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ORIGINAL ARTICLE – MELANOMA

Management of Sentinel Lymph Node Metastasis in Merkel Cell Carcinoma: Completion Lymphadenectomy, Radiation, or Both?

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ABSTRACT

Background. Approximately 30% of patients with clinically localized Merkel cell carcinoma (MCC) show nodal involvement on sentinel lymph node biopsy (SLNB). Optimal management of SLNB-positive disease has not been defined. This study compared outcomes after completion lymphadenectomy (CLND), radiation, and combined CLND plus radiation after a positive SLNB.

Methods. All patients treated at a single institution for SLNB-positive MCC (1998–2015) were retrospectively evaluated, with examination of patient demographics, clinicopathologic characteristics, outcomes, and regional toxicity.

Results. The study identified 71 evaluable patients with SLNB-positive disease. The median age of these patients was 76 years, and 76.1% were men. Of the 71 patients, 11 (15.5%) underwent CLND, 40 (56.3%) received radiation, and 20 (28.2%) underwent CLND plus postoperative radiation. Lymphovascular invasion was significantly more common in the radiation-alone cohort ($p = 0.04$). For the three cohorts, the median percentages of nodal involvement were respectively 2, 10, and 30% ($p = 0.06$). After a median follow-up period of 22.3 months, four patients had recurrence in their regional nodal basin (3 radiation-alone patients and 1 CLND + radiation patient). The three cohorts did not differ significantly in the development of distant metastases ($p = 0.68$) or overall survival ($p = 0.72$). Six patients experienced surgical-site infections (2 CLND and 4 CLND + radiation patients), and three patients experienced symptomatic lymphedema (1 CLND patient and 2 CLND + radiation patients).

Conclusions. Regional failure was infrequent ($\leq 10\%$) regardless of treatment, and morbidity appeared to be low with all approaches. Given that multiple treatment approaches can be successful in treating micrometastatic MCC, future efforts should be directed at refining criteria for allocating patients to a specific method, or possibly no further nodal basin treatment, in an effort to maximize regional control at the lowest cost and morbidity.

Merkel cell carcinoma (MCC) is a rare and aggressive cutaneous malignancy of neuroendocrine origin with a high propensity for regional and distant metastasis.[1] It most often develops on the head and neck of elderly Caucasian patients and has been associated with ultraviolet exposure, immunosuppression, and infection by the Merkel cell polyomavirus.[2–4] As the incidence of MCC continues to rise, so has awareness of and interest in the disease.[5,6]

Excision of the primary tumor with sentinel lymph node biopsy (SLNB) is the mainstay of treatment for clinically localized disease.[7] Merkel cell carcinoma is also highly radiosensitive, and multiple reports have shown improvements in both local and regional control with the use of postoperative radiotherapy.[8,9] About 25–30% of patients who undergo SLNB will have micrometastatic regional lymph node involvement.[10,11]

Given the relative rarity of MCC, evidence-based guidelines for the management of micrometastatic disease in the regional nodal basin are lacking. Historically, completion lymph node dissection (CLND) with or without

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postoperative radiation has been offered after a positive SLNB. Radiation delivered to the primary tumor, regional lymph nodes, or both as definitive therapy also has been described in the literature.[12–14]

We sought to review our experience treating patients at a single institution for SLNB-positive MCC. We evaluated the hypothesis that either CLND or radiation alone provides acceptable rates of regional control for patients with micrometastatic regional nodal involvement after SLNB.

MATERIALS AND METHODS

After institutional review board approval was obtained, we performed a retrospective, single-institution review of patients treated for SLNB-positive MCC between 1998 and 2015. At our institution, all patients with clinically localized MCC routinely undergo SLNB unless severe comorbidities preclude the patient from undergoing general anesthesia.

Patients were stratified by the type of regional nodal basin treatment received as follows: CLND alone, radiation alone, or CLND with postoperative radiation. Patients who underwent radiation therapy received conventionally fractionated radiation to the draining lymphatics with or without radiation to the primary site. All CLNDs were performed at the primary institution.

Of 60 patients, 20 (33.3%) received radiation at the primary institution, whereas the remaining 40 (66.7%) received radiation at an outside facility. Radiation therapy records were available for 55 (91.7%) of the 60 patients undergoing radiation therapy, and the median prescribed radiation dose was 5000 cGy (range 5000–6000 cGy) given in 200 cGy fractions (range 180–300 cGy).

