

Recent updates in the management of Merkel Cell Carcinoma

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Abstract

Merkel cell carcinoma is an aggressive non-melanomatous cutaneous tumour of neuroendocrine origin with an increasing incidence in the recent years. It is a tumour of the elderly and immunosuppressed, which most often appears on sun-exposed areas of the body. The clinical features of the cutaneous or subcutaneous lesions hardly contribute to the diagnosis, and, hence, histopathology and immunohistochemistry play a vital role in diagnosis. The latest staging system by the American Joint Committee on Cancer includes non-nodal invasion to adjacent structures i.e. bone, muscle, fascia, or cartilage into the criteria, in addition to size and depth of invasion. The management relies heavily on a multidisciplinary approach due to rarity of incidence of this disease. According to the international guidelines, surgical management is still the preferred choice. The beneficial role of adjuvant radiotherapy has now been more clearly documented. Data is insufficient to assess whether chemotherapy improves disease-free or overall survival.

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Introduction

Merkel cell carcinoma (MCC) is an aggressive non-melanomatous cutaneous tumour of neuroendocrine origin. It was first described in 1972¹ in a study which observed that the tumour originates from the neuroendocrine cells of the basal epidermis of the skin. Later on, studies described the cell of the origin as epidermal, non-dendritic, non-keratinocytic cell that he referred to as a tactile cell.¹ A number of other terms have also been used to describe this pathology, such as primary small cell carcinoma of the skin, trabecular cell carcinoma, amine precursor uptake decarboxylase (APUDoma) of the skin, and anaplastic cancer of the skin. Being a rare entity, the information pertaining to clinical diagnosis, management, and prognosis of MCC is still in the pipeline.² This review is in series with previous

reviews^{1,2} providing latest updates on staging and management of MCC.

Incidence and Demographics

Although MCC is a rare tumour, its incidence has demonstrated an increasing trend in the past two decades. The annual incidence of MCC in the United States is 0.6 per 100,000. Studies from Australia and New Zealand have documented higher incidence rates.³ The average annual incidence between 2006 and 2010, as reported by the Queensland cancer registry data, is 1.6 per 100,000, with a peak rate of 20.7 per 100,000 for individuals 80 years or older.⁴ In addition, the annual incidence of MCC recorded in the Netherlands increased from 1.7 in 1993-97 to 3.5 in 2003-07. Some of the factors which have been implicated to be the reason behind the rise of incidence of MCC are increased awareness and improved diagnostic techniques, especially the introduction of cytokeratin 20 (CK20) immuno-staining. The median age at diagnosis in women is 76.2 years whereas that for men is 73.6 years. The incidence is rarer in younger age groups. The incidence of MCC is approximately 5-fold to 10-fold greater for people with a solid organ transplant and 11-fold to 13-fold greater in patients with acquired immunodeficiency syndrome (AIDS), suggesting a role of immunosuppression in the pathophysiology of MCC. The National Cancer Database (NCDB) reports that the majority of MCC cases present with local disease (66%), followed by nodal disease (27%), whereas metastatic disease is an even rarer presentation (7%). Relative survival among patients with local disease was 64% at five years compared to 39% in regional nodal disease and 18% in metastatic disease.³

Aetiology

Although a clear aetiology behind the occurrence of MCC has not been defined yet, it does seem to share natural history, clinical features and behaviour (e.g. high recurrence rate and early spread to regional nodes) with melanoma.¹ MCC is a tumour of the elderly and the immunosuppressed, which most often appears on sun-exposed areas of the body. In addition to

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immunosuppression and ultraviolet (UV) light exposure, studies have been conducted focussing on the carcinogenesis of MCC, in particular the role of Merkel cell polyomavirus (MCPyV) and its surrogate marker large T-antigen. Together with CK20, other biomarkers, like human insulin gene enhancer-binding protein islet-1 (ISL1) and octamer-binding transcription factor 4 (OCT4) may provide improved methods for diagnosis and ultimately therapy.⁵ The most common site of the primary lesion is head and neck, comprising roughly 50% of cases (5) and other common sites are extremities (40%) and trunk (8%).^{1,6}

