Review Article

Merkel Cell Carcinoma: A Meticulous Literature Appraisal

Hiba Siddiqui[1], Laraib Khan[2], Mifrah Sherwani[3], Ahmed Nadeem Abbasi[4]

Abstract

Merkel cell carcinoma represents an uncommon yet highly aggressive cutaneous malignancy of neuroendocrine origin, with a steadily rising incidence reported worldwide. This review aims to evaluate and summarize current evidence on the diagnosis, staging, and management of Merkel cell carcinoma. A comprehensive literature search was performed across PubMed, Embase, and Google Scholar to identify studies published between 2005 to 2024 addressing the diagnosis, staging, and management of Merkel cell carcinoma. Search terms included "Merkel cell carcinoma" combined with "diagnosis," "staging," "surgery," "radiotherapy," and "systemic therapy." Merkel cell carcinoma frequently presents as a rapidly enlarging, firm, violaceous nodule on sun-exposed skin. Diagnosis relies on histopathology and immunohistochemistry, with characteristic CK20 and neuroendocrine marker positivity. PET/CT outperforms conventional imaging for detecting nodal and distant metastases. Sentinel lymph node biopsy is critical for staging clinically node-negative cases. Treatment is stage-driven and multidisciplinary. Wide local excision with ≥1–2 cm margins remain the surgical standard. Adjuvant radiation enhances loco-regional control, particularly in cases with positive margins, LVI, or immunosuppression. While chemotherapy offers a limited benefit. Immunotherapy has redefined first-line therapy in advanced disease. Emerging targeted therapies hold promise for patients with refractory disease. Future directions in Merkel cell carcinoma management are predicted to emphasize the identification of predictive biomarkers for treatment response, the advancement of novel immune and molecularly targeted therapies, and the optimization of radiotherapy through hypo-fractionated and image-guided app-roaches. A multidisciplinary, timely, and personalized treatment approach is crucial for optimizing outcomes.

Keywords: Merkel cell carcinoma, Sentinel lymph node biopsy, Radiation, Immunotherapy, Multidisciplinary management

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Authors Affiliation: [1]Dr. Ziauddin Hospital, Karachi; [2,4]Aga Khan University Hospital, Karachi; [3]Karachi Medical and Dental College, Karachi

Corresponding Author: Hiba Siddiqui, Dr. Ziauddin Hospital, Karachi
Email: hibasiddiqui824@gmail.com

Introduction

Merkel cell carcinoma (MCC) typically presents as a glossy, dark, bluish, subcutaneous, raised nodule that grows rapidly. MCCs range in size from less than 1 cm to 2 cm and are usually observed in areas that receive a lot of sunlight.[1] In a large cohort study including 9,387 patients with MCC, the head and neck region emerged as the most common site of primary disease (43%), followed by involvement of the upper extremities and shoulder girdle (24%).[2] In the past, MCC was associated with a poor prognosis and few systemic therapeutic choices. However, significant advancements in radiation, immuno-oncology, and molecular characterisation have completely changed modern management strategies. Adjuvant radiation has a crucial role in improving locoregional control, and current evidence supports broad local

excision with sentinel lymph node biopsy as the cornerstone of localized disease management. Immune-checkpoint inhibitors are now the recommended first-line systemic treatment for patients with advanced or metastatic illness. This review attempts to give physicians a current synthesis of guidelines-based recommendations and new information, given the rarity of MCC and the rapid change of its treatment landscape. In particular, it critically evaluates modern, evidence-based therapy approaches and concentrates on current developments in diagnostic techniques.

Methods

To find research concentrating on MCC treatment approaches, staging frameworks, and diagnostic techniques, a systematic review of the literature was conducted. PubMed, Embase, and Google Scholar were searched electronically for articles published between January 2005 and December 2024. Combinations of pertinent free-text phrases, such as Merkel cell carcinoma, diagnostic, staging, surgery, radiation, and immunotherapy, were used in the search method. Only peer-reviewed, English-language publications with human subjects were included in the search. In order to find relevant papers that were not found during the initial database search, the reference lists of eligible research were also manually examined. In order to support well-informed, evidence-based clinical decision-making, this review aimed to summarize current research and new ideas in MCC management.

