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Radiation therapy in the management of Merkel cell carcinoma: current perspectives

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Abstract

Merkel cell carcinoma (MCC) is a rare cutaneous neuroendocrine neoplasm with a propensity for metastatic spread. When managing MCC, surgical excision is often the initial treatment. As MCC is generally radiosensitive, many institutions include adjuvant radiation therapy (RT) in their standard treatment protocols. In the absence of prospective randomized clinical trials, a number of retrospective reports suggest that adjuvant RT can improve local and regional recurrence rates. Here, we provide an overview of recent studies on the use of RT in MCC treatment and explore the limits of the current knowledge. Ultimately, the benefits and risks associated with using RT in the treatment of MCC remain poorly described and merit more rigorous investigation.

Keywords

brachytherapy; chemoradiation; external-beam radiation; Merkel cell carcinoma; neuroendocrinetumor; radiation therapy

Merkel cell carcinoma

Merkel cell carcinoma (MCC) is a rare cutaneous neuroendocrine neoplasm that presents most often on sun-exposed skin. Approximately two-thirds of patients present with localized disease, with the remaining third presenting with regional advanced or metastatic disease, and their survival is significantly decreased. Although treatment is often successful for early-stage lesions, MCC still carries a mortality rate of 33% [1], with the majority of disease-specific deaths occurring within the first 2 years of follow-up [2]. Individuals most susceptible to MCC comprise a medically vulnerable population: elderly patients (>65 years

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of age) [1,3] and immunosuppressed individuals, including HIV-infected patients [4,5], transplant recipients [6] and patients with hematologic malignancies. Recently, a novel polyomavirus, named Merkel cell polyomavirus, was found to be integrated in approximately 80% of MCC tumors [7]. The clinical and etiological implications of this viral association are actively being investigated. However, the advanced age of MCC onset suggests an accumulation of multiple oncogenic factors [8]. Although MCC is rare (~0.44 per 100,000 age-adjusted person-years), the annual rate of the disease has increased nearly threefold over the last two decades [1]. Part of this increase is attributed to improved diagnostic tools, but an actual increase in disease incidence cannot be excluded, particularly because of the growing elderly population.

Merkel cell carcinoma has long been known to be radiosensitive [9]. As such, both radiation therapy (RT) and chemoradiation have been described for patients with inoperable tumors. In a recent review of the literature, Rao concludes that RT is an effective tool in the management of MCC [10]. However, no randomized controlled clinical trials for the management of MCC have been conducted, and the published literature consists mainly of case reports, retrospective case series and aggregate-level meta-analyses. Owing to the low level of existing evidence, available clinical guidelines for treatment and management of MCC, such as those from the National Comprehensive Cancer Network [101], are based primarily on expert opinion. However, the potential for metastatic spread of MCC, the vulnerability of the populations most susceptible to MCC and the increasing annual rates of the disease all underscore the importance of establishing evidence-based standards of care for patients with this disease.

Here, we provide an overview of studies on the use of RT in MCC treatment and explore the limits of the current knowledge. We also discuss recent findings that may increase available options for MCC treatment with RT.

Clinical presentation & diagnosis of MCC

Merkel cell carcinoma usually presents as a solitary, asymptomatic, rapidly growing skin nodule. The diagnosis is rarely made based on clinical presentation, and biopsy of the lesion is required for definitive identification. Stage I and II disease are limited to the skin, whereas stage III and IV MCC present with lymph node and distant metastases, respectively. Occasionally, metastatic MCC is diagnosed without identifying a primary skin lesion. The histology of MCC is characteristic of neuroendocrine carcinoma; however, histologic diagnosis of MCC may be confounded by its similarity to other small, round blue-cell tumors [101]. Immunohistochemistry with markers such as cytokeratin 20 is required to differentiate MCC from metastatic neuroendocrine tumors and from other tissues, such as small cell lung carcinoma. The need to distinguish similarly appearing tumors and the existence of many histologic variants of MCC makes tissue evaluation by a dermatopathologist advisable.

Management of MCC

Appropriate staging of MCC includes a complete skin and lymph node exam and, when indicated, may include imaging studies (CT, MRI or PET-CT), and needle, open or sentinel lymph node biopsies [101]. The initial treatment for localized MCC is wide excision of the primary tumor with clear surgical margins, and nodal disease can be treated with lymph node dissection [101]. However, RT has played an increasing role in managing MCC. RT has been utilized, in particular, as an adjuvant to surgery but also as an alternative to lymph node dissection and as elective treatment in clinically negative regional lymph node beds. Accordingly, several institutions routinely incorporate RT as part of MCC treatment. Moreover, patients deemed unable to tolerate surgical resection may be recommended

definitive radiation (without surgery) as treatment for their primary tumor or for regional nodal disease. Palliative RT is also used for inoperable, incurable disease. Systemic chemotherapy, often in combination with surgery and/or radiation, is one of the few options for disseminated disease, but is not effective as a curative treatment for MCC.

