Merkel Cell Carcinoma

Daniel J. Lewis, MD[a,*], Joseph F. Sobanko, MD[b], Jeremy R. Etzkorn, MD, MS[b], Thuzar M. Shin, MD, PhD[b], Cerrene N. Giordano, MD[b], Stacy L. McMurray, MD[b], Joanna L. Walker, MD[b], Junqian Zhang, MD[b], Christopher J. Miller, MD[b], H. William Higgins II, MD, MBE[b]

KEYWORDS

• Merkel cell carcinoma • Merkel cell polyomavirus • Wide local excision
• Mohs micrographic surgery • Sentinel lymph node biopsy • Radiation therapy
• Immune checkpoint inhibitors

KEY POINTS

- Merkel cell carcinoma (MCC) is a rare malignancy, but its incidence is rapidly increasing, with 0.79 cases occurring per 100,000 person-years. Most cases of MCC are linked to the Merkel cell polyomavirus (MCPyV). Ultraviolet radiation exposure, immunosuppression, and increased age are other important risk factors.
- Treatment of the primary tumor includes wide or narrow margin excision or Mohs micrographic surgery; adjuvant radiation therapy is administered after narrow excision and can be considered after wide excision or Mohs surgery.
- MCC has a high risk of nodal metastasis, so sentinel lymph node biopsy is recommended in all patients with clinically negative nodes to determine prognosis and to plan comprehensive therapy.
- Immunotherapy has replaced chemotherapy as first-line therapy for metastatic MCC. Avelumab and pembrolizumab inhibit the programmed cell death-1 pathway and are approved by the Food and Drug Administration for MCC.
- Long-term surveillance with MCPyV oncoprotein antibody levels and imaging are recommended due to the high risk of local, regional, and distant recurrence.

INTRODUCTION

Merkel cell carcinoma (MCC) is a rare neuroendocrine carcinoma with high rates of local recurrence and metastasis. Five-year survival rates are 51% for local disease, 35% for nodal disease, and 14% for distant disease.[1] National Comprehensive Cancer Network (NCCN) guidelines for MCC are evolving rapidly. We discuss the epidemiology and pathogenesis of MCC and provide an evidence-based approach to diagnosis, staging, therapy, and surveillance.[2]

EPIDEMIOLOGY AND RISK FACTORS

The incidence of MCC has steadily risen over the past 30 years.[3] Analysis of the Surveillance, Epidemiology, and End Results (SEER) registry in the United States revealed an incidence of 0.79 cases per 100,000 person-years in 2011, or approximately 1600 new cases each year, a 95% annual increase since 2000.[3] European countries, Australia, and China have also seen increasing incidence of MCC over the past several decades.[4–6]

This increase has been primarily attributed to the rising proportion of the worldwide population older than 65 years, as MCC incidence is highest during the eighth decade of life, likely due to immunosenescence as well as higher cumulative exposure to ultraviolet (UV) radiation.[3,7] The rise is also likely partly due to increased reporting as well as improved diagnostics, namely cytokeratin-20

[a] Department of Dermatology, University of Pennsylvania, Hospital of the University of Pennsylvania, 3600 Spruce Street, 2 Maloney, Philadelphia, PA 19104-4283, USA; [b] Department of Dermatology, University of Pennsylvania, 3400 Civic Center Boulevard, Suite 1-330S, Philadelphia, PA 19104, USA
* Corresponding author.
E-mail address: daniel.lewis@pennmedicine.upenn.edu

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(CK-20) immunohistochemical staining, which was introduced in 1992.[8]

The prevalence of MCC varies significantly with geography, race, and sex. UV radiation is a risk factor for MCC; therefore, MCC preferentially affects individuals living in geographic areas with high UVB radiation indices.[9] MCC is also approximately 25-fold more common in white than in other ethnic groups and affects men more than women.[10] Immunosuppressed patients, such as those with hematologic malignancy, human immunodeficiency virus infection, or history of solid organ transplantation, are also at higher risk for MCC.[11]

PATHOGENESIS

Merkel Cell Polyomavirus (Virus-Positive Pathway)

Discovered in 2008, the Merkel cell polyomavirus (MCPyV) is ubiquitous, with 60% to 80% of the population infected based on serology and initial exposure likely occurring during childhood.[12–14] Despite the high incidence of MCPyV infection, MCC is rare likely because of adequate immunosurveillance in the large majority of individuals.[15] Nearly 80% of MCC in the United States is attributed to MCPyV, compared with only 25% in Australia.[16]

In the evolution of MCC, MCPyV DNA is clonally integrated into the host cell genome, resulting in the expression of 2 oncoproteins: small T-antigen (T-Ag) and large T-Ag.[12,17] The small T-Ag promotes transcription and gene expression to transform fibroblasts and is postulated to initiate tumorigenesis.[17] Meanwhile, the large T-Ag inhibits the tumor suppressor genes retinoblastoma (Rb) and p53, producing uncontrolled MCC cell proliferation.[17,18] Notably, the mutational burden of virus-positive MCC is the lowest among all cancers.[19]

Ultraviolet Radiation (Virus-Negative Pathway)

The remaining cases of MCC are attributed to UV exposure, accounting for roughly 20% of cases in the United States and most cases in Australia.[16] MCPyV-negative MCC cells show the highest burden of UV-associated mutations and neoantigen expression of any malignancy, including melanoma and cutaneous squamous cell carcinoma (cSCC).[20,21] An array of loss-of-function mutations in tumor suppressor, DNA repair, and activating genes have been implicated in MCPyV-negative MCC, including inactivation of Rb and p53.[20,21]

