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Recurrence and Survival in Patients Undergoing Sentinel Lymph Node Biopsy for Merkel Cell Carcinoma: Analysis of 153 Patients from a Single Institution

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Abstract

INTRODUCTION—Merkel cell carcinoma (MCC) is a cutaneous neuroendocrine neoplasm with propensity for lymphatic spread. The rarity of MCC has limited analysis of factors associated with a positive sentinel lymph node biopsy (SLNB) and survival.

METHODS—Review of a prospective MCC database was performed. Factors associated with +SLNB were analyzed. Univariate and multivariate analyses of factors associated with recurrence and survival were performed using the cumulative incidence (CI) function, treating death from other causes (DOC) as a competing risk.

RESULTS—From 1996–2010, 153 patients with localized MCC underwent SLNB, of whom 45 (29%) were positive. Factors associated with +SLNB were primary tumor size (25% ≤2 cm v. 45% >2 cm; $p=0.02$) and presence of lymphovascular invasion (LVI; 55% +LVI v. 4% –LVI; $p<0.01$). +SLNB patients were more likely to receive radiation or chemotherapy (60% vs. 7%, $p<0.01$). With median follow-up of 41 months, there were 16 nodal/distant recurrences (10%), 11 deaths from MCC (7%), and 27 DOC's (18%). The 2-year CI's of recurrence or death from MCC were 12% and 6%, respectively. There was no difference in recurrence or death from MCC between +SLNB and –SLNB patients. The 2-year CI's of recurrence or death from MCC for +LVI patients were 30% and 15%, respectively. No –LVI patient recurred or died of MCC.

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CONCLUSION—SLNB identifies occult nodal metastases in 29% of patients with localized MCC. Predictors of +SLNB are tumor size and presence of LVI. Patients with +SLNB are more likely to receive further treatment; however, SLN status is not associated with recurrence or survival. In contrast, LVI is strongly associated with both recurrence and survival.

INTRODUCTION

Originally described as *trabecular carcinoma*, [1] Merkel cell carcinoma (MCC) is a rare cutaneous neuroendocrine neoplasm with an incidence of <0.50/100,000 person-years. [2–6] The natural history of MCC remains poorly characterized and is based on small case series limited by incomplete staging, heterogeneous treatment, short follow-up, and missing recurrence information. [4, 7–12] Large database series, such as those utilizing the Surveillance, Epidemiology and End Results (SEER) Program [13], the National Cancer Data Base (NCDB), [14] and governmental cancer registries [15] have attempted to overcome these limitations, but are constrained by the limited information captured. For example, neither the SEER program nor the NCDB record disease-specific survival (DSS), recurrence patterns, or completely characterize adjuvant therapy.

MCC has a propensity for lymphatic spread: 24–31% of patients present with clinically evident nodal disease, [13, 14, 16] and a similar proportion of the clinically node-negative patients harbor micrometastatic disease. Sentinel lymph node biopsy (SLNB) is a strong predictor of outcome and an established technique to stage the draining nodal basin in breast cancer [17] and melanoma. [18] The use of SLNB in MCC has been described in an effort to identify patients who might benefit from additional treatment. [10, 19–28] However, the small numbers of cases in individual series and lack of detailed staging, recurrence, and follow-up information in the larger database studies have limited a rigorous evaluation of the SLNB procedure in MCC.

Here, we present our experience in patients with localized MCC who underwent SLNB. We describe pre-treatment and pathologic variables associated with a +SLNB. Further, we detail subsequent treatment after SLNB (CLND, RT, and/or chemotherapy) and compare the recurrence and survival between +SLNB and –SLNB patients.

PATIENTS AND METHODS

Patients Selection and Pre-Treatment Evaluation

Patients with histologically confirmed MCC and no evidence of either clinically involved lymph nodes (LN) or metastatic disease (stage I or II, American Joint Commission on Cancer [AJCC] 7th edition [14, 29]) who underwent SLNB were identified from a prospective database at Memorial Sloan-Kettering Cancer Center (MSKCC). The MSKCC Institutional Review Board approved the study design.

