preferred interventions:
    - First sub-bullet revised: Clinical trial ~~(preferred)~~.
  - New bullet added: Other recommended regimen.
    - New sub-bullet added: Retifanlimab-dlwr if patient is not amenable to surgery or RT.
  - New bullet added: If anti-PD-L1 or anti-PD-1 therapy is contraindicated or disease has progressed on this therapy, may consider:
    - New sub-bullets added:
      - Clinical trial (preferred).
      - Useful in Certain Circumstances, new tertiary bullets added:
        - Carboplatin ± etoposide
        - Cisplatin ± etoposide
        - Cyclophosphamide, doxorubicin (or epirubicin), and vincristine (CAV)
        - Ipilimumab ± nivolumab
        - Oncolytic viral therapy (talimogene laherparepvec [T-VEC]) (category 2B).
        - Somatostatin receptor testing; if positive, somatostatin analog therapy (octreotide long acting release [LAR]) (category 2B).
        - Topotecan
        - Tyrosine kinase inhibitors (pazopanib) (category 2B)

Continued

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Updates in Version 1.2023 of the NCCN Guidelines for Merkel Cell Carcinoma from Version 2.2022 include:

MCC-D (2 of 3) (continued)
- Bullet removed: Useful in certain circumstances as clinical judgement dictates for patients with contraindications to checkpoint immunotherapy:
  - Sub-bullets moved:
    - Carboplatin ± etoposide
    - Cisplatin ± etoposide
    - Cyclophosphamide, doxorubicin (or epirubicin), and vincristine (CAV)
    - Topotecan

MCC-D (3 of 3)
- New references added:
  - Grignani G, Rutkowski P, Lebbe C, et al. 545 A phase 2 study of retifanlimab in patients with advanced or metastatic merkel cell carcinoma (MCC) (POD1UM-201). J for Immunother Cancer 2021;9:A574–A575.
  - LoPiccolo J, Schollenberger MD, Dakhil S, et al. Rescue therapy for patients with anti-PD-1-refractory Merkel cell carcinoma: a multicenter, retrospective case series. J Immunother Cancer 2019;7:170.
  - Glutsch V, Kneitz H, Gesierich A, et al. Activity of ipilimumab plus nivolumab in avelumab-refractory Merkel cell carcinoma. Cancer Immunol Immunother 2021;70:2087-2093.
  - Kim S, Wuthrick E, Blakaj D, et al. Combined nivolumab and ipilimumab with or without stereotactic body radiation therapy for advanced Merkel cell carcinoma: a randomised, open label, phase 2 trial. Lancet 2022;400:1008-1019.
  - Nguyen MHK, Leong SP, Abendroth R, Kashani-Sabet M, Kim KB. Complete clinical response to intralesional talimogene laherparepvec injection in a patient with recurrent, regionally advanced Merkel cell carcinoma. JAAD Case Rep 2019;5:849-851.
  - Akaike T, Qazi J, Anderson A, et al. High somatostatin receptor expression and efficacy of somatostatin analogues in patients with metastatic Merkel cell carcinoma. Br J Dermatol 2021;184:319-327.
  - Tarabadkar ES, Thomas H, Blom A, et al. Clinical benefit from tyrosine kinase inhibitors in metastatic Merkel cell carcinoma: A case series of 5 patients. Am J Case Rep 2018;19:505-511.

ABBR-1
- New page added: Abbreviations.

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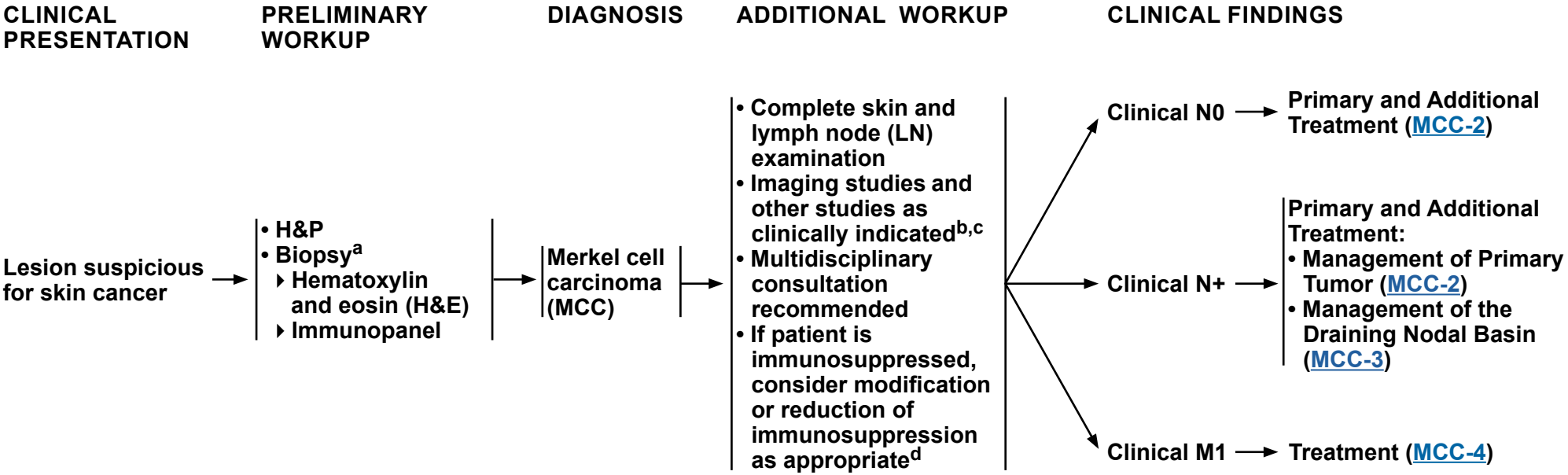

[a] Principles of Pathology (MCC-A).

[b] Imaging is encouraged for staging of most cases of MCC 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 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/brain if clinical suspicion) 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. 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; seronegative patients may have a higher risk of recurrence; in seropositive patients, a rising titer may be an early indicator of recurrence; baseline testing should be performed within 3 months of treatment, because titers are expected to decrease significantly after clinically evident disease is eliminated.

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

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

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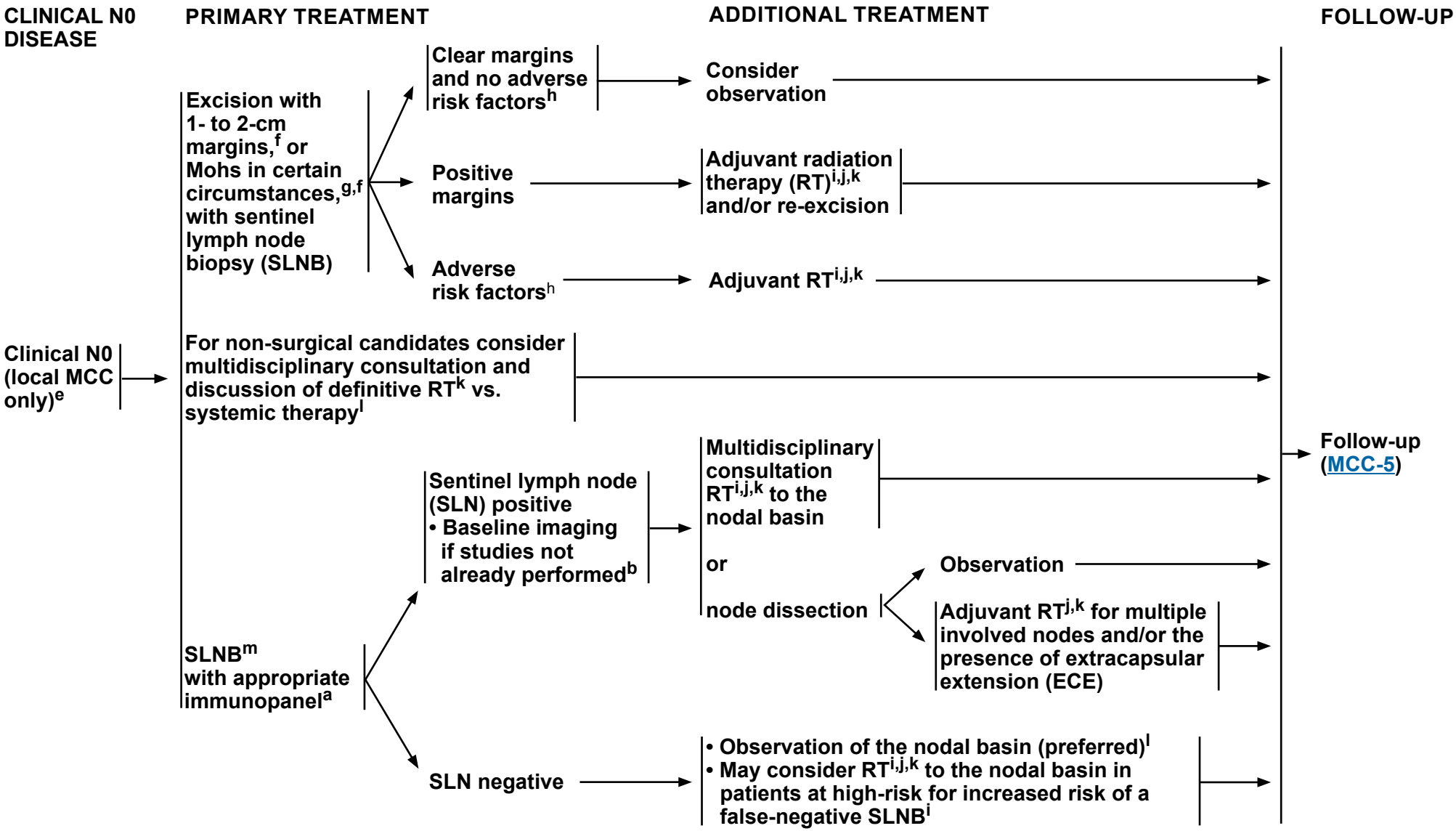

Footnotes on MCC-2A

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FOOTNOTES

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

[b] Imaging is encouraged for staging of most cases of MCC as 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 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/brain if clinical suspicion) 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. The most reliable staging tool to identify subclinical nodal disease is SLNB (George A, et al. Nucl Med Commun 2014;35:282-290; Hawryluk EB, et al. J Am Acad Dermatol 2013;68:592-599; Siva S, et al. J Nucl Med 2013;54:1223-1229).

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

[f] 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 preferred as soon as wound healing permits, as delay has been associated with worse outcomes). See Principles of Excision (MCC-C).

[g] Mohs or other forms of peripheral and deep en face margin assessment (PDEMA) may be appropriate. See NCCN Guidelines for Squamous Cell Skin Cancer - Principles of PDEMA Technique for description of PDEMA.

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

[i] Consider empiric RT to the nodal basin when: 1) the accuracy of SLNB may have been subject to anatomic compromise (lymphoma involved nodes, or history of remote LN excision); 2) when 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); or 3) in cases of profound immunosuppression. See Principles of Radiation Therapy (MCC-B).

[j] Appropriateness of RT should be determined by a radiation oncologist.

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

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

[m] SLNB is an important staging tool. This procedure and subsequent treatment impacts regional control for patients with positive SLNs.

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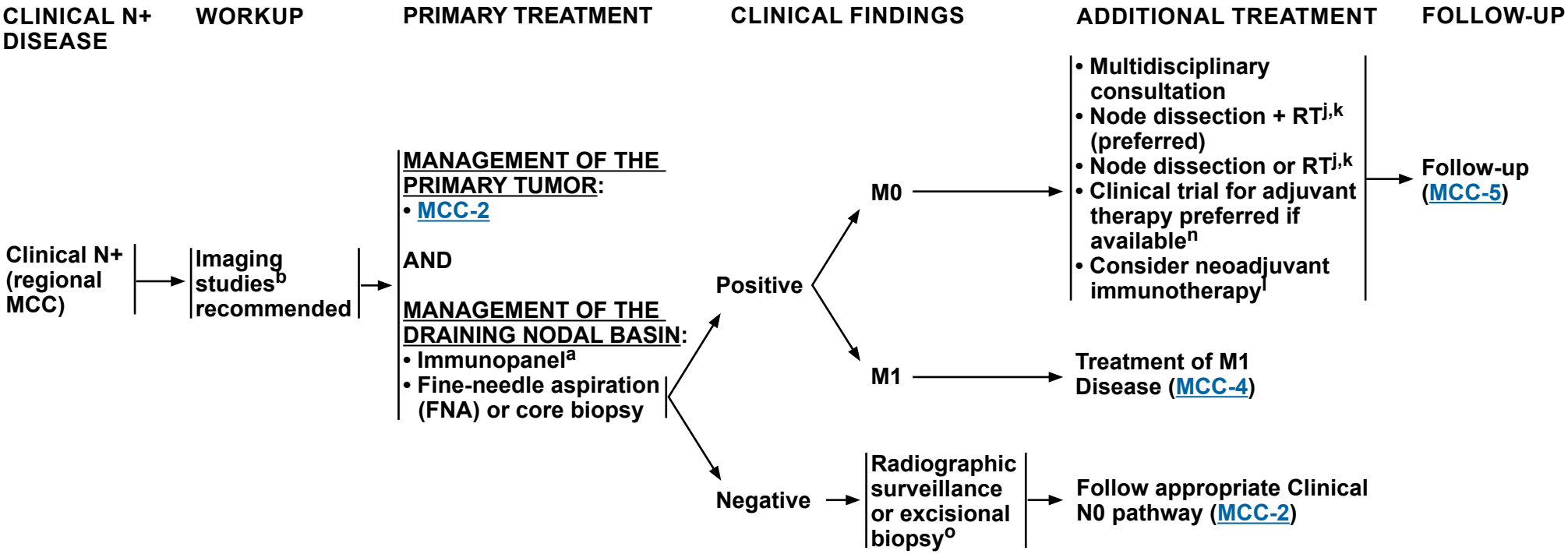

[a] Principles of Pathology (MCC-A).
[b] Imaging is encouraged for staging of most cases of MCC occult metastatic disease resulting in upstaging has been detected in 12%–20% of patients presenting without suspicious H&P findings (Singh N, et al. J Am Acad Dermatol 2021;84:330-339). Several studies indicate whole-body 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/brain if clinical suspicion) 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. The most reliable staging tool to identify subclinical nodal disease is SLNB. (George A, et al. Nucl Med Commun 2014;35:282-290; Hawryluk EB, et al. J Am Acad Dermatol 2013;68:592-599; Siva S, et al. J Nucl Med 2013;54:1223-1229).
[j] Appropriateness of RT should be determined by a radiation oncologist.
[k] Principles of Radiation Therapy (MCC-B).
[l] Principles of Systemic Therapy (MCC-D).
[n] Adjuvant chemotherapy may be considered in select clinical circumstances; however, available retrospective studies do not suggest survival benefit for adjuvant chemotherapy. No data are available to support the adjuvant use of immunotherapy outside of a clinical trial. See Principles of Systemic Therapy (MCC-D).
[o] An excisional biopsy may be considered to confirm a negative initial FNA or core LN biopsy if clinical suspicion remains high.

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[d] As immunosuppression in MCC is a risk factor for poor outcomes, immunosuppressive treatments should be minimized as clinically feasible in consultation with the relevant managing physician. As immunosuppressed patients are at high risk for recurrence, more frequent follow-up may be indicated.
[j] Appropriateness of RT should be determined by a radiation oncologist.
[k] Principles of Radiation Therapy (MCC-B).
[l] Principles of Systemic Therapy (MCC-D).
[p] Under highly selective circumstances, in the context of multidisciplinary consultation, resection of limited metastases can be considered.

