Radiotherapy in the Multidisciplinary Management of Merkel Cell Carcinoma

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Abstract

The management of Merkel cell carcinoma (MCC) requires multidisciplinary care for optimal patient outcomes. Radiotherapy (RT) is most commonly used as adjuvant therapy to improve locoregional control in patients with MCC who undergo surgery. Additionally, it can sometimes be used as definitive monotherapy for patients who decline or are not candidates for surgery and as palliative treatment in those with metastatic MCC. This article discusses the indications, treatment considerations, and recommended dose prescriptions for RT in the management of early- and advanced-stage disease. Considerable hope exists that immunotherapy advances will synergize with RT to further enhance clinical outcomes.

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Merkel cell carcinoma (MCC) is a relatively rare cutaneous malignancy, predominantly diagnosed in elderly individuals (aged >70 years), that is increasing in incidence as the population ages.¹ Due to the rarity of this disease, there is a paucity of prospective randomized studies to guide clinical practice. This review explores the role of radiotherapy (RT) as part of the multimodality management of MCC and presents current areas of consensus and controversy.

MCC arises from epidermal neuroendocrine cells, which synapse with afferent neurons to enable tactile sensation in the skin.² It classically presents as a benign-appearing; small; firm; red, purple, or skin-colored; non-tender papule or nodule on a sun-exposed surface in an elderly individual.³ Diagnosis is made histologically. It is in the family of small round basophilic tumors, but can be distinguished based on S-100–negative, TTF-1–negative, and CK20–positive immunohistochemical staining.⁴ The isolation of clonal polyomavirus integration in MCC has suggested a viral contribution to the development of this disease in a subset of patients.⁵ Although it can occur in young adults, the frequency of the disease

increases markedly in patients aged >70 years, which has been attributed to the burden of chronic mutagenic UV exposure and age-associated diminished immunosurveillance.^{3,6} It is also more common in patients immunosuppressed for other reasons (eg, transplant recipients, chronic lymphocytic leukemia). Prognosis is strongly dependent on the extent of disease at initial presentation and immune status.

Staging reflects the extent of disease, with distinctions made for small (<2 cm) versus moderately sized (>2 cm) localized disease, regional disease involving draining lymph nodes, and disseminated metastatic disease.⁷ A pooled patient-level meta-analysis has confirmed that sentinel lymph node biopsy (SLNB) has increased sensitivity in detecting regional disease compared with CT scans.⁸ National guidelines now recommend that suitable patients with clinically node-negative MCC undergo SLNB, and that those with clinically node-positive MCC undergo biopsy (eg, fine-needle aspiration, core, open) to confirm lymph node involvement.⁹ Although staging with CT and/or PET/CT is encouraged whenever metastatic or unresectable disease is suspected based

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on patients' signs and/or symptoms, it is also recommended for all patients with pathologic evidence of lymph node involvement.^{8,9} The treatment of MCC is dependent on disease extent.

Localized Disease Management

Surgery represents the primary treatment modality for the diagnosis and treatment of localized MCC in medically and technically operable patients.⁹ A National Cancer Database (NCDB) study examining US patients diagnosed from 1985 to 2005 indicated that approximately 50% present with stage I or II disease.¹⁰ In line with the infiltrative nature of neuroendocrine malignancies, historical series have reported local recurrence rates of 100% following excision with only 0.5-cm margins.^{3,11} Therefore, a wider local excision of 1 to 2 cm circumferentially and down to the investing fascia is the recommended surgical approach.

A number of older, single-institution, retrospective studies have indicated that adjuvant RT to the primary site is beneficial in early-stage MCC.^{12–15} Up to 40% of all patients will develop local recurrences after surgery even with wide margins, which can be used to justify the routine use of adjuvant RT to the primary site.¹⁶ In fact, the largest systematic review to date of 1,254 patients with MCC treated from 1966 to 2004 showed a statistically significant reduction in local (hazard ratio [HR], 0.27) and regional (HR, 0.34) recurrence among patients treated with combination RT and surgery compared with surgery alone.¹⁷ Moreover, in one NCDB study, the addition of RT to surgery in patients with stage I and II disease was associated with improved survival.¹⁸ Further, a retrospective evaluation from British Columbia has suggested that RT is highly effective for local control following subtotal resection or microscopically positive margins.¹⁹

