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ORIGINAL ARTICLE – MELANOMA

Completion Lymph Node Dissection or Radiation Therapy for Sentinel Node Metastasis in Merkel Cell Carcinoma

Jay S. Lee, MD[1], Alison B. Durham, MD[2], Christopher K. Bichakjian, MD[2], Paul W. Harms, MD, PhD[3], James A. Hayman, MD, MBA[4], Scott A. McLean, MD, PhD[5], Kelly L. Harms, MD, PhD[2], and William R. Burns, MD[1]

[1]Division of Surgical Oncology, Department of Surgery, Michigan Medicine, University of Michigan, Ann Arbor, MI; [2]Department of Dermatology, University of Michigan, Ann Arbor, MI; [3]Department of Pathology, University of Michigan, Ann Arbor, MI; [4]Department of Radiation Oncology, University of Michigan, Ann Arbor, MI; [5]Department of Otolaryngology, University of Michigan, Ann Arbor, MI

ABSTRACT

Background. For sentinel lymph node (SLN) metastasis from Merkel cell carcinoma (MCC), the benefit of completion lymph node dissection (CLND) versus radiation therapy (RT) is unclear. This study compares outcomes for patients with SLN metastasis undergoing CLND or RT. We also evaluated positive non-SLNs as a prognostic factor.

Methods. Using a prospective database, we identified MCC patients with SLN metastasis who underwent CLND or RT. At our institution, CLND was recommended for patients with acceptable perioperative risk, while therapeutic RT was offered to those with high perioperative risk. Primary outcomes were MCC-specific survival (MCCSS), disease-free survival (DFS), nodal recurrence-free survival (NRFS), and distant recurrence-free survival (DRFS).

Results. From 2006 to 2017, 163 patients underwent CLND ($n = 137$) or RT ($n = 26$). Median follow-up was 1.9 years. CLND had no significant differences for MCCSS (5-year survival 71% vs. 64%, $p = 1.0$), DFS (52% vs. 61%, $p = 0.8$), NRFS (76% vs. 91%, $p = 0.3$), or DRFS (65% vs. 75%, $p = 0.3$) compared with RT. Patients with positive non-SLNs ($n = 44$) had significantly worse MCCSS (5-year survival 39% vs. 87%, $p < 0.001$), DFS (35% vs. 60%, $p = 0.005$), and DRFS (54% vs. 71%, $p = 0.03$) compared with negative non-SLNs ($n = 93$). Multivariate analysis showed positive non-SLNs were independently associated with MCCSS, DFS, and DRFS.

Conclusions. CLND and RT may have similar outcomes for MCC patients with SLN metastasis when treatment aligns with our institutional practices. For patients undergoing CLND, positive non-SLNs is an important prognostic factor associated with poor survival and distant recurrence. This high-risk group should be considered for adjuvant systemic therapy trials.

Merkel cell carcinoma (MCC) is an aggressive cutaneous malignancy, with 31–45% of patients presenting with clinically occult metastases to regional lymph nodes.[1–4] Because of this, sentinel lymph node (SLN) biopsy is recommended for all clinically node-negative patients.[5] Clinical practice guidelines recommend that patients with SLN metastasis from MCC undergo completion lymph node dissection (CLND) or receive therapeutic radiation therapy (RT).[5] However, the use of these treatment modalities varies widely across institutions, with 47–79% of patients undergoing CLND instead of RT or other treatments.[3,6,7]

Despite this variation, it is unclear how CLND compares with RT for long-term survival and recurrence. One single-institution study suggested CLND had similar rates of nodal and distant recurrence compared with RT, but this analysis was limited by a small sample size and many

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W. R. Burns, MD
e-mail: wilburns@med.umich.edu

different treatment approaches.[7] CLND and RT offer distinct advantages and disadvantages. Similar to melanoma, it is possible that CLND may improve regional disease control and provide prognostic information, but not improve disease-specific survival.[8] However, unlike melanoma, patients with SLN-metastasis from MCC who do not undergo CLND are recommended to receive therapeutic RT (and not active surveillance).[5] Furthermore, CLND is generally associated with increased morbidity when compared with SLN biopsy alone,[8–11] or to SLN biopsy with nodal RT[11,12] for patients with breast cancer and melanoma. Although the morbidity of these treatments for patients with MCC is unknown, it is likely similar to that seen with breast cancer and melanoma. Unfortunately, there are no randomized controlled trials comparing CLND and RT for patients with MCC. In this context, further study is needed to directly compare outcomes for CLND and RT.