Limitations of studies describing RT for MCC

The level of evidence supporting the benefits of RT is important to consider when evaluating its use for MCC. The robustness of the current evidence is hampered by inherent limitations of the studies conducted thus far. Case reports, small retrospective case series or meta-analyses of the same are prone to bias and often lack sufficient numbers to draw definitive conclusions. Moreover, in such reports, the criteria for designating which patients received RT are not often defined. In nonrandomized case series, patient selection can introduce bias that is impossible to control for. For example, during clinical management, physicians will sometimes avoid RT in patients with poor performance status because these patients may not tolerate the treatments. By contrast, some centers may reserve RT for patients with prognostic signs that portend worse outcomes, such as large primary tumors, lymphovascular invasion, positive or close surgical margins or infiltrative growth patterns. Regardless of what motivates the selection, such nonrandom assignments create patient groups that are not comparable in their expected outcomes.

Many reports on MCC treatment lack standardized management protocols. As such, there can be variability in the use of RT (e.g., dose, fractions, margins, inclusion of in-transit or lymph node beds), as well as variability in surgical techniques and additional interventions such as chemotherapy or lymph node dissections among the patients included in a study. Such uncontrolled variability is amplified because MCC is a rare tumor and publishing a large case series requires the inclusion of patients from multiple centers or patients seen over many years at the same center. In either case, it is likely that treatments will vary by institution or over time. These differences may account for the broad range of reported recurrence rates for MCC. For example, published local recurrence rates after surgical resection alone range from 8 to 100% [2,11]. Accounting for such variability when interpreting data can be problematic.

Another limiting factor in MCC studies is that the selected end points often include locoregional recurrence and overall survival (OS) but not disease-specific survival (DSS). Considering the high likelihood of intercurrent mortality from comorbid conditions in the advanced-age population affected by MCC, DSS is often more informative than OS. In addition, in retrospective studies, follow-up surveillance can be of limited duration and often does not occur according to a fixed schedule, possibly resulting in noncaptured events.

In most studies, disease stage at diagnosis is a significant predictor of MCC survival. However, staging systems that do not include microscopic assessment of lymph nodes may fail to adequately stratify risk, thus leading to comparison of patients with non-equivalent prognoses. Interpretation of staging data is confounded by the many institutional staging systems that have been used for MCC, thereby complicating data comparisons across medical centers. Any future randomized, controlled clinical trials would require a uniform risk stratification system, based on an accurate assessment of factors predictive of recurrence and disease-specific mortality. An attempt to address this need was made by the staging system recently adopted by the American Joint Committee on Cancer (AJCC) [12]. This staging system does distinguish between patients who have undergone microscopic nodal interrogation and those who have not, as well as those with clinically detected nodal disease. The current AJCC staging (7th Edition) is based on an outcomes analysis of over 5000 patients with MCC from the National Cancer Data Base (NCDB) [13]. Unfortunately, the

NCDB does not capture DSS and clinical nodal information was not available on many patients. These limitations and others make accurate prognostication with the AJCC7 questionable. Validation and possible refinement of the system will be needed to develop a reliable risk stratification system for MCC.

Finally, many studies inadequately report adverse events associated with the use of RT and other therapies. As a consequence, quality-of-life changes attributable to disease and treatments are often not assessed. These omissions raise questions that will be particularly relevant for patients who might avoid adverse side effects associated with unnecessary RT, either when surgery alone could provide similar benefits as surgery with adjuvant RT or when hypofractionated palliative RT may be more appropriate than aggressive RT for patients with incurable disease and poor performance status.

The lack of prospective randomized treatment trials for MCC is understandable considering its low incidence. Yet, without such trials, no conclusive statements can be made about the efficacy of RT in the management of MCC. It is noteworthy that most published retrospective studies describing RT for MCC (Table 1) report an association between RT use and an improvement in locoregional control rates or relapse-free survival (RFS) in selected patients. Nonetheless, when considering these studies, it is imperative to recall the above caveats and understand that these studies may overestimate the benefit of RT, especially for patients who receive adequate surgical treatment.

Adjuvant RT for MCC

Several retrospective studies report on the use of adjuvant RT, which is typically performed within weeks after excision of primary tumors or after surgical dissection for node-positive regional disease. The concept motivating adjuvant RT is based on the hypothesis that residual subclinical disease in the surgical bed is responsible for surgical-site recurrences. The use of RT after surgery is intended to treat the potential residual disease and prevent disease progression.