Results

The existing literature on MCC covers a broad array of subjects, including epidemiological trends, molecular mechanisms, diagnostic assessments, and current treatment approaches. Due to the broad range of the search, a thorough examination of all published research was neither feasible nor planned. This review emphasizes recent, high-quality, clinically relevant evidence that corresponds with the established goals, focusing specifically on diagnostic evaluation, staging, and management strategies based on guidelines. The synthesized data highlights the importance of an exhaustive diagnostic and staging evaluation and illustrates the changing treatment landscape of MCC, where surgical intervention, radiotherapy, and systemic immunotherapy are combined as essential elements of care. Growing evidence points to better clinical results with immune checkpoint inhibitors, in addition to more clearly established roles for adjuvant radiotherapy, underscoring the essential importance of a multidisciplinary, stage-adjusted treatment approach that considers individual patient factors and comorbidities

Diagnosis and Workup

Histopathology

The diagnostic evaluation of MCC typically begins with histopathological assessment of the primary lesion through biopsy, accompanied by a thorough dermatologic examination to assess for additional cutaneous involvement. Hematoxylin-eosin (H&E)-visualized MCC tumors are made of filaments, blue cells with very little cytoplasm, and small, ordinary nucleoli, according to histopathology.[3] Other possible features include perineural invasion, lympho-vascular invasion, numerous mitoses, single-cell necrosis, and epidermal involvement by pagetoid spreading. MCC tumor cells are made up of para-nuclear electron-dense neurosecretory granules, commonly referred to as dense core granules, desmosomes, and 10 nm filaments, just like normal Merkel cells.[4]

Immunochemistry

Immunohistochemistry (IHC) staining demonstrates the significant part in the primary diagnosis of MCC. A relevant immuno-panel should contain cytokeratin 20 (CK20) and thyroid transcription factor (TTF-1), chromogranin, synaptophysin, CD56, neuron-specific enolase (NSE), and neurofilament.[5,6] The combination of these markers can help diagnose difficult instances, even though they are not very specific for MCC. This includes tumors with unusual characteristics, including squamous differentiation or epidermotropism, as well as those that are CK20-negative.

Pathology reporting

Important information, including tumor size, the

condition of the deep and peripheral margins, the existence of lymphovascular invasion (LVI), and extent to bone, cartilage, and muscle fascia should all be included in the pathology report. These characteristics are crucial for prognostication. Further details of the primary tumor should also be recorded, such as its growth pattern (nodular or infiltrative), depth of invasion (measured in millimeters as Breslow thickness). Evaluation should also document whether tumor-infiltrating lymphocytes (TILs) are present, and identify any concurrent malignancies within the same tissue sample, such as squamous cell carcinoma (SCC).[7]

Table 1: *8th ed. AJCC T-Staging of MCC.*

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

Radiology

Data on the emergence and detection of MCC tumors using a variety of imaging techniques, such as computed tomography (CT), ultrasonography, magnetic resonance imaging (MRI), and positron emission tomography (PET), have been published in a number of retrospective analyses. Cross-sectional imaging techniques such as computed tomography (CT) and 18F-fluorodeoxyglucose positron emission tomography/computed tomography (FDG PET/CT) are commonly employed in the detection and staging of MCC along with any distant metastases, across various anatomical locations.[8,9] Whole-body PET is more profound for recognizing occult metastatic disease at baseline.[10] Colgan et al, compared CT-scan and FDG PET data to sentinel lymph node biopsy (SLNB) in a retrospective study, showing the computed sensitivity of FDG PET was considerably higher than that of CT-scan (83% vs. 47%).[11]

Sentinel Lymph Node Biopsy

Sentinel lymph node biopsy (SLNB) is optimally performed before excision of the primary lesion to preserve lymphatic drainage pathways and ensure accurate pathological staging. The procedure is advised for all eligible patients presenting with clinically negative lymph nodes. However, the complex and variable lymphatic drainage routes, especially in the head and neck area, might diminish diagnostic reliability, raising the possibility of false-negative results. These constraints underscore the importance of careful interpretation of results and emphasize the necessity of a thorough evaluation that combines detailed clinical assessment with suitable cross-sectional and functional imaging to enhance overall diagnostic precision.

Staging

Tumor staging is categorized based on the updated criteria specified in the 8th edition of the American Joint Committee on Cancer (AJCC) staging system, as explained below:

Table 2: *8th ed. AJCC clinical-N Staging of MCC.*

Category	Definition
NX	Regional lymph nodes cannot be clinically assessed (e.g., previously removed for another reason, or due to body habitus).
N0	No regional lymph node metastasis was detected on clinical and/or radiologic examination.
N1	Metastasis in regional lymph node(s).
N2	In-transit metastasis (discontinuous from primary tumor; located between the 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 the primary tumor and draining regional nodal basin, or distal to the primary tumor) with lymph node metastasis.

Table 3: *8th ed. AJCC pathological-N Staging of MCC.*

Category	Definition
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 was 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 the primary tumor; located between primary tumor and the draining regional nodal basin, or distal to the primary tumor) with lymph node metastasis.