To better inform decision making, we used a prospective institutional database to compare MCC-specific survival (MCCSS) and recurrence for patients with SLN metastasis who underwent CLND or therapeutic RT. At our institution, patients with SLN metastasis are generally recommended to undergo CLND. Patients considered to be at high perioperative risk or who decline CLND are offered therapeutic RT to the nodal basin instead of additional surgery. We hypothesized that CLND and RT would have similar MCCSS and distant recurrence-free survival (DRFS), while CLND would be associated with improved nodal recurrence-free survival (NRFS). For patients undergoing CLND, we also evaluated metastasis to non-SLNs as a prognostic factor. Furthermore, we hypothesized positive non-SLNs would be associated with worse outcomes.

METHODS

Study Cohort and Data Source

This study was approved by the Institutional Review Board at the University of Michigan. We used a prospective institutional database of MCC patients[4,13] to identify patients with histologically confirmed SLN metastasis who were treated with CLND or therapeutic RT from 2006 to 2017. Study data were collected and managed using REDCap electronic data capture tools.[14] This database includes all patients with MCC evaluated or treated at our institution. Pathologic data for the primary tumor included primary tumor size, tumor thickness, mitotic rate, angiolymphatic invasion, and ulceration. Pathologic data for lymph nodes included number of lymph nodes, number of nodes with metastases, tumor burden, and extracapsular/extranodal extension. We also calculated the total number of positive lymph nodes (total number of lymph nodes with metastasis in the SLN biopsy and CLND specimens). For patients undergoing CLND, we specifically identified those with positive non-SLNs (metastasis identified in lymph nodes from the CLND specimen). Follow-up data included date of last follow-up, date of death, cause of death, date of recurrence, and type of recurrence (local, nodal, or distant). Mortality data were determined using the electronic medical record, outside hospital records, and by phone contact with patients if data were missing.

Sentinel Lymph Node (SLN) Biopsy and Management of SLN Metastasis

Our technique for SLN biopsy has been previously described.[15] At our institution, patients with SLN metastasis are recommended to undergo CLND. Patients considered to be at high perioperative risk, and patients who decline CLND, are offered therapeutic RT to the nodal basin. For patients who undergo CLND, adjuvant RT to the nodal basin is recommended for those with metastasis to multiple lymph nodes or where extracapsular invasion is identified.[5]

Study Outcomes

Primary outcomes for this study were MCCSS, disease-free survival (DFS), NRFS, and DRFS. Time zero was the date of the first biopsy or tissue sample positive for MCC. MCCSS was determined at the date of MCC-related death; DFS was determined at the date of the first recurrence; NRFS was determined at the date of first recurrence in the draining nodal basin; and DRFS was determined at the date of distant recurrence. A secondary outcome was the use of therapeutic RT to the nodal basin instead of CLND.

Statistical Analysis

Patients were divided into two groups—CLND and RT. Patients undergoing CLND were further divided based on the presence of positive non-SLNs. We then compared outcomes among these groups. To better evaluate positive non-SLNs as a prognostic factor, we also specifically examined patients with two to four total positive lymph nodes, and compared outcomes for patients with positive and negative non-SLNs. This subset analysis focused on patients with a similar total burden of nodal disease.

Survival curves were generated using the Kaplan–Meier method, and survival between groups was compared using the log-rank test. Multivariate Cox proportional hazard regression models were used to evaluate the covariate-adjusted association between study variables and the primary outcomes. A multivariate logistic regression model was used to identify factors independently associated with receiving RT instead of CLND. Study variables with a p value ≤ 0.2 on univariate analysis were included in the multivariate models. Data were analyzed using Stata version 14.2 (StataCorp LLC, College Station, TX, USA). Two-sided p-values < 0.05 were considered statistically significant.