In a retrospective analysis of 110 patients with head and neck MCC from three institutions (Westmead Hospital, Sydney, Australia; Princess Margaret Hospital, Toronto, Canada; Royal Prince Alfred Hospital, Sydney), Clark *et al.* report their analysis of surgery plus RT versus either surgery alone or RT alone with a median follow up of 1.8 years (combination therapy [n = 66]; surgery monotherapy [n = 36]; RT monotherapy [n = 8]) [14]. In a univariate analysis, surgery plus adjuvant RT improved RFS compared with monotherapy ($p = 0.013$) but did not improve the rate of distant recurrence ($p = 0.82$) or DSS ($p = 0.67$). However, the study does not differentiate between the two types of mono-therapy (surgery alone versus RT alone), making it impossible to assess the benefit of adding RT as a surgical adjuvant. On multivariate analysis, combination therapy was associated with longer time to relapse; however, it was not an independent contributor to either RFS or DSS. *Post hoc* subgroup analysis using two different staging systems suggests the association between multimodal therapy and better local control may be stronger in patients with more advanced local disease but no lymph node involvement, and the same patients may show a DSS benefit as well. However, when interpreting these results, it is important to note that 35 out of 93 (38%) patients had incomplete excisions of their MCC (positive surgical margins), suggesting a high baseline need for postsurgical therapy in this population.

Lewis *et al.* present a systematic meta-analysis of published data that compares surgery alone with surgery plus adjuvant local RT in the management of MCC [15]. The authors included 1254 patients in the analysis according to the following criteria: histopathologic diagnosis of MCC; a single, primary tumor of the skin; treatment with surgical excision with or without the use of adjuvant RT (which may have included other treatments, such as

chemotherapy or lymph node dissection); negative surgical margins; and postoperative follow-up of at least 1 month documenting disease recurrence, progression, survival and/or duration of event-free interval. Statistically significant reductions in local and regional recurrence were reported among patients who received adjuvant RT compared with surgery alone, whereas neither distant metastasis, OS nor DSS was significantly different between the two groups. A *post hoc* subgroup analysis (n = 382) excluding single-patient case reports, studies of only one treatment group and studies with only aggregate-level data, demonstrates a significantly increased OS (hazard ratio [HR]: 0.63; p = 0.02) and DSS (HR: 0.62; p = 0.04) after treatment with adjuvant RT. However, considering the limitations of comparing such disparate and inherently flawed datasets, it is unclear how much weight can be placed on either the overall analysis or the subgroup analysis. Although the analysis supports the idea that adjuvant RT can improve locoregional control, it is noteworthy that the observed rates of local (40%) and regional (56%) recurrence seen in the patients treated with surgery alone are markedly higher than many published studies, once more suggesting that RT was making up for inadequate surgical treatment. Moreover, as there was no consistency in the RT used across the studies, this analysis does little to delineate a standard treatment approach.

Mojica *et al.* report on the Surveillance, Epidemiology and End Results (SEER) survey from the National Cancer Institute to investigate the association between the use of adjuvant RT and OS in patients with MCC from 1973 to 2002 [16]. In 1665 cases of MCC, 40% of the surgical patients were noted as having received adjuvant RT. The authors report that the median survival for patients receiving adjuvant RT was 63 months compared with 45 months for those treated with surgery alone (p < 0.0001), with the greatest benefit seen in patients with larger tumor size. A multivariate analysis of OS in 603 patients also identified adjuvant RT as an independent survival factor (relative risk = 0.85; p = 0.0122). As the authors point out, there are several critical limitations to the study, in part, because of limitations of the SEER database. The database does not report on completeness or the margin status of primary tumor resections, only a small number of cases reported lymph node dissection, the number of patients who completed their adjuvant RT is unknown, no details regarding RT treatment fields (local vs nodal, vs both) or dosages are available, no information regarding the use of chemotherapy is provided and no information regarding recurrences or DSS is available. The likelihood of a patient bias in the selective application of RT across this registry-based population is strongly suggested by the younger average age (72 vs 76 years; p < 0.0001) and more advanced MCC stage (37% with regional disease vs 31%; p = 0.0377) of patients who received adjuvant RT. Although age, stage and RT use were all independently associated with OS, it is likely that the younger patients who received RT had a higher average performance status and baseline life expectancy. This fact and the difficulties of interpreting OS in an elderly patient population make drawing definitive conclusions from this study impossible.

