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ORIGINAL ARTICLE – MELANOMA

Patterns of Metastasis in Merkel Cell Carcinoma

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ABSTRACT

Background. Merkel cell carcinoma (MCC) is a cutaneous neuroendocrine malignancy with a propensity for regional and distant spread. Because of the relative infrequency of this disease, the patterns of metastasis in MCC are understudied.

Methods. Patients with American Joint Committee on Cancer (8th edition) stage I–IV MCC treated at our institution were identified (1/1/2008–2/28/2018). The first site of metastasis was classified as regional [regional lymph node (LN) basin, in-transit] or distant. Distant metastasis-free (DMFS) and MCC-specific (MSS) survival were estimated.

Results. Of 133 patients, 64 (48%) had stage I, 13 (10%) stage II, 48 (36%) stage III, and 8 (6%) stage IV disease at presentation. The median follow-up time in patients who remained alive was 36 (interquartile range 20–66) months. Regional or distant metastases developed in 78 (59%) patients. The first site was regional in 87%, including 73% with isolated LN involvement, and distant in 13%. Thirty-seven (28%) patients eventually developed distant disease, which most commonly involved the abdominal viscera (51%) and distant LNs (46%) first. The lung (0%) and brain (3%) were rarely the first distant sites. Stage III MCC at presentation was significantly associated with worse DMFS (hazard ratio 4.87, $P = 0.001$) and stage IV disease with worse MSS (hazard ratio 6.30, $P = 0.002$).

Conclusions. Regional LN metastasis is the most common first metastatic event in MCC, confirming the importance of nodal evaluation. Distant disease spread appears to have a predilection for certain sites. Understanding these patterns could help to guide surveillance strategies.

Merkel cell carcinoma (MCC) is an aggressive neuroendocrine cutaneous malignancy, which was first described by Toker.[1] It often presents in sun-exposed areas as a rapidly growing, firm, nontender nodule and has been associated with immunosuppression, comorbid malignancies, exposure to ultraviolet radiation, and infection by the Merkel cell polyomavirus.[2–4] Although its incidence has been rising in recent years, it remains a relatively rare malignancy, with only approximately 2500 cases diagnosed per year in the United States.[5] MCC is known to have a propensity for regional and distant metastasis and has been associated with a high mortality rate, with estimated 5-year overall survival rates of 14–51% depending on the extent of disease at presentation.[6]

The current approach to staging for MCC includes primary tumor biopsy, complete skin and regional lymph node (LN) examination, and consideration of cross-sectional imaging for metastatic screening.[7] Because of frequent regional LN involvement, sentinel lymph node biopsy (SLNB) is generally recommended for patients with clinically localized MCC, although a survival benefit has not been clearly demonstrated.[7–11] Distant metastasis also occurs frequently; institutional series demonstrate that approximately one-third of patients with MCC will eventually develop distant disease.[12,13] However, because of the relative infrequency of this disease, the timing and frequencies of regional and distant disease spread have not been well characterized, resulting in relatively vague baseline and surveillance imaging recommendations. The National Comprehensive Cancer Network guidelines propose that baseline imaging with computed tomography

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(CT) or whole-body positron emission tomography with fused CT (PET/CT) may be useful for MCC, especially in the setting of LN-positive disease.[7] On follow-up, guidelines recommend consideration of imaging as clinically indicated.

The purpose of the current study was to describe the patterns of regional and distant metastasis in 133 patients treated for MCC at our institution. The frequencies of the first sites of metastasis and time to distant metastasis were determined. A better understanding of these patterns of disease spread may help to guide imaging and disease surveillance strategies.

METHODS

Approval for this study was obtained from the institutional review board of the University of Pennsylvania. Consecutive adult patients age 18 years or older who were treated at our institution for biopsy-proven MCC diagnosed between January 1, 2008 through February 28, 2018 were identified. One patient was excluded for insufficient clinical information and loss to follow-up. The final study cohort consisted of 133 patients.