SLNB Procedure and Examination of SLN

Patients underwent excision of their primary tumor and SLNB as previously described. [23, 24] Briefly, a combination of technetium 99m (⁹⁹Tc)-radiolabeled sulfur colloid injected

preoperatively and lymphazurin blue injected intraoperatively at the site of the tumor were used for SLN identification.

SLNB specimens were analyzed as previously described.[23] Briefly, specimens were processed for hematoxylin and eosin (H&E). One initial level per LN was stained for H&E and examined. If metastatic MCC was identified, no further studies were performed. If no tumor was found, three additional sections were taken from the tissue block. The first and last were stained for H&E. The section in between was analyzed via immunohistochemistry (IHC) as previously described.[23] If the primary tumor was known to be positive for CK20, Cam5.2, or chromogranin, the stronger of those markers was used. If the immunophenotype of the primary tumor was unknown, additional sections were taken and IHC was performed using all of the aforementioned markers.

Subsequent Treatment, Follow-Up, and Recurrence

After SLNB, treatment decisions were made at the discretion of treating physician(s). RT is defined as 50 Gy to the draining nodal basin of the primary tumor for five days/week over a 5–6 week course performed within eight weeks of surgery. Chemotherapy consisted of cisplatin or carboplatin with etoposide for 4–6 cycles over 8–12 weeks and was initiated within eight weeks of surgery, or after RT (when given). In follow-up, patients were seen every 2–3 months for one year and every 6–12 months thereafter. Follow-up consisted of a complete skin/LN evaluation, with laboratory and imaging studies obtained as clinically indicated. Recurrence was defined as any patient, physician, or radiographically discovered evidence of nodal or distant tumor. Local or *in transit* recurrences were not included as a variable in this analysis, as SLNB status would not be predicted to impact local or *in transit* recurrences. Date of first recurrence was defined as the first notation in the medical record indicating the nodal or distant recurrence. Vital status and cause of death were obtained for every patient from the medical record, direct patient/family contact, and correspondence with referring physicians.

Statistical Analysis

Statistical analysis was performed using SAS (version 9.1, Cary, North Carolina, U.S.A.) and R software (version 2.1, www.r-project.org). Fisher's exact test was used to examine covariate differences based on SLN status. The cumulative incidence (CI) function was used to estimate the probabilities of time from treatment to nodal/distant recurrence or death due to MCC. Patients with MCC who died of other causes or died without nodal/distant recurrences were treated as competing events for analysis of survival and recurrence, respectively.[30, 31] Gray's test was used to determine differences in CI outcomes between groups.[32]

RESULTS

Patient Characteristics

One hundred fifty-three patients presented with clinically localized MCC and underwent SLNB from 1996–2010. Seven of these patients had their SLNB procedure done prior to presenting at MSKCC and had complete pre-treatment and SLNB procedure information

available for review. They are included in the analysis of factors associated with a +SLNB, but excluded from the recurrence and survival analysis to prevent bias due to their presentation status after SLNB with a recurrence.

Differences in Patient, Tumor, and Treatment Characteristics Between +SLNB and –SLNB Patients

There were 45 patients (29%) with a +SLNB. Table 1 summarizes differences in pretreatment characteristics based on SLN status. Patients with +SLNB had larger primary tumors (14mm v. 12mm; $p=0.03$); thus, size (defined by clinical stage 1 vs. 2) was a predictor of +SLNB (25% ≤ 2 cm v. 48% >2 cm; $p<0.01$). Notably, of the 66 patients with primary tumors ≤ 1 cm in maximal diameter who underwent SLNB, there were 17 (26%) with +SLNB (Figure 1a).

Table 2 summarizes differences in surgical, pathologic, and post-SLNB treatment based on SLN status. Patients with +LVI were more likely to have +SLNB (55% +LVI v. 4% –LVI, $p<0.01$; Figure 1b). Of the 45 +SLNB patients, the median number of +SLN was 1 (range of 1 – 4). Thirty-six (80%) of +SLN were detected on H&E with the remaining nine (20%) identified via IHC. Of the 45 patients with a +SLNB, 21 (47%) underwent CLND. Six (29%) of these patients had additional positive non-SLN (mean = 4.3, range 1 – 8).

