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Radiotherapy for inoperable Merkel cell carcinoma: a systematic review and pooled analysis

Parth Patel¹, Chirag Modi², Beth McLellan¹, Nitin Ohri²

1 Department of Medicine, Division of Dermatology, Montefiore Medical Center, Albert Einstein College of Medicine, Bronx, New York
2 Department of Radiation Oncology, Montefiore Medical Center, Albert Einstein College of Medicine, Bronx, New York

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Corresponding author: Nitin Ohri, MD, Department of Radiation Oncology, Montefiore Medical Center Albert Einstein College of Medicine, Bronx, NY 10467, USA. Tel. (718) 430-3682; Fax. (718) 430-8618. Email: ohri.nitin@gmail.com

ABSTRACT

Background: Cumulative data on radiation monotherapy for Merkel cell carcinoma (MCC) is lacking.

Objective: We sought to synthesize all available data on treatment outcomes for radiation monotherapy for inoperable stage I-III MCC.

Methods: We performed a systematic review of the current literature. Articles published in English in the PubMed database up to July 29, 2016, were evaluated.

Results: Eight case reports, 4 case series, and 6 retrospective studies, yielding 68 patients, were included in our analysis. Of the 24 stage I/II patients treated with local irradiation, 6 (25%) relapsed and 1 (4%) died from MCC. Of the 24 stage I/II patients treated with local and regional nodal irradiation, 5 (21%) relapsed and 2 (8%) died from MCC. Of the 20 stage III patients treated with local and regional nodal irradiation, 12 (60%) relapsed and 7 (35%) died from MCC.

Conclusions: Radiation monotherapy appears to be a reasonable treatment modality for patients with inoperable stage I-III MCC. Further investigation with prospective studies is needed to draw definitive conclusions.

Introduction

Merkel cell carcinoma (MCC) is an aggressive tumor of the skin and mucous membranes first described by Toker in 1972 [1]. MCC classically presents as a rapidly growing, firm, violaceous nodule and is thought to be due to extensive radiation exposure and/or polyomavirus. Like melanoma, MCC has a strong propensity to recur locally, spread regionally, and disseminate widely, leading to a fatal outcome [1]. However, unlike melanoma, MCC is highly radiosensitive, with in vitro MCC cell lines demonstrating substantially lower surviving fractions (mean: 0.30) than melanoma cell lines (mean: 0.57) when exposed to 2 Gy of radiation [2].

Although there have been few prospective studies to guide management of the disease, it is generally agreed that for the primary tumor, surgery with or without adju-
vant radiation therapy is the preferred treatment modality; for nodal involvement, node dissection and/or radiation therapy is the preferred treatment modality; and for distant metastasis, chemotherapy, radiation therapy and/or surgery should be considered [3]. When surgery is not possible due to tumor location and size, patient comorbidities, and/or patient refusal, radiation monotherapy is typically the preferred treatment modality, regardless of whether the intent is palliative or curative.

Due to the rarity of MCC, with an incidence of only 0.79 per 100,000 [4], the efficacy of radiotherapy for inoperable MCC is not well defined. Here we present a systematic review of the literature to evaluate radiation monotherapy for MCC patients, focusing on the effects of local and regional radiation therapy on relapse and survival. We hope the results of this article help raise awareness that radiation monotherapy, as opposed to other local-regional nonsurgical treatment modalities, is a reasonably effective option for patients with inoperable MCC.

Methods and Materials

Data Search
We searched the PubMed database for articles published in English up to July, 29 2016. The search terms included a combination of “Merkel cell carcinoma” or “merkel-cell carcinoma” and “radiation therapy” or “radiotherapy.” The references of articles selected for full-text evaluation were also considered for additional studies.

Inclusion/Exclusion Criteria
All study types (case reports/series, retrospective studies and prospective studies) were considered in our analysis. Studies with the following criteria were included: 1) published in English, 2) published as a full article, 3) reported known primary MCCs without distant metastasis (M+) or prior treatment, 4) the primary treatment modality was radiation therapy without surgery and/or chemotherapy, and 5) reported tumor staging data, total radiation dose data, and at least one of the following primary outcomes data: recurrence, metastasis, or survival. For studies with aggregate data, if part of the patients in the aggregate data were treated with combination therapy (surgery and/or chemotherapy) the cohort was excluded because we could not determine what part of the data represented those patients who received radiation monotherapy.