In contrast, several series have suggested that local recurrences are less common in patients with very early-stage MCC treated with surgery alone. The University of Michigan examined a cohort of 104 patients with stage I MCC treated from 2006 to 2012 who achieved a gross total resection via a wide local excision with 1- to 2-cm margins and an SLNB. With a median follow-up of 3 years, local recurrences occurred in 1%, satellite recurrences in 1%, and in-transit recurrences in 3.8%.²⁰ At Memorial Sloan

Kettering Cancer Center, only 13% of patients with stage I MCC received adjuvant RT, and a local recurrence rate of 2% was reported.²¹ In summary, retrospective data suggest that adjuvant RT directed to the tumor bed is generally beneficial, but there appears to be a subset of patients with such favorable disease that its omission can be considered.

Medically inoperable patients, patients in whom surgery would result in unacceptable functional or cosmetic outcomes, or those who decline surgery may be candidates for definitive RT alone. Radiobiological studies have indicated that the disease is very radiosensitive.²² Single-institution studies have indicated that local control with RT monotherapy for localized disease can range from 75% to 100%.^{23–25} RT is also effective for head and neck locations in which surgical excision can be challenging.²⁶

Primary Site RT Treatment Considerations

Gross tumor volume (GTV) is defined as the gross primary lesion and involved nodes (if any). Radially, clinical tumor volume typically encompasses the tumor or tumor bed with a 3- to 5-cm margin, although smaller expansions of 2 to 3 cm are sometimes used, depending on anatomic boundaries and adjacent normal tissues (eg, for head and neck sites). The full thickness of the skin and underlying fascia should also be targeted (typically, 5-mm thickness) often using tissue-equivalent material, commonly referred to as *bolus*, to achieve an adequate skin dose. Depending on the location and immobilization used, a 0.5- to 1-cm planning target volume (PTV) expansion can be used (Figure 1). In the adjuvant setting, the prospective phase II TROG 96:07 trial prescribed 50 Gy in 25 fractions using 2D beam arrangements,²⁷ whereas the prospective Groupe de Cancérologie Cutanée of the Société Française de Dermatologie trial advised using the same dose, but frequently patients also received an additional 10-Gy boost to the tumor bed.²⁸ In the setting of gross disease, Canadian data have suggested that cancer-specific survival is improved if >50 Gy is administered.²⁹ RT can be delivered using a number of modalities, including photons, electrons, or brachytherapy. Photon plans can be delivered conformally using 3D and volumetric techniques. Electrons are often used for the primary site because of the superficial nature of the region that needs to be treated. Case reports have indicated

Figure 1. Primary site and regional nodal radiotherapy (RT) fields for Merkel cell carcinoma (MCC). (A) An oblique 3D beam arrangement with photon RT was used to adjuvantly treat the skin and subcutaneous tissues around the primary site (clinical tumor volume [CTV]: red) following wide local excision of a T2,N0 MCC of the left forearm. Bolus was used to ensure full dose to the skin. 95% (dark green), 50% (green), and 10% (blue) isodose lines are shown. (B) Volumetric modulated arc therapy was used to conformally deliver adjuvant photon RT to a patient with stage IIIB MCC of the left cheek involving the parotid gland (CTV: red) following wide local excision and left neck dissection. Again, bolus (yellow) was used to ensure full dose to the skin around the primary site. 95% (dark green), 50% (green), and 10% (blue) isodose lines are shown.

that brachytherapy can be effective in locations such as the lip, which are challenging to treat with external-beam RT.³⁰ Using conventional fractionation of 1.8 to 2 Gy per treatment, the total radiation dose prescription for the primary site ranges from 50 to 56 Gy for negative surgical margins, 56 to 60 Gy for microscopically positive margins, and 60 to 66 Gy for gross disease (Table 1), although some believe that given the very radiosensitive nature of MCC, lower doses could also be used.³¹ Hypofractionated