Figure 2 details the treatment profile of all patients following SLNB. Patients with +SLNB were more likely to undergo CLND (47% v. $<2\%$, $p<0.01$) and were more likely to receive post-SLNB nodal RT (either as *adjuvant* RT after CLND or as *therapeutic* RT after a +SLNB) and/or chemotherapy (60% v. 6%, $p<0.01$). Of the 108 patients with a –SLNB, 99 (92%) underwent no further treatment, 2 (2%) underwent CLND, and 7 (6%) underwent nodal RT.

Nodal or Distant Recurrence and Death from MCC

Median follow-up was 41 months. Figure 2 describes the patterns of recurrence for each treatment group. There were two local recurrences (one with a +SLNB and one with a –SLNB) and six *in transit* recurrences (four +SLNB, two –SLNB) that are not included in further analysis (see methods). Overall, there were ten nodal (7%) and nine distant (6%) recurrences. In the 45 +SLNB patients, there was one nodal (2%) and three distant (7%) recurrences. In the 108 –SLNB patients, there were nine (8%) nodal and six (6%) distant recurrences. Of the 99 –SLNB patients who underwent no further treatment, 8 (8%) developed a nodal recurrence (false negative population), yielding a false negative rate of 15% ($[\text{false negative}]/[\text{false negative} + \text{true positive}] = 8/[8+45]$). Of the 23 patients with a +SLNB who received nodal RT as part of their therapy (adjuvant or therapeutic), none had a nodal recurrence. Of the 13 patients with a +SLNB who received systemic chemotherapy as part of their adjuvant therapy, one had a distant recurrence. Of the 32 patients with a +SLNB who received no adjuvant systemic therapy, two developed systemic recurrence.

Figure 3 shows the CI's of recurrence (top) and death from MCC (bottom). Sixteen patients developed recurrence and 25 patients died without a recurrence (Figure 3, top). Eleven patients died of MCC and 27 died of other causes (Figure 3, bottom). Greater than 90% of

all recurrences and deaths from MCC occurred within two and five years of follow-up, respectively.

Figure 4 summarizes the CI's of recurrence and death from MCC, subdivided by SLNB status, clinical stage, and LVI. The 2-year CI of recurrence was 12%, respectively. There was no difference in the CI of recurrence based on SLNB status (Figure 4, top left; $p=0.86$) and there was an insignificant trend towards increased recurrence based on primary tumor size (Figure 4, middle left; $p=0.26$). However, there was a significant difference in the CI of recurrence based on LVI status of the primary tumor (Figure 3, bottom left). Notably, no -LVI patient developed recurrence during follow-up, while the 2-year CI of nodal/distant recurrence in the +LVI patients was 30% ($p<0.01$).

The 2-year CI of death from MCC was 6%. There was no difference in the CI of death from MCC based on SLN status (Figure 4, top right; $p=0.89$). There was a borderline significant probability of death from MCC based on primary tumor size (Figure 4, middle right; $p=0.05$). There was a significant difference between the 2-year CI of death from MCC based on LVI of the primary tumor (Figure 4, bottom right). Notably, no -LVI patient died from MCC during follow-up, while the 2-year CI of death from MCC in +LVI patients was 15% ($p<0.01$).

Among 83 patients with follow up of 3 years, there were seven recurrences (8.4%; five nodal, two distant). No recurrence occurred after three years. There were three deaths from MCC (3.6%) and 21 deaths from other causes (25%). All deaths from MCC occurred after three years.

DISCUSSION

To our knowledge, this is the largest description of the SLNB procedure in MCC. We found a 29% rate of +SLNB in patients presenting with localized MCC. This is consistent with other reports in the literature which cite +SLNB rates of 19–38%. [8–10, 16, 21, 23, 24, 26–28] Primary tumor size and LVI in the primary tumor were associated with a +SLNB. This is consistent with a previous report from our institution [16] and a recent series from the University of Michigan [28] where larger primary tumors were more likely to have nodal micrometastases. However, we could not define a size of primary tumor for which the probability of a positive SLN was insignificant: 26% of patients with primary tumors ≤ 1 cm had +SLNB. This is in contrast to Stokes' review of the Department of Veterans Affairs database in which only 4% of patients with tumors ≤ 1 cm had +SLNB. [9] Our results are more consistent with other single institution series where the rate of SLN positivity in tumors ≤ 1 cm ranges from 15–42%. [8, 21, 28, 33, 34]

