Chapter 14
Merkel Cell Carcinoma

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Introduction

Merkel cell carcinomas (MCCs) are rare cutaneous neuroendocrine neoplasms that are clinically aggressive due to a relatively high local, regional, and distant metastatic recurrence potential [1]. These tumours behave in a more lethal fashion than melanoma and are associated with an overall 5-year survival rate between 30 and 64 % [2–5]. They are found most commonly in Caucasian (94 %), elderly patients, with the average age at presentation being 72 years [6–8]. The most common sites of involvement include the head and neck (46–48 %), followed by the extremities (35–38 %), and trunk (11–17 %) [6, 7]. Risk factors include extensive sun exposure, immunosuppression, and/or infection with the polyomavirus virus [7, 9–11].

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MCCs usually present as non-tender, rapidly growing, painless, red to violaceous intradermal papules or nodules that can reach considerable size. Given their relatively non-specific clinical presentation, diagnosis is often delayed leading to advanced disease at the time of diagnosis. The "AEIOU" acronym can be used to assist with diagnosis: A—asymptomatic, E—expanding, I—immunosuppressed, O—age >50 years, and U—ultraviolet-exposed fair skin [1]. Ultimately, diagnosis is established by excisional or punch biopsy demonstrating the characteristic small, round, blue cells with large prominent nuclei. Immunohistochemical analysis has been instrumental in identifying markers characteristic of MCC, facilitating its differentiation from other small round, blue cell tumours. Whereas cytokeratin-20 (CK-20) staining is positive in 89–100 % of MCCs, thyroid transcription factor-1 (TTF-1) is generally absent [1].

Presentation [5]	Prognosis [12] 5-Year overall survival (OS)
• Localized disease (66 %)	64 %
• Regional metastasis (27 %)	39 %
• Distant metastasis (7 %)	18 %

The American Joint Committee on Cancer AJCC 7th edition is the current recommended staging system for MCCs. Prognostically, patients who have pathologically proven node-negative disease have improved survival compared to those who are only evaluated clinically. As such, the current AJCC guidelines divide stages I and II into A and B substages based upon the method of nodal evaluation [12].

Management

Localized Merkel Cell Carcinoma [3, 13–15]

Work-up	Surgical excision (margins)	Lymph node assessment	Adjuvant therapy	Follow-up
• History and physical examination • Complete skin and lymph node examination • Biopsy (H + E, IHC) • No labs • Imaging studies at physician discretion	• Wide local excision (1–2 cm margins) to investing fascia • Mohs micrographic surgical excision with negative margins and then re-excision (0.5–1.0 cm margins)	• Discuss and offer SLNB	• Refer to radiation oncology for consideration of adjuvant RTX to the primary site • No role for systemic chemotherapy in the adjuvant or neoadjuvant setting	• History and physical exam every 3–6 months for 3 years and then every 6–12 months thereafter

H + E hematoxylin and eosin staining, *IHC* immunohistochemistry, *SLNB* sentinel lymph node biopsy, *RTX* radiation therapy

Regional Metastatic Merkel Cell Carcinoma [15–17]

Clinical scenario	Work-up[a]	Surgical approach
SLNB positive	• Imaging: – CT chest, abdomen, and pelvis – PET-CT – MRI[b]	• Completion lymphadenectomy (CLND) should be offered and discussed • Level I–III axillary lymph node dissection • Superficial and deep groin dissection • Observation (if patient refuses further surgery or not surgical candidate) • Refer to radiation oncology for treatment to primary site and nodal basin and medical oncology for assessment of adjuvant therapy/clinical trial; there may be a role for radiation to the nodal basin instead of CLND in some patients
Clinically positive lymph nodes	• FNA or core biopsy • Imaging: – CT chest, abdomen, and pelvis – PET-CT – MRI[b]	• Therapeutic lymphadenectomy should be offered and discussed • Refer to radiation and medical oncology for assessment of adjuvant therapy/clinical trial

SLNB sentinel lymph node biopsy, *FNA* fine-needle aspiration, *CLND* completion lymphadenectomy
[a]PET-CT is gaining importance and may be preferred in some instances
[b]MRI can be used if PET-CT is unavailable

Sentinel Lymph Node Biopsy

The single most important prognostic characteristic of clinically localized MCC is the presence or absence of occult nodal metastases [18, 19]. The incidence of sentinel node metastases in MCC ranges anywhere between 11 and 47 % and approximately 30 % of clinically node-negative patients will harbor micrometastatic disease [20–23]. Unfortunately, SLNB is associated with a high false-negative rate (~15 %) likely secondary to lymphatic dysfunction and/or the relatively high number of MCCs on the head and neck leading to multiplicity of nodes compared to other sites. Several factors have been associated with SLN positivity including (a) primary tumour size (25 % for tumours ≤2 cm vs. 45 % for tumours >2 cm), and (b) the presence of lymphovascular invasion (55 % for tumours with lymphovascular invasion vs. 4 % for tumours with no evidence of lymphovascular invasion) [24]. SLNB also has therapeutic implications as patients with a positive sentinel lymph node appear to be at significantly higher risk of distant metastasis and death from MCC and thus may benefit from additional treatment [3, 4, 20, 22, 25–31]. Although SLNB is associated with a significant improvement in MCC-specific survival when compared to wide-local excision alone, well-designed, prospective studies are required to clarify its role particularly given the availability of alternative treatment in the form of chemotherapy and/or radiation therapy [32].

