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Merkel Cell Carcinoma: An Updated Review Focused on Bone and Bone Marrow Metastases

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Simple Summary: Merkel cell carcinoma (MCC) is a rare and aggressive neuroendocrine skin cancer, known for its high recurrence rate and metastatic potential. Bone metastases have been identified as the fourth or even the third most common site of distant spread. Despite growing awareness of bone and bone marrow involvement in MCC, current research lacks a comprehensive focus on their biological and radiological behavior, the pattern of metastatic spread, and related clinical, demographic, and treatment profiles. This review aims to provide a comprehensive overview of the current evidence regarding MCC, with a focus on the characteristics and impact of bone and bone marrow metastases.

Abstract: Background/objectives: Despite advancements in early diagnosis and clinical practices guided by standardized care protocols, Merkel cell carcinoma (MCC) is still marked by an unfavorable prognosis with a 5-year relative survival rate of 65%. Indeed, regional nodal metastases affect 40-50% of MCC patients, while approximately 33% experience distant dissemination. Among these, bone and bone marrow metastases are particularly notable, although the characteristics and clinical implications of this metastatic disease in MCC remain poorly understood. Methods: A comprehensive review was conducted using the Medline database (via PubMed) up to January 2024. The search strategy included the string "(Merkel cell carcinoma AND (bone OR marrow))". Results: A total of 1,133 (69.3% male and 30.7% female) patients diagnosed with advanced MCC were collected. The median (IQR) age at diagnosis was 67.5 (12.65) years old. 201 (20.8%) cases of bone and/or bone marrow metastases were identified and linked to a primary known MCC in 75.7% of cases. Bone metastases (BMs) appear as the third most common metastatic site, following the liver (2nd) and lymph nodes (1st). They show a mixed biological and radiological behavior, with a marked preference for the axial skeleton over the appendicular one. Addressing characteristics of bone metastatic disease, neurological symptoms were the most documented, whereas bone marrow involvement and leukemic spread seemed to be primarily related to immunosuppression. Multimodal treatment including platinum-based chemotherapy and radiotherapy represented the primary approach for effective management. Conclusions: The pattern of metastatic spread in MCC differ among studies, with the bones resulting as the third most common site of distant spread. Excluding head and neck MCC, which seems to be more regularly associated with liver metastases, the relationship between the primary tumor site and the development of bone or bone marrow

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metastases appears inconsistent. Overall, BMs mostly correlated with advanced MCC stages and poorer survival outcomes, with a median OS of 8 months (range 12.75-4). The integration of international guidelines alongside the ongoing findings from clinical trials will contribute to improve systemic disease control and enhance patient care.

Keywords: Merkel cell carcinoma; metastasis; bone; bone marrow; diagnosis; dermoscopy; reflectance confocal microscopy; treatment; therapy; etiology; origin; MCC; MCCUP; RCM

1. Introduction

Merkel cell carcinoma (MCC) is a rare yet highly aggressive neuroendocrine skin tumor that predominantly affects elderly men, with the head and extremities being the most common sites of occurrence [1]. In recent years, notable advancements have been achieved in the diagnosis and management of MCC, particularly through the introduction of immunotherapy for locally advanced, inoperable, and metastatic disease [2].

Clinical practice is further guided by several guidelines, which aim to standardize care for MCC patients [2–4]. Despite these advancements, the overall prognosis remains guarded, with a 5-year relative survival rate of 65% across all Surveillance, Epidemiology, and End Results (SEER) stages combined [5]. Moreover, MCC is associated with a high incidence of local recurrence, particularly within the first 2-3 years following the primary tumor excision. Regional nodal metastases develop in 40–50% of patients, while approximately 33% of them experience distant secondaries affecting various anatomical sites [4]. Among these, bone metastases (BMs) have been identified as the fourth [6] or even the third [7] most common site of distant spread.

Nevertheless, despite the increasing recognition of BMs and bone marrow involvement in MCC, current literature lacks a comprehensive focus on their biological and radiological behavior, the patterns of metastatic spread, and related clinical, demographic, and treatment profiles. This review seeks to offer a comprehensive summary of the latest evidence on MCC epidemiology, etiology, diagnosis, and management, with a focus on the characteristics and impact of bone and bone marrow metastases.

2. Materials and Methods

A comprehensive review was conducted from Medline database (via PubMed) up to January 2024. To address our focus, the search strategy included the string "(Merkel cell carcinoma AND (bone OR marrow))". Additionally, relevant keywords were used in different combinations for free-hand search and bibliography of selected articles was reviewed.

3. Epidemiology of MCC

Determining precise global incidence rates for Merkel cell carcinoma remains challenging due to geographic and demographic variability, as well as the lack of global epidemiological studies. However, between 2000 and 2013 MCC diagnosis surged by 95%, almost doubling the 57% increase of melanoma cases [8].

In the United States, data from the SEER registry revealed an MCC incidence rate of 0.7 cases per 100,000 person-years in 2013, corresponding to approximately 2,488 cases annually [8]. On a global scale, the incidence of MCC is estimated at 0.6 cases per 100,000 people annually, based on data derived from different individual regions and isolated case reports [9].

Notably, countries in the southern hemisphere, such as Australia (2.5 per 100,000) and New Zealand (0.96 per 100,000), report the highest incidence rates, significantly exceeding those observed in the northern hemisphere [9,10]. Furthermore, nations such as Norway, Denmark, and Japan, which

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have shown stable incidence rates over time, represent an exception to the overall increasing trend in MCC incidence [11].

As regard the age of MCC patients, the incidence generally rises with it, peaking between 70 and 80 years [11]. Indeed, MCC is relatively rare in younger individuals with only 0.07% of cases occurring in those under 30 years of age [11]. However, when affecting young adults, MCC is often diagnosed at more advanced stages [12].

Based on these data, the trend of incidence is matter of debate. However, several key factors should be considered to understand the phenomenon, combining demographic shifts with environmental exposures and improved diagnostic accuracy: aging population [10], UV-exposure rates [13], increasing MCC awareness among healthcare providers and patients, use of non-invasive diagnostic tools (e.g., dermoscopy, reflectance confocal microscopy) [14,15], greater efficacy and reliance on immunosuppressive therapies [16,17].

4. Etiology and Risk Factors for MCC

4.1. Two (Viral- and UV-Related) Driving Mechanisms for MCC Onset

Similar to other cutaneous malignancies, the pathogenesis of Merkel cell carcinoma is likely the result of a complex interaction between genetic, molecular, and environmental factors. However, MCC recognize two main determinants of pathogenesis: viral and ultraviolet (UV) exposure-related driving mechanisms.

In 2008, researchers identified the integration of a mutated Merkel cell polyomavirus (MCPyV) genome as a key causative factor in the majority of MCC cases [18]. MCPyV, a circular double-stranded DNA virus, is usually acquired during childhood, as defined by the high prevalence of antibodies detectable in the general population against its capsid protein VP1. Despite this virus' widespread occurrence, primary MCPyV infection is typically asymptomatic, with only a small fraction of individuals developing MCC over time [19]. Therefore, MCC is generally classified as MCPyV-positive or -negative cancer. MCPyV-positive MCC, also defined as Merkel-type sarcoma, represents a pure neuroendocrine carcinoma characterized by the expression of viral oncoproteins, a low tumor mutational burden [20], and a relatively favorable prognosis compared to the counterpart [21]. This variant is thought to arise from dermal fibroblasts or pre/pro B-cells [22,23]. Conversely, patients with MCC often have a history of other cancers, particularly those linked to UV exposure, indicating possible shared etiological factors with these malignancies [24–26].

In this regard, approximately 20% of MCC cases are UV-associated MCPyV-negative, a form referred to as squamous cell carcinoma, Merkel type. This subtype of MCC, which was found to be more prevalent in certain geographic regions with high levels of sun exposure [27], arises from UV-induced DNA damages and displays characteristic oncogenetic features: high mutational burden, high p63 expression, inactivation of tumor suppressor genes such as Retinoblastoma 1 (Rb1) and tumor protein 53 (TP53) [28], and high frequency of NOTCH1 and FAT1 mutated [27]. In addition, UV exposure is also responsible for the inactivation of genes involved in DNA damage repair, including KMT2A, KMT2C KMT2D, ASXL1, ARID1A, ARID1B, SMARCA4, and in chromatin-modifying pathways, such as ATM, MSH2, BRCA1, BRCA2, and BCOR [29]. Moreover, also UV-associated MCPyV-negative MCC has been linked with the activation of JAK-STAT pathway, MAPK (HRAS, NF1) pathway [30], PI3K pathway (PIK3CA, AKT1, PIK3CG) and the receptor tyrosine kinase FGFR2 [27]. This subtype, which is mostly associated with a poorer prognosis [21], appears to originate from keratinocytes, epidermal stem cells, or Merkel cells. It exhibits neuroendocrine characteristics or displays a combination of features from both neuroendocrine and squamous cell carcinoma (SCC) cells[1]: it seems to arise from or in association with SCC [20,31–33].