Study Selection, Quality Assessment and Data extraction
Authors PP and CM independently searched the PubMed database and reviewed all the selected articles using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) selection process (Figure 1). From the selected articles, the following data was extracted: language, author, date of publication, study design, sample size, age of patients at diagnosis, sex of patients, location and size of primary tumor, stage of cancer at diagnosis, total radiation dose, immunocompromised status, recurrence/metastasis, and survival. Discrepancies in opinion about article eligibility, the quality of studies, and/or data extraction, were reviewed jointly by PP and CM to achieve consensus.

Quality Assessment
The quality of the selected studies was evaluated according to the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) guidelines (Table 1) [5]. The level of evidence supporting each article was determined using criteria from the Oxford Center for Evidence-based Medicine (Table 1) [6].

Data Analysis
Survivorship estimates were generated using descriptive statistics and the Kaplan-Meier method in Graphpad Prism 6 (Graphpad Software Inc., La Jolla, CA). For the analysis of relapse-free survival, the endpoint was any recurrence or metastasis; for the analysis of overall survival, the endpoint was death from any cause; and for the analysis of cause-specific survival the endpoint was death from MCC.

Aggregate and individual patient data were combined using the two-stage method, with a fixed- or random-effects approach, in Comprehensive Meta Analysis 2.0 (Biostat Inc., Englewood, NJ) [7,8]. Based on Cochran’s Q test for heterogeneity, the fixed-effects model was only used if the P value > 0.1 [9]. When aggregate data was reported as a median, the mean and variance were estimated using distribution-free formulas [10].

Tumor staging was standardized using the 2010 TNM staging system for MCC [11]. A tumor was considered stage I if it was <2 cm with no metastases; stage II if it was 2-5 cm with no metastases; stage III if there was lymph node metastasis; and stage IV if distant metastasis occurred. Local recurrence was defined as recurrence within or adjacent to the primary site; regional recurrence was defined as recurrence in the regional nodal basin or in-transit metastasis (cutaneous/intradermal metastasis en-route to the regional nodal basin), and distant metastasis was defined as tumor spreading distant to the regional nodal basin.

Results

Description of Studies
An initial search of the PubMed database identified 586 records. A title-abstract screen resulted in 83 arti-
Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) selection process.

TABLE 1. Study characteristics and quality assessment

| Study Characteristics And Quality Assessment |
|-----------------------------------------------|
| Author(s) | Year Published | Study Design | Comparative/Non-comparative† | Sample Size‡ (n = 68) | Level of Evidence | GRADE Quality |
|-----------|----------------|--------------|-------------------------------|-----------------------|------------------|---------------|
| Ashby et al [40] | 1989 | Case series | Non-comparative | 1 | 4 | Very Low |
| Chatzinasiou et al [41] | 2015 | Case report | Non-comparative | 1 | 4 | Very Low |
| Elliot [42] | 1981 | Case report | Non-comparative | 1 | 4 | Very Low |
| Handa et al [43] | 2000 | Case report | Non-comparative | 1 | 4 | Very Low |
| Hasle et al [44] | 1991 | Case report | Non-comparative | 1 | 4 | Very Low |
| Kitamura et al [45] | 2015 | Case report | Non-comparative | 1 | 4 | Very Low |
| Lawenda et al [46] | 2008 | Retrospective | Non-comparative | 2 | 3 | Low |
| Luaces Rey et al [47] | 2008 | Case series | Non-comparative | 1 | 4 | Very Low |
| Magrini et al [48] | 1992 | Case series | Non-comparative | 1 | 4 | Very Low |
| Makino et al [49] | 2005 | Case report | Non-comparative | 1 | 4 | Very Low |
| Pellea et al [50] | 1988 | Retrospective | Non-comparative | 1 | 3 | Low |
| Pape et al [12] | 2011 | Retrospective | Comparative | 25 | 3 | Low |
| Seki et al [51] | 2003 | Case series | Non-comparative | 2 | 4 | Very Low |
| Suntharalingam et al [52] | 1995 | Retrospective | Comparative | 2 | 3 | Low |
| Tuskada et al [53] | 2016 | Case report | Non-comparative | 1 | 4 | Very Low |
| Veness et al [*54, 55] | 2009/2015 | Retrospective | Non-comparative | 25 | 3 | Low |
| Yamakawa et al [56] | 2008 | Case report | Non-comparative | 1 | 4 | Very Low |