Management

The treatment of this rare skin cancer is tailored based on the stage of the disease, the location of the lesions, and the patient's overall health. Optimal care is best attained through coordinated decision-making among multiple disciplines, in which experts from dermatology, plastic and reconstructive surgery, radiation oncology, medical oncology, pathology, and radiology collectively participate in treatment planning, thus guaranteeing a comprehensive and patient-focused approach.

Surgical Intervention

Before determining the management approach, it is necessary to determine the stage of the disease. A meta-analysis demonstrated that, in clinically node-negative (cN0) MCC patients, performing SLNB was linked to superior disease-free survival (DFS) and overall survival (OS) outcomes when compared to observation of nodal status without surgical staging.[13] For an extended period, surgical resection has been the standard of care for MCC confined to the primary tumor with at least 2cm margins.[14] The surgical margins are recommended to enable primary tissue closure. Mohs micrographic surgery (MMS), which entails the meticulous excision of malignant tissue in sequential layers with immediate histological assessment, is considered a suitable approach for MCC involving anatomically or functionally critical areas of the face, where tissue conservation is essential.[15] Completion lymph node dissection (CLND) is suggested for patients with sentinel lymph node-positive or clinically evident MCC.[16] Fields et al, showed a cohort of MCC patients with metastatic disease (stage IV) or clinically detectable lymph node involvement (stage IIIB) exhibited higher disease-specific death (DSD) rates compared to those with microscopic lymph node involvement (stage IIIA) or no lymph node involvement (stages I, II).[17]

Role of Radiation

Radiation therapy (RT) shows a significant role in the treatment of MCC. Though a meta-analysis of 17,179 MCC patients showed that adjuvant radiotherapy improved loco-regional and local disease-free survival (DFS), but had no impact on DFS.[18] Delay in starting adjuvant radiation therapy for more than 79 days is related with worse OS of MCC patients.[19] As per NCCN guidelines,[20] the main indications of adjuvant RT are microscopically positive margins, narrow clinical margin (<1 cm) excision, larger primary tumor (>1 cm); chronic T-cell immunosuppression, HIV, chronic lymphocytic leukemia (CLL), solid organ transplant; head/neck primary site; lymph vascular invasion (LVI) present. It is substantial to note that a higher 5-year locoregional recurrence (LRR) rate was observed, when time to postoperative radiotherapy (ttPORT) exceeded 8 weeks compa-

red to within 8 weeks, with rates of 28.0% versus 9.2%, respectively (P = .006).[21]

A tissue-like material called "bolus" is utilized to enhance the dose of radiation delivered to the skin surface by effectively bringing the point of maximum dose closer to the epidermis. It is employed in radiotherapy to treat superficial lesions, including skin cancers[22]. As per NCCN guidelines, for adjuvant radiotherapy, a dose of 50–56 Gy is recommended for negative surgical margins. In cases of microscopically positive margins, the advised dose is 56–60 Gy. If the resection margins are grossly positive, further surgical resection to achieve negative margins is preferred; however, if resection is not feasible, a radiotherapy dose of 60–66 Gy is recommended. Elective irradiation of in-transit lymphatic pathways is generally considered when the primary tumor is anatomically close to the regional nodal basin, to mitigate the risk of subclinical disease spread. If neither SLNB nor lymph node dissection has been performed, a dose of 60–66 Gy is recommended for clinically involved lymph nodes to target the nodal basin. It is essential to note that after lymph node dissection, if multiple nodes are involved or extracapsular extension (ENE) is present, a dose of 60–66 Gy is mandatory. For negative SLNB without lymph node dissection, observation is recommended. However, if SLNB is positive, a radiotherapy dose of 50–56 Gy to the nodal basin is advised.

A recent retrospective published article regarding hypo-fractionated regimen in MCC showed a similar outcome as conventional fractionation.[23] Over all 10 patients received 4Gy per fraction per day in an adjuvant or definitive setting, in total 10 fractions (total dose 40Gy). This regimen has a more biologically effective dose (BED) than most doses used in a preceding study (30–35 Gy in 10 fractions or 45 Gy in 20 fractions). This limited data of patients with MCC, hypofractionated radiation also attained similar results with similar toxicity as with conventional treatment.

High-dose-rate brachytherapy is a different treatment option that can be considered in the management of MCC. This method has demonstrated promising outcomes in the treatment of other skin cancers, too, as evidenced by multiple studies[24,25,26].

