Sentinel lymph node biopsy in Merkel cell carcinoma: Predictors of sentinel lymph node positivity and association with overall survival

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Background: Merkel cell carcinoma (MCC) is a rare, aggressive malignancy with high rates of recurrence and metastasis.

Objective: To evaluate predictors of sentinel lymph node (SLN) positivity in MCC using the National Cancer Database.

Methods: The National Cancer Database, from 2012 to 2014, was used to identify 3048 patients with MCC, of whom 1174 received an SLN biopsy. Predictors of SLN positivity were evaluated using logistic regression. Overall survival was evaluated using a Cox proportional hazards model.

Results: Of patients who underwent SLN biopsy, those with primary lesions on the trunk (odds ratio, 1.98; 95% confidence interval [CI], 1.23-3.17; *P* = .004), tumor-infiltrating lymphocytes (odds ratio, 1.58; 95% CI, 1.01-2.46; *P* = .04), or lymphovascular invasion (odds ratio, 3.45; 95% CI, 2.51-4.76; *P* < .001) were more likely to have positive SLNs on multivariate analysis. Overall survival was negatively affected by age ≥75 years (hazard ratio [HR], 2.55; 95% CI, 1.36-4.77; *P* = .003), male sex (HR, 1.78; 95% CI, 1.09-2.91, *P* = .022), immunosuppression (HR, 3.51; 95% CI, 1.72-7.13; *P* = .001), and SLN positivity (HR, 3.15; 95% CI, 1.98-5.04; *P* < .001).

Limitations: Lack of disease-specific survival and potential selection bias from a retrospective data set.

Conclusions: Truncal MCC, tumor-infiltrating lymphocytes, and presence of lymphovascular invasion were independent predictors of positive SLNs. Overall survival was negatively affected by advancing age, male sex, immunosuppression, and SLN positivity. (J Am Acad Dermatol 2019;81:364-72.)

Key words: lymphovascular invasion; Merkel cell carcinoma; National Cancer Database; overall survival; sentinel lymph node biopsy; tumor-infiltrating lymphocytes.

Merkel cell carcinoma (MCC) is a rare, aggressive, primary cutaneous neuroendocrine tumor with an uncertain cell of origin.[1] Carcinogenesis ensues via integration of the Merkel cell polyomavirus or ultraviolet-induced DNA damage.[1] Histologically, MCC cells are small to medium in size and round to polygonal in shape, with scant cytoplasm, neuroendocrine nuclei with finely stippled chromatin, absent nucleoli, multiple small chromocenters, frequent nuclear molding, and numerous mitoses and single-cell tumor necrosis. Tumors are typically dermal based and

arranged in nodular, diffuse, or trabecular patterns.[2,3] First described in 1972 by Toker,[3] approximately 2500 cases are diagnosed annually within the United States, with an increasing incidence.[4,5] This increased incidence may be attributed to the rising age in the United States and is expected to rise to 3284 cases by 2025.[5] Risk factors for development include Merkel cell polyomavirus, ultraviolet exposure, increasing age, and immunosuppression.[1]

At presentation, 70% of patients have localized disease, 25% present with regional lymphadenopathy, and 5% have distant metastasis.[1,6-9] However, even those with small primary tumors can have a 24% to 42% risk of nodal disease.[1] Current National Comprehensive Cancer Network guidelines recommend wide local excision of the tumor with possible adjuvant radiation therapy, sentinel lymph node (SLN) biopsy (SLNB), and that primary cutaneous origin (vs secondary cutaneous involvement by small-cell carcinoma of the lung) be confirmed with an immunohistochemical staining panel that includes cytokeratin-20 and thyroid transcription factor-1. The immunohistochemical stains are also used to identify the micrometastatic disease in the draining nodal basin.[10] Among patients whose clinical examination suggested only local disease, those who had pathologically proven negative nodes had better outcomes than those who only underwent clinical nodal evaluation.[9] This suggests pathologic staging is more accurate than clinical staging.[9]

Owing to the rarity of MCC, few small, single-center studies have examined SLN positivity in MCC, with even fewer focusing on predictors of SLN positivity.[2,11-14] Because of this, determining which tumor characteristics are associated with a positive SLN and decreased survival is challenging.[1] To this end, we used the National Cancer Database (NCDB) to evaluate factors affecting SLNB use, predictors of SNL positivity, and association with overall survival (OS) in MCC.