Cell of Origin

The cell of origin in MCC remains unidentified and controversial. It is likely derived from a cell population such as dermal fibroblasts that enter the Merkel cell differentiation pathway before or during neoplastic transformation.[22–24] MCPyV can infect dermal fibroblasts, whereas UV radiation likely stimulates the expression of genes in fibroblasts that encode matrix metalloproteinases, driving MCC development.[25,26] Investigators have recently suggested that MCC may encompass 2 tumors: a neuroendocrine carcinoma related to MCPyV integration derived from fibroblasts and a UV-related squamous cell carcinoma (SCC) with neuroendocrine differentiation derived from keratinocytes or epidermal stem cells.[27] Others have argued that the term MCC is a misnomer and that the cell of origin is a pre-B lymphocyte rather than a Merkel cell.[24]

DIAGNOSIS

Clinical Presentation

The primary lesion in MCC classically manifests as a solitary erythematous or violaceous papulonodule or plaque on sun-exposed skin (**Fig. 1**), most commonly on the head and neck followed by the extremities.[28] It is usually firm and nontender, and it may ulcerate and grow rapidly after it first appears, often doubling in size within 1 to 3 months. Metastatic MCC with no known primary tumor can also occur and accounts for 4% of all cases.[1]

Common features of MCC are captured in the acronym "AEIOU": asymptomatic, expanding rapidly, immunosuppression, older than age 50, and ultraviolet radiation.[28] This acronym is sensitive in that 89% of patients with MCC have at least 3 of these 5 characteristics, but it is not specific.[28] The nonspecific clinical appearance of MCC can have a broad clinical differential diagnosis, including a cyst, lipoma, dermatofibroma, cSCC, basal cell carcinoma (BCC), or amelanotic melanoma.[29] Biopsy is necessary for diagnosis.

Histopathology and Immunohistochemistry

Histopathology often exhibits nodular growth in the dermis and subcutis (**Fig. 2**A) of undifferentiated small, round blue cells with large nuclei containing granular chromatin, scant cytoplasm, high mitotic figures, apoptotic bodies, and necrosis (**Fig. 2**B).[30] The histopathologic differential diagnosis includes BCC, melanoma, Ewing sarcoma, neuroblastoma, leukemia cutis, and metastatic small-cell lung carcinoma.[30] MCC in situ, in which neoplastic cells are confined to the epidermis or

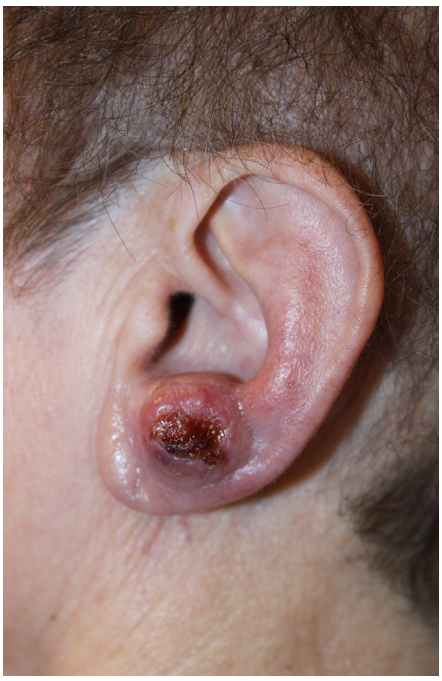

Fig. 1. Classic clinical appearance and anatomic location of MCC: a pink, erythematous nodule with central ulceration on the left ear.

follicular epithelium, may mimic pagetoid intraepidermal neoplasms such as SCC in situ, melanoma in situ, or extramammary Paget disease.[31] Last, a small-cell variant of MCC may share histopathologic features with cutaneous lymphoma.[32]

Immunohistochemistry with neurofilament, CK-20, CK-7, and thyroid transcription factor-1 (TTF-1) exhibits high sensitivity and specificity in distinguishing MCC from common histopathologic mimics (**Table 1**).[30] CK-20 stains MCC in both a diffuse cytoplasmic and a perinuclear dot pattern with 75% sensitivity, with the latter more specific for MCC (**Fig. 2**C).[8,33] Neurofilament promotes detection of CK-20-negative tumors and also frequently exhibits a perinuclear dot pattern.[34] Most MCC lesions are CK7-negative, but a minority of cases demonstrate partial CK-7 positivity.[35] TTF-1 is typically negative and assists in differentiating MCC from metastatic small-cell lung carcinoma.[36] Expression of neuroendocrine markers such as synaptophysin, chromogranin, CD56, and neuron-specific enolase is also characteristic of MCC, but their specificity is low.[34] Lymphovascular invasion can be assessed with D2-40 or CD31 staining.