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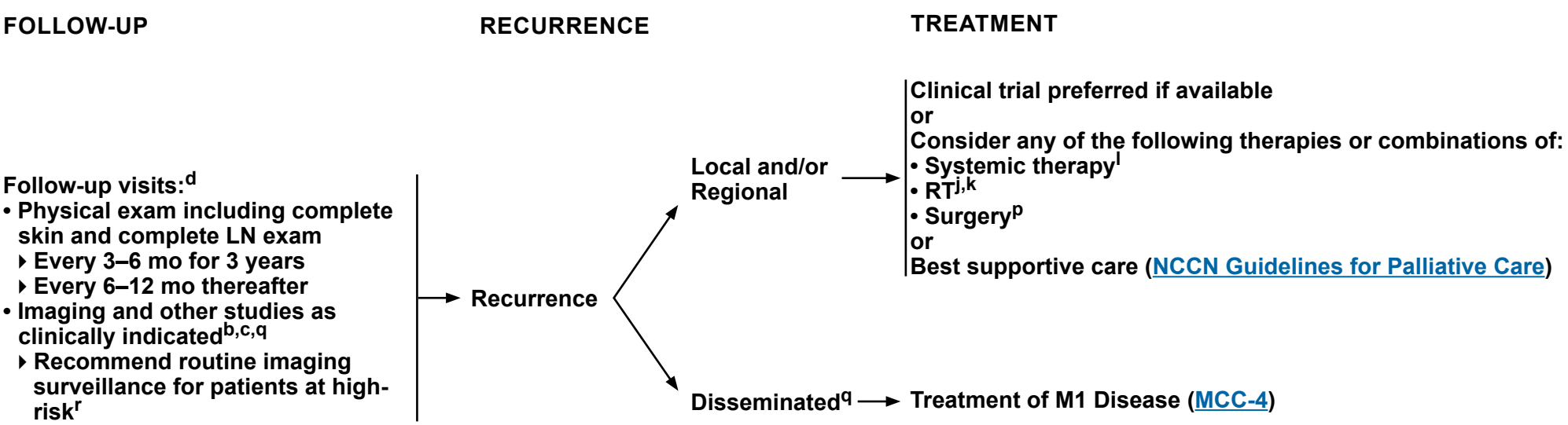

[b] Imaging is encouraged for staging of most cases of MCC occult metastatic disease resulting in upstaging has been detected in 12%–20% of patients presenting without suspicious H&P findings (Singh N, et al. J Am Acad Dermatol 2021;84:330-339). Several studies indicate whole-body PET with fused axial imaging is more sensitive for detecting occult metastatic disease at baseline; however, CT with contrast of chest/abdomen/pelvis (and neck/brain if clinical suspicion) 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. The most reliable staging tool to identify subclinical nodal disease is SLNB. (George A, et al. Nucl Med Commun 2014;35:282-290; Hawryluk EB, et al. J Am Acad Dermatol 2013;68:592-599; Siva S, et al. J Nucl Med 2013;54:1223-1229).

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

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

[j] Appropriateness of RT should be determined by a radiation oncologist.

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

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

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

[q] 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.

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

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

PRINCIPLES OF PATHOLOGY

- **Pathologists should be experienced in distinguishing MCC from cutaneous simulants and metastatic tumors.**
- **Synoptic reporting is preferred.**
- **Minimal elements to be reported include largest tumor diameter (cm), peripheral and deep margin status, lymphovascular invasion (LVI), and extracutaneous extension (ie, bone, muscle, fascia, cartilage).**
- **Strongly encourage reporting of these additional clinically relevant factors (compatible with the American Joint Committee on Cancer [AJCC] and the College of American Pathologists [CAP] recommendations):**
  - **Depth (Breslow, in mm)**
  - **Tumor-infiltrating lymphocytes (not identified, brisk, non-brisk)**
  - **Tumor growth pattern (nodular or infiltrative)**
  - **Presence of a second malignancy within the pathologic specimen itself (ie, concurrent squamous cell carcinoma [SCC])**
- **Immunohistochemistry should be used for confirmation on all newly diagnosed MCC to exclude possible mimickers such as metastatic small cell carcinoma. Staining with CK20 (membranous and/or paranuclear dot-like) and negativity for thyroid transcription factor-1 (TTF-1) are usually sufficient. If an atypical staining pattern is present, AE1/3 keratin (dot-like), or at least one neuroendocrine marker (such as synaptophysin, neurofilament, INSM1 [insulinoma-associated protein 1],[1] chromogranin, CD56, or neuron-specific enolase [NSE]), and/or Merkel cell polyomavirus (MCPyV) T antigen (CM2B4) stains may be employed.**
- **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 immunohistochemistry 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 ECE.**

[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

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

General Treatment Information–Primary MCC Tumor Site

- Treatment Information
  - Bolus is used to achieve adequate skin dose. Wide margins (5 cm) should be used around the primary site, when clinically feasible with consideration given to anatomic constraints. If electron beam is used, an energy and prescription isodose should be chosen that will deliver adequate dose to the lateral and deep margins.
- General Dosing Prescription
  - All doses are at 2 Gy/day standard fractionation.
  - In the palliative setting, a wide range of fractionation schedules may be used, including less protracted fractionation schedules such as 30 Gy in 10 fractions, 20 Gy in 4 or 5 fractions, or 8 Gy in 1 fraction. These schedules are under a clinical trial for curative intent.

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

Note: All recommendations are category 2A unless otherwise indicated.
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PRINCIPLES OF RADIATION THERAPY

General Treatment Information–Draining Nodal Basin

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

Node Dissection Status	RT Dosing
• No SLNB or LN dissection	
▸ Clinically evident lymphadenopathy	60–66 Gy[a,b]
▸ Clinically node negative, but at risk for subclinical disease	46–50 Gy
• SLNB without LN dissection	
▸ SLN negative — RT not routinely indicated[c]	Observation
▸ SLN positive[d]	50–56 Gy
• After LN dissection with multiple involved nodes and/or ECE[e]	60–66 Gy

[a] LN dissection is the recommended initial therapy for clinically evident adenopathy, followed by postoperative RT if indicated.
[b] Shrinking field technique.
[c] Consider empiric RT to the nodal basin when: 1) the accuracy of SLNB may have been subject to anatomic compromise (lymphoma involved nodes, or history of remote LN excision); 2) when 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); or 3) when identified by lymphoscintigraphy in cases of profound immunosuppression (ie, solid organ transplant recipients).
[d] Microscopic nodal disease (SLN positive) is defined as nodal involvement that is neither clinically palpable nor abnormal by imaging criteria, and microscopically consists of small metastatic foci without ECE.
[e] Adjuvant RT following LN dissection is only indicated for multiple involved nodes and/or the presence of ECE. Adjuvant RT following LN dissection is generally not indicated for patients with low tumor burden on SLNB or with a single macroscopic clinically detected LN without ECE.

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

PRINCIPLES OF EXCISION

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

Surgical Approaches:
- **It is recommended, regardless of the surgical approach, that every effort be made to coordinate surgical management such that SLNB is performed at the time of definitive excision.[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 peripheral and deep en face margin assessment [PDEMA]),[b] provided they do not interfere with SLNB when indicated.**
  - **If SLNB is not performed concurrently, it is recommended that SLNB is performed prior to definitive excision with exhaustive histologic margin assessment (ie, Mohs).**

Reconstruction:
- **It is recommended that any reconstruction involving extensive undermining or tissue movement be delayed until negative histologic margins are verified and SLNB is performed if indicated.**
- **Since RT is often indicated postoperatively, closure should be chosen to allow for expeditious initiation of RT (eg, primary closure, avoiding extensive tissue movement).**

[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.

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

PRINCIPLES OF SYSTEMIC THERAPY[a]

Local Disease N0:

- **For primary disease, adjuvant chemotherapy is not recommended.**

- **Recurrent locally advanced:**
  - **Consider pembrolizumab[b,c] if curative surgery and curative RT are not feasible.[1]**
  - **Other recommended regimen:**
    - ◊ **Retifanlimab-dlwr if patient is not amenable to surgery or RT.[2]**

Regional Disease N+:

- **Clinical trial (preferred)**

- **For regional disease, adjuvant chemotherapy is not routinely recommended as survival benefit has not been demonstrated in available retrospective studies, but could be used on a case-by-case basis if clinical judgment dictates. No data are available to support the adjuvant use of immunotherapy outside of a clinical trial.**

- **Useful in certain circumstances as clinical judgment dictates:**
  - **Carboplatin ± etoposide**
  - **Cisplatin ± etoposide**
  - **Neoadjuvant nivolumab[c,3]**

- **Recurrent regional disease:**
  - **Consider pembrolizumab[b,c] if curative surgery and curative RT are not feasible.[1]**
  - **Other recommended regimen:**
    - ◊ **Retifanlimab-dlwr if patient is not amenable to surgery or RT.[2]**

[a] When available and clinically appropriate, enrollment in a clinical trial is recommended.
[b] 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.
[c] NCCN Guidelines for Management of Immunotherapy-Related Toxicities.

References

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

PRINCIPLES OF SYSTEMIC THERAPY[a]

Disseminated Disease M1:

- **Preferred interventions:**
  - **Clinical trial**
  - **Avelumab[b,c]**
  - **Nivolumab[b,c]**
  - **Pembrolizumab[b,c,1]**

- **Other recommended regimen:**
  - **Retifanlimab-dlwr if patient is not amenable to surgery or RT.[2]**

- **If anti-PD-L1 or anti-PD-1 therapy is contraindicated or disease has progressed on this therapy, may consider:**
  - **Clinical trial (preferred)**
  - **Useful in Certain Circumstances:**
    - ◊ **Carboplatin ± etoposide**
    - ◊ **Cisplatin ± etoposide**
    - ◊ **Cyclophosphamide, doxorubicin (or epirubicin), and vincristine (CAV)**
    - ◊ **Ipilimumab ± nivolumab[4,5,6]**
    - ◊ **Oncolytic viral therapy (talimogene laherparepvec [T-VEC])[7] (category 2B)**
    - ◊ **Somatostatin receptor testing;[8] if positive, somatostatin analog therapy (octreotide long acting release [LAR]) (category 2B)**
    - ◊ **Topotecan**
    - ◊ **Tyrosine kinase inhibitors (pazopanib)[9] (category 2B)**

[a] When available and clinically appropriate, enrollment in a clinical trial is recommended.
[b] 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.
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References

PRINCIPLES OF SYSTEMIC THERAPY
REFERENCES

[1] Nghiem P, Bhatia S, Lipson EJ, et. al. Durable tumor regression and overall survival in patients with advanced Merkel cell carcinoma receiving pembrolizumab as first-line therapy. J Clin Oncol 2019;37:693-702.
[2] Grignani G, Rutkowski P, Lebbe C, et al. 545 A phase 2 study of retifanlimab in patients with advanced or metastatic merkel cell carcinoma (MCC) (POD1UM-201). J for Immunother Cancer 2021;9:A574–A575.
[3] Topalian SL, Bhatia S, Amin A, et al. Neoadjuvant nivolumab for patients with resectable Merkel cell carcinoma in the CheckMate 358 Trial. J Clin Oncol 2020;38:2476-2487.
[4] LoPiccolo J, Schollenberger MD, Dakhil S, et al. Rescue therapy for patients with anti-PD-1-refractory Merkel cell carcinoma: a multicenter, retrospective case series. J Immunother Cancer 2019;7:170.
[5] Glutsch V, Kneitz H, Gesierich A, et al. Activity of ipilimumab plus nivolumab in avelumab-refractory Merkel cell carcinoma. Cancer Immunol Immunother 2021;70:2087-2093.
[6] Kim S, Wuthrick E, Blakaj D, et al. Combined nivolumab and ipilimumab with or without stereotactic body radiation therapy for advanced Merkel cell carcinoma: a randomised, open label, phase 2 trial. Lancet 2022;400:1008-1019.
[7] Nguyen MHK, Leong SP, Abendroth R, Kashani-Sabet M, Kim KB. Complete clinical response to intralesional talimogene laherparepvec injection in a patient with recurrent, regionally advanced Merkel cell carcinoma. JAAD Case Rep 2019;5:849-851.
[8] Akaike T, Qazi J, Anderson A, et al. High somatostatin receptor expression and efficacy of somatostatin analogues in patients with metastatic Merkel cell carcinoma. Br J Dermatol 2021;184:319-327.
[9] Tarabadkar ES, Thomas H, Blom A, et al. Clinical benefit from tyrosine kinase inhibitors in metastatic Merkel cell carcinoma: A case series of 5 patients. Am J Case Rep 2018;19:505-511.

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

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

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

ABBREVIATIONS

ECE	**extracapsular extension**
H&E	**hematoxylin and eosin**
H&P	**history and physical**
LN	**lymph node**
LVI	**lymphovascular invasion**
MCC	**Merkel cell carcinoma**
MCPyV	**Merkel cell polyomavirus**
PDEMA	**peripheral and deep en face margin assessment**
RT	**radiation therapy**
SLN	**sentinel lymph node**
SLNB	**sentinel lymph node biopsy**

NCCN Categories of Evidence and Consensus	
Category 1	Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.
Category 2A	Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.
Category 2B	Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate.
Category 3	Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate.

All recommendations are category 2A unless otherwise indicated.

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

All recommendations are considered appropriate.

NCCN Guidelines Version 1.2023
Merkel Cell Carcinoma

Discussion

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

Table of Contents

Overview

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

Literature Search Criteria and Guidelines Update Methodology

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

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

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

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

Risk Factors for MCC

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

Diagnosis and Workup

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

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

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

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

Characteristics and Differential Diagnosis

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

Based on clinical impression, 56% of MCC tumors were initially presumed to be benign cysts/lesions.[7] Other studies confirm that MCCs are frequently clinically misdiagnosed as benign lesions or non-melanoma skin cancers (NMSCs) or other rare malignant skin tumors.[8,9,71] Misdiagnosis is even more prevalent among MCC tumors that are admixed or adjacent to other skin tumors.[9,72]

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

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

Several groups have explored the significance of antibodies to MCPyV in patients with MCC.[104-106] In one prospective validation study that included 219 patients with newly diagnosed MCC, patients who were oncoprotein antibody seronegative at diagnosis had a significantly higher risk of recurrence, suggesting that they may benefit from more intensive surveillance.[58] For patients who were seropositive, the oncoprotein antibody test may be a useful component of ongoing surveillance because a rising titer can be an early indicator of recurrence.[58]

Pathology Report

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

Tumor Size (Diameter)

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

Peripheral and Deep Margin Status

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

stage III MCC.[113] One study of 179 cases found that margin status was correlated with local recurrence in MCC treated with surgery alone, but was far less predictive among patients who received adjuvant radiation therapy (RT).[25]

Lymphovascular Invasion

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

Extracutaneous Extension

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

Tumor Thickness

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

Tumor Infiltrating Lymphocytes

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

Tumor Growth Pattern

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

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

Presence of Secondary Malignancy

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

Imaging

The utility of imaging as part of baseline staging for MCC is an issue of debate in the literature. A number of retrospective analyses have reported data on detection and appearance of MCC tumors using various imaging methods, including conventional x-ray,[74,83,146] CT,[83,146-150] ultrasound,[83,146,149] MRI,[74,146,149,151] scintigraphy,[152-154] and PET or PET/CT.[149,151,155-168] For CT and FDG PET or FDG PET/CT, there are reports showing detection of MCC primary tumors, lymph node metastases, and distant metastases in a wide range of anatomic locations. Though the reported sensitivity and specificity of MRI were lower than CT and FDG PET/CT,[151] it is still the best imaging tool available for rare cases of MCC brain metastases.[169-171] A number of studies have attempted to determine the utility of specific imaging methodologies for detecting MCC tumors, either in terms of the sensitivity, specificity, and positive/negative predictive value, or in terms of making an impact on disease restaging or management. However, many studies are limited by small sample size (N < 30) and did not consistently use pathologic confirmation as a standard of reference for determining positive and negative predictive values.