GRADE, Grading of Recommendations Assessment, Development and Evaluation
* Includes two articles that represent one cohort of patients
† Comparative refers to studies that had multiple treatment groups; non-comparative refers to studies that had only 1 treatment group
‡ Only represents those relevant patients included in our study.
Stage I/II Disease

Of the 68 patients treated with radiation monotherapy, 48 (71%) presented with stage I/II MCC. Of these, 24 (50%) underwent local tumor irradiation, and 24 (50%) underwent local tumor and regional nodal irradiation. The mean duration of follow-up for patients in the local radiation group was 13.4 months (range: 3-42) and that for patients in the local-regional radiation group was 15.1 months (range: 4-35). The duration of follow-up was only available for 7 patients in the local radiation group and 9 patients in the local-regional radiation group. The mean total radiation dose to the primary tumor was 55.2 Gy (range: 20-70) in the local radiation group and 64.5 Gy (range: 38.5-70) in the local-regional radiation group. Patients in the local-regional radiation group also received a mean total radiation dose of 50.8 Gy (range: 40-55) to the regional nodal basin (prophylactically).

The relapse rate in the local radiation group was 25% (n = 6/24) (1 local recurrence, 3 regional recurrences, and 2 distant metastasis) and that in the local-regional radiation group was 21% (n = 5/24) (1 local recurrence, 1 regional recurrence, 2 distant metastasis, and 1 unspecified recurrence/metastasis). There were 5 reported deaths (21%) in the local radiation group, of which 1 (4%) was from MCC. There were 9 reported deaths (38%) in the local-regional radiation group, of which 2 (8%) were from MCC. If we assumed that all patients who were alive with disease at the last follow-up eventually died from MCC and all other patients did not die from MCC, the total number of deaths from MCC would increase to 5 (21%) in the local radiation group and 5 (21%) in the local-regional radiation group (Table 3).

Stage III Disease

Of the 68 patients treated with radiation monotherapy, 20 (29%) presented with stage III MCC. All of these patients were treated with local-regional radiation. The mean duration of follow-up for these patients was 18.9 months (range: 4-53). The mean total radiation dose to the primary tumor was 52.2 Gy (range: 20-70) and that to the regional nodal basin was 51.5 Gy (range: 20-70).

The relapse rate was 60% (n = 12/20) (2 regional recurrences, 4 distant metastasis, and 6 unspecified recurrences/metastases). There were 7 reported deaths (35%) in the local-regional radiation group, all of which were from MCC. If we assumed that those patients who were alive with disease at the last follow-up eventually died from MCC and all other patients did not die from MCC, the number of deaths from MCC would increase to 10 (50%) (Table 3).

Surgery plus Radiation vs. Radiation Monotherapy

A retrospective study by Pape et al [12], compared 25 stage I MCC patients treated with radiation monotherapy to 25 stage I MCC patients treated with surgery + radiation. In the radiation monotherapy group, the total dose of radiation was 70 Gy to the primary tumor for all patients and ~50-55 Gy