MATERIALS AND METHODS

The NCDB is a joint, facility-based, clinical oncology database established by the Commission on Cancer and the American Cancer Society. Patients within the NCDB are aged ≥18 years and have received all or part of their first course of therapy at a reporting cancer program.[15] Approximately 70% of all cancer cases diagnosed in the United States are contained in this database. The NCDB provided the deidentified data after prior approval from the Cleveland Clinic Institutional Review Board.

Patients diagnosed with MCC from 2012 to 2014 were identified using International Classification of Diseases codes. The year 2012 was selected as the starting year because the NCDB no longer provides information on SLNB use before 2012.[16]

Study definitions

Age at diagnosis was categorized into <65, 65 to 75, and >75 years. The Charlson-Deyo comorbidity score was designated as 0 if patients had no comorbidities, 1 if there was 1 comorbidity and 2+ if there were ≥2 comorbidities, with comorbidities defined as previously published.[17] Tumor site was designated as head and neck, upper extremities, trunk, lower extremities, and not specified. The clinical diameter was categorized according to the American Joint Commission on Cancer staging system as ≤2 cm, 2.01 to 5.00 cm, ≥5 cm, or unknown.[18] Tumor growth was classified as diffusely infiltrative, circumscribed/nodular, or unknown. Transection was classified as not transected, transected, or unknown. Tumor-infiltrating lymphocytes (TIL), lymphovascular invasion (LVI), and immunosuppression were classified as present, absent, or unknown. Patients were considered as immunosuppressed if they had diseases such as AIDS, lymphoma, or leukemia or if they were taking immunosuppressive or anticancer drugs.

Statistical methods

Categorical variables are presented as number and percentage, and continuous variables are presented as the mean ± standard deviation. Inferential statistics were performed using the χ^2 test and the t test, without including unknown data. Analyses for factors affecting SLNB use and the probability of SLN positivity were performed using logistic regression. The Cox proportional hazards model was used to evaluate OS. The data were analyzed using R 3.4.1 statistical software (The R Foundation for Statistical Computing, Vienna, Austria).

CAPSULE SUMMARY

- Positive sentinel lymph node biopsy in patients with Merkel cell carcinoma was associated with primary lesions on the trunk, tumor infiltrating lymphocytes, and lymphovascular invasion.

- Following National Comprehensive Cancer Network guidelines and performing sentinel lymph node biopsy on patients with Merkel cell carcinoma without clinically evident nodal metastases could improve prognostic accuracy.

RESULTS

We identified 3048 patients, of whom 1174 (38.5%) received SLNB and 1874 (61.5%) did not (Table I). Patients aged <65 years were more likely to receive SLNB (44.5% [n = 278 of 625]) compared with those >75 years (32.1%, [n = 487 of 1517]), whereas there were no differences in sex (P = .4) and comorbidities (P = .37) between the 2 groups. Patients with extremity MCC were more likely to receive SLNB (53.8% [n = 652] vs 46.2% [n = 560], P < .001), whereas those with head and neck MCC were less likely to receive SLNB (31.8% [n = 406] vs 68.2% [n = 870], P < .001).

Clinical diameter, TIL, LVI, and transection did not differ between the 2 groups. Patients who underwent SLNB had better survival (1.64 ± 0.64 vs 1.37 ± 0.72 years, P < .001). In addition, 2-year survival was 81% (95% confidence interval [CI], 78%-85%) for patients who received SLNB and was 54% (95% CI, 51%-58%) for those who did not.

Factors affecting use of SLNB

Multivariate analysis adjusting for age, sex, comorbidities, presence of immunosuppression, primary site, diameter, transection, TIL, and LVI showed SLNB was more likely to have been performed in patients with MCC on the lower extremity (odds ratio [OR], 1.9; 95% CI, 1.52-2.4; P < .001) and those with MCC on the upper extremity (OR, 2.61; 95% CI, 2.16-3.16; P < .001) (Table II). An SLNB was less likely to be performed in patients who were immunosuppressed (OR, 0.71; 95% CI, 0.5-0.99; P = .04) and in those aged >75 years (OR, 0.53; 95% CI, 0.43-0.65; P < .001). Sex, comorbidities, diameter, transection, TIL, and LVI did not affect the chance of having had an SLNB on multivariate analysis.