Disease stage at presentation was categorized according to the American Joint Committee on Cancer (AJCC) 8th edition staging system.[6,14] Pathologic staging was used for patients with clinically localized MCC (no evidence of regional or distant metastases at presentation) who underwent SLNB. If a SLNB was not performed, patients were clinically staged. Patient characteristics recorded included age at initial diagnosis, sex, history of other malignancies, and immunosuppression. Immunosuppression was defined as having a solid organ transplant, bone marrow transplant, hematologic malignancy, autoimmune disorder, human immunodeficiency virus/acquired immunodeficiency syndrome, or receipt of chemotherapy within the 3 months before MCC diagnosis. Primary tumor characteristics analyzed included location, diameter, and presence of lymphovascular invasion. Baseline imaging, including ultrasound, CT, and PET/CT, was defined as imaging performed within 1 month of MCC diagnosis. The frequency and modality of follow-up surveillance imaging was at the discretion of treating providers. Treatment characteristics recorded included primary tumor excision, SLNB, complete lymph node dissection, and adjuvant or first-line radiation and systemic therapies.

The primary outcome was the first site of metastasis, categorized as regional (regional LN basin and in-transit disease) or distant (distant LNs, distant soft tissue, and other organs). The secondary outcomes were the first site(s) of distant metastasis, distant metastasis-free survival (DMFS), and MCC-specific survival (MSS). DMFS was estimated in patients who presented with stage I through III MCC and defined as the number of months from MCC presentation to diagnosis of first distant metastasis, censoring at last follow-up for those without distant disease. MSS was defined as the interval, in months, from initial diagnosis to MCC-related death. Patients who were alive or died of other causes were censored at last follow-up.

Categorical variables are presented as frequencies and continuous variables as medians with interquartile ranges (IQR). Univariate comparisons were made using the Pearson's Chi squared or Fisher's exact test, as appropriate, for categorical variables, and the Wilcoxon rank-sum test for continuous variables. Survival curves were estimated using the Kaplan–Meier method and compared using the log-rank test. Associations with DMFS and MSS were determined using Cox regression. Multivariable Cox proportional hazards models included factors with $P < 0.10$ by univariate analyses with sequential removal of variables with $P > 0.10$ on multivariable regressions. All tests were two-sided. P values < 0.05 were considered statistically significant. Statistical analyses were performed using R version 3.5.3.[15]

RESULTS

Baseline Characteristics

A total of 133 patients met study criteria, including 64 (48%) with stage I, 13 (10%) with stage II, 48 (36%) with stage III, and 8 (6%) with stage IV MCC at presentation (Table 1). The median age was 74 (IQR 66–82) years, and a majority (61%) of patients were male. Immunosuppression was present in 14% of patients overall and up to 39% of those with stage II MCC. The most common primary tumor location was the head and neck in 41% of patients.

Definitive excision of the primary tumor was not performed in 22 (16%) patients. Fourteen of these patients presented with clinical stage III MCC, which represented 45% of those with clinical stage III disease. All eight patients who presented with stage IV MCC also did not undergo primary tumor resection. When the primary tumor was excised and margin was reported, > 1.0–2.0 cm represented a plurality (31%) of margins utilized.

Among 94 patients who presented with clinically localized disease, 68 (72%) underwent SLNB. SLNB was also performed for one patient with evidence of in-transit disease at presentation. Among the 69 patients who underwent SLNB, 17 (25%) were positive. Twenty (21%) patients with clinically localized MCC did not undergo SLNB, and SLNB failed in another 6 (6%) patients. These patients were clinically staged as stage I/II. Among those with stage III MCC, 31 (65%) presented with clinically