The absence of detected MCPyV in these combined tumors suggests that viral involvement is limited to MCPyV-positive MCC cases [34,35].

Beyond the prolonged exposure to UV radiation and MCPvV infection as established causal mechanisms, several risk factors for MCC are identified. Among these, immunosuppression (e.g.,

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HIV positive or AIDS patients, organ transplant recipients, or patients undergoing immunosuppressive treatments) [16,36,37], advanced age (over 70 years old) [11], male gender [10,11], fair skin [13], personal history of other skin cancers are the main recognized.

4.2. The Debate of MCC Cell of Origin

The identification of the two driving mechanisms in Merkel cell carcinoma pathogenesis has led to a reassessment of its cellular origin, which was originally believed to be the epidermal Merkel cells (from which the tumor gets its name).

Alternative proposed origins for MCC include epithelial progenitor cells, fibroblasts, dermal stem cells, and pre/pro B cells [38–41] (Table 1). Merkel cells are highly specialized epithelial cells that function as mechanoreceptors, located in the basal layer of the epidermis and the external part of the hair follicle. Both Merkel cells and MCC share several features. Firstly, both cell types exhibit high expression of the ion channel Piezo2, a protein that facilitates the conversion of mechanical signals into electrical signals [42,43]. Secondly, the differentiation of Merkel cells is driven by the expression of specific transcription factor known as atonal homolog 1 (ATOH1) [44], which is also represented in MCC [45]. Additionally, immunohistochemical studies have shown that both Merkel cells and MCC express common markers, such as cytokeratin 20 (CK-20) and neuroendocrine markers like chromogranin A and synaptophysin [22].

However, Merkel cells are primarily post-mitotic, thus exhibiting low sensitivity to oncogenic stimuli [44]. Moreover, they are placed in the basal layer of the epidermis, while MCC typically affects the dermis and subcutaneous tissues [41]. Furthermore, Merkel cells are mostly represented in the palms and soles [46], whereas MCC predominantly occurs in sun-exposed areas, such as the head and neck, or limbs [10,38]. Lastly, no reports of Merkel cells being infected by Merkel cell polyomavirus (MCPyV) have been described [47], and MCPyV small T-antigen (ST) has failed to induce Merkel cell proliferation or transformation in transgenic murine models [48]. The similarities between Merkel cells and MCC may be linked to the acquisition of the neuroendocrine phenotype from different cell type during the oncogenic process of MCC [49]. In MCC, both sun exposure and virus-induced oncogenic triggers may act on shared molecular pathways, notably involving the loss of the retinoblastoma protein (Rb). In this sense, the sequestration of the tumor suppressor Rb by MCPyV is a critical step in the pathogenesis of MCPyV-positive MCC [28,50]. Alternatively, MCPyV-negative MCC tumors lose Rb expression due to somatic mutations [28,51]. In other types of skin tumors, the loss of Rb has been demonstrated to play a role in the development of a neuroendocrine phenotype [52–54]. Moreover, Rb inactivation may lead to increased expression of ATOH1, a transcription factor involved in Merkel cell differentiation [55].

Based on these findings, alternative origins for MCC cells have been proposed, including epithelial non-Merkel cells, fibroblastic cells, and B-cell lineages [22]. Among these, epithelial stem cells - considered the most likely progenitors of differentiated Merkel cells [56–58] - have been proposed as a potential cell of origin for MCC [22,41].

Observations of MCC tumors suggest that UV-induced cases likely originate from a progenitor cell within the epidermis [59]. The UV mutation signature observed in MCPyV-negative MCC indicates that this cancer may have an epithelial origin, specifically arising from keratinocyte progenitor in the interfollicular epidermis, and acquiring the ability to differentiate into Merkel cells during the oncogenic process [22,41]. In MCC, this signature is characterized by specific types of mutations, particularly C to T transitions, frequently involving key tumor suppressor genes like tumor protein 53 (TP53) and Rb1. The dual inactivation of the TP53 and Rb1 genes is also observed in small cell lung cancer (SCLC), a neuroendocrine carcinoma that shares significant phenotypic similarities with MCC. In SCLC, the inactivation of these genes drives both transformation and neuroendocrine differentiation in epithelial cells [60,61]. Intriguingly, the notion that an epithelial cell serves also as the origin of MCPyV-positive MCC remains a topic of debate, primarily due to the inability of epidermis-targeted T-antigen expression to produce MCC tumors in pre-clinical models [22,23]. Alternatively, the occurrence of MCPyV-positive MCC could be explained by the integration

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of MCPyV in cutaneous appendages enriched with Merkel cell precursors [22,23]. Nevertheless, the specific cell type in which MCPyV integration occurs is still unclear.

The absence of connection between MCC tumor cells and the epidermis, along with the lack of a UV mutation signature, suggests a potential non-epithelial origin for this neoplasia Indeed, MCPyV-positive MCC may originate from dermal mesenchymal cells for several reasons. First, a non-epithelial origin could account for the low tumor mutational burden and the absence of the UV signature typically seen in MCPyV-negative MCC. Second, the deep localization of fibroblast stem cells might account for the predominantly dermal occurrence of MCC [40]. Moreover, this hypothesis aligns with the virus' natural life cycle, according to studies that shows how dermal fibroblasts support the complete MCPyV cycle in vitro [62,63].

Finally, fibroblasts have the potential to be reprogrammed into pluripotent cells[64] suggesting the possibility that they could adopt a Merkel cell phenotype. However, this theoretical concept still needs to be experimentally validated.

In addition to the absence of epidermal connection, MCC may express B cell markers, such as TdT and PAX5, with some MCPyV-positive MCC cases exhibiting immunoglobulin (Ig) rearrangement. These findings indicate that MCPyV-positive MCC may originate from pre-/pro-B cells [65]. Furthermore, both MCCs often shares phenotypic similarities with B-cell neoplasia, and MCPyV can integrate itself into hematopoietic cells, potentially guiding the transformation of B cells. To date, the failure to acquire a Merkel cell phenotype in these instances argues against B-cell origin of MCC [23].

Table 1. Candidate cell of origin in Merkel cell carcinoma.

Cell of origin	**Driving mechanism**	**Evidence supporting the origin of MCC from the specific candidate cell**	
		Pros	**Cons**
Merkel cell	UV-related	Phenotypic similarities: cytokeratin (CK) 20, neuroendocrine markers (chromogranin A, synaptophysin), Piezo2 and Atoh1.	No mitotic activity. No transformation/proliferation induced by MCPyV T antigens. Different anatomic localization between the candidate cell and MCC. Lack of connection between the tumor cells and the epidermis.
Epithelial progenitor	UV-related	Presence of UV-signature (TP53, Rb inactivation). Ability to differentiate into Merkel cell. Ability to differentiate in MCC. Most likely origin of neuroendocrine carcinoma in other sites (SCLC).	No transformation/proliferation induced by MCPyV T antigens. Lack of connection between tumor cells and the epidermis.

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Fibroblast and dermal stem cell	MCPyV-related	Ability of MCPyV antigens to induce transformation in these cell types. Explain the exclusive dermal/hypodermal localization of MCC.	Lack of UV signature. No evidence to suggest that fibroblasts can acquire a Merkel cell-like phenotype. Unpredicted origin for a neuroendocrine carcinoma.
Pre/Pro B-cell	MCPyV-related	Epidemiologic data on the association between MCC and B-cell neoplasia. Co-expression of B-cell markers (PAX5, TdT, Ig). Detection of MCPyV integration in B-cell neoplasia.	Lack of UV signature. No evidence that B-cells can acquire a Merkel cell-like phenotype. Unpredicted origin for a neuroendocrine carcinoma.

5. Clinical Features and Diagnosis of MCC

The diagnosis of Merkel cell carcinoma is established through a comprehensive approach that includes clinical assessment, noninvasive imaging, and histopathological analysis with immunohistochemistry.