Predictors of SLN positivity

We identified 1174 patients who had an SLNB, of which the SNLB specimen was positive in 361 (30.8%) and negative in 813 (69.2%) (Table III). There was a trend for older age among patients with a positive SLN, with 34.3% (n = 167) of patients with a

positive SLNs aged >75, 28.4% (n = 116) aged 65 to 75, and 28.1% (n = 78) aged <65 years (P = .09). Patients with MCC on the trunk (45.1% [n = 46]) were more likely to have a positive SLN compared with the extremity (29.7% [n = 194], P = .004). Patients who were immunosuppressed trended toward having higher rates of SLN positivity compared with those who were not immunosuppressed (36.6% [n = 26] vs 27.9% [n = 168], P = .08). Patients with diffusely infiltrative MCC growth type had greater rates of positive SLNs compared with those with circumscribed/nodular MCC growth type (41.0% [n = 43] vs 27.6% [n = 54], P = .02). Presence of TIL (37.2% [n = 61] vs 24.4% [n = 74], P = 003) and LVI (52.4% [n = 143] vs 23.2 [n = 124], P < .001) were also associated with greater rates of SLN positivity. Comorbidities (P = .36), male sex (P = .16), clinical diameter (P = .38), and transection (P = .77) did not affect SLN positivity.

On multivariate analysis, patients with MCC on the trunk had an almost 2-fold increase in odds of having a positive SLN (OR, 1.98; 95% CI, 1.23-3.17; P = .004) (Table IV) compared with those with MCC on the head and neck. Presence of TIL increased the odds of a positive SLN by 58% (OR, 1.58; 95% CI, 1.01-2.46; P = .04). Presence of LVI had the strongest association with SLN positivity, with affected patients having 3.45-times greater odds of a positive SLN (OR, 3.45; 95% CI, 2.51-4.76; P < .001). Age, sex, comorbidities, clinical diameter, transection, and presence of immunosuppression did not affect the rate of SLN positivity on multivariate analysis.

Factors associated with OS

Multivariate analysis showed those aged >75 years had 2.55 lower odds of OS (hazard ratio [HR], 2.55; 95% CI, 1.36-4.77; P = .003) (Table V); however, this was most likely the result of older individuals being more likely to die of other causes. Male patients had 78% greater odds of death (HR, 1.78; 95% CI, 1.09-2.91; P = .022). Patients who were immunosuppressed had a 3.5-fold higher risk of death compared with those who were immunocompetent (HR, 3.51; 95% CI, 1.72-7.13; P = .001). Patients who underwent SLNB had 62% higher rates of survival (HR, 0.38; 95% CI, 0.3-0.48). Lastly, patients with positive SLNs had a 3.15-times greater risk of death than those with negative nodes (HR, 3.15; 95% CI, 1.98-5.04; P < .001). Comorbidities, primary site, diameter of lesion, transection, TIL, and LVI had no association with survival.

DISCUSSION

The rate of SLN positivity was 30.8% among this cohort. These findings are in line with prior studies

Table I. Demographic and tumor characteristics of patients based on whether SNLB was performed*