Not unexpectedly, we found that patients with +SLNB were more likely to receive further treatment, in the form of CLND (47%), nodal RT (31%), systemic chemotherapy (9%), or chemotherapy and nodal RT (20%). Importantly, with >3 years of median follow-up, recurrence and death from MCC were low (12% and 6%, respectively, at 2-years), highlighting the ability to achieve disease control in clinically node-negative MCC. Among the 21 patients with a +SLNB who received a CLND $\pm$ adjuvant nodal RT and the 17

patients with a +SLNB who received therapeutic nodal RT (without CLND), there was only one nodal recurrence, occurring in a patient who was treated with a CLND alone. These observations suggest that therapeutic RT may be at least as effective as CLND for nodal basin control after a +SLNB. Treatment decisions should take into account side-effects and patient factors/preferences. Further, 71% of patients with a +SLNB received *no* adjuvant systemic chemotherapy and only 6% developed a distant recurrence. With such a low distant recurrence rate without further treatment, it is unlikely that the addition of unproven adjuvant systemic chemotherapy after a +SLNB will be shown to benefit this patient population.

In patients with a –SLNB, 92% received no further treatment, of whom 13% developed nodal or distant recurrence. Importantly, we found an 8% incidence of nodal recurrence after a –SLNB with no further treatment, corresponding to a 15% false negative rate. To our knowledge, this is the first report of the clinical nodal failure rate and false negative rate of the SLNB procedure in MCC. This rate is remarkably similar to the 18% and 10% false negative rates for the SLNB procedure in melanoma [18] and breast cancer,[35] respectively.

We found additional positive non-SLN in 29% of patients (6/21) who underwent CLND after a +SLNB, which is lower than the 50% rate of positive non-SLN reported in other series.[8, 20] However, each of these series had only eight cases of +SLNB patients who underwent CLND. Only one of the six patients with positive non-SLN in our series developed a recurrence (distant).

SLN status was not associated with recurrence or death from MCC. These results are in contrast to other reports of differences in recurrence and survival based on SLN status. Gupta reported on the Dana-Farber experience and performed a meta-analysis of reported series of patients undergoing SLNB for MCC, identifying a total of 122 cases.[21] He found a 60% 3-year recurrence rate for +SLNB patients compared to 20% for –SLNB patients ($p=0.03$). Similarly, Mehrany performed a meta-analysis of patients undergoing SLNB for MCC, identifying a total of 60 cases.[26] He found a 33% 1-year recurrence rate for +SLNB patients, compared to 3% for –SLNB patients ($p=0.005$). However, as discussed above and delineated by others,[34] relying on large databases and meta-analyses to characterize MCC is misleading. For example, several of the studies included in the above meta-analyses included local recurrence (LR) as an outcome measure. However, we would argue that LR is not a relevant outcome when discussing the prognostic role of SLNB. Furthermore, SLN status was not associated with recurrence in our series, even when local and *in transit* recurrences were included (analysis not shown). In their analysis of 5,823 patients with MCC from the NCDB, Lemos, et. al found that patients with pathologically proven negative LN (i.e. –SLNB) had improved 5-year overall survival compared those who did not undergo the SLNB procedure (76% v. 59%, $p < 0.0001$). This report formed the basis for the most current AJCC staging system, which separates stage I and II into (a) and (b) sub-groups, where (a) denotes a negative pathologic node evaluation, generally by SLNB.[29] However, as the NCDB database does not record recurrence or cause of death, it is impossible to assess the direct impact of SLN status on Merkel-specific outcome in this elderly population, where death from other causes is so common.