Patient demographics (age, gender, immunosuppression status), clinicopathologic characteristics (anatomic site, primary tumor depth, presence of lymphovascular invasion, number of positive nodes, percentage of nodal involvement, presence of extranodal extension, non-sentinel lymph node status [CLND patients only]), and oncologic outcomes were reviewed. Primary tumor diameter could not be accurately characterized in this retrospective study and was therefore not included in the analysis. All surgical pathology was reviewed by a board-certified dermatopathologist.

Statistical Analysis

The primary end point of this study was regional nodal recurrence-free survival (RRFS), considering any recurrence within a nodal basin that contained a positive node. The secondary end points were distant metastasis-free survival (DMFS), overall survival (OS), and disease-specific survival (DSS). Chi square or Fisher's exact test and the Kruskal–Wallis test were used to examine differences among the three treatment groups with categorical and numeric clinicopathologic characteristics, respectively. Survival analysis was calculated using the Kaplan–Meier method, and differences in rates based on individual variables were assessed using the log-rank test. Cox regression analysis with a competing risk of death was used to analyze recurrence. All tests were deemed significant at a significance level of 0.05. All analyses were performed in either SAS version 9.4 (SAS Institute, Inc. Cary, NC, USA) or R software (The R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Patient Demographics and Clinicopathologic Characteristics

The inclusion criteria were met by 71 patients with micrometastatic MCC of the regional nodal basin, as determined by SLNB, who underwent CLND, radiation or both. Among these 71 patients, the median age was 76 years (range 46–90 years), and 76% of these patients were men. The median depth of the primary tumor was 5.4 mm (range 0.5–20 mm). The median number of positive sentinel nodes was 1.0, and the median percentage of nodal involvement was 5%.

Of the 71 patients, 25 (35.2%) were treated for nodal involvement in the head and neck (cervical nodal and/or parotid basin), 28 (39.4%) were treated for nodal involvement in the upper extremity (axilla and/or epitrochlear nodal basin), and 18 (25.4%) were treated for nodal involvement in the lower extremity (groin and/or pelvis). No patients had positive SLNs in multiple major nodal basins (i.e., bilateral axillae, bilateral groin, axilla and groin, axilla and neck). The median follow-up period for the entire study population was 22.3 months (range 0.7–142 months).

Of the 71 patients, 11 (15.5%) underwent CLND alone, 40 (56.3%) received radiation monotherapy, and 20 (28.2%) underwent CLND with postoperative radiation. Patient demographics and clinicopathologic characteristics for the three treatment cohorts are shown in Table 1. The time periods for each treatment group were as follows: CLND alone (2003–2015), radiation monotherapy (2000–2015), and CLND with postoperative radiation (1998–2014).

The only difference among the cohorts reaching statistical significance was that the radiation monotherapy cohort had the highest proportion of patients with lymphovascular invasion at the primary tumor site (45.0 vs.

TABLE 1 Patient demographics and clinicopathologic characteristics by treatment group

Characteristic	CLND (n = 11)	Radiation (n = 40)	CLND + radiation (n = 20)	p Value
Median age: years (range)	79.0 (46.0–83.0)	75.0 (54.0–90.0)	75.5 (57.0–84.0)	0.89
Gender, n (%)				
Female	3 (27.3)	10 (25.0)	4 (20.0)	0.86
Male	8 (72.7)	30 (75.0)	16 (80.0)	
Immunosuppression status; n (%)				
Yes	1 (9.1)	7 (17.5)	2 (10.0)	0.72
No	10 (90.9)	33 (82.5)	18 (90.0)	
Anatomic site; n (%)				
Head & neck	3 (27.3)	12 (30.0)	10 (50.0)	0.56
Upper extremity	5 (45.4)	16 (40.0)	7 (25.0)	
Lower extremity	3 (27.3)	12 (30.0)	3 (15.0)	
Median primary tumor depth: mm (range)	5.5 (1.0– 17.4)	5.6 (0.5–18.0)	4.4 (1.2–20.0)	0.80
Lymphovascular invasion; n (%)				
Yes	1 (9.1)	18 (45.0)	5 (25.0)	0.04
No	10 (90.9)	22 (55.0)	15 (75.0)	
Median no. of positive SLNs (range)	1.0 (1.0–6.0)	1.0 (1.0–4.0)	1.0 (1.0–9.0)	0.44
Median nodal involvement: % (range)	2.0 (1.0– 20.0)	10.0 (1.0–70.0)	30.0 (1.0–75.0)	0.06
Extranodal extension; n (%)				
Yes	2 (20.0)	5 (13.2)	5 (31.2)	0.32
No	8 (80.0)	33 (86.8)	11 (68.8)	
CLND status; n (%)				
Positive	1 (9.1)	NA	6 (31.6)	0.21
Negative	10 (90.9)	NA	13 (68.4)	