STAGING AND PROGNOSIS

American Joint Committee on Cancer Staging

In addition to biopsy of the primary MCC, physical examination, imaging, and lymph node (LN) sampling are necessary to stage patients (**Fig. 3**) to determine prognosis, treatment, and eligibility for clinical trials. Updated in 2018, the American Joint Committee on Cancer (AJCC) 8th Edition staging system implemented changes to stratify patients by prognosis more accurately (**Table 2**).[37] The revision distinguishes between clinical and pathologic staging for LNs and distant metastases, an important distinction, as pathology provides more accurate prognostication than clinical assessment.[38] It also now stratifies patients with nodal disease based on whether the primary tumor is known or unknown, because metastases with unknown primary tumors have better prognoses.[38]

Other Prognostic Factors

Additional factors affect prognosis but are not currently reflected in the AJCC 8th Edition staging. Multiple studies have shown that patient-specific factors, such as male sex, immunosuppression, and increasing age at diagnosis, are associated with decreased survival and increased recurrence rates.[39,40] Infiltrative growth on microscopy has

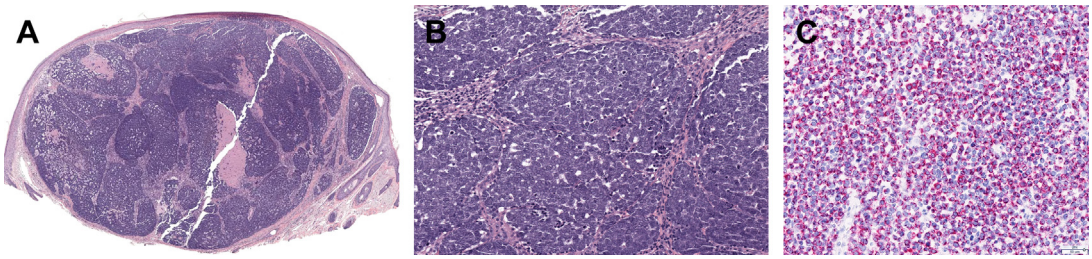

Fig. 2. Typical histopathologic appearance of MCC. (*A*) Nodular collection of monotonous, round blue cells in the dermis; hematoxylin and eosin, original magnification ×25. (*B*) High-power magnification shows atypical cells with round nuclei with finely granular chromatin, scant eosinophilic cytoplasmic rims, and numerous mitotic figures and apoptotic cells; hematoxylin and eosin, original magnification ×150. (*C*) Immunohistochemistry with cytokeratin-20 shows positivity with a characteristic perinuclear dot pattern; magnification ×150.

Table 1
Immunohistochemical staining of Merkel cell carcinoma and histopathologic mimics

Stain	MCC	SCLC	Neuroblastoma	Ewing Sarcoma
Cytokeratin-7	–[a]	+/–	–	–
Cytokeratin-20	+	–	–	–
Thyroid transcription factor-1	–	+	–	–
Neuron-specific enolase	+	+	+	+/–
Chromogranin A	+	+	+	–
Synaptophysin	+	+	+	+/–
Neurofilament	+	–	+	+
CD56	+	+	+	+/–

Abbreviations: CD, cluster of differentiation; MCC, Merkel cell carcinoma; SCLC, small-cell lung cancer.
[a] Cytokeratin-7 (CK-7) is typically negative in MCC; however, a small subset of CK7-positive cases has been described.[36]

also been associated with decreased survival compared with a nodular pattern; evidence remains contradictory on whether Breslow depth affects prognosis.[1] Last, detectable antibodies to T-Ag at diagnosis correlate with lower recurrence rates and increased survival.[41,42]

Baseline Imaging

Up to 13% of patients may exhibit clinically occult metastatic disease on baseline imaging.[43] Therefore, NCCN guidelines now recommend considering baseline imaging at diagnosis for all patients before surgery.[2] PET–computed tomography (PET-CT) is recommended over CT, because PET-CT is twofold more sensitive (17% vs 7%) in upstaging patients.[2,43]

Regional Lymph Nodes

In addition to imaging, clinical assessment of the regional LNs should be performed. Patients with palpable nodes or nodal disease on imaging should undergo fine-needle aspiration, core-needle biopsy, or excisional biopsy.[2] Excisional biopsy should be considered if needle aspiration or core biopsy is negative to exclude a false-negative biopsy result.[2,44] For those with no clinical or radiologic nodal involvement, sentinel lymph node biopsy (SLNB) should be performed,