| TABLE 2. Patient characteristics |
|---------------------------------|
| **Stage I/II** (n = 48) | **Stage III** (n = 20) | **All Stages** (n = 68) |
| **Sex** | | |
| Male | 9 (19%) | 13 (65%) | 22 (32%) |
| Female | 37 (77%) | 7 (35%) | 44 (65%) |
| Unknown | 2 (4%) | 0 (0%) | 2 (3%) |
| **Age at Diagnosis** | | |
| <60 y | 3 (6%) | 2 (10%) | 5 (7%) |
| 60-69 y | 7 (15%) | 1 (5%) | 8 (12%) |
| 70-79 y | 11 (23%) | 7 (35%) | 18 (26%) |
| ≥ 80 y | 25 (52%) | 10 (50%) | 35 (52%) |
| Unknown | 2 (4%) | - | 2 (3%) |
| **Location of Primary Tumor** | | |
| Head and Neck | 35 (73%) | 12 (60%) | 47 (69%) |
| Trunk | - | 3 (15%) | 3 (4%) |
| Upper Extremities | 2 (4%) | 1 (5%) | 3 (4%) |
| Lower Extremities | 10 (21%) | 4 (20%) | 14 (21%) |
| Unspecified Extremity | 1 (2%) | - | 1 (2%) |
| **Lesion Size** | | |
| ≤ 2 cm | 21 (44%) | 6 (30%) | 27 (40%) |
| > 2 cm | 22 (46%) | 13 (65%) | 35 (51%) |
| Unknown | 5 (10%) | 1 (5%) | 6 (9%) |
| **Mean Size cm (range)** | 3.0 (0.4-18) | 4.0 (0.5-10) | 3.3 (0.4-18) |
| **Immunosuppression** | | | |
| Yes | 2 (4%) | 2 (10%) | 4 (6%) |
| No | 46 (96%) | 18 (90%) | 64 (94%) |
to the regional nodal basin for patients in the local-regional group. In the surgery + radiation group, the total dose of radiation was ~50-55 Gy to the surgical bed for all patients and ~50-55 Gy to the regional nodal basin for patients in the local-regional group. There were 2 regional recurrences at 6 and 15 months in the radiation monotherapy group and 4 regional recurrences at 5, 16, 17 and 109 months in the surgery + radiation group. In this study, there was no significant difference in relapse-free survival (log-rank, \( p = .18 \)) or cause-specific survival (log-rank, \( p = .32 \)) between the radiation monotherapy group and surgery + radiation group [12].

**Discussion**

In this review, we have demonstrated that radiation monotherapy appears to be a reasonable treatment modality for patients with inoperable stage I-III MCC. Compared to radiation monotherapy, isolated case reports of other nonsurgical treatment modalities using cryotherapy [13,14], topical immunotherapy (dinitrochlorbenzol [15], imiquimod [14,16,17]), intralesional immunotherapy (interluekin-12 [18], tumor necrosis factor-alpha [19], interferon-alfa [16], interferon-beta [20], glucopyranosyl lipid-A [18]) and/or isolated limb perfusion with chemotherapy (melphalan, tumor necrosis factor-alpha +/- interferon-gamma) [21,22], have shown variable efficacy, often with only transient response or adjuvant radiation therapy required for maintenance.

Despite the fact that patients treated with radiation monotherapy often have adverse prognostic features such as large lesion size and head and neck tumor location [23,24], the incidences of relapse and death from MCC in the studied patients were similar, if not lower, than the

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**TABLE 3. Treatment characteristics and outcomes**

| Treatment                          | Local recurrence | Regional recurrence | Distant metastasis | Unspecified recurrence/metastasis | Death from MCC |
|------------------------------------|------------------|---------------------|--------------------|-----------------------------------|----------------|
| Stage I/II (n = 48)                |                  |                     |                    |                                   |                |
| **Local Radiation monotherapy (n = 24)** |                  |                     |                    |                                   |                |
| Mean duration of follow-up: 13.4 months (range: 3-42) (n = 7)* |                  |                     |                    |                                   |                |
| Event                              |                  |                     |                    |                                   |                |
| Mean Total Radiation Dose: 55.2 Gy (range: 20-70)* |                  |                     |                    |                                   |                |
| Time-to-event (months)             |                  |                     |                    |                                   |                |
| 5                                  |                  | 6,7                 | 18,31              | -                                 | 23             |
| **Local-regional radiation monotherapy (n = 24)** |                  |                     |                    |                                   |                |
| Mean duration of follow-up: 15.1 months (range: 4-35) (n = 9)* |                  |                     |                    |                                   |                |
| Event                              |                  |                     |                    |                                   |                |
| Mean Total Radiation Dose: 64.5 Gy (range: 38.5-70) |                  |                     |                    |                                   |                |
| Time-to-event (months)             |                  |                     |                    |                                   |                |
| 4                                  |                  | 15                  | 4,15               | 10                                | 7,12           |
| **Stage III (n = 20)**            |                  |                     |                    |                                   |                |
| **Local-regional radiation monotherapy (n = 20)** |                  |                     |                    |                                   |                |
| Mean duration of follow-up: 18.9 months (range: 4-53) (n = 20)* |                  |                     |                    |                                   |                |
| Event                              |                  |                     |                    |                                   |                |
| Mean Total Radiation Dose: 52.2 Gy (range: 20-70) |                  |                     |                    |                                   |                |
| Time-to-event (months)             |                  |                     |                    |                                   |                |
| 2                                  |                  | 2 (10%)             | 4 (20%)            | 6 (30%)                           | 7 (35%)        |
| - (in-transit)                    |                  | -                   | 1, 3, 6, 9         | 2, 3, 5, 6, 8, 36                 | 5, 5, 5, 7, 10, 10, 14 |