RESULTS

Patients

From 2006 to 2017, 179 patients were evaluated or treated for SLN metastasis, of whom 16 patients did not receive CLND or RT and were therefore excluded from the study. Of the remaining 163 patients, 137 (84%) underwent CLND and 26 (16%) underwent therapeutic RT. Of those who underwent CLND, 49 (36%) also received adjuvant RT to the nodal basin after CLND. These patients were included in the CLND group because one aim of this study was to evaluate CLND in the treatment of MCC. Furthermore, preliminary analysis demonstrated no statistically significant differences in survival or recurrence compared with patients who underwent CLND but did not receive adjuvant RT to the nodal basin. Table 1 compares the characteristics of patients who underwent CLND versus RT. Patients who underwent CLND were significantly younger (70 ± 16 vs. 78 ± 11 years, $p = 0.001$), were more likely to have two or more positive SLNs (39% vs. 12%, $p = 0.007$), and were more likely to have two or more total positive lymph nodes (59% vs. 12%, $p < 0.001$) compared with those who underwent RT. Of the patients who underwent CLND, 44 (32%) had positive non-SLNs. The median number of positive non-sentinel nodes was two (interquartile range: three). Median follow-up (time from date of diagnosis to date of last follow-up or death) was 1.9 years.

Factors Independently Associated with Receiving Therapeutic Radiation Therapy (RT)

Multivariate logistic regression modeling was performed to evaluate factors independently associated with receiving therapeutic RT instead of CLND (electronic supplementary Table 1). For these models, we adjusted for study variables with $p \leq 0.2$ on univariate analysis (age, sex, immunosuppression, tumor thickness, and number of positive SLNs). After adjusting for these covariates, older age (OR 1.1, 95% CI 1.0–1.2, $p = 0.002$), female sex (OR 3.5, 95% CI 1.3–9.6, $p = 0.02$), and a lower number of positive SLNs (OR 6.4, 95% CI 1.6–25.7, $p = 0.009$) were independently associated with receiving RT instead of CLND.

Comparison of Completion Lymph Node Dissection (CLND) and RT

Figure 1 compares outcomes for patients who underwent CLND or RT. Patients who underwent CLND did not have significantly different MCCSS (5-year survival 71% vs. 64%, $p = 1.0$) (Fig. 1a), DFS (5-year survival 52% vs. 61%, $p = 0.8$) (Fig. 1b), NRFS (5-year survival 76% vs. 91%, $p = 0.3$) (Fig. 1c), or DRFS (5-year survival 65% vs. 75%, $p = 0.3$) (Fig. 1d) compared with those who underwent RT. Table 2 shows results from multivariate Cox proportional hazard regression models comparing CLND and RT. For these models, we adjusted for study variables with $p \leq 0.2$ on univariate analysis for at least two study outcomes (sex, immunosuppression, T stage, ulceration, SLN tumor burden, and total number of positive lymph nodes). After adjusting for these covariates, patients who underwent CLND did not have significantly different MCCSS (HR 0.4, 95% CI 0.1–1.3, $p = 0.1$), DFS (HR 0.7, 95% CI 0.3–1.6, $p = 0.4$), NRFS (HR 1.6, 95% CI 0.3–7.5, $p = 0.6$), or DRFS (HR 0.9, 95% CI 0.2–3.5, $p = 0.9$) compared with those who underwent RT. In addition, patients with immunosuppression had significantly reduced MCCSS (HR 3.3, 95% CI 1.3–8.7, $p = 0.01$), DFS (HR 2.2, 95% CI 1.1–4.4, $p = 0.02$), and DRFS (HR 3.1, 95% CI 1.3–7.2, $p = 0.01$). Finally, patients with two or more total positive lymph nodes had significantly reduced MCCSS (HR 3.6, 95% CI 1.4–9.3, $p = 0.007$) compared with those with only one positive lymph node, but no significant differences for DFS, NRFS, or DRFS.

Positive Non-SLNs and Prognosis After CLND

Figure 2 compares outcomes for patients who underwent CLND and had positive or negative non-SLNs. Patients with positive non-SLNs had significantly reduced MCCSS (5-year survival 39% vs. 87%, $p < 0.001$) (Fig. 2a) and DFS (5-year survival 35% vs. 60%, $p = 0.005$) (Fig. 2b) compared with those with negative non-SLNs. Patients with positive non-SLNs did not have significantly different NRFS compared with those with negative non-SLNs (5-year survival 74% vs. 77%, $p = 0.9$) (Fig. 2c), but did have significantly reduced DRFS (5-year survival 54% vs. 71%, $p = 0.03$) (Fig. 2d).