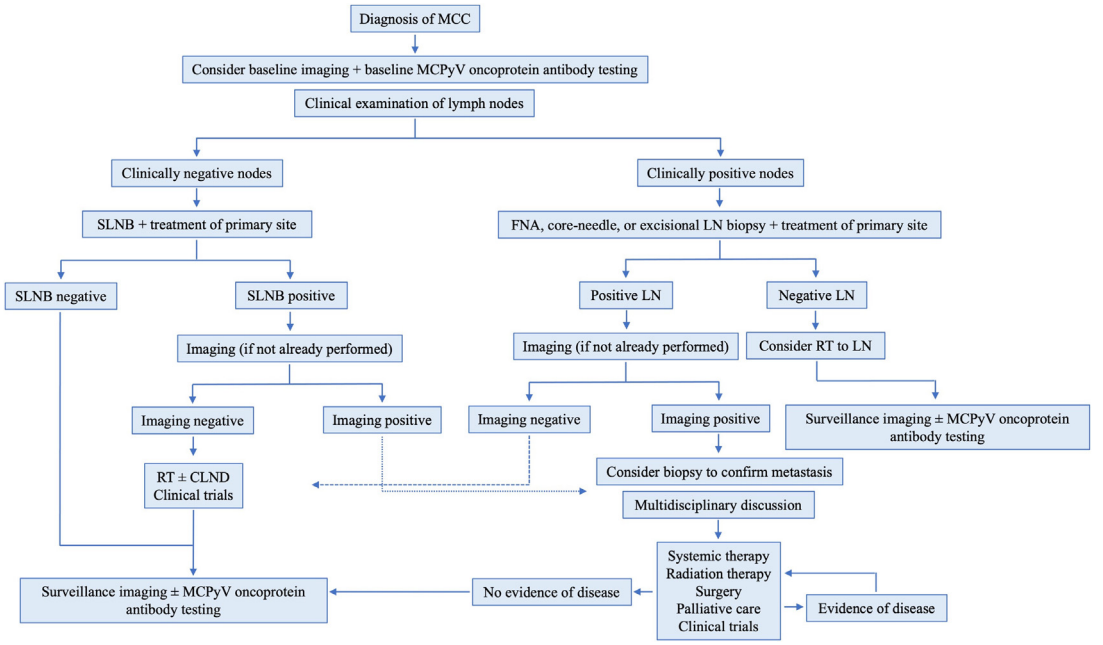

Fig. 3. Overview of evaluation, treatment, and monitoring for MCC. FNA, fine-needle aspiration.

Table 2
American Joint Committee on Cancer 8th Edition staging system for Merkel cell carcinoma

Stage	Method	Primary Tumor	Lymph Node	Metastasis
0	Pathologic	In situ (within epidermis only)	No regional lymph node metastasis	No distant metastasis
I	Clinical[a]	Tumor ≤2 cm in maximum dimension	Negative nodes on clinical exam only (no pathology performed)	No distant metastasis
	Pathologic[b]	Tumor ≤2 cm in maximum dimension	Negative nodes by pathology	No distant metastasis
IIA	Clinical	Tumor ≥2 cm in maximum dimension	Negative nodes on clinical examination only (no pathology performed)	No distant metastasis
	Pathologic	Tumor ≥2 cm in maximum dimension	Negative nodes by pathology	No distant metastasis
IIB	Clinical	Tumor invasion into muscle, fascia, bone, or cartilage	Negative nodes on clinical examination only (no pathology performed)	No distant metastasis
	Pathologic	Tumor invasion into muscle, fascia, bone, or cartilage	Negative nodes by pathology	No distant metastasis
III	Clinical	Any tumor size or invasion	Negative nodes on clinical examination only (no pathology performed)	No distant metastasis
IIIA	Pathologic	Any tumor size or invasion	Positive nodes on pathology only (negative nodes on clinical examination)	No distant metastasis
	Pathologic	Not detected (unknown primary)	Positive nodes on clinical examination and confirmed via pathology	No distant metastasis
IIIB	Pathologic	Any tumor size or invasion	Positive nodes on clinical examination and confirmed via pathology OR in-transit metastasis[c]	No distant metastasis
IV	Clinical	Any tumor size or invasion or unknown primary	Presence or absence of regional nodal disease	Distant metastasis detected via clinical examination
	Pathologic	Any tumor size or invasion or unknown primary	Presence or absence of regional nodal disease	Distant metastasis confirmed via pathology

[a] Clinical detection of nodal or metastatic disease includes inspection, palpation, and imaging.
[b] Pathologic detection of nodal disease includes sentinel lymph node biopsy, fine-needle aspiration, core-needle biopsy, or excisional biopsy. Pathologic confirmation of metastatic disease is via biopsy of the suspected metastasis.
[c] In-transit metastasis represents a tumor distinct from the primary lesion and is located either (1) between the primary lesion and the regional lymph node basin or (2) distal to the primary lesion.

except when contraindicated due to comorbidities.[2,45] All pathologic analysis of nodal tissue should include immunohistochemistry for improved sensitivity.[2]

SLNB is recommended based on evidence that 25% to 30% of patients without lymphadenopathy have occult regional nodal metastasis.[2,46,47] Even patients with small primary tumors have a significant risk of nodal disease: a 0.5-cm tumor confers a 14% risk of regional nodal disease.[1,47,48] In addition, for patients with no nodal disease on imaging, SLNB is still recommended, as PET-CT is less sensitive in detecting micrometastasis and does not replace SLNB as a staging tool.[43] Factors associated with SLNB positivity include large tumor size and pathologic features such as increased thickness, high mitotic rate, and infiltrative growth.[47,49,50]

The effect of SLNB status on survival, particularly disease-specific survival (DSS), remains

unclear. Several studies have shown SLNB status to be a strong predictor of DSS and overall survival (OS).[40,51–53] In some studies, a positive SLNB was associated with a 5-year OS of 50% to 62%, compared with 60% to 80% with a negative SLNB.[1,46] A negative SLNB, compared with negative clinical nodal assessment alone, has been associated with lower rates of recurrence (11% vs 44%) and improved 5-year OS (97% vs 75%).[1,46] However, other single-center studies showed no association between DSS and SLNB status.[49,52] Analysis of 4543 patients with MCC from the SEER registry found a correlation between improved DSS and use of SLNB on univariate but not multivariate analysis.[40] Although the precise effects on DSS remain unclear, SLNB aids in identifying patients who can benefit from therapies for regional control that may improve survival.[54]

Distant Metastasis

Although clinical examination may sometimes detect skin and LN metastases, imaging is often necessary to detect visceral metastases. Although PET-CT should be considered at baseline in all patients, those with pathologic nodal disease should be evaluated for distant metastasis, preferentially with whole-body PET-CT or alternatively with CT with contrast of the neck, chest, abdomen, and pelvis.[2] Imaging is also warranted in patients with unresectable disease or whenever metastasis is suspected based on signs or symptoms.[2] MRI of the brain may be considered for suspected intracranial metastasis.[2] Biopsy may be necessary to confirm metastasis when imaging detects suspicious lesions.