Chemotherapy

In contemporary clinical practice, the role of cytotoxic chemotherapy in managing MCC has markedly diminished, primarily due to the emergence of immunotherapy as a more effective treatment option.[27] Historically, chemotherapy was the standard treatment for advanced or metastatic MCC, but its efficacy was limited to short-term responses. Patients often experienced rapid disease progression after initial improvements, with chemotherapy offering little long-term survival benefit. The multivariate analysis suggests chemotherapy does not affect survival.[28.29] The most frequently administered agents include cisplatin, carboplatin, and etoposide.[30]

Immunotherapy

The role of preexisting skin-resident cells, like CD8 tissue-resident memory T cells and Vδ1 T cells, as mediators of immune checkpoint blockade (ICB) is emerging. In major histocompatibility complex-high (MHC-H) MCC, which typically express higher levels of class I MHC molecules, CD8 Trm cells play a crucial part in driving the immune reaction to ICB therapy. In contrast, in MHC-low MCCs, where the expression of MHC class I molecules is reduced, Vδ1 T cells take on a more significant role. These gamma-delta (γδ) T cells can identify and attack tumor cells self-sufficiently of classical antigen presentation by MHC molecules, thus contributing to the efficacy of ICB in these tumors.[31]

In March 2023, the FDA approved Retifanlimab-dlwr, a newly developed monoclonal antibody that targets and blocks the PD-1 receptor on the basis of the POD1UM-201 trial.[32] Other immune checkpoint inhibitors like Pembrolizumab, Nivolumab alone or in combination, are approved for MCC.[33,34,35] As reported by Bhatia et al, in advanced-stage MCC where curative surgery and radiotherapy are not feasible, treatment with Avelumab has demonstrated enhanced clinical outcomes, resulting in favorable real-world metrics, includeing enhanced tumor response (rwORR), extended

response longevity (rwDOR), prolonged time to disease progression (rwPFS), and improved survival duration (OS).[36]

Targeted Molecular Therapy

As immunotherapy has become the pillar treatment for advanced MCC, research into targeted therapies is ongoing, particularly for patients who do not respond to or are ineligible for immunotherapy.[37] Pazopanib and Cabozantinib are the VEGFR-1, VEGFR-2, and 3, and kit inhibitors[38]. For MCC patients, expressing somatostatin receptors, specifically SSTR2 expression, serves as a prognostic marker and is associated with metastatic disease at the time of diagnosis[39]. Although studies regarding somatostatin analog therapy (such as octreotide) are limited[45]. These therapies work by binding to somatostatin receptors and inhibiting tumor growth. In a cohort of 37 individuals with metastatic MCC treated with peptide receptor radionuclide therapy (PRRT) using 177-Lu- or 90Y-labeled somatostatin analogs over 1 to 5 treatment cycles (total administered activity ranging from 1.5 to 30 GBq), an objective response rate of 31.6% was observed, with a favorable safety profile and no significant treatment-related toxicities observed.[40]

Ongoing investigations are exploring therapeutic strategies aimed at the PI3K/AKT/mTOR signaling cascade, a critical molecular pathway implicated in regulating cellular proliferation and survival in MCC.[41] A significant presence of anaplastic lymphoma kinase (ALK) expression has been reported in Merkel cell carcinoma, with one study showing ALK positivity in almost 87% of tumor specimens and a statistically significant relationship with Merkel cell polyomavirus (MCPyV) status, reinforcing its potential role as a prognostic marker.[42] Simultaneously, treatment approaches aimed at ALK signaling pathways, as well as other molecularly targeted agents addressing specific genomic changes, are being explored as possible therapeutic options for certain patients with MCC.

Multidisciplinary Approach

Effective management of MCC demands collaborative efforts from various specialties, and patient outcomes improve significantly when cases are assessed in a specialized multidisciplinary tumor board environment.[43, 44]

Conclusion

Current research initiatives in MCC increasingly focus on enhancing treatment choices by discovering dependable predictive biomarkers, as well as advancing new immunotherapeutic and Molecularly targeted therapies. Concurrent developments in radiotherapy aim to enhance dose administration via hypofractionated regimens and modern image-guided methods. The growing use of genomic profiling, thorough evaluation of the tumor microenvironment, and liquid biopsy technologies presents considerable opportunity to enhance personalized and flexible treatment approaches. Moreover, the increasing application of artificial intelligence in diagnostic pathology, radiomic analysis, and radiation therapy planning could enhance precision and reliability in clinical decision-making. Ongoing multidisciplinary collaboration and strong translational research will continue to be vital for closing existing therapeutic gaps and enhancing long-term outcomes in this biologically aggressive condition.

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Author's Contribution

HS: Conceptualization and primary writing, outlined the manuscript structure.

LK: Reviewed the manuscript for clinical accuracy, contributes to conception of innovation, data analysis, data interpretation and manuscript writing.

MS: Literature search and manuscript writing.

ANA: Final approval of the version to be published.

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