From a clinical perspective, MCC typically presents as a pink or red-violaceous, painless, firm, rapidly growing nodule or plaque, this last one theoretically more detectable in the early stages of the disease[1]. Four distinct clinical presentations have been proposed and described as representative of MCC: Pinkish plaque, cherry red nodular, ulcerated erythematous nodular, and hyperkeratotic nodular MCC [66]. Interestingly, while the first three clinical findings were histologically consistent with "classic MCC," the final one was identified as MCC associated with SCC [66]. Compared to pure MCC, the coexistence of MCC and SCC is a rare occurrence, more commonly observed in immunosuppressed patients and associated with poorer outcomes [67,68]. Additionally, MCC can occasionally coexist with Bowen's disease (BD), with a recent review identifying 13 cases of MCC overlapping with BD [69]. This combination appears to be more common in females, typically presenting as a rapidly growing single nodule on a red-brownish plaque, often located on the face [69].

Although MCC is commonly found in sun-exposed areas, it can also rarely arise from the oral mucosa and/or lips, which are of dermatological interest as potential primary tumor sites. This has been reported in both adults [70–76] and young individuals, starting from the age of 14 [77–79]. In these cases, MCC typically presents as an ulceroproliferative or pinkish-red, rapidly growing nodule, especially when located at the vermillion border or labial semi-/mucosa [75]. Furthermore, cases of MCC involving the penile or scrotal region have been documented less frequently (n=2) [80,81] compared to those occurring in the vulvar region (n=18) [82,83]. Pain and perilesional erythema have also been noted as additional characteristics for these specific locations.

Along with clinical evaluation, dermoscopy and reflectance confocal microscopy (RCM) represent two non-invasive imaging techniques that have proven to be highly valuable in diagnosing MCC [85]. The primary dermoscopic features of MCC include a variably focused and dilated polymorphous vessels set on homogeneous pinkish, milky red structureless background, togheter with shiny or not-shiny white areas [66,84].

Differently from BD and its glomerular and/or dotted vessels at dermoscopy [86], in MCC the dermoscopic vascular pattern is characterized by irregular linear vessels, either alone or in combination with glomerular or arborizing vessels (vascular polymorphism) supporting the differential diagnosis [66].

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In RCM, MCC displays aggregates of hyporeflective small cells bordered by fibrotic linear septae, which have been previously reported as highly suggestive of the disease [85] in support of a clinical and dermoscopic suspicion of MCC [66]. Additionally, larger polymorphic hyper-reflective cells, likely representing highly proliferative cells, may also be observed [85].

Given the above, MCC final diagnosis relies on histological examination revealing the infiltration of the dermis/hypodermis by small, round, blue proliferating tumor cells (with hematoxylin-eosin staining), which exhibits immunohistochemical features of high-grade neuroendocrine carcinoma [86]. Notably, MCC cells express various cytoskeletal keratins (CKs), including CK20 (membranous and/or paranuclear dot-like), CK8, CK18, CK19; and neuroendocrine markers such as chromogranin A, synaptophysin, cluster of differentiation (CD) 56, and neuron-specific enolase (NSE). Conversely, they are typically negative for thyroid transcription factor 1 (TTF1), leukocyte common antigen (LCA), protein S100, melan A, vimentin and CK7(3). Less than 10% of MCC cases are negative for CK20(3).

Thus, immunohistochemical staining showing neurofilament positivity (+), CK-20 positivity (+), CK-7 negativity (-), and TTF-1 negativity (-) offers high sensitivity and specificity in differentiating MCC from common histopathological mimics, such as SCLC, neuroblastoma, Ewing sarcoma, melanoma, and lymphoma [87–89] (Table 2). In rare cases, MCC may test positive for TTF1 or CK7, so the interpretation of staining patterns for these two antigens should be done with caution [3,90].

No histological markers can selectively differentiate between virus- or UV-associated MCC: a positive staining for MCPyV large T-antigen (LT) strongly indicates MCPyV-associated MCC. Nevertheless, negative staining does not definitively rule out the possibility of viral involvement [91,92].

Table 2. Immunohistochemical differential diagnosis of Merkel cell carcinoma.

Stain	MCC*	SCLC	Neuroblastoma	Ewing sarcoma	Small-cell melanoma	Lymphoma
Neurofilament (NF)	+	−	+	+	−	−
Cytokeratin (CK) 20	+	−	−	−	−	−
Cytokeratin (CK) 7	+/−	+/−	−	−	−	−
Thyroid transcription factor-1 (TTF1)	+/−	+	−	−	−	
Neuron-specific enolase (NSE)	+	+	+	+/−	−	−
Chromogranin A	+	+	+	−	−	−
Synaptophysin (SYP)	+	+	+	+/−	−	−
Neural cell adhesion molecule (NCAM) or CD56	+	+	+	+/−	+	+/−
S100	−	−	−	−	+	−

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Leukocyte common antigen (LCA) or CD45	−	−	−	−	−	+

*A small subset of CK7-positive, TTF-1-positive MCCs has been described. Positive (+): the marker is typically expressed in the tumor type; Positive/Negative (+/−): the expression may vary and is not definitive for that tumor type; Negative (−): the marker is typically not expressed in the tumor type.

6. Staging System (AJCC 8th Edition) and Prognostic Factors

Staging of Merkel Cell Carcinoma involves the TNM system, evaluating the size and extent of the primary tumor (T), the involvement of regional lymph nodes (N), and the presence of distant metastases (M) [93]. The American Joint Committee on Cancer (AJCC) classification (8th edition) refines this by distinguishing lymph node involvement into clinical (N) and pathological (pN) stages, based on whether lymph nodes are assessed through physical examination or histopathological evaluation [93]. According to this system (Table 3), MCC is classified as follows: stages I and II for skin-limited disease; stage III for regional lymph node involvement or an undetectable primary tumor; and stage IV for distant metastatic disease beyond regional lymph nodes [93].

Clinical staging relies on physical examination, lymph node palpation, and imaging studies, though routine baseline imaging is not always recommended [2]. However, 2-deoxy-2-[^{18}F] fluoro-D-glucose ([^{18}F] FDG) positron emission tomography (PET)/computed tomography (CT) (FDG PET/CT) scan is a critical tool for staging and re-staging MCC, as it effectively identifies metastatic disease particularly in the bone and bone marrow, which may be missed by standard CT scans [94].

Sentinel lymph node biopsy (SLNB) represents the most reliable method for detecting subclinical nodal involvement, utilizing a specific immunohistochemical panel [3]. Pathological staging involves microscopic examination of tissue samples obtained through lymph node biopsies, organ biopsies, or needle biopsies [88,93,95].

Table 3. American Joint Committee on Cancer classification (AJCC) 8th edition for Merkel cell carcinoma.

AJCC Stage		TNM staging	Primary Tumor	Lymph Node	Metastasis
0		Tis, N0, M0	In situ (within epidermis only)	No regional lymph node metastasis	No distant metastasis
I	Clinical*	T1, N0, M0	≤ 2 cm maximum tumor dimension	Nodes negative by clinical exam (no pathological exam performed)	No distant metastasis
	Pathologic**	T1, pN0, M0	≤ 2 cm maximum tumor dimension	Nodes negative by pathologic exam	No distant metastasis
IIA	Clinical*	T2-3, N0, M0	> 2 cm tumor dimension	Nodes negative by clinical exam (no pathological exam performed)	No distant metastasis
	Pathologic**	T2-3, pN0, M0	> 2 cm tumor dimension	Nodes negative by pathological exam	No distant metastasis
IIB	Clinical*	T4, N0, M0	Primary tumor invades bone,	Nodes negative by clinical exam	No distant metastasis

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			muscle, fascia, or cartilage	(no pathological exam performed)	
	Pathologic**	T4, pN0, M0	Primary tumor invades bone, muscle, fascia, or cartilage	Nodes negative by pathologic exam	No distant metastasis
III	Clinical*	T0-4, N1-3*****, M0	Any size / depth tumor	Nodes positive by clinical exam (no pathological exam performed)	No distant metastasis
IIIA	Pathologic**	T1-4, pN1a(sn)*** or pN1a, M0	Any size / depth tumor	Nodes positive by pathological exam only (nodal disease not apparent on clinical exam)	No distant metastasis
		T0, pN1b, M0	Not detected ("unknown primary")	Nodes positive by clinical exam, and confirmed via pathological exam	No distant metastasis
IIIB	Pathologic**	T1-4, pN1b-3, M0	Any size / depth tumor	Nodes positive by clinical exam, and confirmed via pathological exam OR in-transit metastasis ****	No distant metastasis
IV	Clinical*	T0-4, any N, M1	Any	+/- regional nodal involvement	Distant metastasis detected via clinical exam
	Pathologic**	T0-4, any pN, M1	Any	+/- regional nodal involvement	Distant metastasis confirmed via pathological exam

* Clinical detection of nodal or metastatic disease may be via inspection, palpation, and/or imaging. ** Pathological detection/confirmation of nodal disease may be via sentinel lymph node biopsy, lymphadenectomy, or fine needle biopsy; and pathological confirmation of metastatic disease may be via biopsy of the suspected metastasis. *** (sn)= sentinel lymph node. The N1 category defines a regional lymph node metastasis without in-transit metastasis. The N1 category is subdivided in N1a(sn) for *clinically occult* lymph node metastasis detected only at SLNB in a patient with clinical stage I-II disease; N1a for *clinically occult* lymph node metastasis detected following lymph node dissection; and N1b for *clinically and/or radiologically detected* metastasis. **** In transit metastasis: a tumor distinct from the primary lesion and located either (a) between the primary lesion and the draining regional lymph nodes or (b) distal to the primary lesion. ***** N2 is defined as

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in-transit metastasis *without* associated lymph node metastasis; N3 is defined as in-transit metastasis *with* lymph node metastasis.