TREATMENT

Primary Tumor Bed

Surgical excision

Surgical excision of the primary tumor is the initial step in treating local MCC (**Fig. 4**). The main objective is to obtain negative microscopic margins when surgically feasible.[2] Regardless of surgical approach, excision should be coordinated with and occur synchronously with or following SLNB, if indicated, to avoid altering lymphatic drainage patterns.[44,54] Reconstruction involving extensive undermining or adjacent tissue rearrangement should be performed only after negative margins are confirmed.[54] Complex reconstruction, especially staged flaps and grafts, also should be avoided in cases in which adjuvant radiation therapy (RT) is planned, as these repair approaches require prolonged postoperative care that may delay RT.[44]

Wide versus narrow margin excision Although the requisite depth of excision is usually to fascia or periosteum, the optimal surgical margin remains poorly defined and typically ranges from 1 to 3 cm.[32] Current NCCN guidelines recommend excision with individualized margins.[2] Margin size should be based on multiple factors: (1) whether adjuvant RT is being considered, (2) associated surgical morbidity, and (3) ability to close the surgical defect based on the margin size.[46,55,56] Some studies have suggested that wide margins of 1 to 2 cm confer lower rates of local recurrence, whereas others have shown no difference in local recurrence with wide (>1 cm) versus narrow (<1 cm) margins.[46,57,58] Importantly, these studies did not account for whether or not adjuvant RT was administered.

Wide local excision (WLE) is the standard and most common surgical method of treating the primary tumor.[2,57] Rates of local recurrence after WLE range are 25% to 40% without adjuvant RT.[57,59,60] However, recent evidence has supported narrow margins if adjuvant RT is planned.[61] In patients with stage I to III disease undergoing surgery without radiation of the primary tumor, local recurrence rate was lower after wide (>1 cm) versus narrow (<1 cm) excision.[62] However, in patients receiving adjuvant RT after excision, local control was excellent with a 1% local recurrence rate regardless of margin size, including patients with positive microscopic margins.[62] Thus, adjuvant RT is powerful in controlling narrow or even positive surgical margins. Based on these findings, NCCN guidelines now recommend either narrow or wide margin excision, allowing the surgical margin to be based on whether adjuvant RT will be administered.[2] Histologically negative margins are recommended when clinically feasible, but surgical margins should be balanced with morbidity of surgery.[2]

Mohs micrographic surgery Mohs micrographic surgery (MMS) represents another surgical approach outlined in NCCN guidelines (**Fig. 5**).[2] Compared with conventional excision, MMS permits complete peripheral and deep margin evaluation before reconstruction, whereas standard excision confers the risk of positive margins from incomplete excision, which occur as often as 10.4% following WLE, or false-negative margins from examination of less than 1% of the surgical margin.[63] The ability to confirm microscopic clearance of the tumor along all margins with MMS may reduce the need for adjuvant RT.[64] MMS also maximizes sparing of normal tissue, a notable benefit in MCC, given it commonly affects cosmetically sensitive areas on the head and neck.

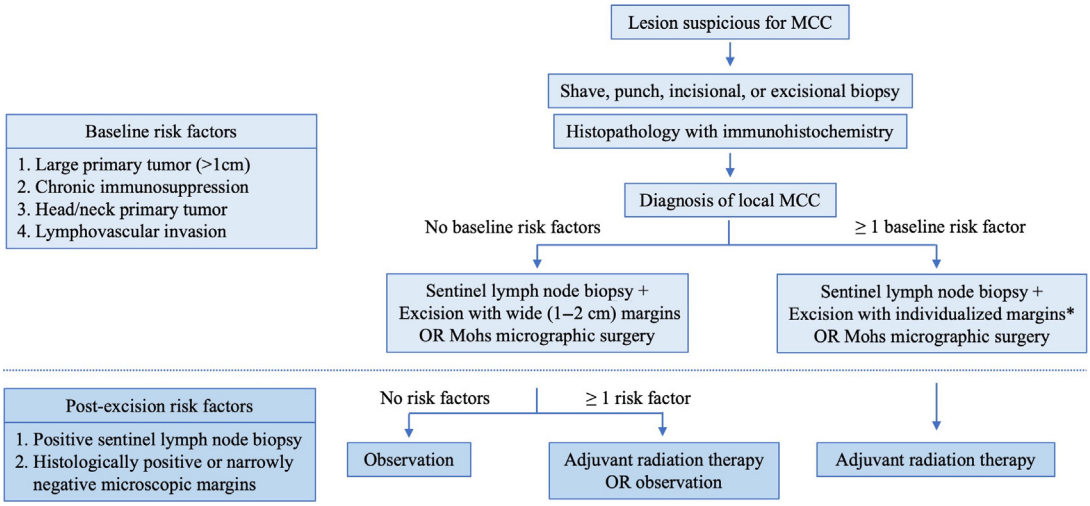

Fig. 4. Diagnosis and treatment of the primary tumor in local MCC. *Narrow (<1 cm) excision margins minimize morbidity, and microscopically positive margins are acceptable when followed by adjuvant RT to the primary site.