To better evaluate positive non-SLNs as a prognostic factor, we also specifically examined patients with two to four total positive lymph nodes and compared outcomes for patients with positive and negative non-SLNs (electronic supplementary Fig. 1). This subset analysis focused on patients with a similar total burden of nodal disease. In this

TABLE 1 Comparison of patient demographics and clinical characteristics (n = 163)

Variable	Completion lymph node dissection (n = 137)	Radiation therapy (n = 26)	p Value
Age at diagnosis, years [median (IQR)]	70 (16)	78 (11)	0.001
Sex			0.07
Female	46 (34)	14 (54)	
Male	91 (66)	12 (46)	
Immunosuppression[a]	16 (12)	1 (4)	0.3
Body site			0.5
Head and neck	47 (34)	11 (42)	
Extremities and trunk	90 (66)	15 (58)	
T stage			0.7
T1 or T2	128 (93)	24 (92)	
T3 or T4	9 (7)	2 (8)	
Tumor thickness			0.2
Smallest tertile: ≤ 5.1 mm	42 (31)	9 (35)	
Middle tertile: > 5.1 mm or ≤ 10.0 mm	43 (31)	12 (46)	
Largest tertile: ≥ 10.0 mm	43 (31)	3 (12)	
Not reported	9 (7)	2 (8)	
Mitotic rate[b], mitoses/mm^2 [median (IQR)]	36 (35)	37 (36)	0.9
Angiolymphatic invasion[c]			0.8
Yes	61 (45)	11 (42)	
No	70 (51)	13 (50)	
Not reported	6 (4)	2 (8)	
Ulceration[c]			0.5
Yes	21 (15)	6 (23)	
No	99 (72)	18 (69)	
Not reported	17 (12)	2 (8)	
Number of positive sentinel lymph nodes			0.007
One positive sentinel lymph node	84 (61)	23 (88)	
Two or more positive sentinel lymph nodes	53 (39)	3 (12)	
Sentinel node tumor burden			0.6
< 5%	65 (47)	15 (58)	
5–10%	13 (9)	1 (4)	
> 10%	34 (25)	4 (15)	
Not reported	25 (18)	6 (23)	
Extracapsular/extranodal extension[d]			0.3
Yes	11 (8)	3 (12)	
No	115 (84)	19 (73)	
Not reported	11 (8)	4 (15)	
Total number of positive lymph nodes[e]			< 0.001
One positive lymph node	56 (41)	23 (88)	
Two or more positive lymph nodes	81 (59)	3 (12)	
Positive non-sentinel lymph nodes	44 (32)	–	–
Number of positive non-sentinel lymph nodes [median (IQR)]	2 (3)	–	–

Data are expressed as n (%) unless otherwise specified

IQR Interquartile range

[a]Immunosuppression was defined as iatrogenic non-transplant, transplant, lymphoma/leukemia, or other

[b]Reported as the median mitotic rate (measured in mitoses per mm^2) and interquartile range for each group

[c]Considered present if the pathologist reported positive, focal, or suspicious; considered absent if the pathologist reported none or equivocal

[d]Extracapsular/extranodal extension in lymph nodes from the sentinel lymph node biopsy specimen

[e]Total number of lymph nodes with metastasis in the sentinel lymph node biopsy and completion lymph node dissection specimens