Survival in MCC is mainly determined by the stage at diagnosis. The 5-year overall survival (OS) rate drops significantly as the stage advances, from 62.8% at stage I to 13.5% at stage IV (AJCC 8th edition) [96,97]. However, a recent cohort study interestingly found that only 65% of deaths were directly attributed to MCC-related causes [98].

In terms of prognosis, MCC is characterized by its high recurrence rates: local recurrence (27-60%), regional lymph node involvement (45-91%), and distant metastasis (13-52%) [93,99,100].

Integrating current evidence, MCC patients are considered as high-risk for recurrence if they exhibit one or more modified adverse risk factors (mARF), including tumor size ≥2 cm (or >1 cm per NCCN guidelines v1.2024), chronic immunosuppression (e.g., HIV, chronic lymphocytic leukemia, or solid organ transplant), head and neck primary sites, lymphovascular invasion, pathologically positive lymph nodes, or incomplete lymph node evaluation [2–4,101,102].

On the other hand, several factors, including Rb protein expression, intratumoral CD8 T-lymphocyte infiltration, and MCPyV LT antigen expression, show promise as positive prognostic markers but need further validation [3]. In this context, testing for MCPyV oncoprotein antibodies should be performed in the initial assessment, as seropositive patients could potentially use antibody levels to monitor recurrence, thereby reducing the need for frequent imaging [103]. Conversely, seronegative patients face a 42% higher recurrence risk and necessitate a closer surveillance [103].

Due to the rarity of MCC, the understanding of metastatic patterns and prognosis at stage IV remains incomplete, with data showing considerable variability. Patients with bone or liver metastases report significantly worse OS ($p < 0.01$) and an increased risk of Merkel-specific death (HR: 3.06 for bone metastases and HR: 2.09 for liver metastases, $p<0.001$) [7]. However, another study found that although liver and brain metastases were significantly associated with poorer disease-specific survival (DSS), bone metastases did not show the same correlation [104]. Additionally, patients with metastases to the bone, liver, and distant lymph nodes seemed to also have a higher risk of regional lymph node involvement [101].

Excluding the following articles due to the lack of individual data [6,104,111,127,131,140,142,157] (Table 4), the median OS for bone and bone marrow metastatic MCC was 8 months (range 12.75-4).

Further studies are needed to provide definitive and comprehensive evaluations.

7. Bone and Bone Marrow Metastases in MCC

7.1. Type of Bone Metastases

Bone metastases (BMs) can be classified in two types according to histopathology: osteoblastic or bone-forming BMs, as reported in prostate cancer and breast cancer; osteolytic or bone-destructive BMs, as metastases from kidney, thyroid, lung cancers, multiple myeloma; and mixed BMs, that is the combination of both osteoblastic and osteolytic processes (as less often reported in breast cancer) [105].

Considering literature data about the biological behavior of these different pathological bone secondaries, the diversification partially influences prognosis since osteolytic lesions are often more aggressive, and generally show quicker progression compared to the sclerotic metastases [105,106]. Additionally, tumor cell proliferation within bone marrow precedes bone destruction, making bone damage a relatively delayed feature of bone metastasis [106,107], and explaining the variable development of bone pain and fractures.

Few data are reported about the nature of BMs in Merkel cell carcinoma. The evidence derived from imaging studies suggests a major mixed behavior for BMs in MCC, as demonstrated by the radiopaque/hyperdense (when osteoblastic) or radiolucent/hypodense (when osteolytic) signal on radiography (X-ray) or computed tomography (CT) scan, respectively [108]. Cases of intracranial metastasis through [109] or without [110] bone destructions have been reported, although arterial or

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venous spread represent the most common via of bone dissemination [110]. The specific venous drainage and veno-lymphatic anastomoses generated by MCC neoplastic clones may explain the evidence.

7.2. Pattern of Metastatic Spread and Association Between Primary MCC and BMs

Merkel cell carcinoma has a high recurrence rate, especially within the first 2-3 years after excision, with 40-50% of patients developing regional lymph node (LN) metastases and about 33% experiencing distant metastases [4].

Common distant metastasis sites include non-regional LNs (41%), skin/soft tissue (25%), liver (23%), bone (21%), pancreas (8%), lung (7%), and brain (5%) (percentages exceeded 100% because some patients had metastatic disease involving multiple sites) [6].

However, the reported patterns of metastatic spread in the literature vary across different studies. In 2024, Kim et al. analyzed 151 patients who had received treatment for MCC and examined the relationship between primary tumor site and distant metastasis. They found that after a median follow-up of 11 months, 58.9% of patients had a single metastatic site, while 41.1% had multiple. The most common metastasis sites were distant LNs (62.3%), followed by skin/soft tissues (26.5%) and bone (26.5%) [7].

Different authors reported different data about the most common distant metastatic sites in MCC, and BMs are typically preceded by other involvements such as non-regional LNs (the most frequent), skin, and lung [96] or abdominal organs [100]. Nevertheless, non-regional LNs are not always the primary sites affected by distant metastases. Gonzalez et al. reported that the most common metastatic sites were the liver (39.3%), followed by distant LNs (38.3%), bone (27.7%), and lung (21.9%) [101]. Similarly, Xia et al. found liver metastasis to be the most common (13.5%), followed by bone (11.3%) and lung (8.4%) secondaries [111].

Regarding the association between the primary MCC and BMs, notably, patients with upper limb/shoulder primaries were less likely to develop distant LNs or liver metastases ($p=0.02$ and $p=0.04$), while those with head and neck primaries were more likely to develop liver metastases ($p<0.01$) [7]. This observation was supported by Maloney et al., who demonstrated that head and neck primary MCC was associated with liver metastases ($p=0.0003$), in contrast to primary tumors in the lower limbs [104]. These findings regarding the likelihood of liver metastasis in MCC are consistent with previously published data, which show a higher incidence in head/neck primary tumors (43% of 58 patients) compared to lower limb primaries (5% of 39 patients; $p<0.0001$) [6].

On the other hand, patients with trunk primary MCCs exhibited higher rates of positive lymph nodes and seemed more prone to developing bone metastases ($p=0.0049$) [112]. Nevertheless, this data is not fully corroborated, as Kim et al. found bone metastases to be more frequently associated with head and neck (37.5%) or upper limb primaries (22.5%) than with trunk primaries (17.5%) [7].

In this review, we summarized the prevalence of single metastatic localizations from SEER databases and retrospective mono-/multi-centric studies, collecting a total of 967 metastatic events at presentation or during follow up reports. In decreasing order of prevalence, the pattern of metastatic spread was as follows: LNs (27.8%, n=269), liver (21.2%, n=205), bone (19%, n=184), lung (10.5%, n=102), skin and subcutaneous tissue (8.6%, n=83), brain (3.1%, n=30), gastric (2.3%, n=23), spinal cord (2.2%, n=21), bone marrow (1.8%, n=17), pancreas (1.4%, n=14), testis (1.2%, n=12), retroperitoneum/thyroid gland (0.4%, n=3 each), and heart (0.1%, n=1) [6,7,102,104,110,111,113–156]. Overall, BMs and bone marrow involvement in MCC are linked to advanced stages [142–144] and associated with poorer survival outcomes [101,113].