MMS for MCC typically involves the intraoperative use of CK-20 immunohistochemistry on frozen section pathology to aid in visualizing tumor cells at the margins and oftentimes within a central debulk specimen. Nevertheless, the central tumor debulk should also be sent for permanent sections for microstaging.[65] Retrospective studies have shown that MMS is effective; however, prospective trials comparing MMS and WLE have not been performed.[63,65,66] Local recurrence rates after MMS are lower than with WLE, ranging from 0% to 22%, whereas survival outcomes are comparable based on limited studies.[59,63,65–67] To ensure accurate LN staging, SLNB is performed first, followed by MMS and reconstruction of the primary tumor in a subsequent operative session.[65]

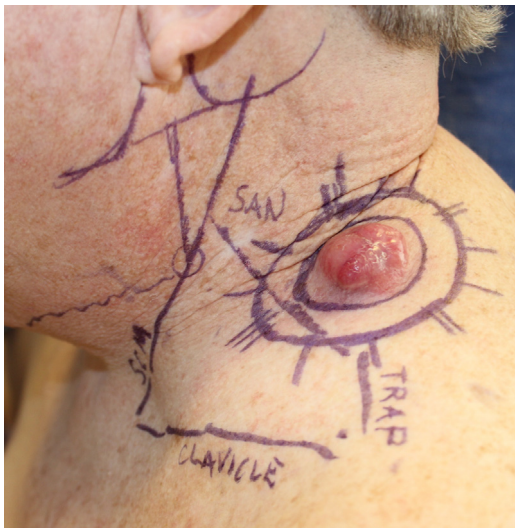

Fig. 5. Preoperative marking during MMS for an MCC on the left neck showing planned incisions for the debulk and initial stage as well as the approximate course of the spinal accessory nerve using surface topographic landmarks.

Radiation therapy

Radiation monotherapy Radiation monotherapy is an alternative to surgery in patients who are poor surgical candidates or who have primary tumor in an anatomic site where excision would produce significant functional compromise.[68] NCCN guidelines recommend higher doses if RT is administered as monotherapy; specifically, 60 to 66 Gy with a field that includes a wide (5-cm) margin around the tumor.[2] However, outcome data on radiation monotherapy remain limited. Although in-field control rates range from 75% to 100%, rates of distant recurrence are increased, and DSS and OS are lower compared with excision.[69] However, these rates are likely influenced by factors unrelated to therapy, because patients selected for radiation monotherapy often have inoperable tumors or comorbidities precluding surgery that may lower OS.

Adjuvant radiation therapy Approximately 50% of patients with MCC in the United States receive local adjuvant RT.[70] Adjuvant RT to the tumor bed provides superb local control, even after narrow excision or positive microscopic margins, and is associated with a trend toward improved disease-free survival (DFS) in multiple retrospective studies.[71,72] Adjuvant RT is indicated in a number of scenarios: (1) narrowly negative microscopic surgical margins, (2) positive microscopic surgical margins, (3) grossly positive

surgical margins when additional surgery is not possible, and (4) in the setting of adverse microscopic features such as lymphovascular invasion.[2,44] NCCN guidelines also recommend adjuvant RT in patients with one or more of the following risk factors: large (>1 cm) primary tumors, head or neck tumors, chronic immunosuppression, and positive SLNB.[2]

Adjuvant RT should be administered within 2 months of surgery to minimize local recurrence.[44] Conventionally fractionated RT consists of 50 to 66 Gy delivered in 25 to 33 fractions.[44] However, this regimen is associated with substantial toxicity, including radiation dermatitis, mucositis, and chronic fibrosis, and requires several treatments over 4 to 6 weeks.[44,73] Preliminary evidence suggests that 8-Gy single-fraction RT (SFRT) provides a high rate of durable local control (94%) while minimizing toxicity.[73,74] SFRT may be considered for tumors with a lower risk of local recurrence, especially those in areas such as the head and neck where higher morbidity associated with RT is anticipated.[44]

The use of adjuvant RT in patients with clear surgical margins remains controversial. Adjuvant RT was not associated with improved local control after margin-negative WLE in one study, and another study failed to show a significant difference in OS, relapse-free survival, or DFS after clear pathologic margins after MMS.[46,64]

Lymph nodes The optimal treatment after assessing LN status has not been defined. Evidence suggests that patients with pathologically negative nodes can be safely observed without adjuvant RT given the low incidence of same nodal basin recurrence after negative SLNB.[75] However, adjuvant RT can be considered in patients at risk for false-negative SLNB, cases in which the primary tumor is located on the head and neck, where SLNB is less accurate due to the complex lymphatic drainage in this region, or in which excision is performed before SLNB, altering lymphatic drainage patterns.[2] Adjuvant RT to regional nodes can also be considered in clinically node-negative patients who decline SLNB.[71,72]

For patients with confirmed nodal disease without distant metastasis, treatment options include complete lymph node dissection (CLND), definitive nodal RT, or both.[44] Patients with SLN-positive disease who undergo either CLND or RT have OS and DSS similar to patients with SLN-negative disease, highlighting the importance of treating the nodal basin.[52] However, data comparing treatment options remain limited. In patients with clinically evident nodal disease, RT provides excellent regional control and has been reported to lower regional recurrence rates; however, it is unclear if these findings apply to occult nodal disease detected by SLNB.[76] Overall, rates of regional recurrence after RT or CLND appear comparable, with no additional benefit derived from RT following CLND.[52] CLND offers the advantage of pathologic evaluation of the entire nodal basin, which may guide the planning of additional RT fields.