Computed Tomography

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

FDG PET/CT

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

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

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

Staging and Treatment of the Primary Tumor

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

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

Because of the high historic risk of local recurrence in MCC, the Panel's tenets for surgical excision emphasize complete extirpation of tumor at the time of initial resection to achieve histologically clear surgical margins when clinically feasible. To minimize morbidity, narrow excision margins resulting in possible microscopically positive margins are acceptable when followed by adjuvant RT to the primary site. Surgical margins should be balanced with morbidity of surgery. Alternative methods for complete removal of the primary tumor include Mohs micrographic surgery (Mohs) and peripheral and deep en face margin assessment (PDEMA), using margins similar to WLE (See NCCN Guidelines for Squamous Cell Skin

Cancer – Principles of PDEMA Technique). These alternative methods ensure complete tumor removal and clear margins, while sparing surrounding healthy tissue. Regardless of the surgical technique employed, the goal should be primary tissue closure to avoid any undue delay in proceeding to RT and allow for initiation of adjuvant RT, if needed, within 3 to 4 weeks. In selected cases in which surgical excision is not possible, surgery is refused by the patient, or surgery would result in significant morbidity, radiation monotherapy may be considered (See *Principles of Radiation Therapy* in the algorithm). In all cases, surgical management should be coordinated so that SLNB is performed prior to or at the same time as definitive surgery.

Surgery for Primary Tumor

Given the potential for rapid growth, surgery has been the most common approach used to treat primary MCC tumors and has been shown to produce superior outcomes compared to non-surgical primary treatment.[45,176] Outcomes for a variety of surgical approaches to remove MCC primary tumors have been reported in the literature, including biopsy approaches, either with or without subsequent re-excision to obtain clear margins, standard excision, local amputation, and Mohs or other approaches with integrated complete margin assessment.[8,25,45,51,177-187] Whereas there are a number of retrospective studies that found that negative margin status was associated with improved local recurrence and survival,[24,25,45,113,181,183,188-190] other analyses did not consistently find such associations.[21,23,118-120,158,191-195] There is evidence that margin status has an impact on survival regardless of adjuvant RT receipt.[190] Among cases with stage I/II disease treated with surgery only, recurrence rates and OS were better for negative versus positive margins.[183] On the other hand, for high-risk local and regional MCC, margin status did not seem to have an impact on recurrence in those who received adjuvant RT.[196,197]

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

Definitive Radiation Therapy for Locoregional Disease

Historically, surgery has been the mainstay of treatment for local and regional MCC; as a result, data on the efficacy of definitive RT are extremely limited. There are a large number of retrospective studies that include very small samples of patients (N < 10) who received definitive RT instead of surgery.[21,24,45,71,118,172,192,193,195,201-209] As mentioned previously, patients 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.[45,176] The largest study (N > 2000) comparing outcomes between definitive RT and surgery showed improved OS with surgery (± adjuvant RT) versus definitive RT,

both among patients with stage I/II disease (median OS, 76 vs. 25 months; *P* < .001) and among those with stage III disease (median OS, 30 vs. 15 months; *P* < .001).[176] However, the patient population 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).[17] Retrospective studies of MCC treated with definitive RT to their primary and/or nodal MCC reported in-field recurrence rates of less than 25%, with median time to in-field recurrence ranging from 4 to 6.3 months.[25,210-215] One meta-analysis of 264 patients with locoregional MCC treated with definitive RT reported that cumulative in-field recurrence rate was 12% per site, and that in-field recurrence was significantly more likely at regional versus primary irradiated sites (16% vs. 7.6%, *P* = .02).[208]

Nodal Staging and Treatment of Regional Disease

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

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

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

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

A clinical N+ diagnosis (palpable lymph nodes) should be confirmed by using fine-needle aspiration (FNA) or core biopsy of the draining nodal basin with an appropriate immunopanel. An open biopsy may be

considered to confirm a negative initial FNA or core lymph node biopsy if clinical suspicion remains high. If negative results are confirmed, MCC should be treated as clinical N0 and follow the clinical N0 pathway including sentinel lymph node biopsy. If initial or subsequent lymph node biopsy results are positive, imaging studies are recommended if not already performed to evaluate the extent of lymph node and/or visceral organ involvement. If a distant metastasis is detected, management should follow the M1 pathway. In case of no detected distant metastases, multidisciplinary consultation and node dissection and/or RT is recommended. Enrollment in a clinical trial for adjuvant therapy is preferred, if available. Neoadjuvant immunotherapy can be considered.

Adjuvant systemic therapy is not routinely recommended because no survival benefit has been reported. Most NCCN Member Institutions only use systemic therapy for stage IV, distant metastatic disease (M1), with or without surgery and/or RT. A few NCCN Member Institutions suggest considering adjuvant systemic therapy for select cases of clinical (macroscopic) regional (N1b or N2) disease. However, available retrospective studies do not suggest that adjuvant chemotherapy provides survival benefit, and most institutions only use adjuvant chemotherapy for MCC in select cases. For select patients for whom adjuvant systemic therapy is considered, treatment in the context of a clinical trial is preferred, when available. Although not routinely recommended for adjuvant treatment of regional disease, if used in select cases the panel recommends cisplatin or carboplatin with or without etoposide, or neoadjuvant nivolumab. For recurrent regional disease, pembrolizumab can be considered if curative surgery and curative RT are not feasible.

Sentinel Lymph Node Biopsy

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

Another issue of debate is whether the SLNB procedure itself offers some protection against recurrence, progression, or death from disease for patients with clinically node-negative disease. One retrospective study of patients with clinical stage I/II MCC found that those who underwent SLNB had improved 5-year DSS compared with those who did not undergo SLNB, although the actual difference was small (79% vs. 74%).[221] Another analysis of a large population database found that compared with patients who had no pathologic nodal evaluation, those with SLNB alone or SLNB plus LND had lower risk of all-cause mortality, and that SLNB plus LND was also associated with improved MCC-specific mortality.[35] There is insufficient information to ascertain whether these associations are due to the SLNB procedure itself or due to subsequent management choices informed by the results of pathologic nodal evaluation. Other retrospective studies have found that among patients presenting with clinically node-negative MCC, SLNB is not significantly associated with improved LRC or OS,[8,45] except for one report of significantly longer OS.[179]

SLNB Pathology

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

Fine-Needle Aspiration

Several retrospective studies have reported that FNA biopsy is an accurate method for diagnosing MCC lesions, including primary tumors and nodal and distant metastases.[231-234] One small study compared FNA results with subsequent LND results, and found that the FNA procedure identified all cases of LN metastases that were greater than 6 mm, but did not consistently identify smaller foci.[232] This finding underscores that FNA biopsy is not an appropriate method for detection of clinically occult metastases, but is effective for verifying MCC in palpable nodes. IHC analyses of FNA samples showed that most cases were positive for CK20, AE1/AE3, synaptophysin, NSE, and CD56.[231,233,234] Chromogranin staining was present in a smaller proportion of cases (36%).[233,234] Markers for melanoma (ie, S100, HMB45, Melan A, CD45) or lymphoma (leukocyte common antigen) were nearly always negative.[231,233,234]

Surgery Versus Radiation Therapy for Regional Disease

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

Due to lack of prospective data, however, it is unclear whether surgical approaches or RT are more effective as initial treatment for nodal MCC. For studies with at least 20 patients with MCC lymph node involvement, few reported outcomes for specific nodal treatments.[22,25,51,113,114,172,176,201,206,236-238] Wright et al showed that surgery (with or without adjuvant RT) was associated with better OS compared with definitive RT (median 30 vs. 15 months, P < .001).[176] In contrast, Bhatia et al found no significant difference in OS for surgery alone compared with RT alone or surgery plus RT.[113] Furthermore, while some studies suggest that nodal surgery may improve outcomes,[51,236-238] a few found that patients who received nodal RT alone fared better,[22,25] and others found no clear trends according to nodal treatment.[22,114,172,201,206,239] Perez et al. and Lee et al., retrospectively, evaluated outcomes for 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.[240,241]

There are very few data to inform the extent of nodal surgery needed for patients with biopsy-proven regional disease. Results from retrospective analyses suggest that MCC prognosis worsens with increasing nodal involvement (clinically detectable nodal involvement versus microscopic nodal involvement,[16,24,52,119] increasing number of nodes involved,[17,21,111-113,193,204,215,218,242,243] and the presence of ECE[124,204,218]). These findings suggest that the aggressiveness of nodal treatment should perhaps be commensurate with the extent of nodal disease. The type of LN surgery may not be very important if patients are also treated with RT. A pooled

analysis of several prospective studies found that the margin status of surgically removed lymph nodes was not associated with locoregional recurrence in patients who received RT to the nodal basin.[244] One of these prospective studies also found that among patients with locoregional MCC, all of whom were treated with surgery plus RT (with or without chemotherapy), nodal involvement was not prognostic for DSS or OS.[245]

Postoperative Radiation and Systemic Therapy for Locoregional Disease

Postoperative Radiation

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

Overall, studies reporting results specifically for patients with stage I/II disease agree that adjuvant RT to the primary tumor significantly reduced the rate and time to locoregional recurrence,[19,185,248,252,262,267] while many also reported improvements in survival.[113,182,183,195,248,251] Kang et al examined 42 cases of stage I/II MCC and determined that those who had RT to their primary site had significantly higher 2-year local recurrence-free survival compared to those who did not receive RT (89% vs. 36%, $P < .001$).[248] Of note, three large studies using NCDB data (N > 1000 stage I/II patients) concluded that surgery plus RT or conformal RT (CRT) led to significantly better survival results compared to surgery alone.[113,182,183] Even though benefit has been noted for low-risk stage I MCC,[252,262] local MCC with high-risk features might have the most to gain from adjuvant RT.[25,123,247,249,259] Particularly, a recent study of 1,858 stage I/II patients with 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 ($P = .478$).[251]

Regarding the clinical benefit of adjuvant RT for patients with node-positive versus node-negative MCC, results vary widely between studies.[21,25,49,51,53,113,116,119,120,123,148,195,240,258,263-265] Some studies showed that postoperative RT was associated with improved survival in patients with stage I/II disease, but not for stage III disease.[113,195] In contrast, a retrospective study found that postoperative RT to the primary tumor bed improved LRC and DSS in patients with pathologic or clinically positive nodes, but not in patients with negative nodes.[123] In other studies, nodal RT in patients with positive SLNB significantly reduced 3-year relapse-free survival rate (51% vs. 0%; $P < .01$),[148] as well as 3-year regional control (95% vs. 66.7%; $P = .008$).[268] A large study using NCDB data (N = 447) of 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.[265] Several studies pointed out that the utility of adjuvant RT might be extended to patients with negative nodes.[25,53,116,120,258,268] Specifically, tumor-bed irradiation was significantly associated with prolonged DFS ($P = .006$) and OS ($P = .014$) in patients with negative SLNB.[53] In another study, RT to regional nodes was associated with improved regional control, irrespective of clinical status ($P = .01$).[120] Overall, studies have both supported[25] and refuted[263]

the effectiveness of nodal RT in reducing nodal relapse in node-negative patients.

Postoperative Systemic Therapy

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

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

Treatment of Distant Metastatic Disease

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

The NCCN Panel recommends multidisciplinary consultation for patients with distant metastatic disease (M1). Comprehensive imaging is recommended for all patients with any clinically detected and pathologically proven regional or distant metastases. In general, the 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. Options include avelumab, pembrolizumab, nivolumab (preferred) or cisplatin or carboplatin with or without etoposide, topotecan, cyclophosphamide, doxorubicin (or epirubicin), and vincristine (CAV) (useful in certain circumstances as clinical judgment dictates for patients with contraindications to ICI). Surgery may be beneficial in highly selective

circumstances for resection of oligometastases or symptomatic lesions. All patients should receive best supportive care, and depending on the extent of the disease and other case-specific circumstances, palliative care alone may be the most appropriate option for some patients (See NCCN Guidelines for Palliative Care).

Systemic Therapy for Metastatic or Unresectable Disease

Immunotherapy

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

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

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

The recommendation for neoadjuvant nivolumab is supported by data from the Checkmate 358 phase I/II trial that included 39 patients with resectable MCC.[274] Among 36 patients who underwent surgery, 47.2% achieved a pathologic complete response. Among 33 radiographically evaluable patients who underwent surgery, 54.5% had tumor reductions greater than or equal to 30%.[274]

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

Chemotherapy

Responses to chemotherapy in patients with MCC have been reported for a variety of regimens, including regimens that contain platinum agents (often in combination with etoposide), cyclophosphamide (often in CAV),

cyclophosphamide with methotrexate and 5-fluorouracil (CMF), paclitaxel, nab-paclitaxel, docetaxel, ifosfamide, anthracycline, 5-fluorouracil, topotecan, gemcitabine, and irinotecan.[210,270,275,290-293] In analyses with more than 20 patients, reported overall response rates (ORRs) were usually around 40% to 60%. In several studies the response rate appeared to depend on the number of prior chemotherapy regimens, with reports of response rates up to 70% for first-line chemotherapy, and as low as 9% to 20% in patients who received one or more prior lines of chemotherapy.[210,270,275,290-295] Reported responses to chemotherapy were fairly short-lived, with a median duration ranging from approximately 2 to 9 months.[210,270,275,291-294] Reported rates of toxic death were between 3% and 10%, with patients who are older being at higher risk.[210,270,275]

Follow-up and Recurrence

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

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

The NCCN Panel recommends close clinical follow-up for patients with MCC starting immediately after diagnosis and treatment. The physical examination should include a complete skin and complete lymph node examination every 3 to 6 months for the first 3 years, then every 6 to 12 months thereafter. The recommended frequency of follow-up visits is purposely broad to allow for an individualized schedule based on the risk of recurrence, stage of disease, and other factors such as patient anxiety and clinician preference. The panel's recommendations for frequent clinical exams during the first 3 years also reflect the fact that MCC will recur in up to half of patients, and most recurrences occur within the first few years after diagnosis. Education regarding self-examination of the skin is useful for patients with MCC because of their increased risk for other NMSCs.

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

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

Management of MCC with local, 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 case-specific circumstances, palliative care alone may be the most appropriate option for some patients (See NCCN Guidelines for Palliative Care).