7.3. Clinical and Demographic Data

44. articles retrieved out of 148 reported bone/bone marrow as metastatic site involved (Table 4). A total of 1,133 (69.3% male and 30.7% female) patients diagnosed with advanced MCC were collected. The median (IQR) age at diagnosis was 67.5 (12.65) years old. 201 (20.8%%) cases of bone and/or bone marrow metastasis were identified and linked to a primary known and unknown MCC

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in 75.7% and 24.3%, respectively. Sometimes the nature of the primary MCC was not otherwise specified [104,140].

Except for one istance [131], in single-case reports of bone/bone marrow MCC metastasis specifically detailing primary tumor sites (n=30) [110,116,122,124–139,141–147,149–159], the anatomical distribution of the primary MCC aligned with typical patterns described in literature to date for this neuroendocrine skin tumor, that are the head and neck (12/28), trunk (8/28), upper (6/28) and lower arms (2/28), and hand (1/28). Notably, an extremely rare case of MCC arising on the vulva was described [142].

Considering bone localization among all cases reviewed, the specific type of skeletal involvement other than "bone involvement" was documented in 37 patients, with a notable predilection for the axial skeleton (35 cases) [110,116,122,124–139,141–144,147,149–155,157–159] over the appendicular one (2 cases) [145,146].

17 cases of bone marrow were collected [126–137,139,142,158,159]. When extramedullary intraspinal MCC metastases were documented, the involvement of the epidural space [122,141,143,144,150–152] resulted more common than the intradural one [122,124,142].

Other than pain [144,145,155], the neurological symptoms were the most observed with seizures [138], signs resulting from compression of the spinal nerve roots [152], weakness/numbness [143,150,155], paresthesia [144,156] balance disturbance [122], paraplegias following extra-dural spinal masses [141,150] as the most characteristic; headache was also noted [122]. However, based on detailed case reports, only 10 out of 39 (25%) documented symptomatic disease, suggesting that metastatic bone or bone marrow MCC is typically asymptomatic. Interestingly, leukemic spread during bone marrow disease was documented and linked to certain forms of immunosuppression, suggesting a potential association. These included patients receiving organ transplantation [129,132,158,159], patients with concomitant autoimmune disorders and treated with immunosuppressant therapies (systemic lupus erythematous [126,133], rheumatoid arthritis [128,137,159]), and patients affected by various hematologic conditions (Waldenström macroglobulinemia, plasma cell myeloma, myelodysplastic syndrome, JAK2-positive polycythemia vera, chronic lymphocytic leukemia) [127,130,131,136]. In one case, MCC affected a pregnant woman leading to a rapidly progressing visceral multi-metastatic disease that proved fatal [155].

7.4. Imaging Features of MCC Across Different Diagnostic Techniques

Imaging represents an essential tool in Merkel cell carcinoma management, from early detection to accurate staging. Whole-body FDG-PET/CT or whole-body contrast-enhanced CT scans are mandatory to assess disease extension [3]. PET/CT scan has been reported as more sensitive than CT alone, resulting in an upstage of the disease (7% of cases, mainly stage I/II to stage III) [94,160] and therefore it should be preferred over CT alone when available [161]. Additionally, 8 to 14-megahertz regional lymph nodes ultrasound (US) should be integrated to examine all the main lymph node basins in patients with clinical stage I-II at baseline [3].

To date, the indications about the execution of head/brain imaging slightly differs among the guidelines considered: while ESMO-EURACAN Clinical Practice Guideline indicated brain imaging for head/neck located MCC primaries [3], the European consensus-based interdisciplinary guideline did not routinely recommend brain imaging in asymptomatic stage I/II patients [4].

A synthesis of literature data supports the use of whole-body imaging, such as PET/CT scans, extending to the neck when the primary tumor is located in the head or neck region, as part of the baseline assessment. Additionally, brain MRI should be conducted in cases of neurological symptoms or when a direct cranial extension of the tumor is suspected [2–4]. In our experience, for elderly patients with head and neck MCC presenting with at least one mARF or a negative sentinel lymph node biopsy (SLNB), we typically recommend whole-body PET/CT imaging integrated with head and neck CT or MRI scan.

Primary MCC has nonspecific strictly imaging features [108,162]. Nevertheless, certain suggestive findings can aid in its identification: cutaneous or subcutaneous firm nodule, mass within

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or around muscle tissue; necrosis in larger lesions (>2cm), rare calcifications [108]; significant contrast uptake both for CT and MRI, in accordance with the pathology of fibrovascular separation between clusters of tumor cells and enriched blood sinuses [47]. Among the different imaging techniques available primary MCC mainly appears as follows: a) on US, it shows heterogeneous echogenicity (mainly hypoechoic nodules arising from the dermis/hypodermis), prominent branching/chaotic vascularity, occasional perpendicular hypoechoic linear bands resembling "columns of smoke"; b) on CT, focal skin thickening associated with the cutaneous/subcutaneous nodule, contrast enhancing particularly evident for lesions located in the subcutaneous tissue, signs of tissue edema (fat stranding near the primary lesion); c) on MRI, hypo- to isointensity on T1-weighted images and either hyperintensity or isointensity on T2-weighted images and STIR sequences; d) on FDG PET/CT, hypermetabolic signal is consistent with a malignant proliferation[7,47,162], particularly, for a SUV value of 7.5 ± 3.9 (mean ± SD) [163]. A recent umbrella review of meta-analyses aimed to provide updated evidence to guide appropriate referrals for specific radiopharmaceutical PET/CT or PET/MRI in solid cancers. This review reported a sensitivity and specificity of 0.91 (95% CI 0.85–0.95) and 0.93 (95% CI 0.86–0.97), respectively, for nodal staging in MCC using FDG PET/CT. It also recommended FDG PET/CT for initial lymph node staging and for cases of nodal or distant metastases from unknown primary MCC. Otherwise, DOTA-peptide imaging can be considered in case of FDG PET/CT negativity [163].

Limited data have been published in literature regarding imaging features of bone metastatic MCC. PET/CT, PET/MRI and CT scans are more effective than MRI alone in detecting bone abnormalities (cortical destruction and/or periosteal reaction) and accurately defining bone signals, as particularly demonstrated in well-known metastatic bone cancers [164]. However, MRI for its highly sensitivity can be particularly indicated for detection of bone marrow involvement and extraosseous extension of the tumor [144,165]. Additionally, MRI is the technique of choice in case of cord compression from pathologic vertebral body fracture and/or concomitant spinal cord oedema (focal high T2 phase) [152]. In any case, with the use of intravenous contrast, T1-weighted MRI with fat saturation (STIR) will show intense uptake in the metastatic body, along with any associated variable focal areas of hypointense necrosis [166].

As mentioned above, the mixed nature of BMs in MCC is responsible of the combined response to X-ray-based imaging, depending on the grade of absorption [108]. Practically, on X-ray or CT scan while the osteoblastic lesions appear as round/nodular, well-defined, radiodense or hyperdense bone lesions, the osteolytic BMs in MCC are described as ill-defined, thinned/with absent trabeculae, lucent or hypodense bone lesions [146]. When contrast enhancement is performed, hypervascularity during the arterial phase of enhancement explains the signal increase [167].

On FDG PET/CT, a focal rediotracer uptake in the bones involved is typical (hypermetabolic lesions), with osteolytic metastases presenting as photopenic and characterized by increased activity peripherally [168,169]. Whole-body PET/MRI has demonstrated superior detection of liver metastases compared to PET/CT, although this data has not yet been tested for MCC [170].

Among the other imaging techniques generally adopted to detect BMs and cited in current guidelines, bone scintigraphy is useful and generally used as first-line modality in patient with suspect bone metastasis. Using a radioactive substance, typically technetium-99m (Tc-99m) labeled with a bone-seeking compound like methylene diphosphonate (MDP), it provides whole-body imaging, and although less specific, it needs much smaller change in normal-to-abnormal bone for detection compared to plain radiographs [171]. Moreover, the overall sensitivity among the different radiologic techniques is the following: plain radiographs have low sensitivity (~50%) compared to bone scintigraphy (80%, range 62-100%), CT (85%, range 71-100%), and MRI (90%, range 82-100%) [171,172].

7.5. Treatment of Metastatic Bone/Bone Marrow MCC

The treatment of metastatic bone/bone marrow Merkel cell carcinoma varies widely, ranging from single-modality approaches to multimodal regimens.