Poulsen *et al.* retrospectively reviewed patients with MCC of the lower limb or buttock [11], which they had reported previously to confer a lower survival rate compared with MCC of the upper body [17]. The study included 60 patients from 1986 to 2005 who received combinations of surgery, radiation or chemotherapy as curative treatment with a median follow-up of 4.6 years. The objective of the analysis was to determine factors influencing RFS. Univariate analysis indicated that recurrent disease was associated with worsened RFS (p = 0.03), but the addition of any radiotherapy was associated with improved RFS (HR: 0.30; p < 0.001), as was radiation to the inguinal nodes (HR: 0.20; p = 0.01) or primary site and inguinal nodes (HR: 0.32; p = 0.003). However, RT to the primary site alone failed to show a benefit (p = 0.46). Curiously, RFS did not change with age, surgical margin size or tumor stage. According to multivariate analysis, the only significant factor associated with improved RFS was the addition of radiation (HR: 0.51; p = 0.03). The impact of RT on OS

and DSS was not tested. Once again, the reported benefit of RT in this study may be due to RT compensating for inadequate excisions, as there was an inordinately high rate of local recurrence after surgery alone (17 out of 17 cases [100%]). One strength of this study was that some of the treatment-related adverse events were reported. Two patients required limb amputation after RT: one patient with a history of peripheral vascular disease developed acute arterial thrombosis possibly from high doses of RT over the femoral arteries, resulting in hind-quarter amputation; the other patient required lower-limb amputation for nonhealing ulcers after 45 Gy in 25 fractions.

Taken together, along with prior reports, these recent studies suggest that adjuvant RT after surgery may improve locoregional control for select cases of MCC (Table 1). Any effect of adjuvant RT on distant recurrences or DSS remains to be demonstrated. It is important to note that selection biases and atypically high local and nodal recurrence rates after surgery alone may have exaggerated the apparent benefit of adjuvant RT in these reports. Moreover, the studies do little to help identify the optimal RT treatment parameters or determine which patients merit inclusion of RT in their treatment. The non-necessity of RT is suggested by Allen *et al.* in a single-institution study in which 83% of patients with local or regional MCC received no RT and local relapse rates remained low regardless of RT use [2]. This study illustrates that there is a significant cohort of patients with MCC that is cured with surgical treatment alone. Thus, the routine use of adjuvant RT in all patients who have received surgery with clear pathologic margins likely represents a substantial overuse of RT.

RT as definitive therapy

Patients with MCC often present with comorbidities that complicate treatment decisions. As such, the question of whether RT monotherapy might be as effective as surgery for patients who cannot tolerate an excision has been raised for some time [18–20]. In recent years, the radiosensitivity of MCC and the presence of comorbidities in MCC patients continue to be cited as factors arguing for the use of RT monotherapy. A few studies have reported on the use of RT alone to treat ‘inoperable’ MCC: disease where the patient is not able to tolerate surgery or where tumor size and location would require an excessively morbid excision.

A recent retrospective study describes 43 patients with inoperable MCC who received RT monotherapy to the primary lesion, in-transit tissues and involved lymph nodes between 1993 and 2007 at the Westmead Hospital (Sydney, Australia) and Royal Brisbane/Mater Hospitals (Brisbane, Australia) [21]. All cases were free of distant metastases at the time of initial diagnosis. The authors cite high rates of locoregional control (75% in the irradiated field). However, 26 patients (60%) eventually experienced disease recurrence (median time to relapse: 5 months). Most disease relapses occurred out of the irradiated field (in 23 out of 26 relapsing patients). The high occurrence of disease progression in this study could reflect selective inclusion of patients with advanced disease who already have subclinical disseminated disease at the time of treatment. Alternatively, radiation may be effective at eradicating tumor cells prone to local expansion while sparing a subset of tumor cells more inclined to migration and metastasis. Nonetheless, because reasonable locoregional control was achieved for the duration of the studies, the authors concluded that wide fields of moderate-dose (e.g., 45–50 Gy) RT monotherapy should be considered in select inoperable cases of MCC and that palliative RT, with lower-dose, hypofractionation schedules (e.g., 25 Gy in five fractions), may be appropriate for patients with incurable disease.

In a recent review of the published literature, Koh and Veness note that although high rates of locoregional control with RT monotherapy have been observed, definitive recommendations on RT monotherapy remain confounded by the heterogeneity of patient demographics, disease extent and treatment, and missing data from the studies they cite [22].

While older studies showed similarly high rates of progression with definitive RT for MCC, there is one notable exception. Mortier *et al.* compared two cohorts of patients treated for localized MCC without clinical lymph node involvement at a single institution (Centre Oscar Lambret, Lille, France) between 1991 and 2001: group 1 (n = 9) received RT alone for MCC that was deemed inoperable (median follow-up: 3.0 years); and group 2 (n = 17) received surgery plus adjuvant RT (mean follow-up: 4.6 years) [20]. Both treatment groups received RT at a higher than typical dose of 60 Gy. Most patients also received radiation to the draining lymph nodes, and 40% also received elective RT to in-transit sites. Surprisingly, there were only two recurrences (both in group 2, one in-field and one distant) over the course of the study. It is unclear whether this was due to the broad application of high-dose RT or whether there were other factors contributing to the low progression rate in this study.