Imaging Surveillance

Retrospective studies of follow-up imaging results have reported both local and systemic MCC recurrences detected by a variety of techniques, including MRI,[146] CT,[146,147,157] and FDG PET/CT.[149,155-157,159,163,164,167,298] Data on the accuracy of imaging techniques for follow-up surveillance are limited, because very few report whether or not the imaging findings were histologically confirmed.[147,155,156] The yield from different imaging regimens and techniques is also unknown, as most studies did not clarify the frequency of follow-up or whether the patients had no evidence of disease prior to follow-up imaging. One recent retrospective study of 61 patient 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.[298]

Treatment of Recurrence

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

References

1. Paulson KG, Park SY, Vandeven NA, et al. Merkel cell carcinoma: Current US incidence and projected increases based on changing demographics. J Am Acad Dermatol 2018;78:457-463 e452. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29102486.

2. Fitzgerald TL, Dennis S, Kachare SD, et al. Dramatic Increase in the Incidence and Mortality from Merkel Cell Carcinoma in the United States. Am Surg 2015;81:802-806. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26215243.

3. Goon PK, Greenberg DC, Igali L, Levell NJ. Merkel Cell Carcinoma: rising incidence in the East of England. J Eur Acad Dermatol Venereol 2016;30:2052-2055. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27515234.

4. Rubio-Casadevall J, Hernandez-Pujol AM, Ferreira-Santos MC, et al. Trends in incidence and survival analysis in non-melanoma skin cancer from 1994 to 2012 in Girona, Spain: A population-based study. Cancer Epidemiol 2016;45:6-10. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27639035.

5. Zaar O, Gillstedt M, Lindelof B, et al. Merkel cell carcinoma incidence is increasing in Sweden. J Eur Acad Dermatol Venereol 2016. Available at: http://www.ncbi.nlm.nih.gov/pubmed/27136306.

6. Olsen CM, Pandeya N, Whiteman DC. International Increases in Merkel Cell Carcinoma Incidence Rates between 1997 and 2016. J Invest Dermatol 2021;141:2596-2601 e2591. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33932460.

7. Heath M, Jaimes N, Lemos B, et al. Clinical characteristics of Merkel cell carcinoma at diagnosis in 195 patients: the AEIOU features. J Am Acad Dermatol 2008;58:375-381. Available at: https://www.ncbi.nlm.nih.gov/pubmed/18280333.

8. Tarantola TI, Vallow LA, Halyard MY, et al. Prognostic factors in Merkel cell carcinoma: analysis of 240 cases. J Am Acad Dermatol 2013;68:425-432. Available at: https://www.ncbi.nlm.nih.gov/pubmed/23200197.

9. Suarez AL, Louis P, Kitts J, et al. Clinical and dermoscopic features of combined cutaneous squamous cell carcinoma (SCC)/neuroendocrine [Merkel cell] carcinoma (MCC). J Am Acad Dermatol 2015;73:968-975. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26433246.

10. Leech SN, Kolar AJ, Barrett PD, et al. Merkel cell carcinoma can be distinguished from metastatic small cell carcinoma using antibodies to cytokeratin 20 and thyroid transcription factor 1. J Clin Pathol 2001;54:727-729. Available at: https://www.ncbi.nlm.nih.gov/pubmed/11533085.

11. Cheuk W, Kwan MY, Suster S, Chan JK. Immunostaining for thyroid transcription factor 1 and cytokeratin 20 aids the distinction of small cell carcinoma from Merkel cell carcinoma, but not pulmonary from extrapulmonary small cell carcinomas. Arch Pathol Lab Med 2001;125:228-231. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11175640.

12. Agelli M, Clegg LX. Epidemiology of primary Merkel cell carcinoma in the United States. J Am Acad Dermatol 2003;49:832-841. Available at: http://www.ncbi.nlm.nih.gov/pubmed/14576661.

13. Hodgson NC. Merkel cell carcinoma: changing incidence trends. J Surg Oncol 2005;89:1-4. Available at: https://www.ncbi.nlm.nih.gov/pubmed/15611998.

14. Lemos BD, Storer BE, Iyer JG, et al. Pathologic nodal evaluation improves prognostic accuracy in Merkel cell carcinoma: analysis of 5823 cases as the basis of the first consensus staging system. J Am Acad Dermatol 2010;63:751-761. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20646783.

15. Albores-Saavedra J, Batich K, Chable-Montero F, et al. Merkel cell carcinoma demographics, morphology, and survival based on 3870 cases: a population based study. J Cutan Pathol 2010;37:20-27. Available at: https://www.ncbi.nlm.nih.gov/pubmed/19638070.

16. Harms KL, Healy MA, Nghiem P, et al. Analysis of prognostic factors from 9387 Merkel cell carcinoma cases forms the basis for the new 8th Edition AJCC Staging System. Ann Surg Oncol 2016;23:3564-3571. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27198511.

17. Sridharan V, Muralidhar V, Margalit DN, et al. Merkel cell carcinoma: A population analysis on survival. J Natl Compr Canc Netw 2016;14:1247-1257. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27697979.

18. Akhtar S, Oza KK, Wright J. Merkel cell carcinoma: report of 10 cases and review of the literature. J Am Acad Dermatol 2000;43:755-767. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11050578.

19. Medina-Franco H, Urist MM, Fiveash J, et al. Multimodality treatment of Merkel cell carcinoma: case series and literature review of 1024 cases. Ann Surg Oncol 2001;8:204-208. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11314935.

20. Hitchcock CL, Bland KI, Laney RG, 3rd, et al. Neuroendocrine (Merkel cell) carcinoma of the skin. Its natural history, diagnosis, and treatment. Ann Surg 1988;207:201-207. Available at: http://www.ncbi.nlm.nih.gov/pubmed/3277546.

21. Allen PJ, Bowne WB, Jaques DP, et al. Merkel cell carcinoma: prognosis and treatment of patients from a single institution. J Clin Oncol 2005;23:2300-2309. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15800320.

22. Santamaria-Barria JA, Boland GM, Yeap BY, et al. Merkel cell carcinoma: 30-year experience from a single institution. Ann Surg Oncol 2013;20:1365-1373. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23208132.

23. Youlden DR, Soyer HP, Youl PH, et al. Incidence and survival for Merkel cell carcinoma in Queensland, Australia, 1993-2010. JAMA Dermatol 2014;150:864-872. Available at: https://www.ncbi.nlm.nih.gov/pubmed/24943712.

24. Fields RC, Busam KJ, Chou JF, et al. Five hundred patients with merkel cell carcinoma evaluated at a single institution. Ann Surg 2011;254:465-475. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21865945.

25. Harrington C, Kwan W. Radiotherapy and conservative surgery in the locoregional management of Merkel cell carcinoma: The British Columbia Cancer Agency experience. Ann Surg Oncol 2016;23:573-578. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26286197.

26. Reichgelt BA, Visser O. Epidemiology and survival of Merkel cell carcinoma in the Netherlands. A population-based study of 808 cases in 1993-2007. Eur J Cancer 2011;47:579-585. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21144740.

27. PubMed Overview. Available at: https://pubmed.ncbi.nlm.nih.gov/about/. Accessed November 15th, 2021.

28. Miller RW, Rabkin CS. Merkel cell carcinoma and melanoma: etiological similarities and differences. Cancer Epidemiol Biomarkers Prev 1999;8:153-158. Available at: https://www.ncbi.nlm.nih.gov/pubmed/10067813.

29. Stang A, Becker JC, Nghiem P, Ferlay J. The association between geographic location and incidence of Merkel cell carcinoma in comparison to melanoma: An international assessment. Eur J Cancer 2018;94:47-60. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29533867.

30. Ezaldein HH, Ventura A, DeRuyter NP, et al. Understanding the influence of patient demographics on disease severity, treatment strategy, and survival outcomes in merkel cell carcinoma: a surveillance, epidemiology, and end-results study. Oncoscience 2017;4:106-114. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28966943.

31. Walsh NM. Primary neuroendocrine (Merkel cell) carcinoma of the skin: morphologic diversity and implications thereof. Hum Pathol 2001;32:680-689. Available at: https://www.ncbi.nlm.nih.gov/pubmed/11486166.

32. Higaki-Mori H, Kuwamoto S, Iwasaki T, et al. Association of Merkel cell polyomavirus infection with clinicopathological differences in Merkel cell carcinoma. Hum Pathol 2012;43:2282-2291. Available at: https://www.ncbi.nlm.nih.gov/pubmed/22795182.

33. Lai JH, Fleming KE, Ly TY, et al. Pure versus combined Merkel cell carcinomas: immunohistochemical evaluation of cellular proteins (p53, Bcl-2, and c-kit) reveals significant overexpression of p53 in combined tumors. Hum Pathol 2015;46:1290-1296. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26099430.

34. Lyhne D, Lock-Andersen J, Dahlstrom K, et al. Rising incidence of Merkel cell carcinoma. J Plast Surg Hand Surg 2011;45:274-280. Available at: https://www.ncbi.nlm.nih.gov/pubmed/22250719.

35. Asgari MM, Sokil MM, Warton EM, et al. Effect of host, tumor, diagnostic, and treatment variables on outcomes in a large cohort with Merkel cell carcinoma. JAMA Dermatol 2014;150:716-723. Available at: https://www.ncbi.nlm.nih.gov/pubmed/24807619.

36. Jacobs D, Huang H, Olino K, et al. Assessment of Age, Period, and Birth Cohort Effects and Trends in Merkel Cell Carcinoma Incidence in the United States. JAMA Dermatol 2021;157:59-65. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33146688.

37. Engels EA, Frisch M, Goedert JJ, et al. Merkel cell carcinoma and HIV infection. Lancet 2002;359:497-498. Available at: https://www.ncbi.nlm.nih.gov/pubmed/11853800.

38. Lanoy E, Costagliola D, Engels EA. Skin cancers associated with HIV infection and solid-organ transplantation among elderly adults. Int J Cancer 2010;126:1724-1731. Available at: https://www.ncbi.nlm.nih.gov/pubmed/19810102.

39. Kaae J, Hansen AV, Biggar RJ, et al. Merkel cell carcinoma: incidence, mortality, and risk of other cancers. J Natl Cancer Inst 2010;102:793-801. Available at: https://www.ncbi.nlm.nih.gov/pubmed/20424236.

40. Koljonen V, Kukko H, Tukiainen E, et al. Incidence of Merkel cell carcinoma in renal transplant recipients. Nephrol Dial Transplant 2009;24:3231-3235. Available at: https://www.ncbi.nlm.nih.gov/pubmed/19586970.

41. Koljonen V, Kukko H, Pukkala E, et al. Chronic lymphocytic leukaemia patients have a high risk of Merkel-cell polyomavirus DNA-positive Merkel-cell carcinoma. Br J Cancer 2009;101:1444-1447. Available at: https://www.ncbi.nlm.nih.gov/pubmed/19755994.

42. Koljonen V, Sahi H, Bohling T, Makisalo H. Post-transplant Merkel cell carcinoma. Acta Derm Venereol 2016;96:442-447. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26554531.

43. Clarke CA, Robbins HA, Tatalovich Z, et al. Risk of merkel cell carcinoma after solid organ transplantation. J Natl Cancer Inst 2015;107. Available at: https://www.ncbi.nlm.nih.gov/pubmed/25575645.

44. Paulson KG, Iyer JG, Blom A, et al. Systemic immune suppression predicts diminished Merkel cell carcinoma-specific survival independent of stage. J Invest Dermatol 2013;133:642-646. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23190897.

45. Liang E, Brower JV, Rice SR, et al. Merkel cell carcinoma analysis of outcomes: A 30-year experience. PLoS One 2015;10:e0129476. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26053480.

46. Bryant MK, Ward C, Gaber CE, et al. Decreased survival and increased recurrence in Merkel cell carcinoma significantly linked with immunosuppression. J Surg Oncol 2020. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32562583.

47. Brewer JD, Shanafelt TD, Otley CC, et al. Chronic lymphocytic leukemia is associated with decreased survival of patients with malignant melanoma and Merkel cell carcinoma in a SEER population-based study. J Clin Oncol 2012;30:843-849. Available at: https://www.ncbi.nlm.nih.gov/pubmed/22331952.

48. Yusuf MB, Gaskins J, Rattani A, et al. Immune Status in Merkel Cell Carcinoma: Relationships With Clinical Factors and Independent Prognostic Value. Ann Surg Oncol 2021;28:6154-6165. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33852099.

49. Jouary T, Kubica E, Dalle S, et al. Sentinel node status and immunosuppression: recurrence factors in localized Merkel cell carcinoma. Acta Derm Venereol 2015;95:835-840. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25784178.

50. Arron ST, Canavan T, Yu SS. Organ transplant recipients with Merkel cell carcinoma have reduced progression-free, overall, and disease-specific survival independent of stage at presentation. J Am Acad Dermatol 2014;71:684-690. Available at: https://www.ncbi.nlm.nih.gov/pubmed/24993599.

51. Hui AC, Stillie AL, Seel M, Ainslie J. Merkel cell carcinoma: 27-year experience at the Peter MacCallum Cancer Centre. Int J Radiat Oncol Biol Phys 2011;80:1430-1435. Available at: https://www.ncbi.nlm.nih.gov/pubmed/20708847.

52. Smith FO, Yue B, Marzban SS, et al. Both tumor depth and diameter are predictive of sentinel lymph node status and survival in Merkel cell carcinoma. Cancer 2015;121:3252-3260. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26038193.

53. Servy A, Maubec E, Sugier PE, et al. Merkel cell carcinoma: value of sentinel lymph-node status and adjuvant radiation therapy. Ann Oncol 2016;27:914-919. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26811346.

54. Feng H, Shuda M, Chang Y, Moore PS. Clonal integration of a polyomavirus in human Merkel cell carcinoma. Science 2008;319:1096-1100. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18202256.

55. Rollison DE, Giuliano AR, Becker JC. New virus associated with merkel cell carcinoma development. J Natl Compr Canc Netw 2010;8:874-880. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20870633.

56. Batinica M, Akgul B, Silling S, et al. Correlation of Merkel cell polyomavirus positivity with PDGFRalpha mutations and survivin expression in Merkel cell carcinoma. J Dermatol Sci 2015;79:43-49. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25936870.

57. Santos-Juanes J, Fernandez-Vega I, Fuentes N, et al. Merkel cell carcinoma and Merkel cell polyomavirus: a systematic review and meta-analysis. Br J Dermatol 2015;173:42-49. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25919492.

58. Paulson KG, Lewis CW, Redman MW, et al. Viral oncoprotein antibodies as a marker for recurrence of Merkel cell carcinoma: A prospective validation study. Cancer 2017;123:1464-1474. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27925665.

59. Bhatia K, Goedert JJ, Modali R, et al. Merkel cell carcinoma subgroups by Merkel cell polyomavirus DNA relative abundance and oncogene expression. International Journal of Cancer 2010;126:2240-2246. Available at: https://onlinelibrary.wiley.com/doi/abs/10.1002/ijc.24676.

60. Sihto H, Kukko H, Koljonen V, et al. Clinical factors associated with Merkel cell polyomavirus infection in Merkel cell carcinoma. J Natl Cancer Inst 2009;101:938-945. Available at: https://www.ncbi.nlm.nih.gov/pubmed/19535775.

61. Moshiri AS, Doumani R, Yelistratova L, et al. Polyomavirus-Negative Merkel Cell Carcinoma: A More Aggressive Subtype Based on Analysis of 282 Cases Using Multimodal Tumor Virus Detection. J Invest Dermatol 2017;137:819-827. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27815175.

62. Harms KL, Zhao L, Johnson B, et al. Virus-positive Merkel Cell Carcinoma Is an Independent Prognostic Group with Distinct Predictive Biomarkers. Clin Cancer Res 2021;27:2494-2504. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33547200.