Diagnosis

The usual presentation of MCC is a painless, indurated, solitary dermal nodule with a slightly erythematous to deeply violaceous colour, and, less frequently, an ulcer. In addition, the ability to infiltrate dermal lymphatics, leading to multiple satellite lesions, is also a feature of these lesions. However, the clinical features of the cutaneous or subcutaneous lesions hardly contribute to the diagnosis, and, hence, it is rarely suspected before biopsy.⁷ The clinical features of MCC can be summarised with a mnemonic asymptomatic, expanding rapidly, immunosuppressed, older than 50 years, UV-exposed (AEIOU) skin.⁸ The initial workup for MCC includes ultrasound of the loco-regional lymph nodes and total body scanning examinations.⁷ Histopathology and an incisional or excisional biopsy play a mandatory role in making the diagnosis.

Histopathology

The tumour is composed of strands or nests of monotonously uniform round blue cells, containing large basophilic nuclei with powdery dispersed chromatin and inconspicuous nucleoli, and minimal cytoplasm.⁴ Other features may include single-cell necrosis, frequent mitoses, lymphovascular invasion, perineural invasion, and epidermal involvement via pagetoid spread, which can be further supported by immunohistochemical (IHC) staining.⁷

Immunohistochemistry

On IHC examination, Merkel cells show features of both epithelial and neuroendocrine cells.⁴ On Immunohistochemical staining (IHC), they express epithelial markers, such as cytokeratin AE1/AE3, CAM

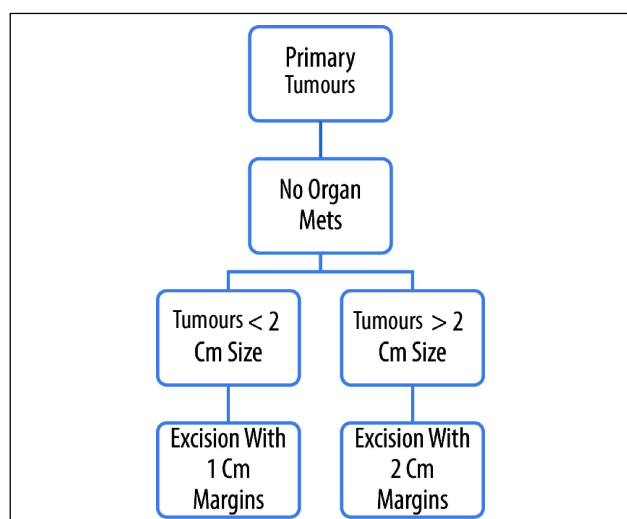


Figure-1 (A): Summarising the key points in incorporating a multidisciplinary approach towards management of Merkel Cell Carcinoma.

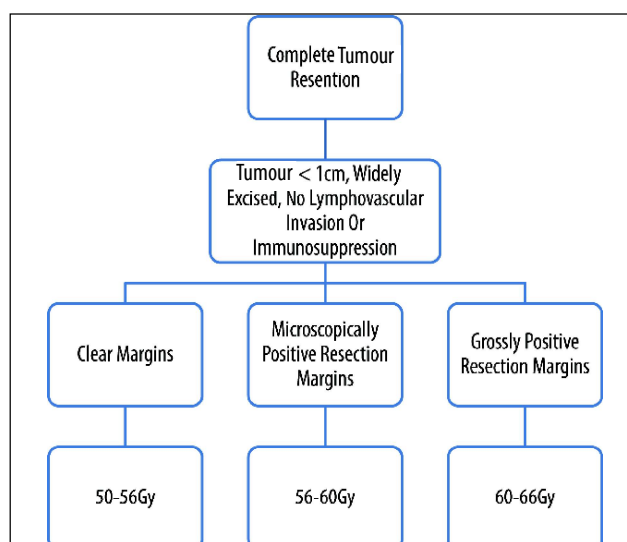
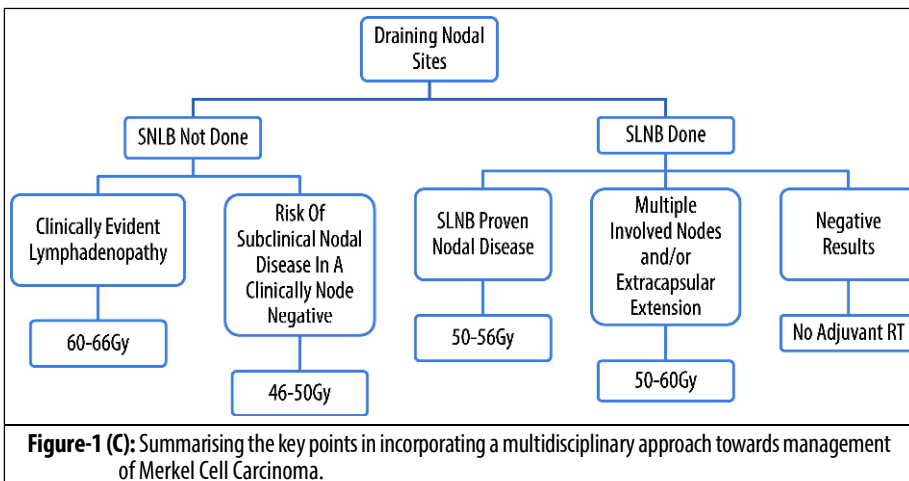


