

## Scientific Article

# Postoperative, Single-Fraction Radiation Therapy in Merkel Cell Carcinoma of the Head and Neck

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## Abstract

**Purpose:** Conventionally fractionated, postoperative radiation therapy (cPORT; 50 Gy in 25 fractions) is considered for patients with Merkel cell carcinoma (MCC) to improve locoregional control. However, cPORT is associated with acute toxicity, especially in the head and neck (H&N) region, and requires daily treatments over several weeks. We previously reported high rates of durable local control with minimal toxicity using 8-Gy single-fraction radiation therapy (SFRT) in the metastatic setting. We report early results on a cohort of patients with localized H&N MCC who received postoperative SFRT if a cPORT regimen was not feasible.

**Methods and Materials:** Twelve patients with localized MCC of the H&N (clinical/pathologic stages I-II) and no prior radiation therapy to the region were identified from an institutional review board-approved prospective registry who underwent surgical resection followed by postoperative SFRT. Time to event was calculated starting from the date of resection before SFRT. The cumulative incidence of in-field locoregional recurrences and out-of-field recurrences was estimated with death as a competing risk.

**Results:** Twelve patients with H&N MCC were identified with clinical/pathologic stages I-II H&N MCC. Median age at diagnosis was 81 years (range, 58-96 years); 25% had immunosuppression. At a median follow-up of 19 months (range, 8-34), there were no in-field locoregional recurrences. A single out-of-field regional recurrence was observed, which was successfully salvaged. There were no MCC-specific deaths. No radiation-associated toxicities greater than grade 1 (Common Terminology Criteria for Adverse Events v5) were observed.

**Conclusions:** Preliminary data suggest that SFRT could offer a potential alternative to cPORT to treat the primary site for localized H&N MCC, particularly in elderly or frail patients, with promising in-field local control and minimal toxicity. Further data with validation in larger cohorts are needed to confirm the sustained safety and efficacy of postoperative SFRT.

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## Introduction

Merkel cell carcinoma (MCC) is a rare and aggressive cutaneous malignancy with an estimated 2488 cases per year in the United States with an exponential increase in incidence.<sup>1</sup> MCC patients have a high (approximately >30%) risk for locoregional recurrences and distant metastases after resection.<sup>2-6</sup> For patients who have localized disease with clinically negative draining lymph nodes (American Joint Committee on Cancer [AJCC] eighth edition stage I-IIIa), initial treatment typically consists of wide excision of the primary tumor and sentinel lymph node biopsy (SLNB).<sup>7</sup> Surgery is then often followed by adjuvant conventionally fractionated postoperative radiation therapy (cPORT) (50 Gy in 25 fractions).<sup>2-6,8</sup>

For patients with MCC of the head and neck (H&N), cPORT provides a locoregional control benefit over observation alone, even among the most favorable low-risk cases.<sup>3,4</sup> However, acute toxicity in the sensitive regions of the H&N can be substantial (eg, skin erythema and desquamation, painful mucositis, xerostomia, altered taste, anorexia, weight loss). In addition, patients often face logistical challenges in attending a protracted course of radiation therapy (RT) for 5 weeks. Logistical considerations are of particular relevance with the increased risk of infection, complications, and death that may occur over a protracted radiation course during the COVID-19 pandemic.<sup>9-11</sup>

Previously, a study found durable local control for gross disease with 8-Gy single-fraction RT (SFRT) among patients with metastatic MCC with minimal toxicity,<sup>12</sup> reflecting the radiosensitivity of MCC. Here, we present the preliminary results of using SFRT treatment in a postoperative, curative setting for patients with H&N disease.