TABLE 1 Characteristics of patients diagnosed with Merkel cell carcinoma

Characteristics	*N* (%)				
	All patients *N* = 133	AJCC 8th edition stage at presentation			
		Stage I *N* = 64 (48%)	Stage II *N* = 13 (10%)	Stage III *N* = 48 (36%)	Stage IV *N* = 8 (6%)
Demographics					
Age in years, median (IQR)	74 (66–82)	76 (65–82)	77 (73–84)	71 (64–80)	70 (69–73)
Sex					
Female	52 (39)	31 (48)	4 (31)	15 (31)	2 (25)
Male	81 (61)	33 (52)	9 (69)	33 (69)	6 (75)
Race					
White	119 (89)	57 (89)	11 (85)	43 (90)	8 (100)
Non-White	14 (11)	7 (11)	2 (15)	5 (10)	0 (0)
Immunosuppression	18 (14)	4 (6)	5 (38)	7 (15)	2 (25)
History of other malignancies	35 (26)	20 (31)	6 (46)	9 (19)	0 (0)
Primary tumor characteristics					
Location					
Head/neck	54 (41)	27 (42)	6 (46)	20 (42)	1 (12)
Upper extremity	28 (21)	19 (30)	3 (23)	6 (12)	0 (0)
Lower extremity	26 (20)	11 (17)	4 (31)	9 (19)	2 (25)
Trunk	12 (9)	7 (11)	0 (0)	4 (8)	1 (12)
Unknown primary	13 (10)	0 (0)	0 (0)	9 (19)	4 (50)
Diameter in cm, median (IQR)	1.2 (0.7–2.1)	0.9 (0.5–1.4)	2.4 (2.2–2.9)	2.5 (1.2–4.0)	2.1 (2.0–2.2)
Depth in mm, median (IQR)	6.0 (3.3–11.0)	5.0 (3.0–8.0)	8.0 (7.5–11.5)	8.5 (5.8–15.5)	17.0 (14.5–19.5)
Lymphovascular invasion					
Absent	44 (33)	28 (44)	5 (39)	11 (23)	0 (0)
Present	41 (31)	19 (30)	6 (46)	14 (29)	2 (25)
Unknown primary/not reported	48 (36)	17 (27)	2 (15)	23 (48)	6 (75)
Initial workup and treatment					
Baseline imaging					
None	14 (11)	10 (16)	2 (15)	2 (4)	0 (0)
Ultrasound	2 (2)	2 (3)	0 (0)	0 (0)	0 (0)
CT	27 (20)	17 (27)	1 (8)	8 (17)	1 (12)
PET/CT	90 (68)	35 (55)	10 (77)	38 (79)	7 (88)
Definitive excision of primary tumor	111 (84)	64 (100)	13 (100)	34 (71)	0 (0)
Primary tumor excision margin (cm)					
No excision	22 (16)	0 (0)	0 (0)	14 (29)	8 (100)
≤ 0.5	22 (16)	13 (20)	3 (23)	6 (12)	0 (0)
> 0.5–1.0	20 (15)	11 (17)	4 (31)	5 (10)	0 (0)
> 1.0–2.0	41 (31)	26 (41)	3 (23)	12 (25)	0 (0)
> 2.0	3 (2)	1 (2)	1 (8)	1 (2)	0 (0)
Not reported	25 (19)	13 (20)	2 (15)	10 (21)	0 (0)
SLNB					
Not performed	58 (44)	15 (23)	5 (38)	30 (62)[a]	8 (100)
Performed	69 (52)	44 (69)	7 (54)	18 (38)[b]	0 (0)
Failed	6 (5)	5 (8)	1 (8)	0 (0)	0 (0)
Adjuvant/first-line treatments					
Complete lymph node dissection					
Not performed	NA	NA	NA	15 (31)	NA

TABLE 1 continued

Characteristics	*N* (%)				
	All patients *N* = 133	AJCC 8th edition stage at presentation			
		Stage I *N* = 64 (48%)	Stage II *N* = 13 (10%)	Stage III *N* = 48 (36%)	Stage IV *N* = 8 (6%)
For positive SLNB	NA	NA	NA	11 (23)	NA
For clinical nodal disease	NA	NA	NA	22 (46)	NA
Primary tumor radiation	46 (35)	18 (28)	5 (38)	23 (48)	0 (0)
Regional nodal basin radiation	37 (28)	2 (3)	1 (8)	32 (67)	2 (25)
Chemotherapy					
None	116 (87)	64 (100)	13 (100)	34 (71)	5 (62)
Neoadjuvant	2 (2)	0 (0)	0 (0)	2 (4)	0 (0)
Adjuvant	10 (8)	0 (0)	0 (0)	10 (21)	0 (0)
Definitive treatment[c]	5 (4)	0 (0)	0 (0)	2 (4)	3 (38)
Immunotherapy					
None	126 (95)	63 (98)	13 (100)	46 (96)	4 (50)
Pembrolizumab	4 (3)	1 (2)	0 (0)	1 (2)	2 (25)
Avelumab	3 (2)	0 (0)	0 (0)	1 (2)	2 (25)

SLNB sentinel lymph node biopsy, *AJCC* American Joint Committee on Cancer, *IQR* interquartile range, *CT* computed tomography, *PET/CT* positron emission tomography/computed tomography, *NA* not applicable

[a]Patients were staged based on clinically evident nodal or in-transit metastases and did not undergo SLNB

[b]Seventeen patients had a positive SLNB. One patient had evidence of in-transit disease and was clinical stage III

[c]Patients did not undergo surgical resection

evident nodal or in-transit disease, and 17 (35%) had microscopic metastases diagnosed by SLNB.