Table 1. Radiotherapy Dose Guidelines for Merkel Cell Carcinoma		
Site	Clinical Scenario	Recommended Dose
Primary	Resected with wide margins (eg, 1–2 cm) and small tumor size (<1–2 cm)	Consider observation
	Resected with negative margins	50–56 Gy
	Resected with microscopically positive margins	56–60 Gy
	Resected with grossly positive margins	60–66 Gy
	Not resected; definitive radiotherapy	60–66 Gy
Nodal basin	Clinically node-negative with SLNB negative	Observation
	Clinically node-negative without SLNB or LN dissection	46–50 Gy
	Clinically node-negative with SLNB positive without LN dissection	50–56 Gy
	LN dissection with extracapsular extension, multiple positive LNs	50–60 Gy
	Clinically involved nodes without SLNB or LN dissection	60–66 Gy

Abbreviations: LN, lymph node; SLNB, sentinel lymph node basin.

regimens are also well tolerated in other cutaneous malignancies,³² and can be considered in patients in whom the delivery of conventionally fractionated RT is logistically challenging. For example, other options for gross disease include 50 Gy delivered in 20 fractions or 50 Gy delivered in 15 fractions. Additional clinical considerations that may influence the dose chosen within these ranges include the location, RT field size, and presence of adjacent critical normal structures.

Regional Nodal Disease Management

The risk of lymph node involvement is directly proportional to the size of the primary tumor.¹⁰ However, as noted, occult regional involvement can occur in 20% to 30% of patients even with <2 cm primary lesions, and therefore SNLB is recommended in all patients who are clinically node-negative.¹⁴ Pathologic features based on the primary-site biopsy that predict SLNB positivity include increasing clinical tumor size, increasing tumor thickness, increasing mitotic rate, and infiltrative tumor growth.³³ For patients with early-stage disease who are clinically node-neg-

ative and decline or are not candidates for SLNB, treatment of the regional nodes with RT alone is supported by the results of the French randomized trial comparing adjuvant regional nodal RT versus observation in patients with stage I MCC following wide local excision and adjuvant RT to the tumor bed.²⁸ Although the trial closed early due to poor accrual following the introduction of SLNB, the addition of nodal RT resulted in a significant improvement in regional recurrence (0% vs 17%; $P=.007$), although it was not associated with a difference in overall or progression-free survival. For patients with a negative SLNB, adjuvant nodal RT is not recommended. In patients with regional lymph node involvement, consensus guidelines favor lymph node dissection more strongly in fit patients with clinically apparent disease versus those with clinically node-negative, SLNB-positive disease, but definitive RT can also be considered in both settings. The advantage of further histologic characterization of disease burden afforded by surgery must be balanced against the potential morbidity of lymphadenectomy (eg, lower-extremity lymphedema following inguinal lymph node dissection). Multiple trials have evaluated the utility of adjuvant RT following complete surgical resection of nodal disease in patients with locally advanced melanoma, but no such data exist for MCC.^{32,34} If extracapsular extension or multiple lymph nodes are found to be involved, adjuvant RT is generally recommended out of concern for locoregional relapse.

Regional nodal disease is also very sensitive to RT.¹⁹ RT can be considered for the definitive or adjuvant treatment of regional lymph nodes. The University of Washington experience of 43 patients with node-positive MCC compared definitive RT for nodal management versus completion lymphadenectomy.³⁵ With 18 months of follow-up, regional lymph node control was 100% in patients with subclinical microscopic disease treated with either RT or lymph node dissection, and was approximately 75% (not statistically significantly different) for clinically involved nodes treated with either RT or lymph node dissection. In summary, RT offers excellent regional control in patients whose nodal disease burden has not been surgically addressed for technical or medical reasons.

Regional Nodal RT Treatment Considerations

The GTV and PTV definitions for regional disease are similar to those used in primary MCC. Clinical target volumes for regional nodes should encompass the entire nodal chain, and radial expansion beyond this volume are not typically used (Figure 1). ¹⁸F-FDG-PET/CT can reveal occult disease and therefore can sometimes be used for more accurate target delineation.³⁶ In cases in which the primary sites and nodes are both being treated and the intervening distance is not too great, treatment of the intervening skin can be considered in hopes of decreasing the likelihood of developing in transit metastases. Our practice is to consider this if the intervening distance is <20 cm. The benefit of improved cutaneous control must be weighed against the potential for increased skin toxicity, especially in patients with head and neck cancer. Notably, TROG 96:07 used 2D beam arrangements and fields were set based on bony anatomy, not using cross-sectional delineation of target volumes. 3D and intensity-modulated RT can significantly reduce the dose received by organs at risk and improve the homogeneity of the radiation dose, which could limit acute skin and other late toxicities.³⁷ Because of the deeper location of most nodal basins, photon RT is typically preferred. The radiation prescription typically ranges from total doses of 46 to 50 Gy for elective nodal radiation, 50 to 56 Gy for known microscopic nodal disease, and 60 to 66 Gy for gross disease (Table 1).^{31,38} NCDB analyses indicate that moderately lower doses of 45 to 50 Gy may be used for subclinical nodal disease.^{39,40}