## Methods and Materials

Twelve patients were identified from an institutional review board-approved prospective registry of 1459 patients with MCC based on the following inclusion criteria: (1) localized MCC of the H&N with clinically negative lymph nodes treated in the initial or recurrent setting (AJCC eighth edition stage I-II), (2) surgical resection with or without SLNB, (3) no residual gross disease, (4) received postoperative 8-Gy SFRT, (5) >90 days of follow-up after SFRT, and (6) no prior RT to the H&N region. Patients provided consent for SFRT after an informed discussion. The patients who opted for this regimen were typically elderly with multiple comorbidities or with significant logistical difficulties and were otherwise willing to forgo RT despite having an indication for cPORT. No tumor-related selection criteria were applied. RT was delivered using electrons (6-8 MeV prescribed to 90% isodose line with a bolus) or photons to

the entire surgical bed plus 3- to 5-cm margins as illustrated in Figure 1. Patients had RT to the primary site alone in 11 of 12 patients, and 1 patient received elective nodal irradiation using an en-block technique (patient no. 9). The patient who received elective nodal RT was immunosuppressed and had a large primary (stage IIB) in close proximity to the first echelon draining lymph nodes.

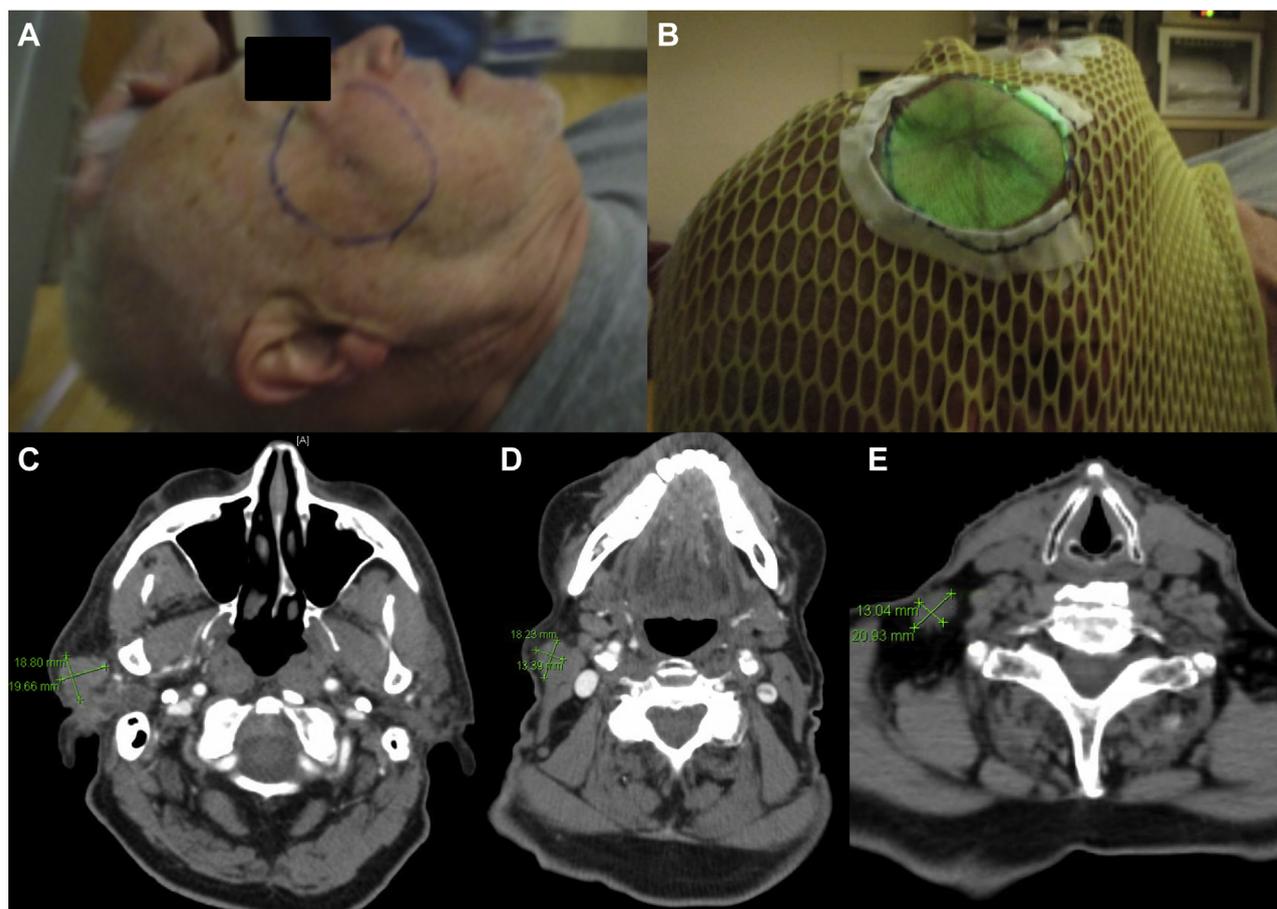
Negative margins were defined as no tumor at the inked edge. In-field recurrences were defined by an event that occurred within the 50% isodose line. Local recurrences were defined by an event that occurred within 2 cm of the primary tumor's surgical bed. Regional recurrences were defined by an event that occurred beyond 2 cm of the primary tumor's surgical bed and within the in-transit pathways or lymph nodal regions of the head and neck that drain the primary site. Common Terminology Criteria for Adverse Events (CTCAE) v5 was employed to grade acute toxicity <90 days and late toxicity ≥90 days after SFRT. Time to event was calculated from the date of resection before SFRT.