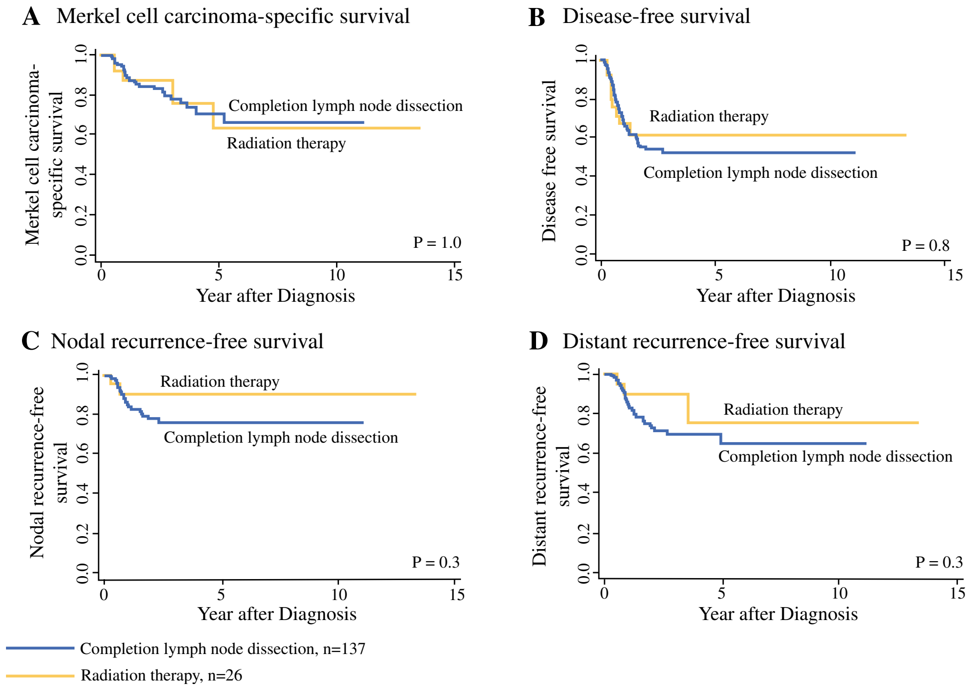

FIG. 1 Comparison of outcomes for completion lymph node dissection and radiation therapy. Patients who underwent completion lymph node dissection did not have significantly different (**a**) Merkel cell carcinoma-specific survival (5-year survival 71% vs. 64%, $p = 1.0$), (**b**) disease-free survival (5-year survival 52% vs. 61%, $p = 0.8$), (**c**) nodal recurrence-free survival (5-year survival 76% vs. 91%, $p = 0.3$), or (**d**) distant recurrence-free survival (5-year survival 65% vs. 75%, $p = 0.3$) compared with those who underwent radiation therapy

subset analysis, patients with positive non-SLNs still had significantly worse MCCSS (5-year survival 51% vs. 90%, $p = 0.04$) (electronic supplementary Fig. 1a) and DFS (5-year survival 33% vs. 64%, $p = 0.04$) (electronic supplementary Fig. 1b) compared with those with negative non-SLNs. Patients with positive non-SLNs did not have significantly different NRFS (electronic supplementary Fig. 1c) or DRFS (electronic supplementary Fig. 1d) compared with those with negative non-SLNs.

Table 3 shows results from multivariate Cox proportional hazard regression models for patients who underwent CLND. For these models, we adjusted for study variables with $p \leq 0.2$ on univariate analysis for at least two study outcomes (positive non-SLNs, sex, immunosuppression, ulceration, SLN tumor burden, total number of positive lymph nodes, and adjuvant radiation to the nodal basin after CLND). After adjusting for these covariates, patients with positive non-SLNs had significantly worse MCCSS (HR 5.9, 95% CI 2.2–16.3, $p = 0.001$), DFS (HR 3.1, 95% CI 1.5–6.5, $p = 0.003$), and DRFS (HR 4.2, 95% CI 1.4–12.1, $p = 0.008$) compared with those with negative non-SLNs, even after adjusting for total number of positive lymph nodes. Patients with positive non-SLNs had no significant differences for NRFS (HR 1.5, 95% CI 0.4–5.1, $p = 0.5$) compared with those with negative non-SLNs. Similarly, patients who received adjuvant radiation to the nodal basin after CLND did not have significantly different outcomes compared with CLND alone. On the other hand, patients with immunosuppression had significantly reduced MCCSS (HR 4.0, 95% CI 1.4–11.4, $p = 0.01$), DFS (HR 2.9, 95% CI 1.4–6.2, $p = 0.005$), and DRFS (HR 5.4, 95% CI 2.0–14.0, $p = 0.001$).

DISCUSSION

In this study, we retrospectively compared outcomes for patients with SLN metastasis from MCC undergoing CLND or therapeutic RT at our institution. This study has two key findings. First, although our study was limited by the small number of patients who underwent therapeutic RT instead of CLND, CLND and RT may have similar cancer-specific outcomes, especially when treatment decisions are based on our institutional preferences. Although a substantial proportion of patients who underwent CLND in this study also received adjuvant RT to the nodal basin, these patients did not have statistically significant differences in survival or recurrence compared with those who underwent CLND without adjuvant RT to the nodal basin. Second, metastasis to non-SLNs is an important prognostic factor for patients undergoing CLND. We demonstrated

TABLE 2 Multivariate models for completion lymph node dissection versus radiation therapy ($n = 163$)