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Among the 201 cases reviewed, chemotherapy (CHT) alone was utilized in 13 cases (6.4%) [110,126,134,135,139,140,148,152,158,159], with median Merkel specific survival (MSS) (IQR) of 8 (8) months. The treatment regimens mainly included platinum-based agents, often combined with etoposide [110,134,135,139,152,158]. Cyclophosphamide, typically in combination with doxorubicin or vincristine, was also utilized [126,139]. Additionally, other agents such as bleomycin [152], 5-fluorouracil, methotrexate [110,159], topotecan hydrochloride, and paclitaxel [110] were sporadically adopted. Furthermore, radiotherapy (RT) alone [116,159] and surgical intervention alone [145,151] were administered in two (1%) cases both, respectively.

Multimodal approaches were more adopted, with CHT combined with RT described in 73 cases (36.3%) [6,128,136,138,142,144,147,150,154,155], or with immunotherapy in 11 cases (5.5%) [113,125]. A comprehensive regimen including CHT, RT, and surgery was applied in 32 cases (16%) [111,153], with immunotherapy instead of CHT utilized in 40 patients (20%) within the triple-therapy regimen group [7]. Dual-modality treatments were also documented, with CHT with immunotherapy in 11 cases (5.5%) [113,125], RT and surgery in 4 cases (2%) [122,141,143,146], and RT combined with immunotherapy in 2 cases (1%) [124,149]. Unfortunately, 7 (3.4%) patients died before receiving the specific adjuvant treatment or immediately after surgery of the primary tumor [129,130,132,133,151,156,158].

For patients undergoing immunotherapy, the treatment involved immune checkpoint inhibitors (ICI), specifically Avelumab, an anti-programmed cell death protein-ligand 1 (PD-L1) human immunoglobulin G1 (IgG1) antibody [124,125,149]. However, this data is not consistently defined [7,113].

In general, the management of metastatic bone MCC needs to be individually tailored. While surgery, potentially involving prosthetic replacement, may be an option for a single metastatic site, stereotactic hypofractionated radiotherapy should be considered for fit patients with oligometastatic bone disease (defined as ≤3 sites). Interestingly, a multivariate analysis by Gonzalez et al. revealed that MCC patients with bone metastases who underwent surgery to remove one of the metastatic sites (bone or other) had 0.92 times lower risk of death [101]. This finding aligns with existing literature, which highlights that incorporating surgery into multimodal treatment can be a favorable prognostic factor for disease-free survival in MCC [173,174]. Nevertheless, systemic immunotherapy should be prioritized in the absence of contraindications with the available options including Avelumab (anti-PD-L1 human monoclonal IgG1 antibody, FDA and EMA approved), Pembrolizumab (anti-PD-1 humanized monoclonal IgG4 antibody, FDA approved), Retifanlimab (anti-PD-1 humanized monoclonal IgG4 antibody, FDA and EMA approved), and Nivolumab (anti-PD-1 human monoclonal IgG4 kappa antibody, not FDA nor EMA approved). Given the limited published data, priority should be given to enrolling patients in clinical trials whenever possible, alongside decisions guided by a multidisciplinary treatment team following tumor board consultation.

Table 4. Summary of the studies investigated bone and bone marrow metastases from Merkel Cell Carcinoma: patient characteristics, nature of the primary MCC, treatment, pattern of metastatic spread, and overall survival.

Author	**Study' type**	**Patient/s**				**Merkel cell carcinoma**				**Another site/s** of distant metastasis (n., %) *	**Overall Survival** for bone/BM metastatic patients
		Number (n.)	Age (years)	Sex		Primary MCC		Bone/bone marrow metastases			
						Known	Unknown				
				Male n (%)	Female n (%)	n. (%)	n. (%)	n. (%)	Therapy		
Khaddour et al. (113)	Original article	34	70.2 (51.4) ***	20 (58.8)	14 (41.2)	14 (41.2)	20 (58.8)	10 (29.4)	CHT, IT	Regional LNs (28, 82.4)	8.2 months (median)
Xia et al. (111)	Original article	273	****	200 (73.3)	73 (26.7)	184 (67.4)	89 (32.6)	31 (11.3) **	CHT, RT, surgery	Liver (37, 13.5)	1-year median OS rate of 38.7% **
Kim et al. (7)	Original article	151	76 (62) ***	101 (66.9)	50 (23.1)	134 (88.8)	17 (11.2)	40 (26.5)	IT, RT, surgery	LNs (94, 62.3), skin/soft tissue (40, 26.5)	15.1 months (median)
Lewis et al. (6)	Original article	215	/	176 (82)	39 (18)	173 (80)	42 (20)	64 (21)	CHT, RT	Non-regional LNs (88, 41%)	/
Pilotti et al. (148)	Original article	50	62 (45) ***	22 (44)	28 (56)	40 (80)	10 (20)	1 (2)	CHT	Skin (4, 8), liver (2, 4), pancreas (2, 4), lung (1, 2)	12 months
Goepfert et al. (140)	Original article	41	66 (55) ***	****	****	****	****	4 (9.8)	CHT	Skin (5, 12.1%), LNs (4, 9.8%)	/

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Maloney et al. (104)	Original article	331	74.6 (15.5) ***	241 (72.8)	90 (27.2)	****	****	6 (1.9)	/	Liver (89, 28.7), lung (51, 16.4), brain (6, 1.9)	5-year median OS rate of 11.2 %
Pectasides et al. (147)	Case report #	1	48	1 (100)	/	1 Buttock	/	1 T11, L2 vertebra	CHT, RT	Regional LNs	5 months
Nguyen et al. (145)	Case report #	1	69	1 (100)	/	1 Cheek	/	1 Tibia	Surgery	/	19 months
Kamijo et al. (146)	Case report #	1	75	/	1 (100)	1 Cheek	/	1 Femur	RT, surgery	Subcutaneous tissue	16 months
Wang et al. (127)	Case report #	1	79	/	1 (100)	/	1	1 BM	/	/	/
Khan et al. (128)	Case report #	1	80	/	1 (100)	1 Trunk	/	1 BM	CHT, RT	Regional LNs	1 month
Morris et al. (129)	Case report #	1	72	1 (100)	/	1 Shoulder	/	1 BM	Death before starting CHT	Regional LNs	4 months

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Le Gall-Ianotto et al. (136)	Case report #	1	65	1 (100)	/	/	1	1 BM	CHT, RT	/	3 months
Kobrinski et al. (137)	Case report #	1	86	1 (100)	/	1 Trunk	/	1 BM	RT	Regional LNs	12 months
Kressin et al. (130)	Case report #	1	64	1 (100)	/	1 Forehead	/	1 BM	Death before starting CHT	Regional LNs	3 months
Keow et al. (131)	Case report #	1	71	1 (100)	/	1	/	1 BM	/	/	/
Durmus et al. (132)	Case report #	1	60	1 (100)	/	1 Thigh	/	1 BM	Death before starting IT	Regional LNs, liver	7 months
Nemoto et al. (133)	Case report #	1	73	/	1 (100)	1 Cheek	/	1 BM	Death before starting therapy	Regional LNs	8 months
Vlad et al. (139)	Case report #	1	72	1 (100)	/	1 Arm	/	1 BM	CHT	Regional LNs	8 months
Barkdull et al. (110)	Case report #	1	55	1 (100)	/	1 Scalp	/	1 Sternum	CHT	Regional LNs, subcutaneous tissue, pancreas	9 months

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Leão et al. (125)	Case report #	1	61	1 (100)	/	1 Buttock	/	1 Sacrum	CHT, IT (Avelumab)	In-transit metastasis	30 months
Lentz et al. (126)	Case report #	1	55	1 (100)	/	1 Scalp	/	1 BM	CHT	Regional LNs, parotid gland	12 months
Smadja et al. (135)	Case report #	1	34	/	1 (100)	1 Shoulder	/	1 BM	CHT	Lung, brain	4 months
Vijay et al. (150)	Case report #	1	57	/	1 (100)	/	1	1 Extra-dural T8, L4, S1	CHT, RT	Non-regional LNs	1 month
Ng et al. (151)	Case report #	1	73	1 (100)	/	1 Arm	/	1 Extra-dural T5-T7	Surgery, death before starting CHT/RT	/	1 month
Highland et al. (134)	Case report #	1	74	1 (100)	/	1 Lip	/	1 BM	CHT	Regional LNs	13 months
Maugeri et al. (154)	Case report #	1	59	/	1(100)	1 Scalp	/	1 T7-T8 vertebra	CHT, RT	Liver, lung	8 months