Although the findings of these studies support that MCC is a radiosensitive cancer and that RT is a reasonable second-line therapy for inoperable MCC or disease where surgical morbidity is predicted to be excessively high, the true efficacy of definitive RT for MCC remains an open question.

Sentinel node biopsy & RT of regional nodes

Sentinel lymph node biopsy (SLNB) was first described in the late 1990s as a means for detecting metastatic MCC in patients with clinically negative nodes [23–25]. Subsequently, the use of immunohistochemical staining to evaluate SLNB in MCC was reported [26]. As 11–57% of patients presenting with clinically negative lymph nodes are found to have microscopic nodal disease on SLNB [27,28], some investigators have recommended a broad application of the technique for staging purposes. Recently, it has become common for SLNB results to direct the use of post-surgical treatments, including completion lymph node dissection (CLND), adjuvant or definitive nodal RT and/or chemotherapy [29]. None of the currently reported retrospective studies looking at the use of RT in conjunction with SLNB is large enough or designed in a manner that allows assessment of the benefit of nodal RT.

Fang *et al.* describe an analysis of RT monotherapy in 50 patients with MCC involving regional nodes [30]. Two cohorts were followed: patients with microscopic lymph node involvement, as determined by SLNB (n = 26); and patients with clinically palpable lymph node involvement (n = 24). The authors describe three lymph node treatment modalities for these patients: definitive RT, CLND and CLND plus RT. Regardless of treatment modality, none of the patients with microscopic node involvement developed regional disease recurrence (median follow-up: 18 months). For those with clinically palpable disease, regional recurrence was found in two out of nine patients receiving RT alone, three out of 12 patients receiving CLND plus RT, and none out of three patients receiving CLND alone, with an aggregate 2-year regional RFS rate of 75%. DSS within each cohort was independent of treatment received. In an accompanying editorial, Bichakjian *et al.* comment on the limitations of interpreting data from such small cohorts [31]. They observe that:

- Early detection of the disease, and not the selection of treatment, could be the reason for the excellent regional control in the microscopic disease cohort;
- SLNB itself could be therapeutic if the metastatic disease were actually removed during the diagnostic procedure, thereby changing CLND and RT to adjuvant therapies;
- Only six out of the 24 patients cited with palpable lymph nodes were truly treated with RT monotherapy. This was because excision of the clinically apparent lymph node would change the lymph node status from macroscopic to microscopic disease.

In a review of 153 patients with clinically local disease who underwent SLNB at a single institution (median follow-up: 41 months), Fields *et al* identified 23 out of 45 (51%) patients positive for microscopic disease who subsequently received nodal RT with or without CNLD [29]. None of these patients (0%) experienced regional recurrence. Only nine out of 108 (8%) SLNB-negative patients received nodal RT and one of the nine (11%) experienced nodal recurrence. In 22 nonirradiated, SLNB-positive patients, there was one (5%) nodal recurrence in a patient who received CLND only, and there were eight (8%) among the 99 SLNB-negative patients who received no further treatment. Similarly, DSS did not appear to be influenced by treatment. The low recurrence rates associated with these early-stage tumors make it difficult to capture a meaningful number of events. Likewise, patient selection bias in assigning treatments makes it difficult to assess the real impact of nodal RT in treating MCC. Surprisingly, SLNB status itself also was not associated with worse RFS or DSS, whereas lymphovascular invasion of the primary tumor was strongly associated with both.

Chemoradiation for MCC

Systemic chemotherapy (usually a platinum-containing agent with or without etoposide) will often induce a short-lived partial response in disseminated MCC. However, an effective systemic approach to treat advanced MCC has yet to be firmly established.

A few centers have explored the use of combining RT with systemic chemotherapy for the treatment of MCC. A 2003 report demonstrated high toxicity (grade 3 or 4 skin reactions in 64% of patients, grade 3 or 4 neutropenia in 57% of patients) associated with adjuvant or definitive carboplatin and etoposide every 3 weeks during chemoradiation for MCC [32]. A follow-up study, published in 2008, was designed to improve this toxicity profile. The more recent study included a combined weekly regimen of RT (total dose: 50 Gy) and carboplatin, followed by three cycles of adjuvant carboplatin and etoposide [33]. In comparison with the previous trial, improved but persistent toxicity was observed. These studies primarily characterized the tolerability of chemoradiation. Nonetheless, the authors felt that, for high-risk MCC, the results of combined modality therapy exceeded their expectations, based on historical observations. However, this hypothesis has not been tested in a prospective controlled trial.