The cumulative incidence of in-field and out-of-field locoregional recurrence was estimated with death considered a competing risk. Patients who did not experience an event during follow-up were right-censored at the time of last follow-up. Confidence intervals (CIs) for the rate of recurrence at different timepoints were calculated using conventional standard error formulas except when the estimate rate was 0%. In those cases, CIs were calculated using the Clopper–Pearson exact method. All statistical calculations were conducted with the statistical computing language R (version 3.6.1; R Foundation for Statistical Computing, Vienna, Austria).

Surveillance consisted of follow-up visits with physical examination including complete skin and lymph nodes every 3 to 6 months for 3 years, then every 6 to 12 months thereafter.<sup>7</sup> Patients who were seropositive for the Merkel cell polyomavirus oncoprotein antibodies had titers obtained at the follow-up visits, prompting repeat imaging if a notable rise occurred.<sup>1</sup> Computed tomography imaging of the neck, chest, abdomen, and pelvis was performed based on clinical indications or recurrence risk-based assessment approximately every 4 months for the first year, then every 6 to 12 months.<sup>1</sup>

## Results

We identified 12 patients with stage I-II H&N MCC treated from 2017 to 2019. Pathologic staging was obtained in the majority of patients (n = 8 of 12), and the remaining patients were clinically staged due to either a failed SLNB (n = 2 of 12) or excisional biopsy alone due to their advanced age and comorbidities (n = 2 of 12). Patient demographics and treatment characteristics are summarized in Table 1. The patient cohort had a median age of 81 years (range, 58-96 years) with 25% (n = 3 of



**Figure 1** (A-B) Patient no. 5 is an 81-year-old immunosuppressed man with a history of clinical stage I Merkel cell carcinoma of the right cheek status post-wide local excision with negative margins and a technically failed sentinel lymph node biopsy who elected to undergo adjuvant 8-Gy SFRT to his primary surgical tumor bed site with electrons. Four months after SFRT, he exhibited out-of-field regional failure in the lymph nodes in (C) the parotid, (D) level 2A, and (E) level 5. He was successfully salvaged with surgical resection followed by adjuvant conventional fractionated proton radiation therapy. He never failed within his initial SFRT field. *Abbreviation:* SFRT = single-fraction radiation therapy.

12) being immunosuppressed and 8% (n = 1 of 12) positive microscopic margins (R1 resection).

Ten patients (no. 1-10) were treated in the de novo setting. Two patients (no. 11-12) were treated in the recurrent setting after they experienced a local recurrence at the primary site alone. They had prior wide local excision and SLNB or neck dissection followed by observation in the initial setting. No patients had a history of prior radiation therapy to the H&N region or received systemic therapy. The documented rationale for patients pursuing SFRT after an informed consent included: logistics for all patients (no. 1-12) with 16% living within 30 miles of our academic institution; potential for decreased acute side effects (patients no. 7-9); and significant medical comorbidities (patient no. 9).