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Chao et al. (155)	Case report #	1	23	/	1 (100)	1 Back	/	1 Extradural T3-T4	CHT, RT	Lung, heart	23 months
Moayed et al. (144)	Case report #	1	70	1 (100)	/	/	1	1 Lumbosacral spine, epidural S1, hip	CHT, RT	Regional LNs	9 moths
Turgut et al. (152)	Case report #	1	63	1 (100)	/	1 Abdomen	/	1 Extradural L5–S1	CHT	"Massive" ****	2 months
Turgut et al. (157)	-	-	-	-	-	-	-	-	-	-	-
Payne et al. (116)	Case report #	1	77	/	1 (100)	1 Buttock	/	1 T4 vertebra	RT	Bone, lung	12 months
Park et al. (156)	Case report #	1	30	1 (100)	/	1 Hand	/	1 C6 vertebra	Death before starting CHT/RT	/	1 month
Madden et al. (143)	Case report #	1	55	1 (100)	/	1 Neck	/	1 Epidural T6-T8	RT, surgery	bone	4 months

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Goodwin et al. (141)	Case report #	1	76	1 (100)	/	1 Back	/	1 Epidural T5	RT, surgery	bone	15 months
Zhao et al. (153)	Case report #	1	54	1 (100)	/	/	1	1 T6, T12, L2 vertebra	CHT, RT, surgery	Regional LNs, liver	21 moths
Folyovich et al. (138)	Case report #	1	62	/	1 (100)	1 Arm	/	1 skull	CHT, RT	Non-regional LNs	24 months
Haykal et al. (142)	Case report #	1	49	/	1 (100)	1 Vulva	/	1 Intradural *intramedullary* C4-C5	CHT, RT	Regional and non-regional LNs, liver	-
Pennisi et al. (124)	Case report #	1	73	/	1 (100)	1 Face	/	1 Intradural *extramedullary* C6-C7	IT (Avelumab), RT	Skin, subcutaneous tissue	5 months
Principe et al. (149)	Case report #	1	79	1 (100)	/	1 Ear	/	1 T2, T7, T10-11, L3 vertebra	IT (Avelumab), RT	Regional LNs, parotid gland	18 months
Abul-Kasim et al. (122)	Case report #	1	65	1 (100)	/	/	1	1 Epidural and intradural L1, L5	RT, surgery	Non-regional LNs, brain, retroperitoneum, lung	8 months

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Tam et al. (158)	Case report #	1	66	1 (100)	/	1 Forearm	/	1 BM	Death before therapy	/	6 months
-	-	1	55	1 (100)	/	/	1	1 BM	CHT	/	1.5 month
Gooptu et al. (159)	Case report #	1	68	/	1 (100)	1 Leg	/	1 BM	CHT	Non-regional LNs	2 months
-	-	1	55	1 (100)	/	1 Neck	/	1 Vertebra	RT	Non-regional LNs, brain	6 months

Abbreviations: BM (bone marrow), CHT (chemotherapy), IT (immunotherapy), LNs (lymph nodes), MCC (Merkel cell carcinoma), OS (overall survival), RT (radiotherapy). # For individual case reports, we specified the anatomical site involved in the "Bone metastasis" section when provided; age is recorded in years and prognosis in months. * We included the most commonly reported metastatic site/s alongside bone. ** We considered only *single bone-site* metastases. *** Median age (IQR) **** Unable to determine due to limitations in the available published data. / None or not intended by the study.

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8. MCC General Management

Treatment of Merkel cell carcinoma involves a combination of surgery, radiation, and systemic immunotherapy, with this latter playing a significant role in improving patient outcomes and prognosis [175]. The standard of care for early-stage (stage I-II) MCC involves performing a wide local excision (WLE) or Mohs micrographic surgery (MMS), with MMS being preferred when WLE is impractical or for tumors located in the head and neck area to minimize the need for additional procedures [176–180]. After surgery, adjuvant radiotherapy (RT) is recommended for residual macroscopic (R2) (better if < 1cm) or microscopic (R1) disease, or when mARFs are detected despite clear margins [2].

During surgery, a sentinel lymph node biopsy (SLNB) should be also performed. If the results are negative, the decision between observation or adjuvant RT to the nodal basin should be made by a multidisciplinary team. In cases where SLNB is unreliable - due to immunosuppression, anatomical constraints, or atypical lymph node drainage - or if SLNB is not feasible with risk of false negatives (e.g., patients with immunosuppression, unusual lymph node drainage, or multiple lymph node basins, such as in head and neck or midline trunk MCC) [2,3], adjuvant RT to both the primary site and the nodal basin should be considered.

Since the high recurrence risk of stage III MCC, after SLNB or biopsy confirmation of clinically/imaging-detected nodal metastases, adjuvant RT to the nodal basin combined with complete lymph node dissection (CLND) is recommended, especially for patients with multiple affected lymph nodes or extranodal disease extension [3]. This approach aids in reducing recurrence and enhancing survival outcomes.

For patients with clinically evident nodal disease (stage IIIB), the preferred treatment involves combined CLND plus RT, or clinical trials that incorporate neoadjuvant systemic therapy, as neither adjuvant RT nor chemotherapy (CHT) has demonstrated a statistically significant improvement in OS [181]. Similarly, in cases of in-transit metastases (also stage IIIB), treatment typically includes surgery and/or RT, or participation in clinical trials [2]. For these patients, adjuvant CHT is not recommended [3].

Different approaches may be assessed for MCC of unknown primary (MCCUP), which typically is characterized by better outcomes than the primary known' counterpart [97,182,183]. In these cases, after performing a FDG PET/CT scan to rule out distant metastases, the management generally follows the same guidelines as for stage III known MCC [3]. However, due to the better prognosis associated with MCCUP, patients with exclusive nodal involvement may be candidates for CLND or RT alone, before considering a combined treatment approach.

Despite recent advancements in the diagnosis and treatment of MCC, advanced (stage III) and metastatic (stage IV) disease can still be difficult to cure. For these cases, immunotherapy is recommended as a first- or second-line treatment [3]. Particularly, Nivolumab may be proposed in the neoadjuvant setting when curative surgery or radiotherapy are not feasible, potentially allowing for surgical eligibility. Otherwise, systemic immunotherapy alone is also indicated with a preference for Avelumab and Pembrolizumab [2]. In case of recurrent locally advanced disease, Pembrolizumab and Retifanlimab should be indicated as treatment options over Avelumab [2].

Instead, in metastatic disease all four mentioned ICIs, other than clinical trials, are viable treatment options [2,4]. Otherwise, CHT primarily consisting of platinum-based agents and etoposide, is just reserved for specific circumstances [2].

A practical diagnostic-therapeutic flowchart following the current evidence has proposed in Figure 1.

Due to the aggressive nature of MCC and the limited systemic control of the disease, regular follow-up visits are crucial for patients' outcome. Complete skin and lymph node examinations are recommended every 3-6 months for the first 3 years and every 12 months until the 5th year for primary tumors without additional high-risk factors. In case of mARFs or stage III patient the schedule plans should be improved and maintained for a lifetime [4,103,175,176].

