

## Scientific Article

# Should Sentinel Lymph Node Biopsy Status Guide Adjuvant Radiation Therapy in Patients With Merkel Cell Carcinoma?



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## Abstract

**Purpose:** Radiation of the draining lymph node basin remains controversial for Merkel cell carcinoma, particularly in the era of sentinel lymph node biopsy (SLNB).

**Methods and Materials:** Based on a 20-year experience using SLNB-guided adjuvant radiation therapy (RT), we conducted a retrospective review of clinically node-negative patients testing 2 hypotheses: (1) whether nodal RT could be safely omitted in SLNB-negative Merkel cell carcinoma and (2) whether the excised primary site should always be radiated. Clinically node-positive patients were excluded.

**Results:** Among 57 clinically node-negative patients who underwent SLNB and wide local excision (WLE), 42 (74%) had a negative SLNB, and 15 (26%) had a positive SLNB. At a median follow-up of 43 months (range, 5-182), SLNB-negative patients irradiated to the primary site had improved 4-year disease-specific survival (100% vs 65%,  $P = .008$ ), local recurrence-free survival (100% vs 76%,  $P = .009$ ), and distant recurrence-free survival (100% vs 75%,  $P = .008$ ), but not overall survival (87.5% vs 57.7%,  $P = .164$ ) compared with SLNB-positive patients receiving comprehensive RT. Among SLNB-negative patients treated with WLE only, 67% (6/9) had a disease relapse, half of which were local relapses (33%).

**Conclusions:** In this single-institution retrospective review, after negative SLNB and WLE, RT given only to the primary site provided 100% disease control without a need for nodal RT. Among SLNB-negative patients who had WLE, omission of postoperative primary-site RT was associated with 67% cancer relapse, of which half was local.

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## Introduction

Merkel cell carcinoma (MCC) is a rare neuroendocrine tumor that occurs predominantly in the sun-exposed skin of older Caucasian patients.<sup>1</sup> The majority of cases are associated with the Merkel cell polyomavirus, and risk factors include ultraviolet radiation exposure and immunosuppression.<sup>1</sup> From 2000 to 2013, MCC incidence increased 95% with an estimated 2800 new diagnoses in 2020 in the United States, reflecting an aging population.<sup>2</sup> Outcomes remain poor with a 5-year disease-specific survival of 64%.<sup>3</sup>

Sentinel lymph node biopsy (SLNB) and wide local excision (WLE) comprise the standard initial management approach followed by adjuvant radiation therapy (RT) to the primary tumor site.<sup>4</sup> On the other hand, indications for RT to the draining lymph node basin are less clear. Some studies suggest adjuvant nodal RT can be safely omitted in SLNB-negative disease, citing low rates of regional recurrence.<sup>3,5-7</sup> However, other studies demonstrate regional recurrence rates as high as 33% even in SLNB-negative patients, raising concern about the draining lymph nodes in this population.<sup>22</sup>

Here, we report a 20-year experience treating MCC with adjuvant RT according to a policy of excluding the draining nodal basin for SLNB-negative MCC and including the draining nodal basin for SLNB-positive MCC. The goal of this report was specifically to evaluate two hypotheses: (1) if nodal RT could be safely omitted in SLNB-negative MCC and (2) if the excised primary site should always be radiated.

## Methods and Materials

### Procedures

Institutional review board approval was obtained. We identified clinically node-negative patients who underwent SLNB and WLE for MCC between March 1996 and December 2015. The closing date for patient record review was selected to allow for adequate follow-up time. Data were obtained from the institutional cancer registry and radiation oncology department records.

Patients underwent WLE of the primary tumor to establish negative histologic margins except in cases of limitations on resectability. Regional staging via SLNB was performed at the time of WLE, with completion lymph node dissection in cases of positive SLNB. Sentinel lymph node detection used a gamma probe after

peritumoral injection of a radiotracer. The dissection was deemed complete when the activity in the surgical bed was less than 10% of the initially detected activity of the most active node. Adjuvant RT to the primary tumor site was recommended for all patients and given to the draining lymph node basin for SLNB-positive patients. RT consisted of 46 to 50 Gy in 23 to 25 fractions. Patients with positive margins were treated to a dose of 60 Gy in 30 fractions. Primary site irradiation almost always consisted of relatively superficial electron beam therapy, and the nodal basin was irradiated separately with a 3-dimensional conformal photon plan. After 2010, intensity-modulated RT was frequently used to treat draining nodal basins. If the primary site was in immediate anatomic proximity to the draining nodal basin and both were to be irradiated, intensity-modulated RT was used to treat both areas.