At a median follow-up time of 19 months (range, 8-34 months), there were no local recurrences. Eleven of 12 patients received radiation to the postoperative bed alone, and one of these patients (no. 5) experienced a recurrence in the regional draining lymph nodes that were not treated

with PORT. Patient no. 5 was also immunosuppressed but had clinical stage I disease with negative surgical margins and a failed SLNB (Fig 1). The patient was successfully salvaged with a neck dissection and postoperative conventional fractionated radiation therapy. Thus, there was 1 out-of-field recurrence and no in-field recurrences. The overall out-of-field locoregional recurrence rate at 1 year was 8.3% (95% CI, 1.3%-54.4%) and 0% (95% CI, 0.0%-26.5%) in-field (Fig 2).

No patient developed distant metastatic disease. There was 1 patient death during the follow-up period owing to significant cardiac comorbidities, which were present before the MCC diagnosis. No patient experienced any radiation-related toxicity greater than grade 1 (CTCAE v5).

## Discussion

We present a preliminary experience of treating localized MCC in the H&N region with a single fraction

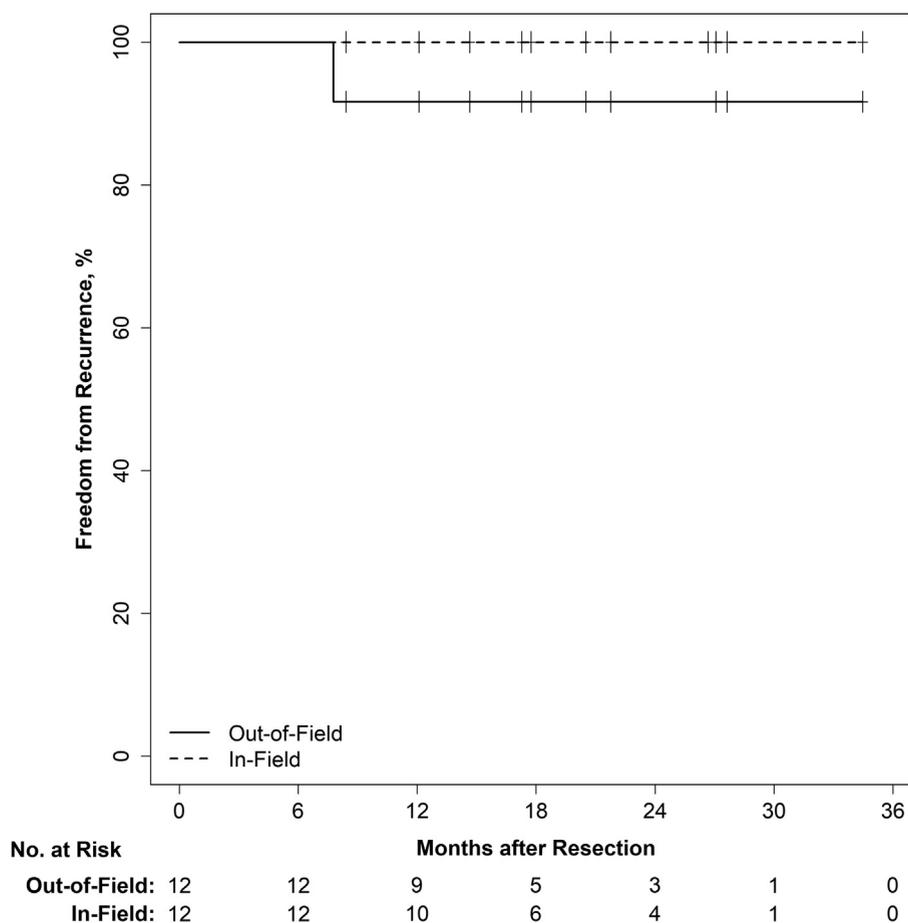
**Table 1** Demographics and treatment summary table of the patient cohort