NCCN guidelines recommend RT to the nodal basin after CLND in patients with multiple involved nodes or pathologic evidence of extracapsular tumor extension.[2] However, until further evidence and more specific guidelines become available, treatment options for managing nodal disease should be discussed with the patient and may vary based on site-specific morbidity, tumor characteristics, and patient comorbidities.[2,54] At present, systemic agents are not considered first-line for nodal disease.[2] However, guidelines may change as data emerge on immunotherapy in the neoadjuvant setting.[2,77]

Metastatic disease For patients with metastatic disease, consensus guidelines recommend multidisciplinary tumor board discussion of options such as systemic therapy, RT, and palliative care based on the clinical scenario.[2,78] Immunotherapy is now considered first-line therapy for metastatic MCC.[2]

Immunotherapy There is significant rationale for the use of immunotherapy in MCC given the host immune system plays an essential role in controlling the malignancy. Immunosuppressed patients have a 10-fold higher incidence of MCC, and a robust CD8+ T-cell infiltrate within MCC tumors is an excellent prognostic factor associated with no reported MCC-related deaths.[41,42] Oncogenic mutations in MCC tumor cells upregulate the programmed death receptor-1 (PD-1)/programmed death ligand-1 (PD-L1) pathway, promoting local immune evasion via impaired T-cell activation. Furthermore, tumor-infiltrating lymphocytes and circulating MCPyV-specific T cells appear exhausted in MCC.[79–81] PD-1 or PD-L1 blockade with immune checkpoint inhibitors (ICIs) reinvigorates exhausted T cells and stimulates the antitumor response. Response rates with ICIs are approximately 50% to 70% for treatment-naïve disease and 30% for refractory disease, with 70% to 80% response durability at 2 years in both groups.[82–87]

Avelumab, a monoclonal antibody inhibiting PD-L1, was approved by the US Food and Drug Administration (FDA) in 2017 as first-line therapy for metastatic MCC based on the JAVELIN Merkel 200 trial.[85] This trial was a phase II, open-label,

multicenter study in which avelumab was given intravenously every 2 weeks in 88 patients with stage IV disease refractory to chemotherapy.[85] Twenty-eight (33%) patients responded to therapy, with an 11% complete response (CR) rate and with 82% of responses persisting over 10.4 months of follow-up.[85] Median OS was 12.6 months, with a 5-year OS rate of 26%.[87]

Pembrolizumab, an anti-PD-1 monoclonal antibody, was FDA-approved in 2018 for recurrent locally advanced or metastatic MCC. A multicenter phase II trial investigated intravenous pembrolizumab as first-line systemic therapy every 3 weeks for up to 2 years.[83,86] The overall response rate was 58% in 50 patients with metastatic or recurrent locoregional MCC.[83,86] Median progression-free survival (PFS) was 16.8 months and PFS at 3 years was 39%.[83,86]

Nivolumab, another PD-1 inhibitor, is currently under investigation, particularly in combination with ipilimumab, an antibody that inhibits cytotoxic T-lymphocyte associated antigen-4 (CTLA-4).[88,89] Like PD-1/PD-L1, CTLA-4 inhibits T-cell activation, and its blockade can potentiate an antitumor response. Ipilimumab may be particularly useful, either as monotherapy or in combination with a PD-1/PD-L1 inhibitor, in patients in whom PD-1 blockade remains or becomes ineffective.

Use of ICIs as neoadjuvant and adjuvant therapy is a novel approach in MCC actively being studied. In the neoadjuvant setting, a recent trial studied 39 patients with higher-risk local or regional disease treated with 2 doses of nivolumab followed by definitive excision.[77] Approximately 50% patients demonstrated CR, and recurrence-free survival significantly correlated with disease response at the time of surgery.[77] With additional study, neoadjuvant therapy may reduce the extent of therapy to the tumor bed in select patients.

Although the success of ICIs remains encouraging overall, more than 50% of patients demonstrate no response or develop progressive disease after an initial response.[44] In addition, patients receiving immunosuppression for a solid organ transplant or with severe autoimmune disease are poor candidates for ICIs because of the risk of transplant failure or worsened autoimmune disease.

Chemotherapy With the adoption of immunotherapy, chemotherapy is now reserved for palliative therapy or for patients who cannot receive immunotherapy. Common regimens include etoposide with carboplatin or cyclophosphamide, doxorubicin, and vincristine.[90,91] These regimens lead to tumor regression in 53% to 76% of patients but fail to produce a lasting response and lack an OS benefit.[90,91] The duration of response is often as short as 3 months, and median PFS is a mere 3 to 8 months, with fewer than 5% of responders continuing to benefit at 2 years after starting therapy.[90,91] Chemotherapy is also associated with a high risk of toxicity, particularly in patients older than 65, including myelosuppression, renal injury, and sepsis.[90,91]

Radiation therapy A brief course of RT as palliative therapy may be considered in patients with oligometastatic disease. Reported regimens consist of 8 Gy administered as a single fraction or via 3 fractions.[74,92] Regardless of the specific regimen, short-course RT is well-tolerated and may yield response rates as high as 94% with an in-field control rate of 77% at 8 months.[74,92] Combinations of hypofractionated RT and immunotherapy are under active investigation in clinical trials based on the immunologic rationale that radiation induces the release of tumor antigens, essentially priming the cytotoxic T cells reinvigorated by immunotherapy.[93]

Future therapies Other treatment modalities under investigation as either single or adjuvant therapy include immunostimulatory agents such as Toll-like receptor agonists, interleukin-12, MCPyV vaccination, and talimogene laherparepvec.[94–97] Targeted molecular therapies such as Ataxia telangiectasia mutated and Rad3-related kinase inhibitors, double minute 2 protein inhibitors, and histone deacetylase inhibitors are also being studied.[98–100] These molecular therapies may become especially relevant for patients who are poor candidates for immunotherapy.