Characteristics	SLNB performed, No. (%) (n = 1174)	SLNB not performed, No. (%) (n = 1874)	P value
Age at diagnosis			<.001
<65 y	278 (44.5)	347 (55.5)	
65-75 y	409 (45.1)	497 (54.9)	
>75 y	487 (32.1)	1030 (67.9)	
Sex			.40
Male	747 (37.9)	1222 (62.1)	
Female	427 (39.6)	652 (60.4)	
Charlson-Deyo Comorbidity			.37
0	871 (39.2)	1353 (60.8)	
1	226 (37.5)	376 (62.5)	
2+	77 (34.7)	145 (65.3)	
Immunosuppressed[†]			.001
No	603 (42.1)	831 (57.9)	
Yes	71 (37.8)	117 (62.2)	
Primary site[‡]			<.001
Head and neck	406 (31.8)	870 (68.2)	
Extremity	652 (53.8)	560 (46.2)	
Trunk	102 (36.7)	176 (63.3)	
Clinical diameter[§]			.81
<2 cm	541 (44.6)	672 (55.4)	
2.01-5 cm	37 (48.1)	40 (51.9)	
>5 cm	11 (42.3)	15 (57.7)	
Growth type[‖]			.69
Circumscribed/nodular	196 (49.9)	197 (50.1)	
Diffusely Infiltrative	105 (48.2)	113 (51.8)	
Margins[¶]			<.001
Negative	1072 (49.1)	1112 (50.9)	
Positive	76 (23.5)	248 (76.5)	
Transection[#]			.27
Not transected	297 (43.9)	380 (56.1)	
Transected	246 (47.0)	277 (53.0)	
Tumor infiltrating lymphocytes[**]			.39
Absent	308 (49.1)	319 (59.9)	
Present	164 (52.1)	151 (47.9)	
Lymphovascular invasion[††]			.11
Absent	535 (46.8)	609 (53.2)	
Present	273 (42.9)	364 (57.1)	
Living patients	487 (45.9)	574 (54.1)	<.001

SLNB, Sentinel lymph node biopsy.
*Unknown values are not included in the *P* value.
[†]Immunosupression status was unknown for 500 patients who had SLNB and 926 who did not.
[‡]Primary site was unknown for 14 patients who had SLNB and 268 who did not.
[§]Clinical diameter was unknown for 585 patients who had SLNB and 1147 who did not.
[‖]Growth type was unknown for 873 patients who had SLNB and 1564 who did not.
[¶]Margin status was unknown for 26 patients who had SLNB and 514 who did not.
[#]Transection was unknown for 631 patients who had SLNB and 1217 who did not.
[**]Tumor-infiltrating lymphocytes were unknown for 702 patients who had SLNB and 1404 who did not.
[††]Lymphovascular invasion was unknown for 366 patients who had SLNB and 901 who did not.

where SLN positivity has ranged between 11% and 57%.[11,19] In contrast to other skin cancers, such as squamous cell carcinoma, which show very low risks of nodal involvement for small tumors, most prior studies of MCC show a risk of nodal involvement between 24% and 42%, even in patients with tumors ≤1 cm.[2,6,14,20,21] In contrast, Stokes et al[7] examined 54 patients with tumors ≤1 cm, of which only 2 (3.7%) had positive SLNs, and concluded that node evaluation was not useful in these patients. In our

Table II. Predictors of receiving sentinel lymph node biopsy

Predictor	OR	95%CI	P value
Age			
<65 y	Reference		
65-75 y	0.98	0.79-1.23	.88
>75 y	0.53	0.43-0.65	<.001
Sex			
Female	Reference		
Male	0.99	0.84-1.17	.93
Charlson-Deyo Comorbidity			
0	Reference		
1	0.9	0.74-1.1	.32
2+	0.79	0.57-1.07	.13
Immunosuppressed			
No	Reference		
Yes	0.71	0.5-0.99	.04
Unknown	0.9	0.76-1.07	.24
Primary site			
Head and neck	Reference		
Extremities	2.3	1.89-2.78	<.001
Trunk	1.19	0.89-1.57	.23
Not specified	0.12	0.07-0.2	<.001
Depth			
<2.0 cm	Reference		
2.01-5 cm	1.08	0.66-1.76	.77
>5 cm	1.03	0.44-2.34	.95
Unknown	0.82	0.68-0.98	.03
Transection			
Not transected	Reference		
Transected	0.92	0.72-1.17	.49
Unknown	0.73	0.6-0.91	.003
Tumor-infiltrating lymphocytes			
Absent	Reference		
Present	1	0.75-1.34	.99
Unknown	0.75	0.61-0.92	.007
Lymphovascular invasion			
Absent	Reference		
Present	0.87	0.71-1.07	.2
Unknown	0.67	0.55-0.81	<.001

CI, Confidence interval; *OR,* odds ratio.

cohort, however, there were 468 tumors ≤1 cm, of which 143 (31%) had positive SLNs, indicating that this issue may need further exploration.