63. Hall BJ, Pincus LB, Yu SS, et al. Immunohistochemical prognostication of Merkel cell carcinoma: p63 expression but not

polyomavirus status correlates with outcome. J Cutan Pathol 2012;39:911-917. Available at: https://www.ncbi.nlm.nih.gov/pubmed/22882157.

64. Schrama D, Peitsch WK, Zapatka M, et al. Merkel cell polyomavirus status is not associated with clinical course of Merkel cell carcinoma. J Invest Dermatol 2011;131:1631-1638. Available at: https://www.ncbi.nlm.nih.gov/pubmed/21562568.

65. Harms PW, Vats P, Verhaegen ME, et al. The distinctive mutational spectra of polyomavirus-negative Merkel cell carcinoma. Cancer Res 2015;75:3720-3727. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26238782.

66. Wong SQ, Waldeck K, Vergara IA, et al. UV-associated mutations underlie the etiology of MCV-negative Merkel cell carcinomas. Cancer Res 2015;75:5228-5234. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26627015.

67. Goh G, Walradt T, Markarov V, et al. Mutational landscape of MCPyV-positive and MCPyV-negative Merkel cell carcinomas with implications for immunotherapy. Oncotarget 2016;7:3403-3415. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26655088.

68. Singh N, Alexander NA, Lachance K, et al. Clinical benefit of baseline imaging in Merkel cell carcinoma: Analysis of 584 patients. J Am Acad Dermatol 2021;84:330-339. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32707254.

69. Saqlain F, Shalhout SZ, Emerick KS, et al. Diagnostic yield of staging brain magnetic resonance imaging is low in Merkel cell carcinoma: A single-institution cohort study. J Am Acad Dermatol 2021. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34499987.

70. Tseng YD, Nguyen MH, Baker K, et al. Effect of Patient Immune Status on the Efficacy of Radiation Therapy and Recurrence-Free Survival Among 805 Patients With Merkel Cell Carcinoma. Int J Radiat Oncol Biol Phys 2018;102:330-339. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30191867.

71. Goepfert H, Remmler D, Silva E, Wheeler B. Merkel cell carcinoma (endocrine carcinoma of the skin) of the head and neck. Arch Otolaryngol 1984;110:707-712. Available at: https://www.ncbi.nlm.nih.gov/pubmed/6487123.

72. Ball NJ, Tanhuanco-Kho G. Merkel cell carcinoma frequently shows histologic features of basal cell carcinoma: a study of 30 cases. J Cutan Pathol 2007;34:612-619. Available at: https://www.ncbi.nlm.nih.gov/pubmed/17640231.

73. Llombart B, Monteagudo C, Lopez-Guerrero JA, et al. Clinicopathological and immunohistochemical analysis of 20 cases of Merkel cell carcinoma in search of prognostic markers. Histopathology 2005;46:622-634. Available at: https://www.ncbi.nlm.nih.gov/pubmed/15910593.

74. Anderson SE, Beer KT, Banic A, et al. MRI of merkel cell carcinoma: histologic correlation and review of the literature. AJR Am J Roentgenol 2005;185:1441-1448. Available at: https://www.ncbi.nlm.nih.gov/pubmed/16303995.

75. Gollard R, Weber R, Kosty MP, et al. Merkel cell carcinoma: review of 22 cases with surgical, pathologic, and therapeutic considerations. Cancer 2000;88:1842-1851. Available at: https://www.ncbi.nlm.nih.gov/pubmed/10760761.

76. Henderson SA, Tetzlaff MT, Pattanaprichakul P, et al. Detection of mitotic figures and G2+ tumor nuclei with histone markers correlates with worse overall survival in patients with Merkel cell carcinoma. J Cutan Pathol 2014;41:846-852. Available at: https://www.ncbi.nlm.nih.gov/pubmed/25263506.

77. Warner TF, Uno H, Hafez GR, et al. Merkel cells and Merkel cell tumors. Ultrastructure, immunocytochemistry and review of the literature. Cancer 1983;52:238-245. Available at: https://www.ncbi.nlm.nih.gov/pubmed/6344978.

78. Johansson L, Tennvall J, Akerman M. Immunohistochemical examination of 25 cases of Merkel cell carcinoma: a comparison with

small cell carcinoma of the lung and oesophagus, and a review of the literature. APMIS 1990;98:741-752. Available at: https://www.ncbi.nlm.nih.gov/pubmed/1698390.

79. Haag ML, Glass LF, Fenske NA. Merkel cell carcinoma. Diagnosis and treatment. Dermatol Surg 1995;21:669-683. Available at: http://www.ncbi.nlm.nih.gov/pubmed/7633811.

80. Schmidt U, Muller U, Metz KA, Leder LD. Cytokeratin and neurofilament protein staining in Merkel cell carcinoma of the small cell type and small cell carcinoma of the lung. Am J Dermatopathol 1998;20:346-351. Available at: https://www.ncbi.nlm.nih.gov/pubmed/9700371.

81. Bobos M, Hytiroglou P, Kostopoulos I, et al. Immunohistochemical distinction between merkel cell carcinoma and small cell carcinoma of the lung. Am J Dermatopathol 2006;28:99-104. Available at: https://www.ncbi.nlm.nih.gov/pubmed/16625069.

82. Kolhe R, Reid MD, Lee JR, et al. Immunohistochemical expression of PAX5 and TdT by Merkel cell carcinoma and pulmonary small cell carcinoma: a potential diagnostic pitfall but useful discriminatory marker. Int J Clin Exp Pathol 2013;6:142-147. Available at: https://www.ncbi.nlm.nih.gov/pubmed/23329999.

83. Eftekhari F, Wallace S, Silva EG, Lenzi R. Merkel cell carcinoma of the skin: imaging and clinical features in 93 cases. Br J Radiol 1996;69:226-233. Available at: https://www.ncbi.nlm.nih.gov/pubmed/8800866.

84. Byrd-Gloster AL, Khoor A, Glass LF, et al. Differential expression of thyroid transcription factor 1 in small cell lung carcinoma and Merkel cell tumor. Hum Pathol 2000;31:58-62. Available at: https://www.ncbi.nlm.nih.gov/pubmed/10665914.

85. Hanly AJ, Elgart GW, Jorda M, et al. Analysis of thyroid transcription factor-1 and cytokeratin 20 separates merkel cell carcinoma from small cell carcinoma of lung. J Cutan Pathol 2000;27:118-120. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10728812.

86. Ordonez NG. Value of thyroid transcription factor-1 immunostaining in distinguishing small cell lung carcinomas from other small cell carcinomas. Am J Surg Pathol 2000;24:1217-1223. Available at: https://www.ncbi.nlm.nih.gov/pubmed/10976695.

87. Busam KJ, Jungbluth AA, Rekthman N, et al. Merkel cell polyomavirus expression in merkel cell carcinomas and its absence in combined tumors and pulmonary neuroendocrine carcinomas. Am J Surg Pathol 2009;33:1378-1385. Available at: https://www.ncbi.nlm.nih.gov/pubmed/19609205.

88. Sidiropoulos M, Hanna W, Raphael SJ, Ghorab Z. Expression of TdT in Merkel cell carcinoma and small cell lung carcinoma. Am J Clin Pathol 2011;135:831-838. Available at: https://www.ncbi.nlm.nih.gov/pubmed/21571955.

89. Panse G, McNiff JM, Ko CJ. Basal cell carcinoma: CD56 and cytokeratin 5/6 staining patterns in the differential diagnosis with Merkel cell carcinoma. J Cutan Pathol 2017;44:553-556. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28403527.

90. Koljonen V, Haglund C, Tukiainen E, Bohling T. Neuroendocrine differentiation in primary Merkel cell carcinoma--possible prognostic significance. Anticancer Res 2005;25:853-858. Available at: https://www.ncbi.nlm.nih.gov/pubmed/15868919.

91. Knopf A, Bas M, Hofauer B, et al. Clinicopathological characteristics of head and neck Merkel cell carcinomas. Head Neck 2017;39:92-97. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27447124.

92. Mott RT, Smoller BR, Morgan MB. Merkel cell carcinoma: a clinicopathologic study with prognostic implications. J Cutan Pathol 2004;31:217-223. Available at: https://www.ncbi.nlm.nih.gov/pubmed/14984573.

93. Kukko HM, Koljonen VS, Tukiainen EJ, et al. Vascular invasion is an early event in pathogenesis of Merkel cell carcinoma. Mod Pathol 2010;23:1151-1156. Available at: https://www.ncbi.nlm.nih.gov/pubmed/20473275.

94. Asioli S, Righi A, de Biase D, et al. Expression of p63 is the sole independent marker of aggressiveness in localised (stage I-II) Merkel cell carcinomas. Mod Pathol 2011;24:1451-1461. Available at: https://www.ncbi.nlm.nih.gov/pubmed/21765392.

95. Sihto H, Kukko H, Koljonen V, et al. Merkel cell polyomavirus infection, large T antigen, retinoblastoma protein and outcome in Merkel cell carcinoma. Clin Cancer Res 2011;17:4806-4813. Available at: https://www.ncbi.nlm.nih.gov/pubmed/21642382.

96. Zaragoza J, Kervarrec T, Touze A, et al. A high neutrophil-to-lymphocyte ratio as a potential marker of mortality in patients with Merkel cell carcinoma: A retrospective study. J Am Acad Dermatol 2016;75:712-721 e711. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27544490.

97. Smith KJ, Skelton HG, 3rd, Holland TT, et al. Neuroendocrine (Merkel cell) carcinoma with an intraepidermal component. Am J Dermatopathol 1993;15:528-533. Available at: https://www.ncbi.nlm.nih.gov/pubmed/8311181.

98. Acebo E, Vidaurrazaga N, Varas C, et al. Merkel cell carcinoma: a clinicopathological study of 11 cases. J Eur Acad Dermatol Venereol 2005;19:546-551. Available at: https://www.ncbi.nlm.nih.gov/pubmed/16164706.

99. Saeb-Lima M, Montante-Montes de Oca D, Albores-Saavedra J. Merkel cell carcinoma with eccrine differentiation: a clinicopathologic study of 7 cases. Ann Diagn Pathol 2008;12:410-414. Available at: https://www.ncbi.nlm.nih.gov/pubmed/18995205.

100. Martin B, Poblet E, Rios JJ, et al. Merkel cell carcinoma with divergent differentiation: histopathological and immunohistochemical study of 15 cases with PCR analysis for Merkel cell polyomavirus. Histopathology 2013;62:711-722. Available at: https://www.ncbi.nlm.nih.gov/pubmed/23530585.

101. D'Agostino M, Cinelli C, Willard R, et al. Epidermotropic Merkel cell carcinoma: a case series with histopathologic examination. J Am Acad Dermatol 2010;62:463-468. Available at: https://www.ncbi.nlm.nih.gov/pubmed/20159312.

102. Miner AG, Patel RM, Wilson DA, et al. Cytokeratin 20-negative Merkel cell carcinoma is infrequently associated with the Merkel cell polyomavirus. Mod Pathol 2015;28:498-504. Available at: https://www.ncbi.nlm.nih.gov/pubmed/25394777.

103. Pulitzer MP, Brannon AR, Berger MF, et al. Cutaneous squamous and neuroendocrine carcinoma: genetically and immunohistochemically different from Merkel cell carcinoma. Mod Pathol 2015;28:1023-1032. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26022453.

104. Paulson KG, Carter JJ, Johnson LG, et al. Antibodies to merkel cell polyomavirus T antigen oncoproteins reflect tumor burden in merkel cell carcinoma patients. Cancer Res 2010;70:8388-8397. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20959478.

105. Samimi M, Molet L, Fleury M, et al. Prognostic value of antibodies to Merkel cell polyomavirus T antigens and VP1 protein in patients with Merkel cell carcinoma. Br J Dermatol 2016;174:813-822. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26600395.

106. Touze A, Le Bidre E, Laude H, et al. High levels of antibodies against merkel cell polyomavirus identify a subset of patients with merkel cell carcinoma with better clinical outcome. J Clin Oncol 2011;29:1612-1619. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21422439.

107. Amin MB, Edge S, Greene F, et al., eds. AJCC Cancer Staging Manual (ed 8th). New York: Springer International Publishing; 2017.

108. Rao P, Balzer BL, Lemos BD, et al. Protocol for the examination of specimens from patients with merkel cell carcinoma of the skin. Arch Pathol Lab Med 2010;134:341-344. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20196661.

109. Smoller BR, Bichakjian CK, Brown JA, et al. Protocol for the Examination of Specimens From Patients With Merkel Cell Carcinoma of the Skin, Version 4.0.0.1. College of American Pathologists Cancer

Protocol Templates 2017. Available at: http://www.cap.org/ShowProperty?nodePath=/UCMCon/Contribution%20Folders/WebContent/pdf/cp-skin-merkelcell-17protocol-4001.pdf.

110. Marcoval J, Ferreres JR, Penin RM, et al. Merkel cell carcinoma: differences between sun-exposed and non-sun-exposed variants--a clinical analysis of 36 cases. Dermatology 2014;229:205-209. Available at: https://www.ncbi.nlm.nih.gov/pubmed/25278300.

111. Smith VA, Camp ER, Lentsch EJ. Merkel cell carcinoma: identification of prognostic factors unique to tumors located in the head and neck based on analysis of SEER data. Laryngoscope 2012;122:1283-1290. Available at: https://www.ncbi.nlm.nih.gov/pubmed/22522673.

112. Iyer JG, Storer BE, Paulson KG, et al. Relationships among primary tumor size, number of involved nodes, and survival for 8044 cases of Merkel cell carcinoma. J Am Acad Dermatol 2014;70:637-643. Available at: https://www.ncbi.nlm.nih.gov/pubmed/24521828.

113. Bhatia S, Storer BE, Iyer JG, et al. Adjuvant radiation therapy and chemotherapy in Merkel cell carcinoma: survival analyses of 6908 cases from the National Cancer Data Base. J Natl Cancer Inst 2016;108. Available at: http://www.ncbi.nlm.nih.gov/pubmed/27245173.

114. Fields RC, Busam KJ, Chou JF, et al. Recurrence and survival in patients undergoing sentinel lymph node biopsy for merkel cell carcinoma: analysis of 153 patients from a single institution. Ann Surg Oncol 2011;18:2529-2537. Available at: https://www.ncbi.nlm.nih.gov/pubmed/21431988.

115. Schwartz JL, Griffith KA, Lowe L, et al. Features predicting sentinel lymph node positivity in Merkel cell carcinoma. J Clin Oncol 2011;29:1036-1041. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21300936.

116. Gillenwater AM, Hessel AC, Morrison WH, et al. Merkel cell carcinoma of the head and neck: effect of surgical excision and radiation on recurrence and survival. Arch Otolaryngol Head Neck Surg 2001;127:149-154. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11177031.

117. Sandel HDt, Day T, Richardson MS, et al. Merkel cell carcinoma: does tumor size or depth of invasion correlate with recurrence, metastasis, or patient survival? Laryngoscope 2006;116:791-795. Available at: https://www.ncbi.nlm.nih.gov/pubmed/16652089.

118. Poulsen M, Round C, Keller J, et al. Factors influencing relapse-free survival in Merkel cell carcinoma of the lower limb--a review of 60 cases. Int J Radiat Oncol Biol Phys 2010;76:393-397. Available at: https://www.ncbi.nlm.nih.gov/pubmed/19515508.