The lack of association between SLN status and outcome is puzzling. Unlike breast cancer and melanoma, pathologic nodal status in patients with clinically negative nodes is not predictive of outcome in MCC, yet patients with clinically apparent nodal metastases have substantial disease-specific mortality. One hypothesis is that treatment for microscopically positive nodal disease in MCC is so effective that it interrupts the progression to systemic spread. This observation is in contrast to both melanoma and breast cancer, where +SLN patients also receive more treatment, yet SLN status remains a strong independent predictor of outcome. Alternatively, in patients with clinically negative nodes, prognosis may be driven by more powerful histologic features of the primary tumor, such as LVI. Although our current report is the largest to describe the SLNB procedure in MCC, selection bias in subsequent treatment decisions makes a causal relationship between SLNB status and outcome impossible. Currently, we offer SLNB to all patients with invasive MCC.

In contrast to SLN status, we found that LVI in the primary tumor was highly associated with recurrence and death from MCC. In fact, there were no recurrences or deaths from MCC in patients without LVI. The presence of LVI was also highly predictive of a +SLNB, which consistent with our previous report of the association between histologic features of the primary tumor (depth of invasion, LVI, and tumor growth pattern) [36] and +SLNB and outcomes, but in contrast to the findings of Schwartz from the University of Michigan[28] where depth and growth pattern, but not LVI, were associated with a +SLNB. In the present report, only 4% of patients with –LVI had a +SLNB, compared to 55% in those patients with +LVI. However, the 95% confidence intervals for the 4% rate of +SLNB in patients without LVI is 2–14%. Thus, although the predicted rate of +SLNB in –LVI patients is near the threshold for which SLNB is generally *not* recommended for patients with melanoma, clearly observations of many more patients are required before any recommendation can be made on the use of SLNB based solely on LVI status or other histologic parameters of the primary tumor.

In summary, SLNB is positive in 29% of patients with clinically node-negative MCC. Patients with larger primary tumors are more likely to have a +SLNB; however, there is a significant rate of +SLNB in small (< 1 cm) tumors. Less than 5% of patients with –LVI of their primary tumor had a +SLNB. The false negative rate of the SLNB procedure in MCC is 15%. Patients with +SLNB are more likely to receive further treatment, but SLN status is *not* associated with increased recurrence or death from MCC. In contrast, LVI in the primary tumor is strongly associated with recurrence and death from MCC. Thus, LVI may be more informative than SLNB status in predicting outcomes in MCC. The low rates of recurrence and death from MCC in patients with a +SLNB argues against the use of adjuvant systemic chemotherapy. Inclusion of LVI into subsequent staging and treatment algorithms may allow for both improved definition of what subset of patients with MCC should undergo SLNB and, of the patients that undergo SLNB, what subset should undergo further treatment for clinically localized MCC.

In conclusion, this analysis highlights the importance of accurate, complete, and detailed natural history observations in rare diseases (where prospective randomized trials are neither available nor practical) to guide staging, treatment, and follow-up recommendations.

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Figure 1.

SLN status stratified by primary tumor size and LVI. (A) There is no difference in the rate of +SLNB between tumors ≤1 cm vs. 1–2 cm in size. There is a significant difference in the rate of +SLNB between tumors ≤2 vs. >2 cm in size ($p = 0.02$). (B) There is a significant difference in the rate of +SLNB based on LVI status of the primary tumors ($p < 0.01$ for +LVI v. -LVI). **ABBREVIATIONS:** LVI = lymphovascular invasion, SLNB = sentinel lymph node biopsy, Unk = unknown.

Figure 2.

Treatment and recurrence in 153 patients undergoing SLNB for clinically node-negative MCC. **ABBREVIATIONS:** chemo = systemic chemotherapy, CLND = completion lymph node dissection, MCC = Merkel cell carcinoma, RT = nodal radiation therapy, SLNB = sentinel lymph node biopsy.

Figure 3. Cumulative incidence of nodal/distant recurrence (TOP PANEL) and death (BOTTOM PANEL) from MCC in patients undergoing SLNB.

Figure 4.