Few studies have focused on factors affecting use of SLNB and predictors of SLN positivity. Patients with lower or upper extremity MCC were more likely to undergo an SLNB, possibly owing to the highly aggressive nature of the cancer or to less difficulty in accessing the nodal basin compared with head and neck or truncal MCC. Patients who are older or immunosuppressed received SLNB at a lower rate, potentially because of their high surgical risk. Schwartz et al[2] examined 97 patients who were node positive and found that type of growth (infiltrative vs circumscribed) and mitotic rate or type of growth and tumor thickness were significant predictors of SLN positivity. Fields et al[14] examined 45 patients who were node positive patients and also found that larger tumor size and presence of LVI increased the rate of positive SLNs. Finally, Smith et al[12] found that lower extremity tumor, higher tumor depth, and diameter were associated with higher rates of positive SLNs in a cohort of 191 patients.

In contrast to these studies, we did not find a significant association between tumor diameter and SLN positivity. This could be due to selection bias in the single-institution cohorts and to more modest numbers resulting in fewer predictors being accounted for. In addition, there may be institutional differences in the type of biopsy performed (shave vs excisional) and variable ability to measure tumor diameter based on level of experience of the dermatopathologist, the effects of which may have less impact in a larger data set.

The impact of growth pattern on SLN positivity could not be assessed in a multivariate model owing to few available cases with infiltrative type growth. Similarly, mitotic rate was not available in the NCDB. LVI was significantly associated with SLN positivity in the current cohort and in that described by Fields et al.[14] The presence of TIL in our study was also found to increase the risk of positive SLNs. Previous reports have not examined the effect of TIL on SLN status, because this parameter has gained more recent attention in the anti−programmed cell death protein-1 era.[2,14]

Others, however, evaluated TIL in MCC in survival analyses separate from SLN status. After studying gene expression profiles for a collection of MCC tumors categorized by prognosis, Paulson et al[22] concluded that TIL is independently linked to better MCC-specific survival and may provide prognostic guidance related to staging. Furthermore, Andea et al[23] determined that TIL is one of several histologic features that can assist in determining prognosis in MCC and that the presence of TIL is associated with better survival rates in lymph node−negative disease.[22] Studies evaluating survival based on the presence of TIL in patients with SLN-positive MCC are necessary.

Furthermore, there is some evidence that the pattern of SLN involvement, as evaluated by histology and immunohistochemistry (ie, sheet-like solid disease vs nonsolid disease) can be associated with survival, as seen in breast cancer.[24,25]

Lower OS was noted among individuals aged >75 years; however, some prior studies noted that there is no association between disease-specific survival and advancing age in MCC.[8,26] OS was

Table III. Demographic and tumor characteristics of patients based on sentinel lymph node positivity*

| Characteristics | Sentinel lymph node, No. (%) | | P value |
	Negative (n = 813)	Positive (n = 361)	
Age at diagnosis			.086
<65 y	200 (71.9)	78 (28.1)	
65-75 y	293 (71.6)	116 (28.4)	
>75 y	320 (65.7)	167 (34.3)	
Sex			
Male	506 (67.7)	241 (32.3)	.16
Female	307 (71.9)	120 (28.1)	
Charlson-Deyo Comorbidity			.36
0	613 (70.4)	258 (29.6)	
1	150 (66.4)	76 (33.6)	
2+	50 (64.9)	27 (35.1)	
Immunosuppressed[†]			.12
No	435 (72.1)	168 (27.9)	
Yes	45 (63.4)	26 (36.6)	
Primary site[‡]			.004
Head and neck	291 (71.7)	115 (28.3)	
Extremity	458 (70.2)	194 (29.7)	
Trunk	56 (54.9)	46 (45.1)	
Clinical diameter[§]			.66
<2 cm	365 (67.5)	176 (32.5)	
2.01-5 cm	25 (67.6)	12 (32.4)	
>5 cm	6 (54.5)	5 (45.5)	
Growth type[‖]			.02
Circumscribed/nodular	142 (72.4)	54 (27.6)	
Diffusely Infiltrative	62 (59.0)	43 (41.0)	
Margins[¶]			<.001
Negative	762 (71.1)	310 (28.9)	
Positive	39 (51.3)	37 (48.7)	
Transection[#]			.48
Not transected	210 (70.7)	87 (29.3)	
Transected	167 (67.9)	79 (32.1)	
Tumor-infiltrating lymphocytes**			.003
Absent	233 (75.6)	75 (24.4)	
Present	103 (62.8)	61 (37.2)	
Lymphovascular invasion[††]		<0.001	
Absent	411 (76.8)	124 (23.2)	
Present	130 (47.6)	143 (52.4)	
Living patients	352 (72.3)	135 (27.7)	<.001