Figure-1 (B): Summarising the key points in incorporating a multidisciplinary approach towards management of Merkel Cell Carcinoma.

5.2, pan-cytokeratin, epithelial membrane antigen, and Ber-EP4, and may stain for various neuroendocrine markers, including chromogranin, synaptophysin, somatostatin, calcitonin, and vasoactive intestinal peptide.

The classic IHC feature of MCC which distinguishes it from other undifferentiated tumours is the immunoreactivity for low-molecular-weight cytokeratins (e.g., CK20, CK5/6).⁴ MCC consistently stains positively for low-molecular-weight CK20, which is a fairly specific and sensitive marker for MCC, with a characteristic paranuclear dot-like positivity.⁴



have worse survival compared to those who are staged after pathological examination e.g. Sentinel lymph node biopsy (SLNB).^{10,12}

The staging and prognosis of MCC has now been further updated in the eighth edition of the tumour, node, metastasis (TNM) staging system, which has been recommended by both the AJCC and the UICC.¹³ This system has been developed after an analysis of 9387 patients with MCC from

Staging

MCC can be staged according to the staging system proposed by the American Joint Committee on Cancer (AJCC).¹ Alternatively, a relatively simple system⁹ can be used for stage grouping:

Stage I: patients with localised disease; those with tumour of less than 2cm are considered stage 1A, whereas those with tumour of 2cm or more are considered stage 1B.

Stage II: with regional lymph node metastasis.

Stage III: with distant metastasis.

At the time of first consultation, 70-80% patients with MCC have been reported to be have stage I, 10-30% stage II, and 4-15% stage III disease.⁹

Another consensus staging system was then established in 2010 by AJCC and Union for International Cancer Control (UICC) based on an extensive literature review and an analysis of over 5,000 patients using the NCDB.¹⁰ This staging system defined stages I and II of MCC as disease localised to the skin at the primary site. The primary lesions less than or equal to 2cm were classified as stage I, while those greater than 2cm in size were classified as stage II. The involvement of nearby lymph nodes (regional lymph nodes) was the criterion for disease to be classified as stage III, whereas, stage IV disease went beyond the regional lymph nodes. In this system, the disease was divided into stages depending on the severity of the disease. The chance for spread (metastasis), treatment options, and chance for recovery were mainly determined by the stage at the time of diagnosis. It has been estimated that about a third of nodal metastases are missed on clinical nodal examination,¹¹ and patients who staged only clinically

the NCDB who were diagnosed between 1998 and 2012, and it provides more detailed correlation with clinical outcomes. The eighth edition provides separate criteria for clinical and pathological staging in contrast to the former staging system. Based upon the TNM information, patients are assigned to prognostic stage groups. These can be summarised as follows:

Stage I: Primary tumours ≤2 cm maximum tumour dimension, without evidence of regional lymph node involvement (Table-1).^{14,15}

Stage II: Primary tumours >2cm (T2 or T3) or a primary tumour with invasion into bone, muscle, fascia, or cartilage (T4), without evidence of lymph node involvement. Stage II is divided into two subgroups based upon the size and depth of invasion of the primary tumour.