### Statistical analysis

Demographic and clinical covariates included: age (continuous), sex, race (Caucasian, non-Caucasian), primary site (head and neck [HN] vs non-HN), primary size ( $\leq 2$  cm vs  $> 2$  cm, grouped at the median based on pT stage), American Joint Committee on Cancer (AJCC) prognostic group (I/II vs III/IV), number of pathologically involved lymph nodes ( $\leq 1$  vs  $> 1$ , grouped at the median for SLNB-positive patients), and number of regional nodes examined ( $\leq 3$  vs  $> 3$ , grouped at the median for all patients). Dichotomization of AJCC prognostic group resulted in an equivalent variable to SLNB status. Outcomes included death, local recurrence (arising within or adjacent to primary excision site), regional recurrence (arising in draining lymph node basin or in-transit), or distant recurrence (metastasis). Survival endpoints included overall survival (OS), disease-specific survival ([DSS] defined as death due to MCC), local recurrence-free survival (LRFS), regional recurrence-free survival, and distant recurrence-free survival (DRFS).

Survival time was calculated from the date of diagnosis. Descriptive data were summarized and compared using Fisher's exact test and *t* test. Survival endpoints were estimated using the Kaplan-Meier method and compared using the log-rank test. Multivariate analysis, including propensity score, was not possible because there were less than 10 events.<sup>8</sup> Two-sided *P* values less than .05 were considered statistically significant. Data were analyzed using STATA software version 15 (Stata-Corp, College Station, TX).

## Results

### Patient and treatment characteristics

Over the study period, 183 patients treated for MCC were identified. We excluded patients with clinically-positive nodes ( $n = 19$ ), WLE without SLNB ( $n = 57$ ), and inconclusive AJCC staging ( $n = 27$ ), as these patients were treated per different clinical algorithms. Of the remaining 80 patients in the dataset, 23 were excluded owing to: inadequate treatment information contained in older records (12); unavailable outside records (4); non-standard treatments (3 chemotherapy only, 1 surgery and chemotherapy, 1 RT only, and 1 hospice shortly after surgery); and inconclusive SLNB (1).

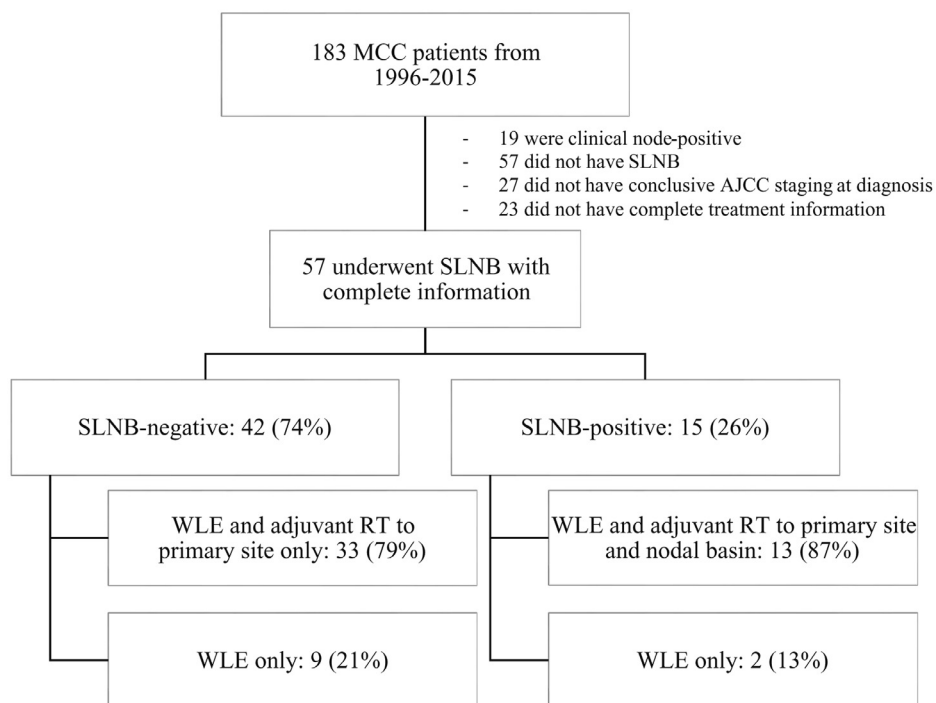
Of the remaining 57 patients who underwent WLE and SLNB, 42 (74%) had a negative SLNB and 15 (26%) had a positive SLNB. Thirty-three (79%) SLNB-negative patients underwent adjuvant RT to the primary site only and 9 (21%) were observed. Thirteen (87%) SLNB-positive patients underwent RT to the primary site plus nodal basin and 2 (13%) were observed. Figure 1 is a diagram summarizing SLNB status and subsequent treatment. The median age at diagnosis was 70 years (range, 43-89), and most patients were male ( $n = 33$ , 58%). The most common primary location was in the head and neck ( $n = 28$ , 49%). Demographic and clinical characteristics are summarized in Table 1. There were no significant differences