CLND completion lymph node dissection; *SLN* sentinel lymph node

9.1% for CLND and 25% for CLND + radiation; $p = 0.04$) Although not statistically significant, there was a trend for patients undergoing both CLND and radiation to have a higher burden of nodal involvement in the sentinel node. As a measure of tumor burden, the median percentage of nodal involvement in the sentinel node was 2% for the CLND-alone patients, 10% for the radiation monotherapy patients, and 30% for the CLND patients with postoperative radiation treatment ($p = 0.06$). Only 1 (9.1%) of 11 patients who underwent CLND alone had a positive non-sentinel lymph node, whereas 6 (30%) of 20 patients in the combined CLND and radiation cohort had at least one positive non-sentinel lymph node. The treatment cohorts did not differ significantly in number of positive sentinel nodes or the presence of extranodal extension.

Regional Recurrence

Four patients experienced regional recurrence in the primary lymph node basin (3 [7.5%] of 40 treated in the radiation monotherapy cohort and 1 [5%] of 20 in the cohort that had CLND with postoperative radiation). One of these four patients was immunosuppressed. The key clinicopathologic characteristics of each patient who experienced a regional recurrence are listed in Table 2. All three patients in the radiation monotherapy group who experienced recurrence subsequently underwent a therapeutic lymphadenectomy and maintained regional control at the last follow-up assessment. The one patient who experienced a regional recurrence after CLND and postoperative radiation also had a synchronous distant metastatic lesion, for which systemic chemotherapy was initiated.

The univariate analysis showed no significant correlation between regional recurrence and any clinicopathologic feature evaluated in this study. The 2-year regional recurrence-free survival rate was 100% for CLND, 93% for radiation, and 94% for CLND with postoperative radiation, as shown in Fig. 1a.

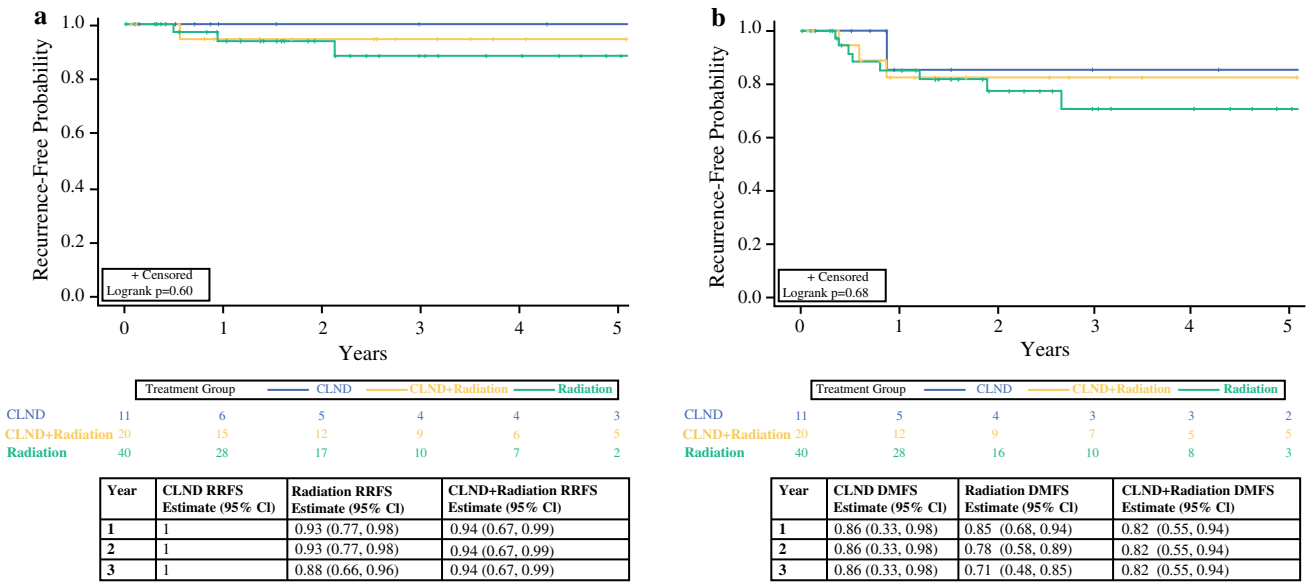
Distant Metastasis

Of the 71 patients, 12 (16.9%) experienced distant metastases (1 in the CLND-alone cohort, 8 in the radiation-alone cohort, and 3 in the CLND + radiation cohort). The DMFS rate at 2 years was 86% for CLND, 78% for