*Unknown values are not included in the P value.

[†]Immunosupression status was unknown for 333 patients who had negative sentinel lymph node biopsy (SLNB) and 167 patients with positive SLNB.

[‡]Primary site was unknown for 8 patients who had negative SLNB and 6 patients with positive SLNB.

[§]Clinical diameter was unknown for 417 patients who had negative SLNB and 168 patients with positive SLNB.

[‖]Growth type was unknown for 609 patients who had negative SLNB and 264 patients with positive SLNB.

[¶]Margin status was unknown for 12 patients who had negative SLNB and 14 patients with positive SLNB.

[#]Transection was unknown for 436 patients who had negative SLNB and 195 patients with positive SLNB.

**Tumor-infiltrating lymphocytes were unknown for 477 patients who had negative SLNB and 225 patients with positive SLNB.

[††]Lymphovascular invasion was unknown for 272 patients who had negative SLNB and 94 patients with positive SLNB.

lower among men in this cohort, confirming several smaller studies.[13] Similarly, in a Surveillance, Epidemiology, and End Results cohort of 1193 patients, male sex was associated with lower 5-year MCC-specific survival (70.4% vs 83.2% in women)[27] as well as previously associated with a lower progression-free survival in a study of 108 patients.[28]

In this cohort, immunosuppression was associated with worsened OS. Similarly, Taratola et al[13] found decreased survival in those with immunosuppression in a cohort of 240 patients. In addition,

Table IV. Predictors of sentinel lymph node positivity

Predictor	OR	95% CI	P value
Age			
<65 y		Reference	
65-75 y	0.97	0.68-1.39	.86
>75 y	1.22	0.87-1.73	.25
Sex			
Female		Reference	
Male	1.19	0.9-1.57	.22
Charlson-Deyo Comorbidity			
0		Reference	
1	1.18	0.85-1.64	.32
2+	1.08	0.63-1.81	.77
Primary site			
Head and neck		Reference	
Extremities	1.22	0.85-1.82	.26
Trunk	1.98	1.23-3.17	.004
Not specified	2.34	0.74-7.04	.13
Depth			
<2.0 cm		Reference	
2.01-5 cm	0.89	0.41-1.86	.77
>5 cm	1.7	0.44-6.25	.42
Unknown	0.97	0.72-1.31	.86
Transection			
Not transected		Reference	
Unknown	1.09	0.74-1.62	.65
Transected	1.01	0.72-1.42	.95
Tumor-infiltrating lymphocytes			
Absent		Reference	
Present	1.58	1.01-2.46	.04
Unknown	1.24	0.88-1.76	.22
Immunosuppressed			
No		Reference	
Yes	1.57	0.9-2.68	.11
Unknown	1.34	1.01-1.77	.04
Lymphovascular invasion			
Absent		Reference	
Present	3.45	2.51-4.76	<.001
Unknown	1.11	0.8-1.55	.52

CI, Confidence interval; *OR,* odds ratio.