in patient age, sex, race, polyomavirus positivity, anatomical site, tumor size, and number of nodes examined between SLNB-positive and SLNB-negative patients and between patients treated with or without adjuvant radiation. However, SLNB-positive patients were more likely than SLNB-negative patients to be immunosuppressed ( $P = .016$ ) and to have a higher AJCC prognostic group and number of positive nodes ( $P < .001$ ).

### Recurrence and survival outcomes

Among the 57 patients treated with WLE and SLNB, there were a total of 11 recurrences (19%), including 7 patients (64%) observed after WLE and 4 SLNB-positive patients (36%) treated with adjuvant radiation to the primary site and nodal basin. Among patients treated with WLE only, the proportion of SLNB-negative patients ( $n = 9$ ) who had any disease failure was 67% ( $n = 6$ ); 3 (33%) had local relapse and 2 (22%) had regional relapse. One of the 2 (50%) SLNB-positive patients observed after WLE had a distant relapse. Table 2 enumerates the recurrences by treatment modality.

SLNB-negative patients, who were irradiated to the primary site only, had improved 4-year DSS (100% vs 65%,  $P = .008$ ), LRFS (100% vs 76%,  $P = .009$ ), and DRFS (100% vs 75%,  $P = .008$ ), but not OS (87.5% vs



**Figure 1** Merkel cell carcinoma (MCC) study sample by sentinel lymph node biopsy (SLNB), wide local excision (WLE), and radiation therapy (RT) treatments received.

**Table 1** Baseline characteristics and disease outcomes of patients with MCC treated with wide local excision with or without adjuvant radiation therapy, by SLNB status