Effective dose & volume of RT

The paucity of data regarding the optimal dose and volume of RT is an important limitation to establishing a standard RT protocol for MCC. To address this issue, a recent study analyzed curative RT in 112 patients diagnosed with MCC between 2000 and 2005 who were identified through the Queensland Oncology Repository database (Australia) [34]. Most patients received adjuvant RT to the primary tumor and nodal fields using a minimum of 3-cm margins when possible. For comparison, the authors translated RT prescriptions into 2-Gy equivalent doses with no correction for overall treatment time, and they reviewed follow-up data to determine patient relapse rates. As with other studies, the authors noted a high rate of in-field control at the primary site among patients who received local RT (in-field relapse: 3%). Patients who received doses of 50 Gy had the lowest local relapse rate. The in-field nodal relapse rate was 11% among those who received nodal RT (8% of cases receiving elective nodal RT for clinically node-negative disease). The authors report that nodal recurrence was much higher (33%) among the 12 clinically node-negative patients who did not elect to receive nodal RT. The authors propose doses of 50 Gy for subclinical disease and 55 Gy for gross disease. Although this study describes the use of adjuvant RT in a well-characterized patient population and suggests a dose threshold, it fails to report on

the adverse effects associated with RT and does not include a no-RT treatment population for comparison of outcomes.

Novel applications of RT for MCC

Whereas local and nodal external-beam RT have been used extensively in MCC, alternative modalities of RT are evolving. A novel application of brachytherapy has recently been described in a patient with MCC of the right upper calf [35]. After wide local excision of the primary tumor and a negative SLNB, the patient was treated with external-beam radiation (50 Gy in 25 fractions) to the tumor bed and inguinal lymph node basin. A month after the prescribed RT, the patient developed 14 palpable dermal nodules on the ipsilateral lower extremity. The investigators then administered surface-mold computer-optimized high-dose-rate brachytherapy (SMBT). This procedure involves a moldable applicator designed to administer high-dose-rate treatment at a rate of 12 Gy/h directly at the skin surface. The intent of this treatment was palliative. However, the authors report a durable treatment response with 25 months of follow-up, suggesting that this method holds promise as a treatment strategy for in-transit cutaneous lesions of MCC. Hopefully, the future application of modalities such as SMBT and intensity-modulated radiation therapy will continue to improve the therapeutic ratio of RT in the treatment of MCC.

Expert commentary

There is general acceptance that surgery remains first-line treatment for clinically localized MCC [101]. Although the use of adjuvant RT in treating MCC is becoming routine in some centers, existing studies of RT for MCC are limited by small numbers and their retrospective nature. Nonetheless, there are general consistencies among published studies that point to RT as an effective adjuvant to surgery for controlling local and nodal recurrences in select patients with MCC. Conclusions regarding the impact of RT on DSS, elective irradiation of uninvolved lymph node beds, and RT monotherapy seem to be less clear. Owing to the limited evidence, the exact benefit of RT in the management of MCC cannot be determined. Unfortunately a risk stratification system to accurately predict those patients most likely to experience local or regional recurrence is also lacking. Despite this uncertainty, it is unlikely that the blanket administration of adjuvant RT to all patients with resected locoregional MCC will be appropriate, given the relatively low rates of local and regional recurrence after surgical resection with clear pathologic margins. Adjuvant RT is most likely to be beneficial for tumors where achieving clear surgical margins can be challenging, such as head and neck MCC and in other high-risk cases where local or regional recurrence rates are anticipated.

Until specific recommendations for RT can be better established, practitioners will have to rely on expert opinion and their own experience to guide their application of RT for MCC. At this time, it seems reasonable to consider the use of adjuvant RT to the primary excision site in patients with features suggesting higher risk of local recurrence (larger tumors, invasive histological pattern, presence of lymphovascular invasion or positive/narrow surgical margins). Similarly, use of nodal RT (definitively or as an adjuvant to CLND) can be considered in patients with clinically involved nodes or positive SLNB. For patients in whom the primary site and regional lymph node bed are in close proximity (e.g., tumors of the head and neck), including the in-transit region in the RT treatment field should be considered. When considering RT for nodal MCC, it is important to consider the site-specific morbidity risks of the various treatment options. In our experience, RT to the groin may be better tolerated than an inguinofemoral lymph node dissection, yet the risks associated with an axillary dissection performed by an experienced surgeon may be substantially less than RT.