SURVEILLANCE

Risk of Recurrence

MCC is associated with a high risk of local, regional, and distant recurrence, estimated to be approximately 40% across multiple studies.[25] However, this risk varies by stage: 20% for stage I disease to 75% for stage III disease and by patient-specific factors such as age, sex, tumor location, MCPyV seropositivity, and immunosuppression.[25,44] The median time to recurrence is 7 to 9 months, with 80% to 90% of cases manifesting within the first 2 years.[101] In local disease, recurrence tends to occur locally or in the nodal basin (40%–60%), whereas distant recurrence occurs frequently (80%) in advanced-stage disease.[44]

Follow-Up and Imaging

Prompt recognition of recurrence allows for earlier initiation of therapy. Follow-up visits with complete

skin and nodal examination and review of systems can be considered every 3 to 6 months for 2 to 3 years, and every 6 to 12 months thereafter in disease-free patients.[2,44] Immunosuppressed patients are at a higher risk for recurrence and, as such, more frequent follow-up may be indicated.[44] Immunosuppressive agents should be minimized as clinically feasible.

Surveillance studies should be based on patient-specific risk factors or symptoms, as no guidelines exist.[2,54] A personalized, web-based risk calculator (https://merkelcell.org/recur/) integrating the aforementioned patient risk factors, may assist in quantifying the risk of recurrence and guiding the frequency of surveillance studies. Routine surveillance imaging with PET-CT or CT, with the former exhibiting higher sensitivity, warrants consideration in patients with high-risk tumor features, nodal disease, or immunosuppression.[54] Surveillance imaging may not be necessary in immunocompetent patients with low-risk tumors and negative SLNB.[54]

Merkel Cell Polyomavirus Oncoprotein Antibody Testing

Antibodies targeting MCPyV oncoproteins are detected in approximately 50% of patients with MCC.[102,103] Baseline MCPyV oncoprotein antibody titers can assist with risk stratification and subsequent detection of disease recurrence. An immunologic response to the MCPyV T-Ag oncoprotein appears protective, as seropositive patients have a better prognosis and a 30% lower rate of recurrence than seronegative patients.[102,103] In addition, in patients who are seropositive at baseline, changes in titers over time reflect changes in MCC disease burden, making MCPyV oncoprotein antibodies a useful serum tumor marker for surveillance.[102,103] These titers can be measured via an anti-Merkel cell panel available through the University of Washington.

NCCN guidelines recommend MCPyV oncoprotein antibody titers as part of initial workup and for surveillance in seropositive patients.[2] A baseline level should be obtained ideally within 3 months of initiating therapy.[44] For seropositive patients, levels can then be repeated every 3 months.[2,44] Two consecutive increasing titers of greater than 20% have a 99% positive predictive value for disease recurrence and should prompt imaging studies to evaluate for recurrence.[44] An increase in titers enables detection of 90% of recurrences within 45 days of the first elevated titer.[44] Conversely, a decreasing titer by more than 20% is associated with a 99% negative predictive value for clinically residual disease.[44] For seronegative patients, surveillance should be centered around imaging studies, although the recent emergence of a circulating tumor DNA assay may offer a more sensitive method of surveillance in these patients.[104]

SUMMARY

The past 2 decades have produced advances in cancer biology, molecular genetics, and immunology that have further characterized the pathophysiology of MCC and expanded our therapeutic armamentarium. New immunotherapies such as those targeting the PD-1/PD-L1 pathway have shown promise in yielding durable responses in nearly half of patients with advanced disease and are now first-line agents for advanced-stage MCC. In addition to offering greater efficacy, therapy for MCC has shifted to a less toxic approach, including narrower excision margins, lower doses of RT, and limited use of chemotherapy. Furthermore, discovery of the MCPyV and its role in pathogenesis has led to the introduction of MCPyV oncoprotein antibody testing, the first serologic tool for surveillance in most patients with MCC. However, there is an ongoing need for continued investigation because survival rates, although improved, remain modest. As further studies enhance our understanding and treatment of MCC, guidelines for managing this aggressive malignancy will continue to evolve.

CLINICS CARE POINTS

- Surgical treatment of the primary MCC tumor consists of individualized margin (wide versus narrow) excision or Mohs micrographic surgery. Adjuvant radiation therapy is recommended after narrow excision and can be considered after wide excision or Mohs surgery.
- Sentinel lymph node biopsy is recommended in all patients without clinically apparent nodal disease or distant metastasis and should be performed prior to surgical treatment of the primary tumor.
- MCC is highly immunogenic and thus PD-1/PD-L1 inhibitors such as avelumab and pembrolizumab are now first-line agents for metastatic MCC.
- MCPyV oncoprotein antibody testing can indicate prognosis at time of diagnosis and can be used to monitor for recurrence following treatment.

AUTHOR CONTRIBUTIONS

D. Lewis: Conceptualization, visualization, and original draft preparation.
J. Sobanko: Review and editing.
J. Etzkorn: Review and editing.
T. Shin: Review and editing.
C. Giordano: Review and editing.
S. McMurray: Review and editing.
J. Walker: Review and editing.
J. Zhang: Review and editing.
C. Miller: Project administration, supervision, review and editing.
H. William Higgins: Conceptualization, methodology, project administration, supervision, review and editing.
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