Characteristic	SLNB-negative		All SLNB-negative	SLNB-positive		All SLNB-positive	All SLNB
	Adjuvant radiation	No adjuvant radiation		Adjuvant radiation	No adjuvant radiation		
n	33 (79)	9 (21)	42	13 (87)	2 (13)	15	57 (100)
Median follow-up (range, months)	43 (5-128)	49 (14-97)	48 (5-128)	28 (1-182)	16 (7-25)	25 (6-182)	43 (5-182)
Median age at diagnosis (range, years)	68 (48-85)	76 (52-85)	69 (48-85)	75 (43-89)	75 (68-81)	75 (43-89)	70 (43-89)
Sex							
Male	16 (48)	7 (78)	23 (55)	8 (62)	2 (100)	10 (67)	33 (58)
Female	17 (52)	2 (22)	19 (45)	5 (38)	0 (0)	5 (33)	24 (42)
Race							
Caucasian	31 (94)	9 (100)	40 (95)	9 (69)	2 (100)	11 (73)	51 (89)
Non-Caucasian	2 (6)	0 (0)	2 (5)	3 (23)	0 (0)	3 (20)	5 (9)
Unknown	0 (0)	0 (0)	0 (0)	1 (8)	0 (0)	1 (7)	1 (2)
Immunosuppressed							
Yes	4 (12)	1 (11)	5 (12)*	4 (31)	1 (50)	5 (33) *	10 (18)
No	26 (79)	7 (78)	33 (79) *	6 (46)	0 (0)	6 (40) *	39 (68)
Unknown	3 (9)	1 (11)	4 (10) *	3 (23)	1 (50)	4 (27) *	8 (14)
Polyomavirus							
Positive	7 (21)	1 (11)	8 (19)	2 (15)	0 (0)	2 (13)	10 (18)
Negative	1 (3)	2 (22)	3 (7)	2 (15)	0 (0)	2 (13)	5 (9)
Unknown	25 (76)	6 (67)	31 (74)	9 (69)	2 (100)	11 (73)	42 (74)
Primary tumor site							
Head and neck	16 (48)	4 (44)	20 (48)	8 (62)	0 (0)	8 (53)	28 (49)
Trunk and buttocks	5 (15)	1 (11)	6 (14)	0 (0)	0 (0)	0 (0)	6 (11)
Extremities	12 (36)	4 (44)	16 (38)	5 (38)	2 (100)	7 (47)	23 (40)
AJCC prognostic group							
I	27 (82)	0 (0)	27 (64)	0 (0)	0 (0)	0 (0)	27 (47)
II	6 (18)	0 (0)	6 (14)	0 (0)	0 (0)	0 (0)	6 (11)
III	0 (0)	0 (0)	0 (0)	13 (100)	2 (100)	15 (100)	15 (26)
Pathologic T category							
pT1	25 (76)	0 (0)	25 (60)	8 (62)	1 (50)	9 (60)	34 (60)
pT2	5 (15)	0 (0)	5 (12)	1 (8)	0 (0)	1 (7)	6 (11)
pT3	1 (3)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	1 (2)
pT4	1 (3)	0 (0)	1 (2)	1 (8)	0 (0)	1 (7)	2 (4)

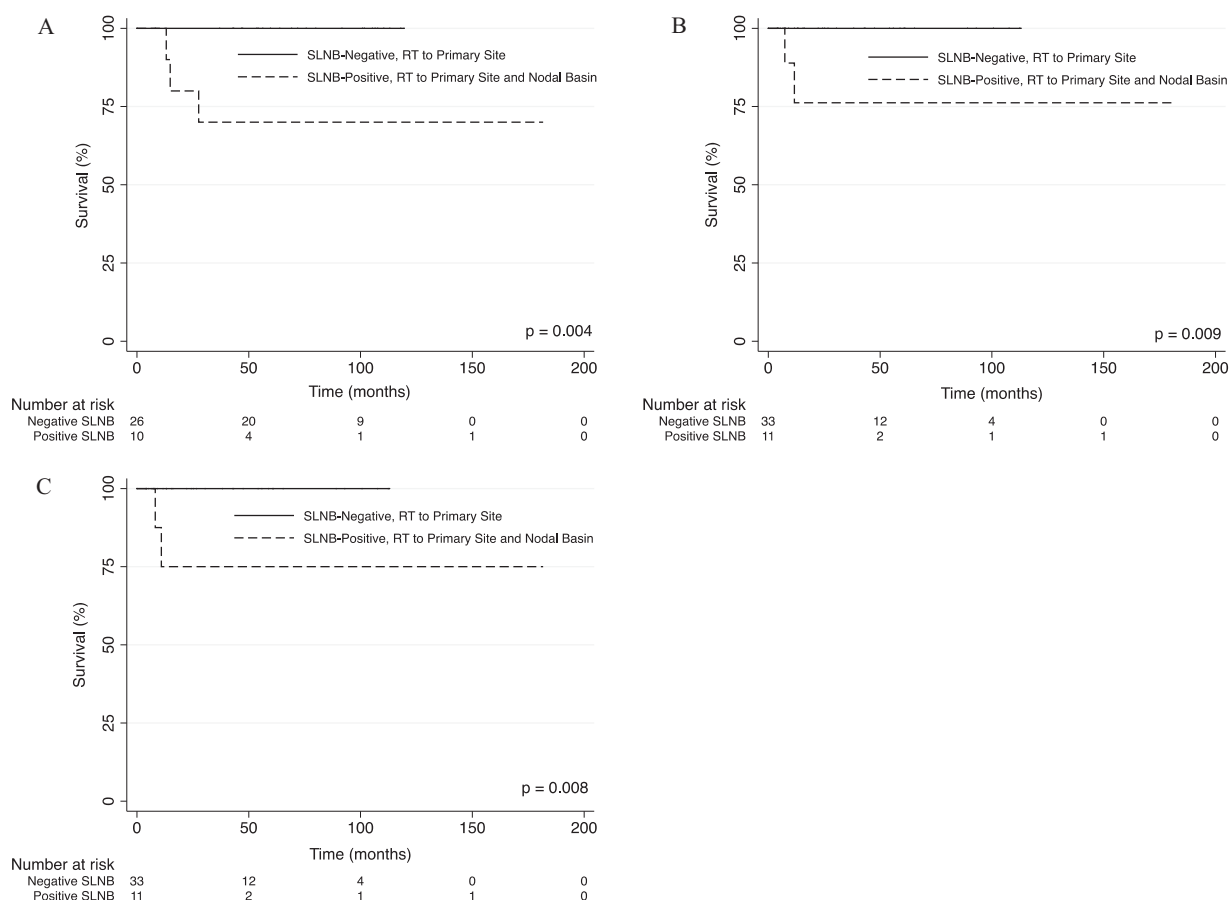
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**Table 1** (Continued)