Typical dosing for adjuvant RT would involve delivering 50 Gy in 25 fractions using electrons, megavoltage photons or orthovoltage photons. The treatment volume should be designed to target the tumor and surrounding tissues to achieve a wide RT field, attempting to attain at least 3-cm margins when feasible. When using RT for definitive treatment of inoperable disease, a similar dose and volume could be considered, but some experts would recommend higher doses (55–60 Gy) for treating bulky disease. When using RT for palliation of incurable disease, clinicians must weigh effects on quality of life and risk for adverse events against the potential benefit of RT. Such patients may benefit more from a lower-dose, hypofractionated RT protocol. Finally, the combination of RT with chemotherapy leads to an increase in toxicity and morbidity with little proven benefit. Thus, the application of chemoradiation, either in the adjuvant or palliative setting, should be employed judiciously.

Further studies are needed to identify which patients benefit the most from including RT in the treatment of their MCC. Ideally, prospective studies would identify which patients are at higher risk for disease progression and thus have sufficient increased benefit to warrant the risks associated with RT. In general, RT is well tolerated once patients are educated about the treatment-related toxicities they should expect. However, receiving RT is not without risks, especially when lymph node beds are irradiated. Risks of RT include acute toxicities (radiation dermatitis, desquamation, pigment alterations, mucositis, alopecia and fatigue) and chronic toxicities (fibrosis, lymphedema, skin ulceration, telangiectasias, xerostomia and malignancy). The impact of these toxicities and the hardship of having to travel to daily RT treatments for multiple weeks are the primary reasons why RT is not applied indiscriminately to all patients with MCC. Further studies to better define the risks of RT treatment in this patient population are warranted.

Five-year view

Without prospective randomized controlled clinical trials, investigators are confronted with a number of challenges when drawing conclusions about the use of RT to treat MCC. Unfortunately, the rarity of this tumor makes conducting such studies at single institutions unlikely. However, in the coming years, implementation of a uniform staging system and adoption of standardized management protocols may facilitate the comparisons of institutional experiences with treating MCC. Continued clinical work studying the natural history of MCC and the execution of intelligently designed and creative treatment protocols will continue to increase our understanding of MCC and hopefully improve its diagnosis and management. One area of notable promise is the potential introduction of immunotherapy in treating MCC [36]. The ability of RT to release tumor antigens while shrinking tumor size may one day be combined with immune-enhancing therapies to synergize an anti-tumor host response.

More research on the etiology of MCC is anticipated in the future. The pathogenesis of MCC is an area of active investigation. This is especially true concerning the role of Merkel cell polyomavirus in MCC. The basic nature of such work makes it difficult to predict the potential translational benefits that may come. How these developments will influence the use of RT in treating MCC remains to be seen.

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Key issues

- Merkel cell carcinoma (MCC) is a rare cutaneous neoplasm with a propensity for lymphatic spread.
- The primary treatment for clinically localized MCC is surgical excision.
- The published literature regarding the use of radiation therapy (RT) in MCC consists mainly of case reports, retrospective case series and aggregate-level meta-analyses, all of which have substantial limitations that prevent meaningful conclusions about the disease outcome.
- Many institutions use surgery plus adjuvant RT to treat localized MCC.
- Adjuvant RT for primary MCC may improve local control in high-risk patients but is unlikely to benefit all patients, recurrence rates for localized disease excised with clear pathologic margins.
- The influence of adjuvant RT on distant recurrence and disease-specific survival is unclear.
- Nodal RT has been used as definitive treatment or as an adjuvant to lymphadenectomy in patients with lymph node involvement, with possible improvement in the regional control of MCC.
- RT can be considered for definitive or palliative treatment of inoperable MCC.
- Chemoradiation for MCC is associated with substantial toxicity and the benefit of this type of treatment has not been firmly established.
- Rigorous clinical and pathological study is needed to define the natural history of MCC, help identify patients at risk for local and nodal relapse, and identify optimal treatment protocols that will likely include RT for select high-risk patients.

Table 1
Select studies on the association of radiation therapy and locoregional control of Merkel cell carcinoma.