119. Fields RC, Busam KJ, Chou JF, et al. Recurrence after complete resection and selective use of adjuvant therapy for stage I through III Merkel cell carcinoma. Cancer 2012;118:3311-3320. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22072529.

120. Balakrishnan V, Berry S, Stew B, Sizeland A. Benefits of combined modality treatment of Merkel cell carcinoma of the head and neck: single institution experience. J Laryngol Otol 2013;127:908-916. Available at: https://www.ncbi.nlm.nih.gov/pubmed/23952972.

121. Andea AA, Coit DG, Amin B, Busam KJ. Merkel cell carcinoma: histologic features and prognosis. Cancer 2008;113:2549-2558. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18798233.

122. Harounian JA, Molin N, Galloway TJ, et al. Effect of Sentinel Lymph Node Biopsy and LVI on Merkel Cell Carcinoma Prognosis and Treatment. Laryngoscope 2021;131:E828-E835. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32663337.

123. Strom T, Carr M, Zager JS, et al. Radiation therapy is associated with improved outcomes in Merkel cell carcinoma. Ann Surg Oncol 2016;23:3572-3578. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27251134.

124. Lim CS, Whalley D, Haydu LE, et al. Increasing tumor thickness is associated with recurrence and poorer survival in patients with Merkel

cell carcinoma. Ann Surg Oncol 2012;19:3325-3334. Available at: https://www.ncbi.nlm.nih.gov/pubmed/22820936.

125. Fleming KE, Ly TY, Pasternak S, et al. Support for p63 expression as an adverse prognostic marker in Merkel cell carcinoma: report on a Canadian cohort. Hum Pathol 2014;45:952-960. Available at: https://www.ncbi.nlm.nih.gov/pubmed/24746200.

126. Butala AA, Jain V, Reddy VK, et al. Impact of Tumor-Infiltrating Lymphocytes on Overall Survival in Merkel Cell Carcinoma. Oncologist 2021;26:63-69. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32886418.

127. Johnson ME, Zhu F, Li T, et al. Absolute lymphocyte count: a potential prognostic factor for Merkel cell carcinoma. J Am Acad Dermatol 2014;70:1028-1035. Available at: https://www.ncbi.nlm.nih.gov/pubmed/24666998.

128. Paulson KG, Iyer JG, Tegeder AR, et al. Transcriptome-wide studies of merkel cell carcinoma and validation of intratumoral CD8+ lymphocyte invasion as an independent predictor of survival. J Clin Oncol 2011;29:1539-1546. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21422430.

129. Paulson KG, Iyer JG, Simonson WT, et al. CD8+ lymphocyte intratumoral infiltration as a stage-independent predictor of Merkel cell carcinoma survival: a population-based study. Am J Clin Pathol 2014;142:452-458. Available at: https://www.ncbi.nlm.nih.gov/pubmed/25239411.

130. Kervarrec T, Gaboriaud P, Berthon P, et al. Merkel cell carcinomas infiltrated with CD33(+) myeloid cells and CD8(+) T cells are associated with improved outcome. J Am Acad Dermatol 2018;78:973-982 e978. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29273486.

131. Feldmeyer L, Hudgens CW, Ray-Lyons G, et al. Density, distribution, and composition of immune infiltrates correlate with survival in Merkel cell carcinoma. Clin Cancer Res 2016;22:5553-5563. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27166398.

132. Pilotti S, Rilke F, Bartoli C, Grisotti A. Clinicopathologic correlations of cutaneous neuroendocrine Merkel cell carcinoma. J Clin Oncol 1988;6:1863-1873. Available at: https://www.ncbi.nlm.nih.gov/pubmed/3199169.

133. Skelton HG, Smith KJ, Hitchcock CL, et al. Merkel cell carcinoma: analysis of clinical, histologic, and immunohistologic features of 132 cases with relation to survival. J Am Acad Dermatol 1997;37:734-739. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9366819.

134. Schwartz JL, Bichakjian CK, Lowe L, et al. Clinicopathologic features of primary Merkel cell carcinoma: a detailed descriptive analysis of a large contemporary cohort. Dermatol Surg 2013;39:1009-1016. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23551620.

135. Howard RA, Dores GM, Curtis RE, et al. Merkel cell carcinoma and multiple primary cancers. Cancer Epidemiol Biomarkers Prev 2006;15:1545-1549. Available at: https://www.ncbi.nlm.nih.gov/pubmed/16896047.

136. Koljonen V, Kukko H, Tukiainen E, et al. Second cancers following the diagnosis of Merkel cell carcinoma: a nationwide cohort study. Cancer Epidemiol 2010;34:62-65. Available at: https://www.ncbi.nlm.nih.gov/pubmed/20061203.

137. Bzhalava D, Bray F, Storm H, Dillner J. Risk of second cancers after the diagnosis of Merkel cell carcinoma in Scandinavia. Br J Cancer 2011;104:178-180. Available at: https://www.ncbi.nlm.nih.gov/pubmed/21081931.

138. Youlden DR, Youl PH, Peter Soyer H, et al. Multiple primary cancers associated with Merkel cell carcinoma in Queensland, Australia, 1982-2011. J Invest Dermatol 2014;134:2883-2889. Available at: https://www.ncbi.nlm.nih.gov/pubmed/24991966.

139. Koljonen V, Rantanen M, Sahi H, et al. Joint occurrence of Merkel cell carcinoma and non-Hodgkin lymphomas in four Nordic countries. Leuk Lymphoma 2015;56:3315-3319. Available at: https://www.ncbi.nlm.nih.gov/pubmed/25899400.

140. Saxena A, Rubens M, Ramamoorthy V, Khan H. Risk of second cancers in merkel cell carcinoma: a meta-analysis of population based cohort studies. J Skin Cancer 2014;2014:184245. Available at: https://www.ncbi.nlm.nih.gov/pubmed/25574398.

141. Brenner B, Sulkes A, Rakowsky E, et al. Second neoplasms in patients with Merkel cell carcinoma. Cancer 2001;91:1358-1362. Available at: https://www.ncbi.nlm.nih.gov/pubmed/11283937.

142. Ly TY, Walsh NM, Pasternak S. The spectrum of Merkel cell polyomavirus expression in Merkel cell carcinoma, in a variety of cutaneous neoplasms, and in neuroendocrine carcinomas from different anatomical sites. Hum Pathol 2012;43:557-566. Available at: https://www.ncbi.nlm.nih.gov/pubmed/21940035.

143. Ishida M, Okabe H. Merkel cell carcinoma concurrent with Bowen's disease: two cases, one with an unusual immunophenotype. J Cutan Pathol 2013;40:839-843. Available at: https://www.ncbi.nlm.nih.gov/pubmed/23672777.

144. Iwasaki T, Matsushita M, Kuwamoto S, et al. Usefulness of significant morphologic characteristics in distinguishing between Merkel cell polyomavirus-positive and Merkel cell polyomavirus-negative Merkel cell carcinomas. Hum Pathol 2013;44:1912-1917. Available at: https://www.ncbi.nlm.nih.gov/pubmed/23664542.

145. Heenan PJ, Cole JM, Spagnolo DV. Primary cutaneous neuroendocrine carcinoma (Merkel cell tumor). An adnexal epithelial neoplasm. Am J Dermatopathol 1990;12:7-16. Available at: https://www.ncbi.nlm.nih.gov/pubmed/2138434.

146. Kouzmina M, Koljonen V, Leikola J, et al. Frequency and locations of systemic metastases in Merkel cell carcinoma by imaging. Acta Radiol Open 2017;6:2058460117700449. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28540062.

147. Gollub MJ, Gruen DR, Dershaw DD. Merkel cell carcinoma: CT findings in 12 patients. AJR Am J Roentgenol 1996;167:617-620. Available at: https://www.ncbi.nlm.nih.gov/pubmed/8751663.

148. Gupta SG, Wang LC, Penas PF, et al. Sentinel lymph node biopsy for evaluation and treatment of patients with Merkel cell carcinoma: The Dana-Farber experience and meta-analysis of the literature. Arch Dermatol 2006;142:685-690. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16785370.

149. Peloschek P, Novotny C, Mueller-Mang C, et al. Diagnostic imaging in Merkel cell carcinoma: lessons to learn from 16 cases with correlation of sonography, CT, MRI and PET. Eur J Radiol 2010;73:317-323. Available at: https://www.ncbi.nlm.nih.gov/pubmed/19108971.

150. Girard R, Djelouah M, Barat M, et al. Abdominal metastases from Merkel cell carcinoma: Prevalence and presentation on CT examination in 111 patients. Diagn Interv Imaging 2022;103:41-48. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34465553.

151. Colgan MB, Tarantola TI, Weaver AL, et al. The predictive value of imaging studies in evaluating regional lymph node involvement in Merkel cell carcinoma. J Am Acad Dermatol 2012;67:1250-1256. Available at: https://www.ncbi.nlm.nih.gov/pubmed/22552001.

152. Kwekkeboom DJ, Hoff AM, Lamberts SW, et al. Somatostatin analogue scintigraphy. A simple and sensitive method for the in vivo visualization of Merkel cell tumors and their metastases. Arch Dermatol 1992;128:818-821. Available at: https://www.ncbi.nlm.nih.gov/pubmed/1599271.

153. Guitera-Rovel P, Lumbroso J, Gautier-Gougis MS, et al. Indium-111 octreotide scintigraphy of Merkel cell carcinomas and their metastases. Ann Oncol 2001;12:807-811. Available at: https://www.ncbi.nlm.nih.gov/pubmed/11484956.

154. Durani BK, Klein A, Henze M, et al. Somatostatin analogue scintigraphy in Merkel cell tumours. Br J Dermatol 2003;148:1135-1140. Available at: https://www.ncbi.nlm.nih.gov/pubmed/12828740.

155. Belhocine T, Pierard GE, Fruhling J, et al. Clinical added-value of 18FDG PET in neuroendocrine-merkel cell carcinoma. Oncol Rep

2006;16:347-352. Available at: https://www.ncbi.nlm.nih.gov/pubmed/16820914.

156. Concannon R, Larcos GS, Veness M. The impact of (18)F-FDG PET-CT scanning for staging and management of Merkel cell carcinoma: results from Westmead Hospital, Sydney, Australia. J Am Acad Dermatol 2010;62:76-84. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20082888.

157. Maury G, Dereure O, Du-Thanh A, et al. Interest of (18)F-FDG PET-CT scanning for staging and management of merkel cell carcinoma: a retrospective study of 15 patients. J Eur Acad Dermatol Venereol 2011;25:1420-1427. Available at: https://www.ncbi.nlm.nih.gov/pubmed/21366705.

158. Siva S, Byrne K, Seel M, et al. 18F-FDG PET provides high-impact and powerful prognostic stratification in the staging of Merkel cell carcinoma: a 15-year institutional experience. J Nucl Med 2013;54:1223-1229. Available at: https://www.ncbi.nlm.nih.gov/pubmed/23753187.

159. Hawryluk EB, O'Regan KN, Sheehy N, et al. Positron emission tomography/computed tomography imaging in Merkel cell carcinoma: a study of 270 scans in 97 patients at the Dana-Farber/Brigham and Women's Cancer Center. J Am Acad Dermatol 2013;68:592-599. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23127473.

160. Ibrahim SF, Ahronowitz I, McCalmont TH, et al. 18F-fluorodeoxyglucose positron emission tomography-computed tomography imaging in the management of Merkel cell carcinoma: a single-institution retrospective study. Dermatol Surg 2013;39:1323-1333. Available at: https://www.ncbi.nlm.nih.gov/pubmed/23777452.

161. Treglia G, Kakhki VR, Giovanella L, Sadeghi R. Diagnostic performance of fluorine-18-fluorodeoxyglucose positron emission tomography in patients with Merkel cell carcinoma: a systematic review and meta-analysis. Am J Clin Dermatol 2013;14:437-447. Available at: https://www.ncbi.nlm.nih.gov/pubmed/23959776.

162. Buder K, Lapa C, Kreissl MC, et al. Somatostatin receptor expression in Merkel cell carcinoma as target for molecular imaging. BMC Cancer 2014;14:268. Available at: https://www.ncbi.nlm.nih.gov/pubmed/24742330.

163. George A, Girault S, Testard A, et al. The impact of (18)F-FDG-PET/CT on Merkel cell carcinoma management: a retrospective study of 66 scans from a single institution. Nucl Med Commun 2014;35:282-290. Available at: https://www.ncbi.nlm.nih.gov/pubmed/24240193.

164. Byrne K, Siva S, Chait L, et al. 15-year experience of 18F-FDG PET imaging in response assessment and restaging after definitive treatment of Merkel cell carcinoma. J Nucl Med 2015;56:1328-1333. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26159592.

165. Liu J, Larcos G, Howle J, Veness M. Lack of clinical impact of (18) F-fluorodeoxyglucose positron emission tomography with simultaneous computed tomography for stage I and II Merkel cell carcinoma with concurrent sentinel lymph node biopsy staging: A single institutional experience from Westmead Hospital, Sydney. Australas J Dermatol 2017;58:99-105. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26459330.

166. Sollini M, Taralli S, Milella M, et al. Somatostatin receptor positron emission tomography/computed tomography imaging in Merkel cell carcinoma. J Eur Acad Dermatol Venereol 2016;30:1507-1511. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26446694.

167. Ben-Haim S, Garkaby J, Primashvili N, et al. Metabolic assessment of Merkel cell carcinoma: the role of 18F-FDG PET/CT. Nucl Med Commun 2016;37:865-873. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27092665.

168. Poulsen M, Macfarlane D, Veness M, et al. Prospective analysis of the utility of 18-FDG PET in Merkel cell carcinoma of the skin: A Trans Tasman Radiation Oncology Group Study, TROG 09:03. J Med Imaging Radiat Oncol 2018. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29405630.

169. Feletti A, Marton E, Rossi S, et al. Pituitary metastasis of Merkel cell carcinoma. J Neurooncol 2010;97:295-299. Available at: https://www.ncbi.nlm.nih.gov/pubmed/19806319.

170. Abul-Kasim K, Soderstrom K, Hallsten L. Extensive central nervous system involvement in Merkel cell carcinoma: a case report and review of the literature. J Med Case Rep 2011;5:35. Available at: https://www.ncbi.nlm.nih.gov/pubmed/21269448.

171. Caramanti RL, Chaddad Neto FE, Meguins LC, et al. Brain metastasis of Merkel cell carcinoma - A rare case report. Surg Neurol Int 2019;10:172. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31583169.

172. Foote M, Veness M, Zarate D, Poulsen M. Merkel cell carcinoma: the prognostic implications of an occult primary in stage IIIB (nodal) disease. J Am Acad Dermatol 2012;67:395-399. Available at: https://www.ncbi.nlm.nih.gov/pubmed/22030017.

173. Tarantola TI, Vallow LA, Halyard MY, et al. Unknown primary Merkel cell carcinoma: 23 new cases and a review. J Am Acad Dermatol 2013;68:433-440. Available at: https://www.ncbi.nlm.nih.gov/pubmed/23182060.

174. Chen KT, Papavasiliou P, Edwards K, et al. A better prognosis for Merkel cell carcinoma of unknown primary origin. Am J Surg 2013;206:752-757. Available at: https://www.ncbi.nlm.nih.gov/pubmed/23835211.