Characteristic	SLNB-negative		All SLNB-negative	SLNB-positive		All SLNB-positive	All SLNB
	Adjuvant radiation	No adjuvant radiation		Adjuvant radiation	No adjuvant radiation		
Unknown	1 (3)	3 (33)	4 (10)	3 (23)	1 (50)	4 (27)	8 (14)
Total number of positive nodes							
0	33 (100)	9 (100)	42 (100)	0 (0)	0 (0)	0 (0)	42 (74)
1	0 (0)	0 (0)	0 (0)	9 (69)	2 (100)	11 (73)	11 (19)
2-4	0 (0)	0 (0)	0 (0)	3 (23)	0 (0)	3 (20)	3 (5)
≥5	0 (0)	0 (0)	0 (0)	1 (8)	0 (0)	1 (7)	1 (2)
Total number of nodes examined							
1	8 (24)	4 (44)	12 (29)	4 (31)	1 (50)	5 (33)	17 (30)
2	6 (18)	0 (0)	6 (14)	3 (23)	0 (0)	3 (20)	9 (16)
3	5 (15)	1 (11)	6 (14)	0 (0)	0 (0)	0 (0)	6 (11)
4	4 (12)	0 (0)	4 (10)	2 (15)	0 (0)	2 (13)	6 (11)
≥5	10 (30)	4 (44)	14 (33)	4 (31)	1 (50)	5 (33)	19 (33)
Disease relapse							
None	33 (100)	3 (33)	36 (86)	9 (69)	1 (50)	10 (67)	46 (81)
Local	0 (0)	3 (33)	3 (7)	2 (15)	0 (0)	2 (13)	5 (9)
Regional	0 (0)	2 (22)	2 (5)	0 (0)	0 (0)	0 (0)	2 (4)
Distant	0 (0)	1 (11)	1 (2)	2 (15)	1 (50)	3 (20)	4 (7)
Local, regional, or distant	0 (0)	6 (55)	6 (55)	4 (36)	1 (9)	5 (45)	11 (100)
Median recurrence time (range, months)	-	10 (7-12)	10 (7-12)	10 (4-48)	14	10 (4-48)	11 (4-48)
Status at last follow-up							
Alive without MCC	26 (79)	4 (44)	30 (71)	6 (46)	0 (0)	6 (40)	36 (63)
Alive with MCC	0 (0)	1 (11)	1 (2)	1 (8)	0 (0)	1 (7)	2 (4)
Died of MCC	0 (0)	1 (11)	1 (2)	3 (23)	0 (0)	3 (20)	4 (7)
Died of other cause	7 (21)	3 (33)	10 (24)	3 (23)	2 (100)	5 (33)	15 (26)

Abbreviations: AJCC = American Joint Committee on Cancer; MCC = Merkel cell carcinoma; SLNB = sentinel lymph node biopsy.