Metastatic Merkel Cell Carcinoma

Distant Metastatic Merkel Cell Carcinoma [15]

Work-up	Surgical approach	Systemic therapy
• Imaging: – CT chest, abdomen, and pelvis – PET-CT – MRI • No specific labs	May be considered for patients with oligometastasis after multidisciplinary tumour board consultation [33] For palliation of symptoms such as bleeding, pain, intestinal obstruction, or perforation of intestinal metastases	• Refer to radiation and medical oncology for assessment of combination therapy ± clinical trial enrollment • Multi-agent chemotherapy: – Cyclophosphamide/doxorubicin/vincristine – Carboplatin/etoposide – Cisplatin/etoposide

Notes: Combining chemotherapy and radiation therapy may provide better palliation of advanced locoregional disease compared to chemotherapy alone

Adjuvant Therapy for Merkel Cell Carcinoma

Radiation Therapy for Merkel Cell Carcinoma

Study	Treatment	Conclusions	Comment
Mojica P et al. [34]	• Surgery ± adjuvant RTX to the primary site • *N* = 1187	• OS was significantly increased with adjuvant RTX vs. surgery alone	• SEER registry data; no information on RFS or DSS • RTX-treated patients significantly younger than surgery-alone patients
Clark et al. [35]	• Surgery + adjuvant RTX to the primary site and regional nodal basin vs. surgery alone or RTX alone • *N* = 110	• Combined therapy improved both local regional control and DFS but not DSS	• Retrospective review of head and neck cases only; a high percentage of cases with positive surgical margins (38 %) • No differentiation between surgical and RTX monotherapies
Lewis et al. [36]	• Surgery ± adjuvant RTX to the primary site and regional nodal basin • *N* = 1254	• Reduction in local and regional recurrence associated with combination therapy vs. surgery alone • Rates of distant metastasis and OS were not significantly different	• Meta-analysis • Rates of local (40 %) and nodal (56 %) recurrence in the surgery-alone cohort notably high, calling into question the relevance of the conclusions

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Study	Treatment	Conclusions	Comment
Jouary T et al. [37]	• Surgery + RTX to the primary site and regional nodal basin vs. surgery + observation • *N* = 83	• Adjuvant RTX associated with improvement in regional recurrence compared to observation (10 % vs. 16.7 %); no improvement in OS	• RCT of patients with stage I disease • Prematurely closed due to a drop in recruitment with the advent of SLNB

RTX radiation therapy, *OS* overall survival, *DFS* disease-free survival, *DSS* disease-specific survival, *RFS* recurrence-free survival, *RCT* randomized controlled trial

Indications for Post-operative Radiation Therapy [15]

- Radiation to the Primary Site
  - Primary tumour >1 cm in diameter
  - Salvage operation for recurrent disease
  - Positive margins that cannot be surgically re-excised
- Radiation to the Nodal Basin
  - Absence of surgical assessment of lymph node basin
  - Positive sentinel node without completion of node dissection
  - Bulky nodal disease with multiple (4+ axillary and 10+ inguinal) lymph node metastases
  - Extracapsular spread

Systemic Chemotherapy for Merkel Cell Carcinoma

Although there is sparse literature on chemotherapeutic options for MCC, at most institutions chemotherapy is used with or without surgery and/or radiation for stage III (regional nodal disease) or stage IV (distant metastatic disease) [15, 38]. Available date from retrospective studies, however, does not suggest a prolonged survival benefit for adjuvant chemotherapy [39, 40]. Enrollment in clinical trials is encouraged whenever available and appropriate.

Referring to Medical Oncology

- All patients with histologically confirmed MCCs, other than those with localized disease, should be referred to medical oncology to (1) evaluate the risk of tumour recurrence; and (2) to establish the role of systemic chemotherapy. If any doubt exists regarding patient risk stratification, referral to medical oncology is warranted.

Referring to Radiation Oncology

- All patients with histologically confirmed MCCs should be referred to radiation oncology for consideration of adjuvant, neoadjuvant, or primary therapy.

Referring to Multidisciplinary Cancer Conference (MCC)

- All patients with a diagnosis of MCC should be discussed to confirm pathologic diagnosis, and evaluate the indications for adjuvant or therapy.

Toronto Pearls

- The multidisciplinary management of MCCs is the cornerstone of evidence-based treatment.

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