Patient ID	Age, y	Stage (AJCC eighth edition)	Sex	Immune-suppressed	Type of immune suppression	Setting	ECOG	Site of RT	Field size, EQ SQ	Late toxicity grade	Surgery type	Path margin status	Recurrence status
1	85	p-I	F	No	-	Initial	0	Glabella	8	1	WLE and SLNB	Negative	None
2	96	c-I	M	No	-	Initial	1	Right cheek	3.3	0	Excisional biopsy	Negative	None
3	86	c-I	F	Yes	CLL	Initial	3	Left ear	10.2	0	Excisional biopsy	Positive	None
4	64	p-I	F	No	-	Initial	0	Left cheek	8.5	0	WLE and SLNB	Negative	None
5	81	c-I	M	Yes	Hairy cell leukemia	Initial	0	Right cheek	6	0	WLE and failed SLNB	Negative	Regional
6	71	p-I	M	No	-	Initial	0	Left lip/cheek	8	0	WLE and SLNB	Negative	None
7	82	c-I	F	No	-	Initial	0	Right cheek	7	0	WLE and failed SLNB	Negative	None
8	68	p-I	F	No	-	Initial	0	Left nose	10	0	WLE and SLNB	Negative	None
9	70	p-IIB	M	Yes	CML	Initial	2	Left cheek/elective neck	PTV 342 cm <sup>3</sup>	0	WLE and SLNB	Negative	None
10	83	p-I	M	No	-	Initial	0	Nose	8.5	0	WLE and LN dissection	Negative	None
11	58	p-I	F	No	-	Recurrent	0	Left scalp	N/A*	N/A*	WLE <sup>†</sup>	Negative	None
12	80	p-IIB	M	No	-	Recurrent	0	Left upper lip	8.4	1	WLE <sup>†</sup>	Negative	None

*Abbreviations:* AJCC = American Joint Committee on Cancer; c = clinical; CLL = chronic lymphocytic leukemia; CML = chronic myelogenous leukemia; ECOG = Eastern Cooperative Oncology Group; EQ SQ = equivalent square of radiation therapy field (cm); LN = lymph node; p = pathologic; PTV = planning target volume; RT = radiation therapy; SLNB = sentinel lymph node biopsy; WLE = wide local excision.

\* N/A denotes “not available” due to radiation treatment at an outside institution.

† WLE denotes surgical procedure performed in the recurrent setting after WLE and ipsilateral SLNB or neck dissection followed by observation in the initial setting.



**Figure 2** Freedom from in-field (100%) and out-of-field (92%) locoregional recurrence in patients treated with single-fraction radiation therapy.

of 8 Gy in the postoperative setting. With a median follow-up of 19 months, there were no in-field or local failures. This compares favorably to the results of historical H&N MCC series of cPORT. Takagishi et al reported a 5-year local recurrence rate of 26.3% with surgery alone versus 0% with adjuvant cPORT ( $P = .02$ ) in patients with H&N MCC, suggesting a benefit for PORT over observation alone in patients with favorable pathologic stage I tumors with negative surgical margins and negative sentinel node biopsy and without immunosuppression.<sup>3</sup> The median time to local recurrence was 11 months. Compared with the patients reported by Takagishi et al, this study had patients with worse prognostic features, including recurrent tumors ( $n = 2$ ), stage II ( $n = 2$ ), failed or no sentinel node biopsy ( $n = 4$ ), positive margin ( $n = 1$ ), and immunosuppression ( $n = 3$ ). Strom et al also showed a significant improvement in 3-year local control (89.4% vs 68.1%;  $P = .005$ ) and regional control (95% vs 66.7%;  $P = .008$ ) among 113 patients with clinical stages I-III H&N MCC who received cPORT versus observation, respectively.<sup>4</sup>