175. Vandeven N, Lewis CW, Makarov V, et al. Merkel Cell Carcinoma Patients Presenting Without a Primary Lesion Have Elevated Markers of Immunity, Higher Tumor Mutation Burden, and Improved Survival. Clin Cancer Res 2018;24:963-971. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29246939.

176. Wright GP, Holtzman MP. Surgical resection improves median overall survival with marginal improvement in long-term survival when compared with definitive radiotherapy in Merkel cell carcinoma: A propensity score matched analysis of the National Cancer Database. Am J Surg 2018;215:384-387. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29157891.

177. Kukko H, Bohling T, Koljonen V, et al. Merkel cell carcinoma - a population-based epidemiological study in Finland with a clinical series of 181 cases. Eur J Cancer 2012;48:737-742. Available at: https://www.ncbi.nlm.nih.gov/pubmed/21729823.

178. Kim JA, Choi AH. Effect of radiation therapy on survival in patients with resected Merkel cell carcinoma: a propensity score surveillance, epidemiology, and end results database analysis. JAMA Dermatol 2013;149:831-838. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23864085.

179. Sattler E, Geimer T, Sick I, et al. Sentinel lymph node in Merkel cell carcinoma: To biopsy or not to biopsy? J Dermatol 2013;40:374-379. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23414107.

180. Haymerle G, Fochtmann A, Kunstfeld R, et al. Merkel cell carcinoma: Overall survival after open biopsy versus wide local excision. Head Neck 2016;38 Suppl 1:E1014-1018. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26041367.

181. Chen MM, Roman SA, Sosa JA, Judson BL. The role of adjuvant therapy in the management of head and neck merkel cell carcinoma: an analysis of 4815 patients. JAMA Otolaryngol Head Neck Surg 2015;141:137-141. Available at: https://www.ncbi.nlm.nih.gov/pubmed/25474617.

182. Vargo JA, Ghareeb ER, Balasubramani GK, Beriwal S. RE: Adjuvant radiation therapy and chemotherapy in Merkel cell carcinoma: Survival analyses of 6908 cases from the National Cancer Data Base. J Natl Cancer Inst 2017;109. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28423400.

183. Singh B, Qureshi MM, Truong MT, Sahni D. Demographics and outcomes of stage I-II Merkel cell carcinoma treated with Mohs micrographic surgery compared with wide local excision in the National

Cancer Data Base. J Am Acad Dermatol 2018. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29408552.

184. O'Connor WJ, Roenigk RK, Brodland DG. Merkel cell carcinoma. Comparison of Mohs micrographic surgery and wide excision in eighty-six patients. Dermatol Surg 1997;23:929-933. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9357504.

185. Boyer JD, Zitelli JA, Brodland DG, D'Angelo G. Local control of primary Merkel cell carcinoma: review of 45 cases treated with Mohs micrographic surgery with and without adjuvant radiation. J Am Acad Dermatol 2002;47:885-892. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12451374.

186. Senchenkov A, Barnes SA, Moran SL. Predictors of survival and recurrence in the surgical treatment of merkel cell carcinoma of the extremities. J Surg Oncol 2007;95:229-234. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17323336.

187. Kline L, Coldiron B. Mohs micrographic surgery for the treatment of Merkel cell carcinoma. Dermatol Surg 2016;42:945-951. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27467228.

188. Mattavelli I, Patuzzo R, Torri V, et al. Prognostic factors in Merkel cell carcinoma patients undergoing sentinel node biopsy. Eur J Surg Oncol 2017;43:1536-1541. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28583789.

189. Bajetta E, Celio L, Platania M, et al. Single-institution series of early-stage Merkel cell carcinoma: long-term outcomes in 95 patients managed with surgery alone. Ann Surg Oncol 2009;16:2985-2993. Available at: https://www.ncbi.nlm.nih.gov/pubmed/19609619.

190. Maloney NJ, Nguyen KA, So NA, et al. Risk factors for and prognostic impact of positive surgical margins after excision of Merkel cell carcinoma. J Am Acad Dermatol 2021. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34537251.

191. Jabbour J, Cumming R, Scolyer RA, et al. Merkel cell carcinoma: assessing the effect of wide local excision, lymph node dissection, and radiotherapy on recurrence and survival in early-stage disease--results from a review of 82 consecutive cases diagnosed between 1992 and 2004. Ann Surg Oncol 2007;14:1943-1952. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17356954.

192. Lok B, Khan S, Mutter R, et al. Selective radiotherapy for the treatment of head and neck Merkel cell carcinoma. Cancer 2012;118:3937-3944. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22180314.

193. Howle JR, Hughes TM, Gebski V, Veness MJ. Merkel cell carcinoma: an Australian perspective and the importance of addressing the regional lymph nodes in clinically node-negative patients. J Am Acad Dermatol 2012;67:33-40. Available at: https://www.ncbi.nlm.nih.gov/pubmed/21996296.

194. Timmer FC, Klop WM, Relyveld GN, et al. Merkel cell carcinoma of the head and neck: emphasizing the risk of undertreatment. Eur Arch Otorhinolaryngol 2016;273:1243-1251. Available at: https://www.ncbi.nlm.nih.gov/pubmed/25759258.

195. Han AY, Patel PB, Anderson M, et al. Adjuvant radiation therapy improves patient survival in early-stage merkel cell carcinoma: A 15-year single-institution study. Laryngoscope 2018. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29314048.

196. Jaouen F, Kervarrec T, Caille A, et al. Narrow resection margins are not associated with mortality or recurrence in patients with Merkel cell carcinoma: A retrospective study. J Am Acad Dermatol 2021;84:921-929. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33253832.

197. Tarabadkar ES, Fu T, Lachance K, et al. Narrow excision margins are appropriate for Merkel cell carcinoma when combined with adjuvant radiation: Analysis of 188 cases of localized disease and proposed management algorithm. J Am Acad Dermatol 2021;84:340-347. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32711093.

198. Dancey AL, Rayatt SS, Soon C, et al. Merkel cell carcinoma: a report of 34 cases and literature review. J Plast Reconstr Aesthet Surg 2006;59:1294-1299. Available at: https://www.ncbi.nlm.nih.gov/pubmed/17113506.

199. Andruska N, Fischer-Valuck BW, Mahapatra L, et al. Association Between Surgical Margins Larger Than 1 cm and Overall Survival in Patients With Merkel Cell Carcinoma. JAMA Dermatol 2021;157:540-548. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33760021.

200. Yan L, Sun L, Guan Z, et al. Analysis of cutaneous Merkel cell carcinoma outcomes after different surgical interventions. J Am Acad Dermatol 2020;82:1422-1434. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30296537.

201. Veness MJ, Perera L, McCourt J, et al. Merkel cell carcinoma: improved outcome with adjuvant radiotherapy. ANZ J Surg 2005;75:275-281. Available at: https://www.ncbi.nlm.nih.gov/pubmed/15932436.

202. McAfee WJ, Morris CG, Mendenhall CM, et al. Merkel cell carcinoma: treatment and outcomes. Cancer 2005;104:1761-1764. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16136596.

203. Tsang G, O'Brien P, Robertson R, et al. All delays before radiotherapy risk progression of Merkel cell carcinoma. Australas Radiol 2004;48:371-375. Available at: https://www.ncbi.nlm.nih.gov/pubmed/15344989.

204. Clark JR, Veness MJ, Gilbert R, et al. Merkel cell carcinoma of the head and neck: is adjuvant radiotherapy necessary? Head Neck 2007;29:249-257. Available at: https://www.ncbi.nlm.nih.gov/pubmed/17163472.

205. Koh CS, Veness MJ. Role of definitive radiotherapy in treating patients with inoperable Merkel cell carcinoma: the Westmead Hospital experience and a review of the literature. Australas J Dermatol 2009;50:249-256. Available at: https://www.ncbi.nlm.nih.gov/pubmed/19916967.

206. Fang LC, Lemos B, Douglas J, et al. Radiation monotherapy as regional treatment for lymph node-positive Merkel cell carcinoma. Cancer 2010;116:1783-1790. Available at: https://www.ncbi.nlm.nih.gov/pubmed/20162707.

207. Samimi M, Touze A, Laude H, et al. Vitamin D deficiency is associated with greater tumor size and poorer outcome in Merkel cell carcinoma patients. J Eur Acad Dermatol Venereol 2014;28:298-308. Available at: https://www.ncbi.nlm.nih.gov/pubmed/23368852.

208. Gunaratne DA, Howle JR, Veness MJ. Definitive radiotherapy for Merkel cell carcinoma confers clinically meaningful in-field locoregional control: A review and analysis of the literature. J Am Acad Dermatol 2017;77:142-148 e141. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28495499.

209. Mendenhall WM, Morris CG, Kirwan JM, et al. Management of cutaneous Merkel cell carcinoma. Acta Oncol 2018;57:320-323. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28712323.

210. Fenig E, Brenner B, Katz A, et al. The role of radiation therapy and chemotherapy in the treatment of Merkel cell carcinoma. Cancer 1997;80:881-885. Available at: https://www.ncbi.nlm.nih.gov/pubmed/9307187.

211. Veness M, Foote M, Gebski V, Poulsen M. The role of radiotherapy alone in patients with merkel cell carcinoma: reporting the Australian experience of 43 patients. Int J Radiat Oncol Biol Phys 2010;78:703-709. Available at: https://www.ncbi.nlm.nih.gov/pubmed/19939581.

212. Sundaresan P, Hruby G, Hamilton A, et al. Definitive radiotherapy or chemoradiotherapy in the treatment of Merkel cell carcinoma. Clin Oncol (R Coll Radiol) 2012;24:e131-136. Available at: https://www.ncbi.nlm.nih.gov/pubmed/22626522.

213. Harrington C, Kwan W. Outcomes of Merkel cell carcinoma treated with radiotherapy without radical surgical excision. Ann Surg Oncol 2014;21:3401-3405. Available at: https://www.ncbi.nlm.nih.gov/pubmed/25001091.

214. Veness M, Howle J. Radiotherapy alone in patients with Merkel cell carcinoma: the Westmead Hospital experience of 41 patients. Australas J Dermatol 2015;56:19-24. Available at: https://pubmed.ncbi.nlm.nih.gov/25369110/.

215. Bishop AJ, Garden AS, Gunn GB, et al. Merkel cell carcinoma of the head and neck: Favorable outcomes with radiotherapy. Head Neck 2016;38 Suppl 1:E452-458. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25645649.

216. Straker RJ, 3rd, Carr MJ, Sinnamon AJ, et al. Predictors of False Negative Sentinel Lymph Node Biopsy in Clinically Localized Merkel Cell Carcinoma. Ann Surg Oncol 2021;28:6995-7003. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33890195.

217. Gunaratne DA, Howle JR, Veness MJ. Sentinel lymph node biopsy in Merkel cell carcinoma: a 15-year institutional experience and statistical analysis of 721 reported cases. Br J Dermatol 2016;174:273-281. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26480031.

218. Sims JR, Grotz TE, Pockaj BA, et al. Sentinel lymph node biopsy in Merkel cell carcinoma: The Mayo Clinic experience of 150 patients. Surg Oncol 2018;27:11-17. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29549898.

219. Conic RR, Ko J, Saridakis S, et al. Sentinel lymph node biopsy in Merkel cell carcinoma: Predictors of sentinel lymph node positivity and association with overall survival. J Am Acad Dermatol 2019. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30902726.

220. Shibayama Y, Imafuku S, Takahashi A, Nakayama J. Role of sentinel lymph node biopsy in patients with Merkel cell carcinoma: statistical analysis of 403 reported cases. Int J Clin Oncol 2015;20:188-193. Available at: https://www.ncbi.nlm.nih.gov/pubmed/24687530.

221. Kachare SD, Wong JH, Vohra NA, et al. Sentinel lymph node biopsy is associated with improved survival in Merkel cell carcinoma. Ann Surg Oncol 2014;21:1624-1630. Available at: https://www.ncbi.nlm.nih.gov/pubmed/24378985.

222. Frohm ML, Griffith KA, Harms KL, et al. Recurrence and Survival in Patients With Merkel Cell Carcinoma Undergoing Surgery Without Adjuvant Radiation Therapy to the Primary Site. JAMA Dermatol 2016;152:1001-1007. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27248515.

223. Fritsch VA, Camp ER, Lentsch EJ. Sentinel lymph node status in Merkel cell carcinoma of the head and neck: not a predictor of survival. Head Neck 2014;36:571-579. Available at: https://www.ncbi.nlm.nih.gov/pubmed/24446426.

224. Stadelmann WK, Cobbins L, Lentsch EJ. Incidence of nonlocalization of sentinel lymph nodes using preoperative lymphoscintigraphy in 74 consecutive head and neck melanoma and Merkel cell carcinoma patients. Ann Plast Surg 2004;52:546-549; discussion 550. Available at: https://www.ncbi.nlm.nih.gov/pubmed/15166975.

225. Hoetzenecker W, Guenova E, Bottinger TU, et al. Mapping of specific sentinel node locations for skin cancer of the head. Eur J Dermatol 2011;21:354-358. Available at: https://www.ncbi.nlm.nih.gov/pubmed/21680279.

226. Willis AI, Ridge JA. Discordant lymphatic drainage patterns revealed by serial lymphoscintigraphy in cutaneous head and neck malignancies. Head Neck 2007;29:979-985. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17525953.

227. Allen PJ, Busam K, Hill AD, et al. Immunohistochemical analysis of sentinel lymph nodes from patients with Merkel cell carcinoma. Cancer 2001;92:1650-1655. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11745244.

228. Su LD, Lowe L, Bradford CR, et al. Immunostaining for cytokeratin 20 improves detection of micrometastatic Merkel cell carcinoma in sentinel lymph nodes. J Am Acad Dermatol 2002;46:661-666. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12004304.

229. Schmalbach CE, Lowe L, Teknos TN, et al. Reliability of sentinel lymph node biopsy for regional staging of head and neck Merkel cell carcinoma. Arch Otolaryngol Head Neck Surg 2005;131:610-614. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16027284.

230. Loyo M, Schussel J, Colantuoni E, et al. Detection of Merkel cell virus and correlation with histologic presence of Merkel cell carcinoma in sentinel lymph nodes. Br J Cancer 2012;106:1314-1319. Available at: https://www.ncbi.nlm.nih.gov/pubmed/22415238.

231. Collins BT, Elmberger PG, Tani EM, et al. Fine-needle aspiration of Merkel cell carcinoma of the skin with cytomorphology and immunocytochemical correlation. Diagn Cytopathol 1998;18:251-257. Available at: https://www.ncbi.nlm.nih.gov/pubmed/9557258.

232. Righi A, Asioli S, Caliendo V, et al. An ultrasonography-cytology protocol for the diagnostic management of regional nodes in a subset of patients with Merkel cell carcinoma of the skin. Br J Dermatol 2013;168:563-570. Available at: https://www.ncbi.nlm.nih.gov/pubmed/23106631.

233. Shield PW, Crous H. Fine-needle aspiration cytology of Merkel cell carcinoma-a review of 69 cases. Diagn Cytopathol 2014;42:924-928. Available at: https://www.ncbi.nlm.nih.gov/pubmed/24678011.

234. Cipolletta Campanile A, Malzone MG, Sanna V, et al. Cytological and immunocytochemical features of Merkel cell carcinoma on fine needle cytology samples: A study of 22 cases. Endocr Pathol 2015;26:243-249. Available at: https://www.ncbi.nlm.nih.gov/pubmed/25982258.