Model variable	HR (95% CI)			
	Merkel cell carcinoma-specific survival	Disease-free survival	Nodal recurrence-free survival	Distant recurrence-free survival
Treatment for sentinel node metastases				
Radiation therapy	Reference	Reference	Reference	Reference
Completion lymph node dissection	0.4 (0.1–1.3)	0.7 (0.3–1.6)	1.6 (0.3–7.5)	0.9 (0.2–3.5)
Male sex	1.4 (0.6–3.1)	1.2 (0.7–2.1)	2.4 (0.9–6.4)	2.2 (0.9–5.0)
Immunosuppression[a]	3.3 (1.3–8.7)*	2.2 (1.1–4.4)*	2.4 (0.8–7.6)	3.1 (1.3–7.2)*
T stage				
T1 or T2	Reference	Reference	Reference	Reference
T3 or T4	1.7 (0.4–7.8)	2.2 (0.9–5.3)	2.8 (0.9–9.2)	1.8 (0.5–6.5)
Ulceration[b]				
No	Reference	Reference	Reference	Reference
Yes	1.7 (0.7–4.5)	1.6 (0.8–3.0)	0.5 (0.1–2.0)	2.1 (0.9–5.0)
Not reported	0.8 (0.2–2.9)	0.8 (0.4–2.0)	1.3 (0.4–4.0)	0.9 (0.3–2.9)
Sentinel lymph node tumor burden				
< 5%	Reference	Reference	Reference	Reference
5–10%	2.4 (0.7–7.9)	1.9 (0.8–4.6)	4.1 (1.2–13.5)*	2.4 (0.8–7.2)
> 10%	1.8 (0.7–4.7)	1.9 (0.9–3.7)	1.8 (0.5–6.4)	1.9 (0.8–4.9)
Not reported	1.6 (0.5–4.7)	1.5 (0.7–3.1)	5.4 (1.9–15.3)**	1.6 (0.6–4.5)
Total number of positive lymph nodes[c]				
One positive lymph node	Reference	Reference	Reference	Reference
Two or more positive lymph nodes	3.6 (1.4–9.3)**	1.5 (0.8–2.5)	1.0 (0.4–2.2)	1.9 (0.9–4.2)

HR Hazard ratio, *CI* confidence interval, * $p < 0.05$, ** $p < 0.01$

[a]Immunosuppression was defined as iatrogenic non-transplant, transplant, lymphoma/leukemia, or other

[b]Considered present if the pathologist reported positive, focal, or suspicious; considered absent if the pathologist reported none or equivocal

[c]Total number of lymph nodes with metastasis in the sentinel lymph node biopsy and completion lymph node dissection specimens

that non-SLN metastasis is independently associated with worse MCCSS, DFS, and distant recurrence. In contrast, other variables, including primary tumor characteristics, SLN features, and total number of positive lymph nodes, were not significantly associated with survival or recurrence.

These findings have several potentially practice-changing implications. First, because CLND and RT may have similar rates of MCCSS and recurrence in our institutional experience, we hypothesize these two approaches could be associated with similar outcomes for all patients with SLN metastasis from MCC. It would be ideal to test this hypothesis in a multicenter, randomized controlled trial, although this would be challenging because of the low incidence of MCC. Alternatively, outcomes for CLND versus RT could be compared using a cohort study with a larger number of patients from multiple institutions. If CLND and RT truly lead to equivalent outcomes, this would guide treatment decisions for SLN metastasis from MCC, similar to the AMAROS trial demonstrating equivalent outcomes for CLND versus RT for SLN metastasis from breast cancer.[12] Patients would need to be counseled carefully on the risks, benefits, and expected outcomes of CLND versus RT. CLND is generally associated with increased morbidity compared with SLN biopsy alone[8–11] or SLN biopsy with nodal RT,[11,12,16] but CLND may provide important prognostic information as positive non-SLNs are independently associated with MCCSS and recurrence.

We also found that patients who underwent CLND trended towards higher rates of nodal recurrence, but this difference was not statistically significant. This could be due to the higher burden of nodal disease in patients undergoing CLND. Patients undergoing CLND also had