* Duration of follow-up (time from date of diagnosis to either outcome of interest or date of last follow-up) was not available for all patients

† Fixed-effects model was used (heterogeneity Q = .221, I² < .001, P = .638)

‡ All stage III patients were treated with local-regional radiation therapy
incidences in similarly staged patients treated with surgery +/- radiation (Figure 2) [1,25-27]. We additionally found that in the absence of nodal disease (stage I/II) in patients with inoperable MCC, prophylactic radiation to the nodal basin resulted in a similar incidence of relapse and death as no prophylactic radiation to the nodal basin. Interestingly, in the only randomized trial evaluating prophylactic radiation to the nodal basin in MCC patients, nodal irradiation with a dose of 50 Gy was associated with a significant decrease in regional recurrences (log-rank, p = .007) but no difference in overall survival (log-rank, p = .989) or progression-free survival (log-rank, p = .400) [28]. When considering nodal disease (stage III), however, radiation is typically provided to the nodal basin in patients with inoperable MCC, as was the case for all stage III patients included in this review. In fact, in a study where all the patients underwent surgery +/- radiation to the primary tumor, it was suggested that radiation to nodal disease is comparable to nodal dissection +/- radiation, with no difference in 2-year regional recurrence-free survival (log-rank, p = 1, p = .8) or disease-specific survival (log-rank, p = .7, p = .9) [29].

Currently, for inoperable stage I-III MCC, the 2016 NCCN (National Comprehensive Cancer Network) guidelines recommend a total radiation dose of 60-66 Gy to the primary tumor. Radiation monotherapy to the nodal basin is only recommended if there is clinical or microscopic nodal involvement, or if the patient is at risk for subclinical nodal disease. Unfortunately, the NCCN guidelines do not define who is at risk for subclinical nodal disease, leaving it to the treating physician’s discretion. For clinical lymphadenopathy, 60-65 Gy is given; for microscopic nodal involvement, 50-56 Gy is given; and for patients at risk for subclinical nodal disease, 46-50 Gy is given. Typically, radiation of intransit lymphatics is not feasible unless the primary site is in close proximity to the nodal basin. In most settings, conventional radiotherapy fraction sizes of approximately 2 Gy/day are utilized (Figure 3). At this time, the NCCN guidelines do not recommend chemotherapy for inoperable stage I-III MCC. Chemotherapy is generally reserved for stage IV MCC (metastatic disease), although there is no high-level evidence demonstrating that chemotherapy prolongs overall survival in this setting [30]. While adding chemotherapy to radiation monotherapy has the theoretical advantage of radiosensitizing MCC, there is limited data justifying this approach for local or regional radiation, and it could possibly even worsen prognosis due to immunosuppression [26,31]. Systemic immunotherapy with recently developed checkpoint inhibitors is a promising approach for the treatment of advanced MCC [32]. Anecdotal data [33] and results from early phase trials [34] for other malignancies suggest that the combination of systemic immunotherapy and radiotherapy should be explored in MCC.

While the response of MCC to radiation therapy is impressive, radiation therapy is not without toxicity; cumulative experience from the treatment of non-melanoma skin cancer indicates that nearly all patients treated with potentially curative radiotherapy doses will develop at least mild-to-moderate acute side effects such as atrophy, pigment change,
Conclusions

To our knowledge, this is the first review to collectively present the outcomes of MCC patients treated with radiation monotherapy. Available data suggest that radiation monotherapy may be able to provide reasonable outcomes for MCC patients unable to undergo surgery. Prospective studies are sorely needed to guide the management of this rare and potentially fatal disease.

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