\*  $P < .05$ . Parentheses contain column percentages except as indicated for ranges and for variables contained within a single row, which represent row percentages.



**Figure 2** Disease-specific survival of patients with Merkel cell carcinoma treated with wide local excision who received adjuvant radiation therapy, by sentinel lymph node biopsy (SLNB) status.

57.7%,  $P = .164$ ) compared with SLNB-positive patients who received comprehensive RT. Female sex was associated with improved 4-year OS (100% vs 65%,  $P = .008$ ) and DSS (100% vs 80%,  $P = .038$ ). No regional recurrences were observed in either group. Patient age, anatomical site, tumor size, immunosuppressed state, polyomavirus positivity, number of positive nodes, and number of nodes examined were not associated with any endpoint in univariate analysis. See Figure 2 for survival curves by SLNB status and treatment.

## Discussion

In this study, we found that SLNB status was useful for determining the extent of subsequent RT. RT to the primary site was important for optimizing local control. Regional RT may not be necessary in cases of negative SLNB, which demonstrated a low risk of relapse in the nodal bed. For SLNB-positive patients, the 4-year DSS was 65%, LRFS was 76%, and DRFS was 75% despite comprehensive adjuvant RT, underscoring the prognostic importance of SLNB status.

MCC is highly radiosensitive, and a systematic review of more than 17,000 MCC cases across 29 studies identified improved locoregional control and OS with adjuvant RT, even in the lowest-risk subset.<sup>9</sup> However, most studies do not describe the RT details, and other studies question the need for adjuvant RT to small, low-risk lesions.<sup>3,10,11</sup> Surgery alone has been associated with a recurrence rate of 26% to 32% after WLE<sup>23,24</sup> and even higher rates after limited excision.<sup>25,26</sup> One large series reported that among 108 SLNB-negative patients, 2 (2%) were given completion nodal dissection and 9 (8%) underwent nodal RT with or without chemotherapy; subsequently, 9 (8%) of these patients had nodal recurrence, and 6 (6%) had distant recurrences, but, of note and unlike our series, no primary site recurrences occurred.<sup>13,27</sup> Among patients in our cohort who had surgery but not adjuvant RT, 50% to 67% (SLNB-positive,  $n = 1/2$ ; SLNB-negative,  $n = 6/9$ ) experienced some form of disease relapse, and among unirradiated SLNB-negative patients, half of these relapses were local failures (33%).

MCC has a propensity to spread to the draining lymph nodes, and accordingly, 27% of patients present with regional disease,<sup>13</sup> whereas up to a third present with

**Table 2** Detailed characteristics of patients with MCC with disease relapse after wide local excision with or without adjuvant radiation therapy

Sex	Primary tumor site	SLNB	AJCC prognostic group	Treatment	Number of positive nodes	Number of nodes examined	Type of recurrence	Time to recurrence (months)	Status at last follow-up	Immuno-suppressed	Polyomavirus
1 Male	Head and neck	Negative	Stage I	No adjuvant radiation	0	3	Local	15	Alive without MCC	No	Negative
2 Female	Trunk and buttocks	Negative	Stage I	No adjuvant radiation	0	8	Distant	48	Died of MCC	No	Unknown
3 Female	Head and neck	Negative	Stage I	No adjuvant radiation	0	1	Local	4	Died of other cause	Yes	Unknown
4 Male	Head and neck	Negative	Stage I	No adjuvant radiation	0	1	Local	13	Alive with MCC	No	Negative
5 Male	Extremities	Negative	Stage I	No adjuvant radiation	0	1	Regional	4	Alive without MCC	No	Positive
6 Male	Head and neck	Negative	Stage I	No adjuvant radiation	0	1	Regional	7	Died of other cause	No	Unknown
7 Female	Extremities	Positive	Stage III	Adjuvant radiation	2-4	4	Local	7	Died of other cause	Yes	Unknown
8 Male	Extremities	Positive	Stage III	No adjuvant radiation	1	33	Distant	14	Died of other cause	Yes	Unknown
9 Male	Extremities	Positive	Stage III	Adjuvant radiation	5+	41	Distant	11	Died of MCC	No	Unknown
10 Female	Extremities	Positive	Stage III	Adjuvant radiation	1	2	Local	12	Alive with MCC	No	Positive
11 Male	Head and neck	Positive	Stage III	Adjuvant radiation	1	4	Distant	8	Died of MCC	No	Unknown