TABLE 2 Key clinicopathologic characteristics for each patient who experienced a regional recurrence

Patient	Treatment group	Recurrent disease location	Immunosuppressed	Primary tumor depth (mm)	Lymphovascular invasion	No. of positive SLNs	Nodal involvement (%)	Extranodal extension
1	Radiation	Pelvis	No	10.4	Absent	2	1	Absent
2	CLND + Radiation	Pelvis	No	3.2	Absent	2	30	Absent
3	Radiation	Superficial inguinal	Yes	17.0	Present	1	1	Absent
4	Radiation	Axilla	No	4.1	Absent	2	10	Absent

SLN sentinel lymph node; *CLND* completion lymph node dissection



Year	CLND RRFS Estimate (95% CI)	Radiation RRFS Estimate (95% CI)	CLND+Radiation RRFS Estimate (95% CI)
1	1	0.93 (0.77, 0.98)	0.94 (0.67, 0.99)
2	1	0.93 (0.77, 0.98)	0.94 (0.67, 0.99)
3	1	0.88 (0.66, 0.96)	0.94 (0.67, 0.99)

Year	CLND DMFS Estimate (95% CI)	Radiation DMFS Estimate (95% CI)	CLND+Radiation DMFS Estimate (95% CI)
1	0.86 (0.33, 0.98)	0.85 (0.68, 0.94)	0.82 (0.55, 0.94)
2	0.86 (0.33, 0.98)	0.78 (0.58, 0.89)	0.82 (0.55, 0.94)
3	0.86 (0.33, 0.98)	0.71 (0.48, 0.85)	0.82 (0.55, 0.94)

FIG. 1 Kaplan–Meier curves for **a** regional recurrence-free survival (RRFS) and **b** distant metastasis-free survival (DMFS)

radiation, and 82% for CLND with postoperative radiation ($p = 0.68$), as shown in Fig. 1b.

Overall and Disease-Specific Survival

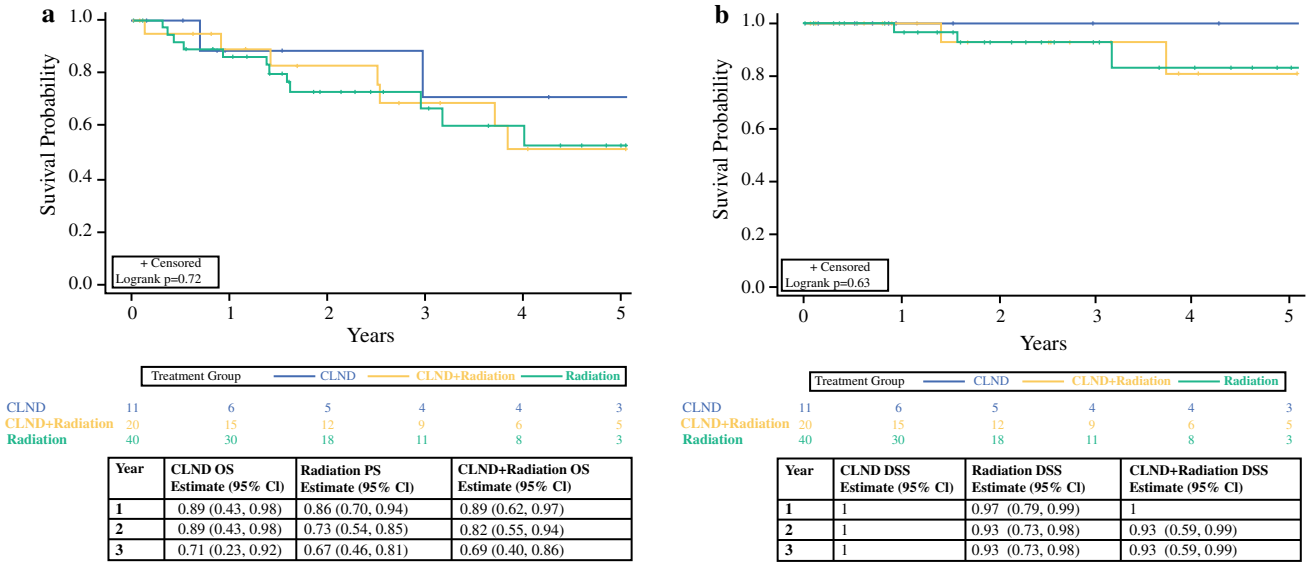
At the time of analysis, 25 of the 71 patients were deceased. Hence, median overall survival was not reached. The 3-year OS rate was 71% for CLND, 67% for radiation, and 69% for CLND with postoperative radiation. Only 6 of 71 patients, however, died of MCC, and the 3-year DSS rate was 100% for CLND, 93% for radiation, and 93% for CLND with postoperative radiation, as shown in Fig. 2a and b. No significant difference in OS ($p = 0.72$) or DSS ($p = 0.63$) was observed among the three cohorts.