In total, 46 (35%) of patients received primary tumor irradiation. Frequency of primary tumor radiation therapy increased with increasing AJCC stage from I (28%) to III (48%). Regional lymph node basin radiation therapy was utilized in 32 (67%) patients who presented with stage III and 2 (25%) with stage IV MCC. Receipt of chemotherapy was uncommon in only 17 (14%) patients and limited to those with regional or distant metastases at disease presentation.

A total of 117 patients underwent baseline cross-sectional imaging (CT or PET/CT). Of these, 30 (26%) patients had regional and 8 (7%) had distant metastases. Only 2 (2%) patients had isolated distant metastases without concurrent regional disease on imaging.

First Metastatic Event

The median follow-up time for patients who remained alive was 36 (IQR 20–66) months. In addition to the 56 patients who presented with stage III or IV MCC, another 22 patients developed regional or distant metastases during the follow-up period, for a total of 78 (59%) patients with disease spread. The first site of metastasis was regional in 87% of patients, including 73% limited to the regional LN basin, 8% with in-transit disease only, and 6% with both nodal and in-transit disease (Fig. 1). Only 13% of patients had distant disease spread as the first metastatic event.

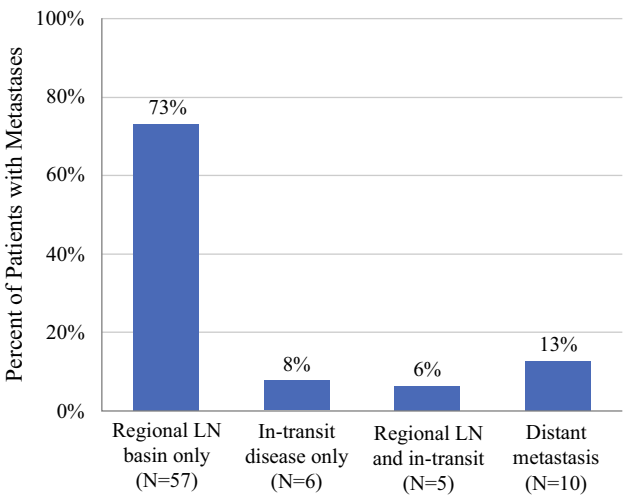

FIG. 1 First site of metastasis among 78 patients who developed regional or distant metastases. *LN* lymph node

The first site of recurrence was additionally characterized among patients who underwent full pathologic staging at the time of disease diagnosis. Of the 51 patients who had a negative SLNB (pathologic stage I/II), 11 (22%)

subsequently developed regional-first recurrence. Five patients recurred within the regional LN basin first for a SLNB false negative rate of 22% [5 false negative/(5 false negative + 18 true positive)]. Three (60%) of these five patients had a head/neck primary. Six additional patients recurred with in-transit disease. Distant-first metastasis was rare in the SLNB-negative population and occurred for only one (2%) patient.

Among the 48 patients who presented with either microscopic (diagnosed by SLNB) or clinically evident stage III MCC, 16 (33%) recurred. The first site of recurrence in these pathologically staged patients was in-transit in four (25%), concurrent in-transit and distant disease in three (19%), and distant metastases in nine (56%) patients.

First Distant Metastasis and Distant Metastasis-Free Survival

A total of 37 (28%) patients eventually developed distant metastases, including 8 patients on presentation and 29 during the follow-up period. The most common first sites of distant metastasis were the abdominal viscera (51%) and distant LNs (46%) (Fig. 2). The lung (0%) and brain (3%) were rarely the first distant sites.

Among patients who initially presented with stage I through III MCC and subsequently developed distant disease ($N = 29$), 40% metastasized within 1 year of MCC diagnosis, 73% within 3 years, and 100% within 5 years. Unadjusted DMFS curves in these patients did not differ significantly by stage (log-rank $P = 0.13$; Fig. 3). The 5-year DMFS rates were 71.2% (95% confidence interval [CI] 56.0–90.4%) for stage I, 61.4% (95% CI 32.7–100.0%) for stage II, and 61.6% (95% CI 47.4–80.0%) for stage III patients. Median DMFS time had not been reached in any group. By multivariable Cox regression analysis, presentation with stage III disease was significantly associated with worse DMFS (stage III vs. I, hazard ratio [HR] 4.87, 95% CI 1.84–12.9, $P = 0.001$; Table 2). Additionally, DMFS decreased with increasing age (HR 1.05, 95% CI 1.01–1.09, $P = 0.018$), whereas an unknown primary tumor location (HR 0.18, 95% CI 0.04–0.91, $P = 0.038$) and irradiation of the primary tumor (HR 0.24, 95% CI 0.09–0.65, $P = 0.005$) were associated with improved DMFS.