Other series have reported on the efficacy of RT for the treatment of MCC of the H&N region.<sup>13,14</sup> Lok et al

reported a 10% crude rate of locoregional failures (4% local and 6% regional) at a median follow-up of 51 months among 48 patients with H&N MCC (clinical stages I-III and recurrent) treated with cPORT.<sup>13</sup> Bishop et al demonstrated excellent 5-year local and regional control outcomes (96% and 92%, respectively) for 102 patients with MCC of the H&N region (clinical stages I-III and recurrent) treated with definitive radiation therapy (61%) or cPORT (39%) to the postoperative bed and ipsilateral neck.<sup>14</sup>

Our study, albeit with a small sample size, had patients with the highest percentage of immunosuppression of 25% ( $n = 3$  of 12) compared with other H&N series reported rates of 0 to 10%.<sup>3,4,13,14</sup> The only regional recurrence noted in this study was in an immunosuppressed patient, who developed an out-of-field recurrence in the regional lymph nodes. This patient also had a failed sentinel lymph node biopsy. However, there was no radiologic evidence of regional nodal disease at the time of SFRT. This is consistent with the observation noted in the literature that immunosuppression is a negative prognostic factor associated with an increased probability of recurrence and death from MCC.<sup>15,16</sup>

There were no observed acute or late toxicities >grade 1 (CTCAE v5) within this cohort after SFRT. A previous study demonstrating the durability of SFRT for gross metastatic MCC in all anatomic sites similarly demonstrated no acute or late toxicities when treating tumors in the H&N region with a median follow-up of 9 months.<sup>12</sup> In regard to acute toxicity after cPORT, Lok et al reported 10% and 2% rates of Radiation Therapy Oncology Group grade 3 dermatitis and mucositis, respectively.<sup>13</sup> For late toxicity after cPORT, Bishop et al reported a 5% Radiation Therapy Oncology Group grade  $\geq 3$  or greater event rate (4 ocular, 1 mandible).<sup>14</sup>

In addition to the minimal toxicity, another attractive feature of this 8-Gy SFRT approach is that it would not significantly interfere with salvaging a potential in-field failure given the low dose of radiation therapy.

This study is limited by its retrospective design, a small sample size, and a relatively short follow-up period of 19 months, although with MCC most locoregional recurrences occur within 1 year. Patient selection was not based on any specific tumor-related factors. All patients expressed logistical considerations as the primary reason for preferring SFRT to cPORT. These data apply to treatment of the primary site in patients with localized H&N MCC. The safety and efficacy of SFRT for patients with higher-stage MCC with clinical or pathologic node-positive disease (AJCC eighth edition stage III) remains unknown. It is possible that the biology of the primary site and regional nodes may differ. Moreover, there was only 1 patient in this study who received elective nodal RT. Caution should be applied with using this approach for elective nodal RT for an aggressive primary in the setting of a failed or no SLNB.

This study suggests that favorable in-field locoregional control may be achieved with SFRT, including in a patient who had microscopically positive margins. In addition, consistent with MCC typically being very radiosensitive, SFRT using a lower biologically equivalent dose ( $BED_{\alpha/\beta = 10}$ ) of 14.4 Gy compared with 50 Gy with cPORT was able to achieve promising in-field local control. Despite the lower BED of SFRT, the similar local control may be explained by emerging data demonstrating that higher dose per fraction may potentiate a greater immune-mediated effect compared with conventionally fractionated RT.<sup>17-19</sup> This is relevant given MCC is a highly immunogenic malignancy.<sup>20</sup> Ongoing work will refine the ideal patient population for postoperative SFRT. To the best of our knowledge, this is the first study to demonstrate promising outcomes with single-fraction postoperative radiation therapy in localized MCC of the H&N region. This approach can also address a need to shorten the course of radiation therapy while maintaining excellent oncologic outcomes during the COVID-19 pandemic.<sup>9-11</sup>

## Conclusion

This study provides preliminary data for prospective evaluation to determine the long-term durability and toxicity of postoperative SFRT for MCC of the H&N region. Further work is needed to identify which patients with MCC may benefit from abbreviated versus protracted postoperative radiation therapy.

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