Cumulative incidence of nodal/distant recurrence and death in patients undergoing SLNB for MCC. TOP PANELS: There is no difference in recurrence (left) or death from MCC (right) based on SLN status. MIDDLE PANELS: There is a slight trend towards decreased recurrence (left) and a nearly significant improvement in death from MCC (right) between clinical stage I and II patients. BOTTOM PANELS: There is a significant association between +LVI and nodal/distant recurrence (left) and death from MCC (right). All recurrences and deaths from MCC occurred in patients with +LVI, with 2-year CI's of

nodal/distant recurrence and death from MCC in +LVI patients of 30% and 15%, respectively. ABBREVIATIONS: CI = cumulative incidence, LVI = lymphovascular invasion, MCC = Merkel cell carcinoma, SLNB = sentinel lymph node biopsy; *Primary tumor size in accordance with AJCC 7th Edition staging system, 2 cm = stage 1, >2 cm = stage 2; †Gray's test).

Table 1

Pre-treatment characteristics of 153 patients undergoing sentinel lymph node biopsy for Merkel cell carcinoma at Memorial Sloan-Kettering Cancer Center from 1996–2010.

Variable	Number (%)			<i>p</i> Value*
	All Patients n=153	–SLNB Patients n=108	+SLNB Patients n=45	
Median age at diagnosis (years, IQR)	69 (61–75)	69 (60–75)	70 (63–74)	0.70
Sex (female)	62 (41%)	45 (42%)	17 (38%)	0.71
Year of diagnosis				
1996–2004	78	59 (76%)	19 (24%)	0.21
2005–2010	75	49 (65%)	26 (35%)	
Location of primary				
Extremity	88	58 (66%)	30 (34%)	0.22
Head/Neck	33	26 (79%)	7 (21%)	
Buttock/Trunk	32	24 (75%)	8 (25%)	
Prior or synchronous other malignancy				
Any	76	55 (72%)	21 (28%)	0.82
Leukemia/lymphoma	13	10 (77%)	3 (23%)	
Skin	53	38 (72%)	15 (28%)	
Solid tumor	21	15 (71%)	6 (29%)	
Median primary tumor size, (mm, IQR)	12 (8–20)	12 (7–18)	14 (10–27)	0.03
Clinical Stage [#]				
Stage I (primary tumor ≤ 2cm)	122	92 (75%)	30 (25%)	0.02
Stage II (primary tumor > 2cm)	31	16 (52%)	15 (48%)	

* Fisher's exact test

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ABBREVIATIONS: IQR = interquartile range, SLNB = sentinel lymph node biopsy

Table 2

Treatment characteristics of 153 patients undergoing sentinel lymph node biopsy for Merkel cell carcinoma at Memorial Sloan-Kettering Cancer Center from 1996–2010.

Variable	Number (%)			<i>p</i> Value [*]
	All Patients n=153	–SLNB Patients n=108	+SLNB Patients n=45	
Margin status of primary tumor excision				
Negative	143	102 (71%)	41 (29%)	0.48
Positive	10	6 (60%)	4 (40%)	
Median margin width in patients with a margin negative excision (mm, IQR)	10 (10–20)	10 (10–20)	13 (10–20)	0.61
Number of SLN removed (median, IQR)	2 (1–3)	2 (1–3)	2 (1–3)	0.30
Number of positive SLN (median, range)	–	0	1 (1–4)	N/A
Determination of positive SLN				
H&E (+)	–	N/A	36 (80%)	N/A
H&E (–), IHC (+)			9 (20%)	
Primary tumor with lymphatic emboli or vascular invasion (LVI)				
Yes	75	34 (45%)	41 (55%)	
No	69	66 (96%)	3 (4%)	<0.01
Unknown	9	8 (89%)	1 (11%)	
CLND after SLNB				
Yes	23	2 (<2%)	21 (47%)	<0.01
No	130	106 (98%)	24 (53%)	
Adjuvant treatment				
None	119 (78%)	101 (94%)	18 (40%)	
Nodal RT	21 (14%)	7 (6%)	14 (31%)	
Chemotherapy	4 (2%)	0	4 (9%)	<0.01
Chemotherapy + Nodal RT	9 (6%)	0	9 (20%)	

* Fisher's exact test

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ABBREVIATIONS: AWD = alive with disease, DOC = died of other causes, DOD = died of disease, H&E = hematoxylin and eosin, IHC = immunohistochemistry, IQR = interquartile range, LVI = lymphovascular invasion, N/A = not applicable, NED = no evidence of disease, RT = radiation therapy, SLNB = sentinel lymph node biopsy.