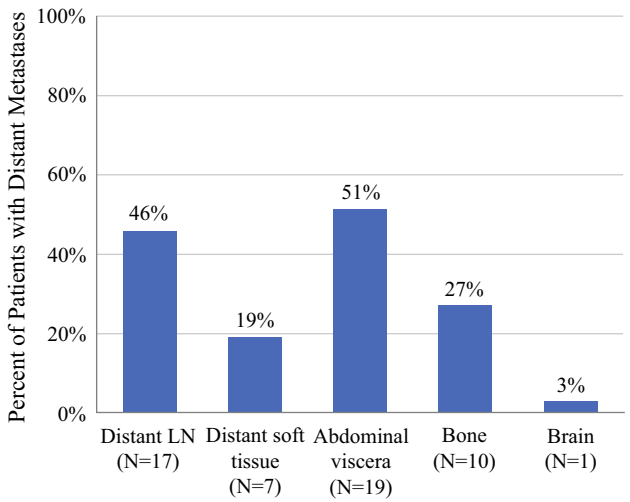

FIG. 2 First site(s) of distant metastasis among 37 patients who developed distant disease. *LN* lymph node. Percentages do not add up to 100% as patients may have had multiple sites involved

Merkel Cell-Specific Survival

The overall 5-year MSS rate for the study cohort was 71.9% (95% CI 62.9–82.1%). The MSS curves differed significantly by stage at presentation (log-rank $P < 0.001$) (Fig. 4). In particular, patients with stage IV MCC at presentation experienced substantially worse survival with a 5-year MSS rate of only 25.0% (95% CI 7.5–83.0%). Presentation with stage IV disease remained associated with worse MSS by multivariable analysis (stage IV vs. I, HR 6.30, 95% CI 1.93–20.5, $P = 0.002$; Table 3). Primary tumor excision margin was associated with MSS by univariate analysis, but not after adjusting for AJCC stage, and was therefore not included in the final multivariable regression. Patients who received primary tumor radiation therapy experienced improved MSS (HR 0.23, 95% CI 0.08–0.71, $P = 0.011$).

DISCUSSION

MCC is an uncommon but aggressive cutaneous neuroendocrine malignancy. Because of the relative infrequency of this disease, the patterns of metastasis in MCC have not been adequately evaluated. In the current study, the regional LN basin was confirmed as a frequent first site of metastasis, preceding the development of distant disease. Distant metastasis, however, was common and developed in nearly one-third of study patients. MCC appears to have a predilection for certain sites, with the abdominal viscera and distant LNs frequently representing the first distant sites of disease.

Among patients who developed disease spread in the current study, 73% had isolated regional nodal involvement as the first metastatic event. The early and high rate of regional LN basin metastasis confirms the importance of SLNB for patients with clinically localized MCC. The SLN positivity rate was 25%, consistent with the range reported in the literature for MCC (23–45%) and comparable to that for thick melanoma (26–33%), for which SLNB is typically recommended.[8,10,11,16–27] Frequent regional LN