Treatment-Related Morbidity

In this retrospective study, lymphedema details were not reported in a systematic manner. Lymphedema reportedly developed in 3 (4.2%) of the 71 patients (1 patient who underwent CLND alone and 2 patients who underwent CLND and postoperative radiation). No patients in the radiation monotherapy cohort were reported to have developed lymphedema. Post-radiation changes such as moist desquamation of the skin and dermatitis were reported in 19 (31.7%) of the 60 patients who received radiation therapy. Two patients who underwent CLND alone and four patients who underwent CLND with post-operative radiation experienced surgical-site infections, whereas one patient in the radiation monotherapy group experienced an abscess at the treatment site.

DISCUSSION

The current study reported a regional recurrence rate lower than 10% with all treatment methods assessed (CLND alone, radiation monotherapy, and CLND with postoperative radiation) for micrometastatic MCC in the regional lymph nodes. In the analysis of the differences in clinicopathologic characteristics between the different



Year	CLND OS Estimate (95% CI)	Radiation PS Estimate (95% CI)	CLND+Radiation OS Estimate (95% CI)
1	0.89 (0.43, 0.98)	0.86 (0.70, 0.94)	0.89 (0.62, 0.97)
2	0.89 (0.43, 0.98)	0.73 (0.54, 0.85)	0.82 (0.55, 0.94)
3	0.71 (0.23, 0.92)	0.67 (0.46, 0.81)	0.69 (0.40, 0.86)

Year	CLND DSS Estimate (95% CI)	Radiation DSS Estimate (95% CI)	CLND+Radiation DSS Estimate (95% CI)
1	1	0.97 (0.79, 0.99)	1
2	1	0.93 (0.73, 0.98)	0.93 (0.59, 0.99)
3	1	0.93 (0.73, 0.98)	0.93 (0.59, 0.99)

FIG. 2 Kaplan–Meier curves for **a** overall survival (OS) and **b** disease-specific survival (DSS)

treatment cohorts, only the rate of lymphovascular invasion at the primary site was found to be statistically different, potentially reflecting the fact that these patients routinely receive radiation to the primary tumor site and hence might be assumed more likely also to receive radiation to the affected regional basin. However, the patients who underwent CLND with postoperative radiation showed a trend toward a higher burden of nodal disease, defined as percentage of nodal involvement, which likely reflects a selection bias. The risk of lymphedema also likely was a contributing factor in terms of potential selection bias, because the combined-method treatment cohort contained the largest percentage of head and neck cases and the lowest percentage of lower extremity cases.

Multiple previous studies have shown improvements in both locoregional control and survival with radiation in the adjuvant setting.[9,15] Ghadjar et al.[15] published a series of 180 patients who received postoperative radiation and reported improvements in local and regional recurrence-free survival and DMFS with no difference in OS. However, Strom et al.[9] examined a group of 171 patients with MCC who received postoperative radiation and observed both higher locoregional control and OS.

Prior studies have reported on patients who received radiation monotherapy for MCC. These studies, however, included a combination of micro- and macroscopic disease in primary tumors, regionally metastatic disease, or both at the initial diagnosis or in the relapse setting. Veness et al.[14] reported an in-field control rate of 75% for 43 patients with primary MCC, regionally metastatic disease, or both treated with radiation monotherapy, whereas Sundaresan et al.[13] described an in-field control rate of 89% for 26 patients, also for a combination of primary MCC and regionally metastatic disease treated with definitive radiation therapy. Fang et al.[12] reported on a series of 26 patients with micrometastatic regional nodal disease together with 24 patients who had clinically evident or macroscopic lymph node involvement. In their series, 19 of the 26 patients with micrometastatic disease after SLNB were treated with radiation alone, whereas seven patients underwent CLND with or without postoperative radiation. During a median follow-up period of 18 months, no regional recurrences were reported.