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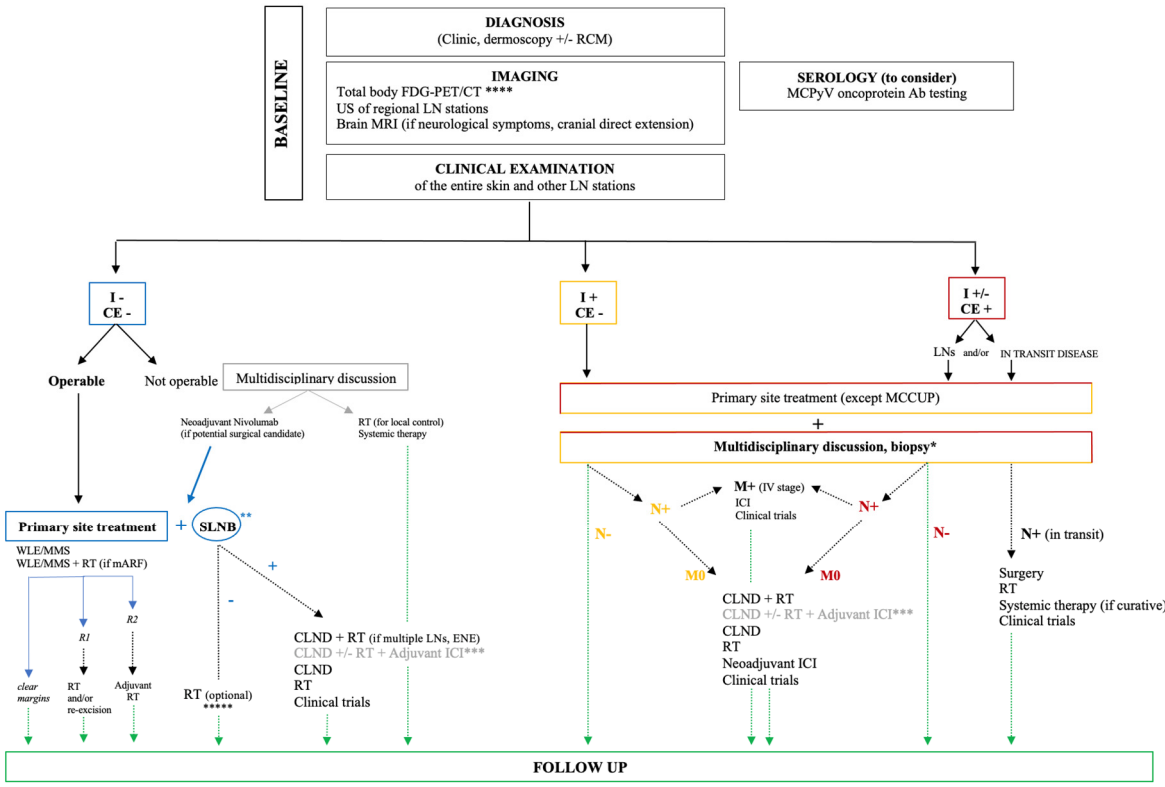
US of the primary scar, as well as the surrounding area and lymph nodes, should go with the clinical visits [4]. Additionally, stage III patients should also receive whole-body FDG PET/CT scan or contrast-enhanced CT scan of the neck, thorax, abdomen, and pelvis, along with brain MRI or CT (when indicated), every 3-6 months during the first 3 years. Afterward, follow-up imaging should take place every 6-12 months for the next 2 years. For frail patients and those with stage IV disease, a personalized monitoring plan should be implemented [4].

Recent clinical trials have explored the use of adjuvant immunotherapy in surgically treated Merkel cell carcinoma to enhance systemic disease control. Adjuvant immunotherapy with Ipilimumab, when compared to observation in completely resected MCC, has been found to be ineffective in preventing disease progression and is associated with significant toxicity [184]. In contrast, Nivolumab has demonstrated a reduction in the absolute risk of recurrence, with disease-free survival (DFS) rates of 85% at 12 months and 84% at 24 months, compared to 77% and 73%, respectively, in the observation group [185].

Furthermore, a post hoc analysis of DFS by disease stage revealed that although median DFS was not reached for stage IIIA versus IIIB patients, at 48 months, stage IIIB patients receiving immunotherapy had a 70% two-year DFS, compared to just 32% in those who did not receive adjuvant treatment [185]



* Confirmation biopsy: FNA, core needle, excisional biopsy; this last one may be considered to confirm a negative lymph node FNA or core needle biopsy. ** If SLNB unreliable or not feasible, consider adjuvant RT to both the primary site and nodal basin. *** Future directions: ongoing clinical trials seem to support the use of ICI in an adjuvant setting (NCT03271372, NCT04291885, NCT03712605). **** In case of negativity, DOTA-peptide imaging can be considered. ***** False-negative SLNB outcomes may be in patients with immunosuppression, those with anatomical constraints, individuals with atypical LN drainage, in presence of multiple LNs basins (e.g., head and neck or midline trunk MCC). mARF resulting from the integration of current guidelines and evidence: tumor size ≥2 cm (or >1 cm per [3]), chronic immunosuppression (e.g., HIV, chronic lymphocytic leukemia, or solid organ transplant), head and neck primary sites, lymphovascular invasion, pathologically positive lymph nodes, or incomplete lymph node evaluation.

Legenda

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Ab (Antibodies)
mARF (modified Adverse Risk Factors)
CE (Clinical Examination)
CLND (Complete Lymph Node Dissection)
ENE (ExtraNodal Extension)
FNA (Fine Needle Aspiration)
I (Imaging)
ICI (Immune Checkpoint Inhibitor)
LN/s (Lymph Node/s)
MCC (Merkel Cell Carcinoma)
MCCUP (Merkel Cell Carcinoma of Unknown Primary)
MCPyV (Merkel Cell PolyomaVirus)
R1 ("microscopic residual disease")
R2 ("macroscopic residual disease")
RT (RadioTherapy)
RCM (Reflectance Confocal Microscopy)
SLNB (Sentinel Lymph Node Biopsy)
WLE (Wide Local Excision)

Figure 1. Evidence-Based Diagnostic and Therapeutic Flowchart for Merkel Cell Carcinoma.

Several ongoing clinical trials are investigating ICIs, either in combination with RT for advanced MCC or as monotherapy for earlier stages of the disease (NCT04291885, NCT03712605, NCT03271372). Notably, the phase 3 randomized, placebo-controlled ADAM trial (NCT03271372) is expected to provide crucial insights, evaluating Avelumab monotherapy as an adjuvant treatment for stage III MCC patients who have completed definitive therapy, including surgery and/or RT, for clinically detected metastases.

9. Conclusions

Merkel cell carcinoma (MCC) is a rare and aggressive neuroendocrine skin cancer, whose prognosis is still largely dependent on early diagnosis and accurate staging.

While two primary mechanisms (UV-induced and MCPyV-related) have been defined in MCC etiopathology, the precise cellular origin remains unclear.

According to our results, the pattern of metastatic spread in MCC differ among studies, with the bones resulting as the third most common site of distant spread after the liver (2nd) and lymph nodes (1st). Excluding head and neck MCC, which seems to be more regularly associated with liver metastases, the relationship between the primary tumor site and the development of bone or bone marrow metastases appears inconsistent. Furthermore, bone involvement does not reliably correlate with the poorest prognosis among metastatic sites. Nevertheless, the median OS for patients with metastatic bone/bone marrow MCC was 8 months (range 12.75-4).

Addressing the characteristics and impact of bone metastases (BMs), BMs exhibit a mixed biological (osteoblastic/osteolytic) and radiological behavior, with a marked preference for the axial skeleton over the appendicular skeleton. Neurological symptoms are the most observed, whereas leukemic spread during bone marrow disease in immunosuppressed patients may suggest a reasonable correlation.

Due to the absence of approved adjuvant treatments for systemic disease control following surgery, early diagnosis through clinical assessment and non-invasive imaging techniques for primary MCC remains critical to improve patient outcomes. Moreover, routine baseline total-body imaging, including PET/CT scans and regional lymph node ultrasounds, is recommended to detect micro-metastatic or clinically occult disease.

Multimodal treatment, primarily involving platinum-based chemotherapy and radiotherapy, represents the primary approach for effective management of bone/bone marrow disease in MCC.

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Finally, integrating international guidelines alongside the ongoing findings from clinical trials will contribute to enhance patient care.

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Abbreviations

The following abbreviations not otherwise mentioned in the text are used in this manuscript:

AIDS	Acquired Immunodeficiency Syndrome
ATM	Ataxia-Telangiectasia Mutated
AKT1	A serine/threonine kinase
ARID1	AT-Rich Interactive Domain-Containing Protein 1
ASXL1	Additional Sex Combs-Like 1
BCOR	BCL6 Corepressor
BRCA1/2	Breast Cancer 1/2
DNA	Deoxyribonucleic Acid
DOTA	1,4,7,10-Tetraazacyclododecane-1,4,7,10-tetraacetic acid
EMA	European Medicines Agency
FAT1	FAT Atypical Cadherin 1
FDA	Food and Drug Administration
HRAS	Harvey Rat Sarcoma Viral Oncogene Homolog
HIV	Human Immunodeficiency Virus
HR	Hazard Ratio
ICI	Immune Checkpoint Inhibitor
IQR	Interquartile Range
JAK-STAT	Janus Kinase-Signal Transducer and Activator of Transcription
KMT2	Lysine Methyltransferase 2
MAPK	Mitogen-Activated Protein Kinase
MSH2	MutS Homolog 2
NCCN	National Comprehensive Cancer Network
NF1	Neurofibromin 1
NOTCH1	Notch homolog 1
PAX5	Paired Box 5
Piezo2	Piezo-type mechanosensitive ion channel component 2
PIK3CA	Phosphatidylinositol-4,5-Bisphosphate 3-Kinase Catalytic Subunit Alpha
PI3K	Phosphoinositide 3-Kinase
SMARCA4	SWI/SNF Related, Matrix Associated, Actin Dependent Regulator of Chromatin Subfamily A, Member 4
STIR	Short Tau Inversion Recovery
TdT	Terminal deoxynucleotidyl Transferase
VP1	Viral Protein 1

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