Table V. Overall survival

Characteristic	HR	95% CI	P value
Age			
<65 y		Reference	
65-75 y	1.43	0.71-2.85	.315
>75 y	2.55	1.36-4.77	.003
Sex			
Female		Reference	
Male	1.78	1.09-2.91	.022
Charlson-Deyo Comorbidity			
0		Reference	
1	1.24	0.74-2.07	.414
2+	1.49	0.74-2.98	.264
Primary site			
Head and neck		Reference	
Extremities	0.63	0.58-1.03	.078
Trunk	0.62	0.28-1.37	.235
Not specified	0.41	0.05-3.17	.396
Depth			
<2.0 cm		Reference	
2.01-5 cm	1.74	0.67-4.55	.255
>5 cm	0.92	0.10-1.3	.994
Unknown	0.88	0.55-1.42	.61
Transection			
Not transected		Reference	
Unknown	0.73	0.39-1.37	.321
Transected	1.01	0.6-1.7	.961
Tumor-infiltrating lymphocytes			
Absent		Reference	
Present	0.75	0.36-1.53	.425
Unknown	1.01	0.58-1.74	.979
Immunosuppressed			
No		Reference	
Yes	3.51	1.72-7.13	.001
Unknown	1.06	0.65-1.71	.82
Lymphovascular invasion			
Absent		Reference	
Present	0.74	0.44-1.25	.255
Unknown	0.81	0.46-1.42	.461
Sentinel lymph node positivity			
Negative		Reference	
Positive	3.15	1.98-5.04	<.001

CI, Confidence interval; *HR,* hazard ratio.

Jouary et al[28] found that immunosuppression was associated with lower progression-free survival. In contrast, Santamaria-Barria et al[29] and Smith et al[12] found no difference in MCC-specific survival between patients who were and were not immunosuppressed. However, it is important to note that male sex and immunosuppression are associated with worse OS in general, highlighting the need to evaluate these parameters in MCC-specific survival.

Positive SLNB in this cohort is associated with decreased OS, despite only 3 years of available survival data. Some studies have not found SLN positivity to affect survival.[11,12,14,29-31] These include Fields et al,[14] whose cohort included 153 patients, and a separate meta-analysis study of 403 patients where SLN status was not found to associate with total or nodal recurrence, as well as others.[11,12,19,32-34] Nevertheless, our findings are similar to those reported by Sridharan et al,[35] who analyzed 4543 patients in Surveillance, Epidemiology, and End Results and showed decreased overall and disease-specific survival. In addition, Kachare et al[27] found a 5.4% 5-year MCC-specific survival advantage for SLNB and that those with a negative SLNB had 84.5% 5-year MCC survival compared

with 64.6% in those with a positive SLNB. Furthermore, Lemos et al[9] analyzed 5283 patients with MCC and found that those with pathologically negative nodes on SLNB had 76% 5-year survival compared with 59% in the clinical nodal assessment group. Another study that focused on regional node positivity in 8044 patients from the NCDB found that the number of positive regional nodes was strongly predictive of survival.[6] In addition, Jouary et al[28] found that SLN positivity was associated with lower progression-free survival. Several smaller retrospective studies also agreed with our findings.[8,32,36,37] Disagreement in previous studies regarding the impact of SLNB status may relate to the lack of consistent use and interpretation guidelines for immunohistochemistry in the setting of MCC.[24]

This study has several limitations. First, because of its retrospective nature, there is a potential selection bias in this data set. Next, disease-specific survival is not available within the NCDB. In addition, data regarding SLNB are only available to researchers starting in 2012, with 4 years of follow-up, and we cannot evaluate trends in SLNB performance by year. Finally, in the case of extensive comorbidities and immunosuppression, the treating team may decide to treat the draining lymph node basin regardless of the SLNB result, owing to the likelihood for regional recurrence, and bypass performing SLNB because of lack of added treatment value.[38]

CONCLUSION

We found that MCC on the trunk, TIL, and presence of LVI were independent predictors of positive SLNs. OS was affected by advancing age, immunosuppression, and sentinel lymph node positivity. In the future, additional histopathologic characteristics, such as primary tumor Merkel cell polyomavirus status and mitotic rate, could improve prediction of positive SLNs. In addition, better tracking in the NCDB of LVI, TIL, histologic, or immunohistochemical staining pattern of tumor involvement in SLNB is desirable to be able to assess the effect of their impact on SLN positivity. We strongly encourage following National Comprehensive Cancer Network guidelines and performing SLNB on patients without clinically evident nodal metastases.

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