Radiation to a non-sampled sentinel lymph node basin or even a negative sentinel lymph node basin also has been described. However, this currently is not a practice of our team.[7] We routinely follow MCC patients who do not undergo SLNB for any reason, as well as selected SLNB-negative patients we believe to be at higher risk for nodal relapse, with serial ultrasonography.

The current study represents the largest series of patients who underwent definitive lymph node radiation for micrometastatic regional lymph node MCC reported to date. Our study reported an overall regional recurrence rate of 5.6% for all patients, showing none after CLND alone, 7.5% after radiation monotherapy, and 5% after CLND with postoperative radiation. Additionally, no statistically significant difference in DMFS, OS, or DSS was observed. However, although comparisons of recurrence rates and survival among the different treatment groups were made in this study, the main objective was rather to test our hypothesis that regardless of treatment method, regional recurrence rates would be acceptable, defined as lower than 10%.

Given the similar survival among the treatment groups, perhaps age and tumor biology play a more significant role than the treatment method for these patients because the majority of patients who died succumbed to non-MCC related disease. Additionally, given that only 7 (22.6%) of the 31 patients who underwent CLND had a positive non-sentinel lymph node, it may be reasonable to suggest that a group of patients may exist who do not need any further nodal basin treatment, and for whom SLNB alone is sufficient. This notion is only strengthened by the recently reported results of the Multicenter Selective Lymphadenectomy Trial II (MSLT-II), which showed no survival benefit for SLNB-positive melanoma patients who underwent immediate CLND versus a delayed therapeutic lymphadenectomy.[16] However, as with melanoma, this should be studied in the setting of a prospective trial in which patients can be closely monitored with serial nodal ultrasounds.

Given that a majority of the patients underwent radiation therapy at an outside center, adverse events likely were underreported in this retrospective study secondary to missing outside records and patients lost to follow-up evaluation. However, treatment-related morbidity related to CLND and regional radiation is well described in prior prospective, randomized trials. The risk of general anesthesia, neurovascular injury, surgical-site infections, and postoperative lymphedema all are well-known risks to patients undergoing CLND for more common diseases such as melanoma and breast cancer.[17–20] Treatment-related adverse events of radiation to the regional nodal basin include cutaneous changes such as fibrosis, lymphedema, and infection and site-specific side effects such as xerostomia, in addition to the logistical difficulty of undergoing daily treatments during multiple weeks.[21,22] Furthermore, it is worth noting that patients who undergo radiation monotherapy to the regional nodal basin and experience recurrence likely will be at higher risk for procedure-related morbidity when undergoing a therapeutic lymphadenectomy in a previously irradiated field.

The limitations of this study were consistent with the inherent flaws of a retrospective study, including incomplete data, inconsistent follow-up evaluation, selection bias among the different treatment methods used, and non-systematic reporting of treatment-related morbidities. Given these limitations, together with lower rates of lymphedema for these treatment methods compared with other published data from prospective trials, adverse events likely were underreported in this retrospective study. The inability to characterize accurately the primary tumor diameter, a key component in the AJCC staging system, also was a significant limitation of this study and may have played a role in selection bias among the treatment methods used.[23] In addition, the sample sizes in this study remained small although it is the largest published series to date with respect to radiation monotherapy.

Given these limitations, the authors do not suggest that one therapy is superior to another, but rather that both CLND and radiation monotherapy appear to be sufficient with regard to regional control in these patients. This retrospective review highlights the need for a prospective, randomized trial allocating patients to specific treatment methods or possibly no further nodal treatment in an effort to maximize regional control at the lowest morbidity and cost. In the absence of such a trial, an informed discussion with patients, including both CLND and radiation monotherapy and their procedure-related risks and benefits, needs to be conducted on an individual basis.

CONCLUSIONS

As the incidence of MCC continues to rise, so does the number of patients who undergo SLNB, and it is imperative to define an optimal treatment pathway for patients after a positive SLNB. With no prospective clinical trial data available, this retrospective review shows that CLND alone or radiation monotherapy appears to be sufficient in the management for the majority of patients with micrometastatic regional lymph node MCC.

DISCLOSURE There are no conflicts of interest relevant to the subject matter presented in this manuscript.

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