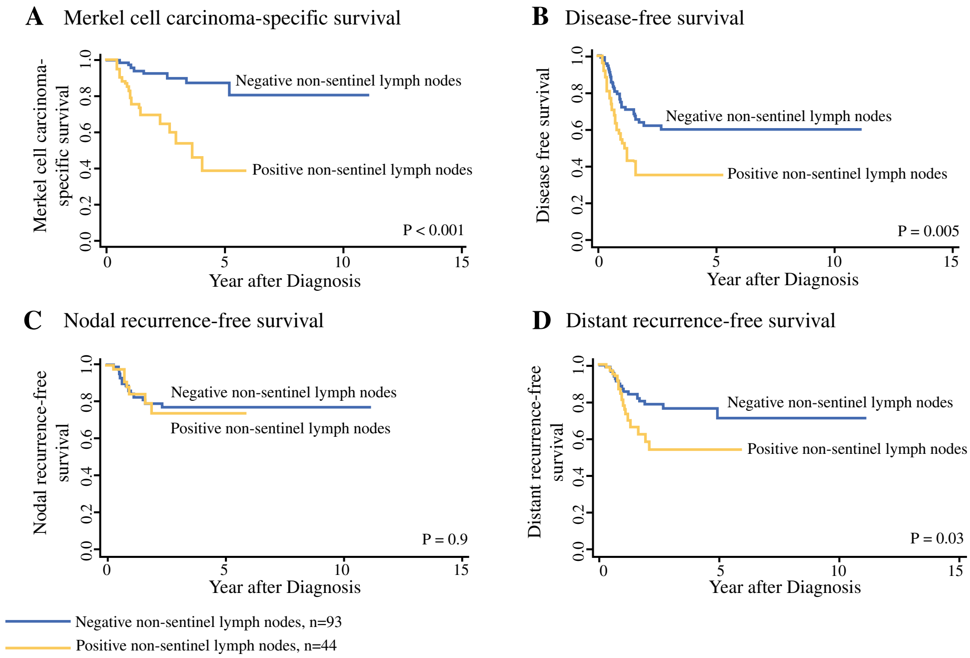

FIG. 2 Positive non-sentinel lymph nodes and prognosis after completion lymph node dissection. Patients with positive non-sentinel node lymph nodes had significantly reduced (**a**) Merkel cell carcinoma-specific survival (5-year survival 39% vs. 87%, $p < 0.001$) and (**b**) disease-free survival (5-year survival 35% vs. 60%, $p = 0.005$) compared with those with negative non-sentinel lymph nodes. Patients with positive non-sentinel lymph nodes did not have (**c**) significantly different nodal recurrence-free survival compared with those with negative non-sentinel lymph nodes (5-year survival 74% vs. 77%, $p = 0.9$), but did have (**d**) significantly reduced distant recurrence-free survival (5-year survival 54% vs. 71%, $p = 0.03$)

lower, but not significantly different, MCC-specific mortality, which could be due to these patients being significantly younger. This is in contrast to melanoma patients with SLN metastasis, for whom CLND is associated with improved DFS and reduced nodal recurrence when compared with active surveillance (without therapeutic RT).[8] Finally, patients with positive non-SLNs should be considered a high-risk group because positive non-SLNs are independently associated with MCCSS, DFS, and distant recurrence, even after adjusting for total number of positive lymph nodes. This high-risk group should be considered for adjuvant systemic therapy trials, particularly as the role for manipulation of the programmed cell death-1 (PD-1/PD-L1) pathway and other immunologic checkpoints becomes more prominent in the treatment of MCC.[17,18]

This study adds to previous work describing the management and outcomes for patients with SLN metastasis from MCC.[3,6,7] Similar to these studies, we describe rates of using CLND versus RT for SLN metastasis. CLND was used more frequently at our institution (84%) compared with other studies (55–79%).[3,6,7] However, unlike previous studies, we directly compared outcomes for patients who underwent CLND versus RT, which was not possible in previous studies due to the relatively small number of patients with SLN metastasis (fewer than 50 patients in each study). This study also identifies positive non-SLNs as a poor prognostic factor for survival and recurrence, which has not been reported in previous studies.[3,6,7] This finding is similar to the prognostic value of positive non-SLNs for melanoma patients,[8,19–21] and may help inform treatment decisions for patients. Similar to melanoma, SLNs may also act as a barrier against further metastasis for MCC.[20,22,23]

This study has several limitations. First, it is a single-institution, retrospective study, which limits the generalizability of our findings. Nonetheless, because MCC is a rare disease, current treatment guidelines[5] rely heavily on single-institution studies with higher treatment volumes.[1–4,7,24] Although large multi-institutional databases such as the National Cancer Database have been used to study MCC in previous work,[25] this database has several limitations for MCC patients: it does not explicitly capture whether SLN biopsy was performed; does not identify the site of RT (primary site vs. nodal basin); and provides no information on MCCSS. Another limitation was selection bias because our institutional practice is to recommend CLND as first-line treatment for patients with SLN metastasis, while therapeutic RT is recommended for patients who are considered high surgical risk or who decline surgery. Patients who underwent CLND also had higher disease burden in their SLNs. To mitigate this, we used multivariate Cox regression models to adjust for