Role of Concurrent RT and Chemotherapy

Single-institution data have repeatedly demonstrated that although RT can provide effective local control, up to 60% of patients treated definitively experience out-of-field relapses.^{24,25} This has led to treatment intensification studies in which concurrent chemotherapy was added to RT. The TROG 96:07 trial enrolled 53 patients with MCC with at least one of the following high-risk features: recurrence after local therapy, stage III disease, grossly positive surgical margins, tumors >1 cm, or an unidentified primary site.²⁷ Patients received 50 Gy of RT in 25 fractions to the primary site and regional

lymph nodes with a 3- to 5-cm margin, along with concurrent carboplatin and etoposide. Treatment was well tolerated aside from common acute skin toxicity (64% grade 3/4). The 3-year overall survival, locoregional control, and distant control rates were 76%, 75%, and 76%, respectively. Multivariate analysis on a matched historical cohort did not identify receipt of chemotherapy as improving overall survival.⁴¹ The lack of benefit from cytotoxic chemotherapy has been further validated in NCDB studies.¹⁸ Therefore, despite the risk for systemic failures, adjuvant chemotherapy is not indicated in patients with locally advanced disease.

Metastatic Disease Management

The goal of treatment in patients with widely disseminated disease is to palliate symptoms. Locoregional techniques including surgery and RT can sometimes have significant therapeutic impact on achieving this goal. Palliation of bone metastases and other sites of extracranial metastatic disease can be achieved with as much as 30 Gy in 10 fractions and as little as 8 Gy delivered in a single fraction, depending on the clinical situation. The University of Washington has used single 8-Gy fractions to treat metastases in a variety of anatomic sites, and reported complete responses in 45% and local control in 77% of tumors treated. Brain metastases are rare with MCC; single case reports describe the use of whole-brain and stereotactic RT for treatment.^{42–44} As with other diseases, the approach used would typically depend on the extent of the intracranial and extracranial disease.

RT and Immunotherapy

Considerable advances have recently been made in harnessing antitumoral immunity for therapeutic gain. Immunosuppression increases the incidence of MCC and diminishes the prognosis of patients. Further, intratumoral immune response has been

suggested to be prognostic in MCC.⁴⁵ Randomized phase II trials in the metastatic setting have shown that pembrolizumab (anti-PD-1; overall response rate [ORR], 56%) and avelumab (anti-PD-L1; ORR, 33%) are effective in MCC.⁴⁶ Although durable responses are common, only a subset of patients experience clinical benefit. Considerable interest has been shown in improving outcomes through combination of immunotherapy with other agents, including RT. Preclinical models have indicated that RT is more effective with an intact adaptive immune system, and retrospective reviews have suggested that local control after RT is diminished in immunocompromised compared with immune-intact patients.^{47–49} Emerging evidence has not found increased toxicities when RT is administered concurrently with immune checkpoint blockades in melanoma.⁵⁰ Adjuvant trials in MCC are ongoing and the hope is that information on the toxicity and efficacy of combination therapy will soon be available (ClinicalTrials.gov identifier: NCT03304639). Accordingly, a significant need exists to determine how best to combine immunotherapy and RT to improve outcomes in the adjuvant and metastatic settings.

Conclusions

The role of RT in the management of MCC is somewhat challenging to define because of the relative lack of data from prospective clinical trials. Nevertheless, a consistent finding in the literature is that RT is highly effective in providing locoregional control benefits in patients with MCC. Mostly single-institution experiences have confirmed that RT can be considered for the definitive, adjuvant, and palliative treatment of patients with MCC within a multidisciplinary framework. Similar to other disease sites, significant hope exists that future improvements in systemic control with immunotherapy will accentuate the importance of achieving locoregional control.

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