Stage III: Any primary tumour with regional lymph node disease. Pathological stage III is divided into subgroups based upon the extent of regional lymph node involvement (Table 2).^{14,15}

Stage IV: Metastasis beyond the regional lymph nodes regardless of the status of the primary tumour and regional nodes (Tables 3-4).^{14,15}

Table-1: Tumour, node, metastasis (TNM) staging with respect to size of primary lesion of Merkel Cell Carcinoma according to American Joint Committee on Cancer (AJCC) 8th edition Staging System.(14, 15).

Primary Tumour (T)	
TX	Primary tumour cannot be assessed (e.g., curetted)
T0	No evidence of primary tumour
Tis	In situ primary tumour
T1	Maximum clinical tumour diameter less than or equal to 2 cm
T2	Maximum clinical tumour diameter >2 but less than or equal to 5 cm
T3	Maximum clinical tumour diameter >5 cm
T4	Primary tumour invades fascia, muscle, cartilage, or bone

Table-2: Tumour, node and metastasis (TNM) staging with respect to clinical and pathological nodal status of Merkel Cell Carcinoma according to American Joint Committee on Cancer (AJCC) 8th edition Staging System. (14, 15).

Regional Lymph Nodes (N) Clinical (N)	
NX	Regional lymph nodes cannot be clinically assessed (e.g., previously removed for another reason, or because of body habitus)
N0	No regional lymph node metastasis detected on clinical and/or radiologic examination
N1	Metastasis in regional lymph node(s)
N2	In-transit metastasis (discontinuous from primary tumour; located between primary tumour and draining regional nodal basin, or distal to the primary tumour) without lymph node metastasis
Pathological (pN)	
pNX	Regional lymph nodes cannot be assessed (e.g., previously removed for another reason or not removed for pathological evaluation)
pN0	No regional lymph node metastasis detected on pathological evaluation
pN1	Metastasis in regional lymph node(s)
pN1a(sn)	Clinically occult regional lymph node metastasis identified only by sentinel lymph node biopsy
pN1a	Clinically occult regional lymph node metastasis following lymph node dissection
pN1b	Clinically and/or radiologically detected regional lymph node metastasis microscopically confirmed
pN2	In-transit metastasis (discontinuous from primary tumor; located between primary tumour and draining regional nodal basin, or distal to the primary tumour) without lymph node metastasis
pN3	In-transit metastasis (discontinuous from primary tumour; located between primary tumour and draining regional nodal basin, or distal to the primary tumour) with lymph node metastasis

Table-3: Tumour, node, metastasis (TNM) staging with respect to clinical and pathological metastases of Merkel Cell Carcinoma according to American Joint Committee on Cancer (AJCC) 8th edition Staging System.(14, 15).

Distant Metastasis (M) Clinical (M)	
M0	No distant metastasis detected on clinical and/or radiologic examination
M1	Distant metastasis detected on clinical and/or radiologic examination
M1a	Metastasis to distant skin, distant subcutaneous tissue, or distant lymph node(s)
M1b	Metastasis to lung
M1c	Metastasis to all other visceral sites
Pathological (M)	
M0	No distant metastasis detected on clinical and/or radiologic examination
pM1	Distant metastasis microscopically confirmed
pM1a	Metastasis to distant skin, distant subcutaneous tissue, or distant lymph node(s), microscopically confirmed
pM1b	Metastasis to lung, microscopically confirmed
pM1c	Metastasis to all other distant sites, microscopically confirmed

Management

MCC is a rare tumour and due to its low incidence and the subtlety of its presentation, its management involves different modalities of oncological treatment. Like many other malignancies, the management of MCC relies mainly on a multidisciplinary approach.¹⁶⁻¹⁸ After necessary workup, including histopathological diagnosis

Table-4: Tumour, node, metastasis (TNM) staging of Merkel Cell Carcinoma according to American Joint Committee on Cancer (AJCC) 8th edition Staging System.(14, 15).