Abbreviations: AJCC = American Joint Committee on Cancer; MCC = Merkel cell carcinoma; SLNB = sentinel lymph node biopsy.

occult nodal metastases.<sup>14</sup> The first and only prospective MCC trial randomizing stage I patients to adjuvant nodal RT versus observation of the nodal basin was prematurely terminated due to increasing SLNB use.<sup>12</sup> In the absence of prospective data, reports have suggested that RT to the draining lymph node basin can be omitted for SLNB-negative patients, citing a low risk of regional recurrence.<sup>3,5-7</sup> However, in these retrospective studies, regional relapse rates for these patients were 11% to 17% with overall relapse as high as 20% to 30%, and radiation fields were not uniform.<sup>9</sup> In this context, the over-riding goal of our study was to evaluate the low risk of regional recurrence when only the primary site was irradiated after a negative SLNB. In our study of clinically node-negative patients, we observed a zero-failure rate among SLNB-negative patients who underwent postoperative RT to the primary site alone. However, it should be acknowledged that more nodal failures could have been observed with a larger dataset including more patients, particularly because the false negative rate of SLNB in MCC may be as high as 17%.<sup>15</sup>

Of note, patients with HN-MCC have been proposed to constitute a high-risk subgroup of SLNB-negative patients.<sup>16</sup> However, prior analyses included patients who had clinical rather than pathologic node evaluation and hence a higher false negative rate.<sup>14</sup> No increased risk of recurrence was found in lymph node-negative HN-MCC evaluated with SLNB.<sup>6</sup> In our cohort, anatomic site was not associated with any outcome, although it should be noted that our study only included patients for whom SLNB was successfully obtained. The only factor in our study influencing 4-year OS was female sex, consistent with previous studies<sup>13,17,18</sup> but not all.<sup>19,20</sup>

Reported relapse rates for SLNB-positive MCC are high, with recurrence rates of 33% to 49% among SLNB-positive patients treated with WLE and adjuvant nodal RT and/or chemotherapy.<sup>5,21</sup> We confirmed a higher rate of local and distant relapse among these patients, who should be considered for novel therapies. Additionally, these patients were more likely to be immunosuppressed compared with SLNB-negative patients.

It should be noted that we excluded patients where staging was uncertain or SLNB was not successful. The National Comprehensive Cancer Network guidelines advise against overreliance on SLNB if there is high risk for a false negative reading. Reasons for caution include prior large-scale WLE, operator failure or abortive technical factors, inability to conduct complete immunohistochemical analysis, or profound immunosuppression.<sup>4</sup> A history of prior major surgery can complicate drainage patterns particularly in the head and neck region.

A further limitation of this work is the exclusion of patients with incomplete treatment data, including some referred to outside facilities. These patients may systematically differ from the study population reported here. However, we were able to acquire information for

approximately half of these patients and no obvious differences were observed.

In sum, in this single-institution retrospective series, surgical excision followed by adjuvant RT to only the primary site omitting the draining nodal basin provided 100% tumor control for SLNB-negative disease. On the other hand, radiation to the primary site is warranted as omission of this treatment led to a frequent incidence of relapse (67% disease relapse, half being local in nature, in this series). Patients with positive and indeterminant SLNBs had worse outcomes despite comprehensive adjuvant RT, and for them, innovative approaches are needed.

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