TABLE 3 Multivariate models for patients undergoing completion lymph node dissection ($n = 137$)

Model variable	HR (95% CI)			
	Merkel cell carcinoma-specific survival	Disease-free survival	Nodal recurrence-free survival	Distant recurrence-free survival
Positive non-sentinel lymph nodes	5.9 (2.2–16.3)**	3.1 (1.5–6.5)**	1.5 (0.4–5.1)	4.2 (1.4–12.1)**
Male sex	2.3 (0.8–6.2)	1.7 (0.9–3.3)	3.2 (1.1–9.7)*	3.2 (1.2–8.5)*
Immunosuppression[a]	4.0 (1.4–11.4)*	2.9 (1.4–6.2)**	2.8 (0.9–9.2)	5.4 (2.0–14.0)**
Ulceration[b]				
No	Reference	Reference	Reference	Reference
Yes	3.3 (1.1–9.9)*	2.0 (0.9–4.1)	0.8 (0.2–3.0)	3.3 (1.3–8.5)*
Not reported	0.8 (0.2–3.1)	0.9 (0.4–2.3)	1.5 (0.4–5.2)	0.9 (0.3–2.9)
Sentinel lymph node tumor burden				
< 5%	Reference	Reference	Reference	Reference
5–10%	2.8 (0.8–10.2)	2.0 (0.8–4.9)	4.0 (1.2–13.5)*	2.5 (0.8–7.7)
> 10%	1.3 (0.4–4.6)	1.7 (0.8–3.8)	1.6 (0.4–6.2)	1.5 (0.5–4.7)
Not reported	1.6 (0.4–6.9)	1.8 (0.8–4.2)	5.4 (1.7–17.2)**	1.9 (0.5–6.3)
Total number of positive lymph nodes[c]				
One positive lymph node	Reference	Reference	Reference	Reference
Two or more positive lymph nodes	2.1 (0.6–7.6)	1.1 (0.5–2.3)	0.8 (0.3–2.6)	1.2 (0.4–3.4)
Adjuvant radiation to nodal basin	0.8 (0.3–2.5)	0.6 (0.3–1.3)	0.9 (0.2–2.9)	0.6 (0.2–1.8)

HR Hazard ratio, *CI* confidence interval, * $p < 0.05$, ** $p < 0.01$

[a]Immunosuppression was defined as iatrogenic non-transplant, transplant, lymphoma/leukemia, or other

[b]Considered present if the pathologist reported positive, focal, or suspicious; considered absent if the pathologist reported none or equivocal

[c]Total number of lymph nodes with metastasis in the sentinel lymph node biopsy and completion lymph node dissection specimens

differences in patient and pathologic risk factors, including the total number of positive lymph nodes. In addition, we would expect this selection bias to be associated with worse outcomes for the RT group as that group was comprised of patients who were older and perceived to be high-risk surgical candidates. In fact, patients in this study who underwent RT had similar outcomes compared with those who underwent CLND, and even trended towards having improved outcomes for recurrence, although these differences were not statistically significant.

Our study is also limited by a short median follow-up time (1.9 years) and a small sample size of patients who underwent therapeutic RT ($n = 26$). This reduced the power of our analysis to 67% to detect a 20% difference in survival. Nevertheless, previous studies of patients with SLN metastasis who underwent RT have been limited to 17 patients or fewer.[3,7] Despite this limitation, our findings suggest a trend toward reduction in recurrence with therapeutic RT compared with CLND, but these differences were not statistically significant. Our findings may have also been impacted by patients in the CLND group having a greater number of SLN metastasis and more extensive SLN tumor burden, although we adjusted for this in our multivariate analysis. To accurately define best practice, a multicenter, randomized controlled trial is needed to compare CLND and RT for MCC patients with SLN metastasis.

CONCLUSION

We found that CLND and RT may have similar outcomes for patients with SLN metastasis from MCC at our institution, and that positive non-SLNs is an important prognostic factor for patients who undergo CLND. These findings should be considered when deciding between CLND or RT for patients with SLN metastasis. Furthermore, patients who undergo CLND and have positive non-SLNs are at high risk of distant recurrence and mortality due to MCC, and should be considered for adjuvant systemic therapy trials.

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