Clinical (cTNM)			
Tis	N0	M0	0
T1	N0	M0	I
T2-3	N0	M0	IIA
T4	N0	M0	IIB
T0-4	N1-3	M0	III
T0-4	Any N	M1	IV
Pathological (pTNM)			
Tis	N0	M0	0
T1	N0	M0	I
T2-3	N0	M0	IIA
T4	N0	M0	IIB
T1-4	N1a(sn) or N1a	M0	IIIA
T0	N1b	M0	IIIA
T1-4	N1b-3	M0	IIB
T0-4	Any N	M1	IV

and relevant staging workup, each case should be discussed in a multidisciplinary tumour board to reach a decision on further management.¹⁶ The current recommendations are in favour of surgical intervention being the main course of treatment,¹⁹ but the scarcity of prospective trials investigating this modality is a major factor contributing to the variability of opinion among clinicians. The guidelines for the management of MCC, therefore, explore all approaches i.e. surgery, chemotherapy and radiotherapy (RT).

Surgery

In order to address the problem of high risk of recurrence of MCC, it has been recommended that the entire lesion be excised at the time of initial presentation to achieve clear surgical margins whenever feasible, keeping in mind that any planned adjuvant RT should not get significantly delayed. The clinical size of the primary lesion plays an important role in the management. For primary tumours without evidence of organ metastases, excision with 1cm margins for tumours <2cm in size and 2cm margins for those >2cm in size has been recommended (Figure 1-A).²⁰ The size of the safety margins may need to be decreased in cases with head and neck involvement to increase aesthetic and functional outcomes.^{18,21} In terms of surgical approach, Mohs micrographic surgery (MMS) has been widely used as a treatment for MCC and has been shown to be as effective as wide local excision (WLE) in treating localised MCC,²² although the need for concurrent sentinel node

mapping (and/or neck dissection) suggests that WLE of the primary tumour in the same setting could be a better choice in certain circumstances.²⁰ A coordinated surgical management is warranted in all cases, so that sentinel lymph node biopsy could be performed prior to definitive surgical intervention, as lymphatic drainage is prone to be altered otherwise.^{14,15} The role of SLNB in the management of MCC has been reflected in a review of 161 MCC patients which found that SLNB identified micro-metastases in one-third of patients.²³ It has been documented by National Comprehensive Cancer Network (NCCN) panel that identifying patients with nodal disease and subsequently performing nodal dissection and/or RT, enhances the regional control.^{7,14} However, it should be kept in consideration that SLNB may be less reliable in head and neck compared to trunk and body.^{14,15}

After verification of clear margins and performing SLNB, if indicated, reconstruction should be performed as soon as possible after surgery. Maximising the efforts to minimise the extensive tissue movement in reconstruction and the delay in adjuvant radiation (if planned) is related to better outcomes.^{14,15}

Radiation Treatment

The rationale of offering RT in the management of MCC has been under debate for a long time. There is relatively little documentation available identifying patients with MCC who have received RT in adjuvant setting (less than 200 published). A study reviewed the Memorial Sloan-Kettering Cancer Centre's MCC database and identified 251 patients who had been treated between 1970 and 2002.²⁴ It analysed patient, tumour, and treatment-related factors for their association with recurrence and survival, but no association was found between irradiation and loco-regional control.²⁵

The weight of evidence now is in favour of considering adjuvant RT for patients with MCC.^{20,26-28} Adjuvant RT has been advocated in order to control local as well as regional disease.²⁶⁻²⁸ A systemic review suggests that definitive RT for loco-regional macroscopic MCC provides clinically meaningful local and regional control.²⁹ A meta-analysis comparing the role of surgery alone versus surgery with adjuvant RT demonstrated that the use of adjuvant RT significantly reduced the risk of local and regional recurrence. Adjuvant RT might be considered in patients with multiple affected lymph nodes of extracapsular extension.⁷

After complete resection of the tumour, the primary disease site must be observed if the tumour is small (<1cm), widely excised, and without other risk factors i.e. lymphovascular invasion or immunosuppression. Radiation-induced toxicity should be considered and discussed with the patient. According to the guidelines formulated by the National Comprehensive Cancer Network, a dose of 50-56Gy should be delivered if the resected margins are clear of the disease, whereas in cases with microscopically positive resection margins, 56-60Gy should be delivered. In case of grossly positive resection margins, or failure to undergo surgery due to unresectability, patient refusal, or significant morbidity, a dose of 60-66Gy should be delivered to the primary site (Figure 1-B).^{14,15}