Study (year)	n	Treatment	Author conclusions	Comments	Ref.
Fields <i>et al.</i> (2011)	153	SLNB ± combinations of CLND, RT, chemotherapy	SLNB status associated with nodal RT use; nodal recurrence low with (3%) and without RT (7%). DSS also independent of RT	Low use of elective RT to SLNB negative beds (9/108)	[29]
Poulsen <i>et al.</i> (2010)	60	Surgery alone, RT alone and combinations of surgery, RT, chemotherapy	Addition of RT to primary and lymph nodes improves RFS vs surgery alone	Lower limb MCC only; local recurrence after surgery alone was 100%, suggesting that RT was compensating for inadequate surgery	[11]
Veness <i>et al.</i> (2010)	43	RT alone	60% of patients ultimately progressed after RT alone; in-field control rate reasonable in-field control for was 75%	Inoperable localized MCC only; high-risk disease with RT alone	[21]
Fang <i>et al.</i> (2010)	50	Lymph node RT alone vs CLND ± RT	Nodal RT provided regional control comparable to CLND for microscopic and palpable nodal disease; no difference observed in OS	Only nodal MCC analyzed; small number of recurrence events; underpowered to detect differences	[30]
Foote <i>et al.</i> (2010)	112	RT ± surgery and/or chemotherapy	In-field relapse rate of 3% for local and 11% for nodal MCC; forgoing elective nodal RT resulted in higher recurrence rate	Of all patients treated with RT, 96% also received surgery; only 12 patients did not receive elective nodal RT and showed excessively high (33%) recurrence rate	[34]
Hui (2010)	176	Surgery ± RT ± chemotherapy	Multivariate analysis showed RT use was predictive of locoregional control	Only 11 (6%) patients did not receive RT, and their locoregional recurrence rate was atypically high (45%)	[37]
Mojica <i>et al.</i> (2007)	1187	Surgery ± adjuvant RT	OS was significantly increased with adjuvant RT vs surgery alone	SEER registry data; no information on RFS or DSS: RT-treated patients significantly younger than surgery-alone patients	[16]
Senchenkov <i>et al.</i> (2007)	38	Surgery ± adjuvant RT or chemotherapy	Adjuvant RT reduced local recurrence rate but did not improve OS	MCC on extremities only; small number of patients. No-RT recurrence rate was high (47%)	[38]
Clark <i>et al.</i> (2007)	110	Surgery + adjuvant RT vs surgery alone or RT alone	Combined therapy improved both local regional control and DFS but not DSS	Head and neck cases only; a high percentage of cases with positive surgical margins (38%); no differentiation between surgical and RT monotherapies	[14]
Lewis <i>et al.</i> (2006)	1254	Surgery ± adjuvant RT	Reduction in local and regional recurrence associated with combination therapy vs surgery alone; rates of distant metastasis and OS were not significant	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	[15]
Allen <i>et al.</i> (2005)	251	Surgery ± RT and/or chemotherapy	Local recurrence rate similar with RT (10%) vs no RT (8%)	Primarily a study on the natural history of MCC. RT was used in a minority (17%) of patients	[2]
Veness <i>et al.</i> (2005)	86	Combinations of surgery, RT and/or chemotherapy	Local relapse similar with RT (12%) vs no RT (14%); nodal relapse lower with RT (18%) vs no RT (37%); median RFS longer with RT vs surgery alone	Adjuvant RT association with RFS not maintained on multivariate analysis	[39]
Mortier <i>et al.</i> (2003)	28	RT alone vs surgery + adjuvant RT	RT alone showed similar outcomes as surgery plus adjuvant RT	Only 9 patients with RT alone; 0 progressed; median dose 60 Gy	[20]
Boyer <i>et al.</i> (2002)	45	Mohs surgery ± adjuvant RT	RFS and DSS not impacted by adjuvant RT	Median age of RT-treated patients lower (69 years) vs surgery alone (75 years); underpowered to detect differences	[40]

Study (year)	n	Treatment	Author conclusions	Comments	Ref.
Eich <i>et al.</i> (2002)	31	Surgery ± adjuvant RT	DFS improved with adjuvant RT ($p = 0.023$); adjuvant RT associated with improved RFS on multivariate analysis	Local (36%) and nodal (50%) relapse rate notably high in surgery-alone group	[41]
Gillenwater <i>et al.</i> (2001)	18	Surgery ± adjuvant RT	Adjuvant RT associated with improvement in local and nodal control ($p < 0.01$) but not distant metastases or survival	Head and neck MCC only; local (44%) and nodal (85%) recurrence rates notably high in surgery alone group	[42]
Meeuwissen <i>et al.</i> (1995)	80	Surgery ± adjuvant RT	Total relapse rates higher with surgery alone (100%) vs surgery plus RT (29%); but RT after incomplete surgery had no benefit (86%)	31 of the 38 patients treated with surgery alone had recurrent disease at presentation, and relapses were mostly nodal	[43]
Yiengpruksawan <i>et al.</i> (1991)	70	Surgery ± adjuvant RT and/or chemotherapy	Local recurrence with adjuvant RT (20%) was no different from no RT (16%)	Only 10 patients treated with local adjuvant RT	[44]

CLND: Completion lymph node dissection; DFS: Disease-free survival; DSS: Disease-specific survival; MCC: Merkel cell carcinoma; OS: Overall survival; RFS: Relapse-free survival; RT: Radiation therapy; SEER: Surveillance, Epidemiology, and End Results; SLNB: Sentinel lymph node biopsy.