235. Grotz TE, Tarantola TI, Otley CC, et al. Natural history of merkel cell carcinoma following locoregional recurrence. Ann Surg Oncol 2012;19:2556-2562. Available at: https://www.ncbi.nlm.nih.gov/pubmed/22453243.

236. Shaw JH, Rumball E. Merkel cell tumour: clinical behaviour and treatment. Br J Surg 1991;78:138-142. Available at: https://www.ncbi.nlm.nih.gov/pubmed/2015460.

237. Mehrany K, Otley CC, Weenig RH, et al. A meta-analysis of the prognostic significance of sentinel lymph node status in Merkel cell carcinoma. Dermatol Surg 2002;28:113-117; discussion 117. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11860419.

238. Deneve JL, Messina JL, Marzban SS, et al. Merkel cell carcinoma of unknown primary origin. Ann Surg Oncol 2012;19:2360-2366. Available at: https://www.ncbi.nlm.nih.gov/pubmed/22271206.

239. Boyle F, Pendlebury S, Bell D. Further insights into the natural history and management of primary cutaneous neuroendocrine (Merkel cell) carcinoma. Int J Radiat Oncol Biol Phys 1995;31:315-323. Available at: https://www.ncbi.nlm.nih.gov/pubmed/7836085.

240. Perez MC, Oliver DE, Weitman ES, et al. Management of Sentinel Lymph Node Metastasis in Merkel Cell Carcinoma: Completion Lymphadenectomy, Radiation, or Both? Ann Surg Oncol 2019;26:379-385. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30311164.

241. Lee JS, Durham AB, Bichakjian CK, et al. Completion Lymph Node Dissection or Radiation Therapy for Sentinel Node Metastasis in Merkel Cell Carcinoma. Ann Surg Oncol 2019;26:386-394. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30556118.

242. Ko JS, Prieto VG, Elson PJ, et al. Histological pattern of Merkel cell carcinoma sentinel lymph node metastasis improves stratification of Stage III patients. Mod Pathol 2016;29:122-130. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26541273.

243. Nguyen AT, Luu M, Lu DJ, et al. Quantitative metastatic lymph node burden and survival in Merkel cell carcinoma. J Am Acad Dermatol 2021;84:312-320. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31954753.

244. Finnigan R, Hruby G, Wratten C, et al. The impact of preradiation residual disease volume on time to locoregional failure in cutaneous Merkel cell carcinoma--a TROG substudy. Int J Radiat Oncol Biol Phys 2013;86:91-95. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23290441.

245. Poulsen MG, Rischin D, Porter I, et al. Does chemotherapy improve survival in high-risk stage I and II Merkel cell carcinoma of the skin? Int J Radiat Oncol Biol Phys 2006;64:114-119. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16125873.

246. Meeuwissen JA, Bourne RG, Kearsley JH. The importance of postoperative radiation therapy in the treatment of Merkel cell carcinoma. Int J Radiat Oncol Biol Phys 1995;31:325-331. Available at: https://www.ncbi.nlm.nih.gov/pubmed/7836086.

247. Mojica P, Smith D, Ellenhorn JD. Adjuvant radiation therapy is associated with improved survival in Merkel cell carcinoma of the skin. J Clin Oncol 2007;25:1043-1047. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17369567.

248. Kang SH, Haydu LE, Goh RY, Fogarty GB. Radiotherapy is associated with significant improvement in local and regional control in Merkel cell carcinoma. Radiat Oncol 2012;7:171. Available at: https://www.ncbi.nlm.nih.gov/pubmed/23075308.

249. Petrelli F, Ghidini A, Torchio M, et al. Adjuvant radiotherapy for Merkel cell carcinoma: A systematic review and meta-analysis. Radiother Oncol 2019;134:211-219. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31005218.

250. Björn Andtback H, Björnhagen-Säfwenberg V, Shi H, et al. Sex Differences in Overall Survival and the Effect of Radiotherapy in Merkel Cell Carcinoma—A Retrospective Analysis of A Swedish Cohort. Cancers 2021;13:265. Available at: https://www.mdpi.com/2072-6694/13/2/265.

251. Wong WG, Stahl K, Olecki EJ, et al. Survival Benefit of Guideline-Concordant Postoperative Radiation for Local Merkel Cell Carcinoma. J Surg Res 2021;266:168-179. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34015514.

252. Takagishi SR, Marx TE, Lewis C, et al. Postoperative radiation therapy is associated with a reduced risk of local recurrence among low risk Merkel cell carcinomas of the head and neck. Adv Radiat Oncol 2016;1:244-251. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28740894.

253. Eng TY, Boersma MG, Fuller CD, et al. Treatment of merkel cell carcinoma. Am J Clin Oncol 2004;27:510-515. Available at: https://www.ncbi.nlm.nih.gov/pubmed/15596922.

254. Lewis KG, Weinstock MA, Weaver AL, Otley CC. Adjuvant local irradiation for Merkel cell carcinoma. Arch Dermatol 2006;142:693-700. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16785371.

255. Guler-Nizam E, Leiter U, Metzler G, et al. Clinical course and prognostic factors of Merkel cell carcinoma of the skin. Br J Dermatol 2009;161:90-94. Available at: https://www.ncbi.nlm.nih.gov/pubmed/19438439.

256. Ghadjar P, Kaanders JH, Poortmans P, et al. The essential role of radiotherapy in the treatment of Merkel cell carcinoma: a study from the Rare Cancer Network. Int J Radiat Oncol Biol Phys 2011;81:e583-591. Available at: https://www.ncbi.nlm.nih.gov/pubmed/21775069.

257. Joseph K, Wong J, Abraham A, et al. Patterns and predictors of relapse in Merkel cell carcinoma: Results from a population-based study. Radiother Oncol 2021;166:110-117. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34838888.

258. Hoeller U, Mueller T, Schubert T, et al. Regional nodal relapse in surgically staged Merkel cell carcinoma. Strahlenther Onkol 2015;191:51-58. Available at: https://www.ncbi.nlm.nih.gov/pubmed/25293726.

259. Hasan S, Liu L, Triplet J, et al. The role of postoperative radiation and chemoradiation in merkel cell carcinoma: a systematic review of the literature. Front Oncol 2013;3:276. Available at: https://www.ncbi.nlm.nih.gov/pubmed/24294591.

260. Kokoska ER, Kokoska MS, Collins BT, et al. Early aggressive treatment for Merkel cell carcinoma improves outcome. Am J Surg

1997;174:688-693. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9409598.

261. Eich HT, Eich D, Staar S, et al. Role of postoperative radiotherapy in the management of Merkel cell carcinoma. Am J Clin Oncol 2002;25:50-56. Available at: https://www.ncbi.nlm.nih.gov/pubmed/11823697.

262. Jouary T, Leyral C, Dreno B, et al. Adjuvant prophylactic regional radiotherapy versus observation in stage I Merkel cell carcinoma: a multicentric prospective randomized study. Ann Oncol 2012;23:1074-1080. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21750118.

263. Grotz TE, Joseph RW, Pockaj BA, et al. Negative sentinel lymph node biopsy in Merkel cell carcinoma is associated with a low risk of same-nodal-basin recurrences. Ann Surg Oncol 2015;22:4060-4066. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25676844.

264. Fujimura T, Furudate S, Kambayahsi Y, et al. Phospho-STAT5B Expression Is a Prognostic Marker for Merkel Cell Carcinoma. Anticancer Res 2017;37:2335-2341. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28476799.

265. Cramer JD, Suresh K, Sridharan S. Completion lymph node dissection for merkel cell carcinoma. Am J Surg 2020. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32087988.

266. Palencia R, Sandhu A, Webb S, et al. Systematic literature review of current treatments for stage I-III Merkel cell carcinoma. Future Oncol 2021;17:4813-4822. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34494443.

267. Sexton KW, Poteet SP, Hill JB, et al. Adjuvant Radiation Therapy Increases Disease-Free Survival in Stage IB Merkel Cell Carcinoma. Ann Plast Surg 2013. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23657045.

268. Strom T, Naghavi AO, Messina JL, et al. Improved local and regional control with radiotherapy for Merkel cell carcinoma of the head and neck. Head Neck 2017;39:48-55. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27300153.

269. Allen PJ, Zhang ZF, Coit DG. Surgical management of Merkel cell carcinoma. Ann Surg 1999;229:97-105. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9923806.

270. Tai PT, Yu E, Winquist E, et al. Chemotherapy in neuroendocrine/Merkel cell carcinoma of the skin: case series and review of 204 cases. J Clin Oncol 2000;18:2493-2499. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10856110.

271. Nghiem PT, Bhatia S, Lipson EJ, et al. PD-1 blockade with pembrolizumab in advanced Merkel-cell carcinoma. N Engl J Med 2016;374:2542-2552. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27093365.

272. Nghiem P, Bhatia S, Lipson EJ, et al. Durable Tumor Regression and Overall Survival in Patients With Advanced Merkel Cell Carcinoma Receiving Pembrolizumab as First-Line Therapy. J Clin Oncol 2019;37:693-702. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30726175.

273. Nghiem P, Bhatia S, Lipson EJ, et al. Three-year survival, correlates and salvage therapies in patients receiving first-line pembrolizumab for advanced Merkel cell carcinoma. J Immunother Cancer 2021;9. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33879601.

274. Topalian SL, Bhatia S, Amin A, et al. Neoadjuvant Nivolumab for Patients With Resectable Merkel Cell Carcinoma in the CheckMate 358 Trial. J Clin Oncol 2020;38:2476-2487. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32324435.

275. Voog E, Biron P, Martin JP, Blay JY. Chemotherapy for patients with locally advanced or metastatic Merkel cell carcinoma. Cancer 1999;85:2589-2595. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10375107.

276. Lewis CW, Qazi J, Hippe DS, et al. Patterns of distant metastases in 215 Merkel cell carcinoma patients: Implications for prognosis and surveillance. Cancer Med 2020;9:1374-1382. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31883234.

277. Maloney NJ, Nguyen KA, Bach DQ, Zaba LC. Sites of distant metastasis in Merkel cell carcinoma differ by primary tumor site and are of prognostic significance: A population-based study in the Surveillance, Epidemiology, and End Results database from 2010 to 2016. J Am Acad Dermatol 2021;84:568-570. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32781190.

278. Kaufman HL, Russell J, Hamid O, et al. Avelumab in patients with chemotherapy-refractory metastatic Merkel cell carcinoma: a multicentre, single-group, open-label, phase 2 trial. Lancet Oncol 2016;17:1374-1385. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27592805.

279. Kaufman HL, Russell JS, Hamid O, et al. Updated efficacy of avelumab in patients with previously treated metastatic Merkel cell carcinoma after >/=1 year of follow-up: JAVELIN Merkel 200, a phase 2 clinical trial. J Immunother Cancer 2018;6:7. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29347993.

280. D'Angelo SP, Russell J, Lebbe C, et al. Efficacy and Safety of First-line Avelumab Treatment in Patients With Stage IV Metastatic Merkel Cell Carcinoma: A Preplanned Interim Analysis of a Clinical Trial. JAMA Oncol 2018;4:e180077. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29566106.

281. D'Angelo SP, Bhatia S, Brohl AS, et al. Avelumab in patients with previously treated metastatic Merkel cell carcinoma (JAVELIN Merkel 200): updated overall survival data after >5 years of follow-up. ESMO Open 2021;6:100290. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34715570.

282. D'Angelo SP, Bhatia S, Brohl AS, et al. Avelumab in patients with previously treated metastatic Merkel cell carcinoma: long-term data and biomarker analyses from the single-arm phase 2 JAVELIN Merkel 200 trial. J Immunother Cancer 2020;8. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32414862.

283. D'Angelo SP, Lebbe C, Mortier L, et al. First-line avelumab in a cohort of 116 patients with metastatic Merkel cell carcinoma (JAVELIN Merkel 200): primary and biomarker analyses of a phase II study. J Immunother Cancer 2021;9. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34301810.

284. Topalian SL, Bhatia S, Hollebecque A, et al. Non-comparative, open-label, multiple cohort, phase 1/2 study to evaluate nivolumab (NIVO) in patients with virus-associated tumors (CheckMate 358): Efficacy and safety in Merkel cell carcinoma (MCC) [abstract]. Presented at the American Association for Cance Research Annual Meeting; Washington, DC. Abstract CT074.

285. Cowey CL, Liu FX, Kim R, et al. Real-world clinical outcomes with first-line avelumab in locally advanced/metastatic Merkel cell carcinoma in the USA: SPEAR-Merkel. Future Oncol 2021;17:2339-2350. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33709776.

286. Park SY, Church C, Alexander NA, et al. Immune checkpoint inhibitor therapy in HIV-associated Merkel cell carcinoma: A case series of 3 patients. JAAD Case Rep 2021;8:28-33. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33490342.

287. Prescribing information: BAVENCIO (avelumab) injection, for intravenous use 2017. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/761049s002lbl.pdf. Accessed May 3, 2018.

288. Prescribing information: KEYTRUDA (pembrolizumab) for injection, for intravenous use. 2017. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/125514s031lbl.pdf. Accessed May 3, 2018.

289. Prescribing information: OPDIVO (nivolumab) injection, for intravenous use. 2018. Available at:

https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/125554s058lbl.pdf. Accessed May 3, 2018.

290. Sharma D, Flora G, Grunberg SM. Chemotherapy of metastatic Merkel cell carcinoma: case report and review of the literature. Am J Clin Oncol 1991;14:166-169. Available at: https://www.ncbi.nlm.nih.gov/pubmed/2028925.

291. Iyer JG, Blom A, Doumani R, et al. Response rates and durability of chemotherapy among 62 patients with metastatic Merkel cell carcinoma. Cancer Med 2016;5:2294-2301. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27431483.

292. Cowey CL, Mahnke L, Espirito J, et al. Real-world treatment outcomes in patients with metastatic Merkel cell carcinoma treated with chemotherapy in the USA. Future Oncol 2017;13:1699-1710. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28605939.

293. Becker JC, Lorenz E, Ugurel S, et al. Evaluation of real-world treatment outcomes in patients with distant metastatic Merkel cell carcinoma following second-line chemotherapy in Europe. Oncotarget 2017;8:79731-79741. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29108353.

294. Satpute SR, Ammakkanavar NR, Einhorn LH. Role of platinum-based chemotherapy for Merkel cell tumor in adjuvant and metastatic settings. Journal of Clinical Oncology 2014;32:9049-9049. Available at: http://ascopubs.org/doi/abs/10.1200/jco.2014.32.15_suppl.9049.

295. Nghiem P, Kaufman HL, Bharmal M, et al. Systematic literature review of efficacy, safety and tolerability outcomes of chemotherapy regimens in patients with metastatic Merkel cell carcinoma. Future Oncol 2017;13:1263-1279. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28350180.

296. Pitale M, Sessions RB, Husain S. An analysis of prognostic factors in cutaneous neuroendocrine carcinoma. Laryngoscope 1992;102:244-249. Available at: http://www.ncbi.nlm.nih.gov/pubmed/1545650.

297. Tai PT, Yu E, Tonita J, Gilchrist J. Merkel cell carcinoma of the skin. J Cutan Med Surg 2000;4:186-195. Available at: https://www.ncbi.nlm.nih.gov/pubmed/11231196.

298. Mahajan S, Barker CA, Mauguen A, et al. (18)F-FDG PET/CT for post-treatment surveillance imaging of patients with stage III Merkel cell carcinoma. J Nucl Med 2021. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34620729.