Regarding the draining nodal sites, 60-66Gy is recommended for clinically evident lymphadenopathy if the patient has not undergone SLNB or lymph node (LN) dissection, whereas 46-50Gy should be delivered if there is risk of subclinical nodal disease in a clinically node-negative patient in the same setting. For patients who undergo SLNB with negative results, adjuvant RT after surgery is not recommended. However, 50-56Gy should be delivered for SLNB-proven nodal disease. In cases of multiple nodes and/or extracapsular extension, 50-60Gy should be administered after LN dissection (Figure 1-C).^{14,15}

RT has also been under consideration in the management of in-transit metastases (stage IIIB) of MCC as it is not possible to contain the disease and ensure clear margins with surgical approach only.^{30,31} Hence, the role of RT has acquired vital importance in this regard. RT to the primary site and satellite lesions with a 3-5cm margin with 50Gy in 25 fractions,³¹ avoiding interruptions has been recommended, with additional boost to the gross disease (10-16Gy) using electrons.³⁰ This recommendation can be supported by literature that RT can achieve more than 75% in-field control rates.³² Compared to surgery, dermal lymphatics can be widely covered using RT. In addition, RT poses fewer late effects than surgery-plus-RT, especially the risk of lymphoedema.³²

Previously, RT has been shown to improve survival in tumours of all sizes, but in current literature, the greatest impact on survival has been in cases where tumours were >2 cm.²⁰ Data is conflicting as to whether there is any survival benefit from adjuvant primary site or

regional nodal irradiation, partly due to the lack of prospective clinical trials.³³ The only randomised control trial to date comparing excision with RT versus excision with observation showed no overall survival improvement with adjuvant RT, but showed a significant reduction in regional recurrence.⁶

Chemotherapy

The effect of adjuvant radiation on survival is currently unproven, but the benefit of chemotherapy seems to be more clearly lacking and should not be recommended routinely.³³ Chemotherapy is usually reserved for systemic disease, though the success of this treatment is limited, and no chemotherapy protocol has been shown to improve survival.²⁰ Although chemotherapy has been used with or without surgery and/or RT for stage IV i.e. cases with distant metastases (M1), it is also being considered for selected cases of macroscopic regional disease (N1b or N2). For local disease, adjuvant chemotherapy is not recommended.^{14,15}

Nonetheless, data is insufficient to assess whether chemotherapy improves disease-free or overall survival in MCC patients with distant metastases. The most commonly used regimen used is cisplatin or carboplatin with or without etoposide. Topotecan is also considered in some cases of older patients. A regimen comprising cyclophosphamide, doxorubicin and vincristine is commonly considered, but it is associated with significant toxicity. Despite what has been stated, clinicians should exercise evidence-based and patient-centred judgment in choosing chemotherapeutic regimen.^{14,15}

Hyper-thermic isolated limb perfusion

Although not included in practice guidelines, hyperthermic isolated limb perfusion has been shown to confer some clinical benefits in the management of MCC. A retrospective review suggests that regional perfusion is safe and has a high complete response rate in a selected group of patients, providing durable loco-regional control of the disease.³⁴ A multicentre study evaluating the efficacy of isolated limb perfusion in which combination therapy with melphalan and tumour necrosis factor (TNF) was utilised demonstrated an overall response rate (ORR) of 87.5% with a complete response (CR) rate of 62.5%. Median loco-regional progression-free survival (LPFS) was 5 months and median overall survival was 54 months.³⁵

Conclusion

Putting all facts in the equation, features which are important in the management of MCC are the rarity of incidence, nonspecific clinical history, and aggressive nature leading to early loco-regional spread, distant metastases and high relapse rates. These features together make MCC a challenge for the team of treating clinicians. Consequently, it is imperative that each case be discussed in a multidisciplinary expert-panel tumour board before embarking on the first treatment modality. The deficiency of literature on MCC to help construct evidence-based management guidelines for clinicians warrants the need for conducting prospective clinical trials.

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