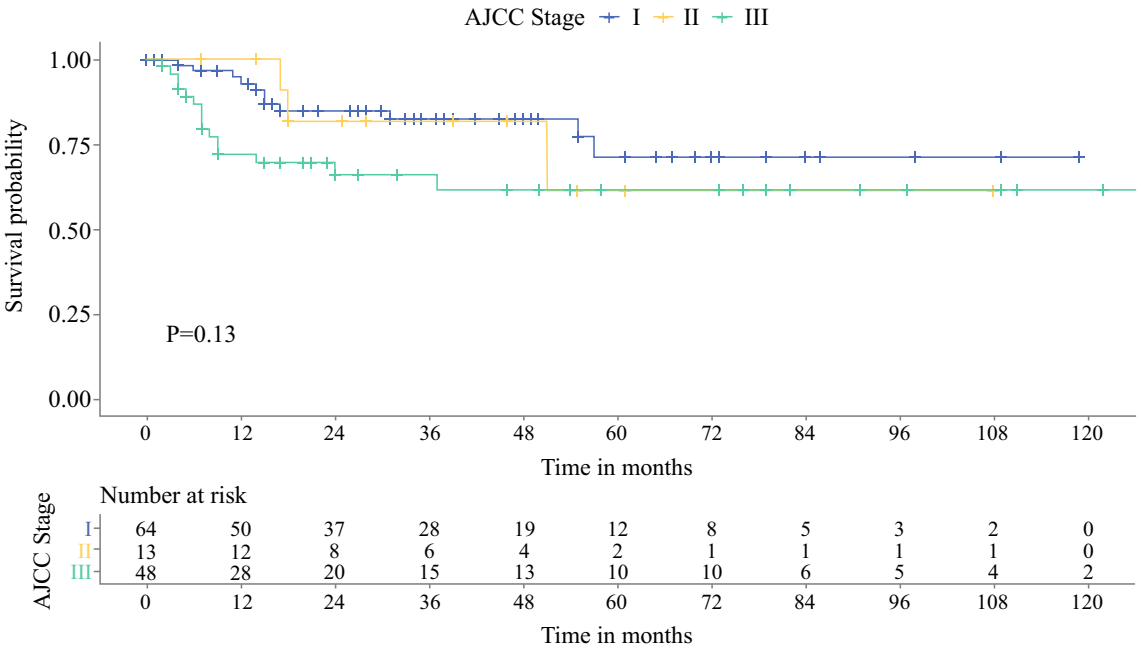

FIG. 3 Kaplan–Meier estimates of distant metastasis-free survival of 125 patients who presented with American Joint Committee on Cancer (AJCC) stage I through III Merkel cell carcinoma

surveillance following initial MCC treatment also should be prioritized. The false-negative rate for SLNB was relatively high at 22% in the present study and in the range of 15–21% in the literature.[8,28–30]

Accurate pathologic staging also could inform risk of distant disease recurrence. Distant-first recurrence was very rare in the SLNB-negative population (pathologic stage I/II), occurring in only one patient, but developed in 56% of patients with stage III MCC who subsequently relapsed. Furthermore, on baseline imaging, only 2% of patients had isolated distant disease without regional nodal involvement, and a minority (13%) of all study patients had distant disease spread as the first metastatic event. These findings suggest that regional LN metastasis likely precedes distant metastasis in a majority of patients. Lymphovascular invasion may be an early occurrence in MCC, present in 90% of primary tumor samples in one study, while isolated blood vascular invasion is much less common in only 3%.[31] By identifying regional nodal metastases early, appropriate treatments could be offered in a timely manner to perhaps prevent distant disease relapse.[10,19]

Additionally, the presence of LN metastases at the time of MCC presentation was associated with significantly worse DMFS, whereas resection margin of the primary tumor was not associated with either DMFS or MSS, consistent with recent findings by Perez et al.[32] It may be appropriate to choose a feasible margin of excision without compromising necessary adjuvant treatments, as recommended by national practice guidelines.[7] In the current study, primary tumor radiation therapy also was associated with improved DMFS and MSS, consistent with findings from a multicenter study that demonstrated improved locoregional disease control, DMFS, and MSS among patients with MCC who received adjuvant primary tumor radiation.[33]

Distant LNs and intra-abdominal organs were most often the first sites of distant metastases in the present study, consistent with previous findings that these sites are frequently involved in metastatic MCC.[12,13,34] While we found that the lung (0%) and brain (3%) were rarely the first sites of distant spread, they may be subsequently involved in 30% and 13% of patients, respectively.[34] Understanding these patterns of metastasis may help to guide follow-up imaging strategies. For example, chest and abdominopelvic imaging, especially in patients who already have regional LN involvement, should be routinely performed for restaging, whereas dedicated brain imaging may be reserved for patients who demonstrate concerning signs and symptoms.

Among patients who initially presented with stage I through III MCC, median DMFS time had not been reached after a median follow-up time of 36 months in the study cohort. Kouzmina et al. reported that the longest latency period between diagnosis and distant metastasis was 14.2 years, but the median time to distant disease was 2.5 years among patients who did not present with stage IV

TABLE 2 Characteristics associated with distant metastasis-free survival among patients who presented with American Joint Committee on Cancer (AJCC) stage I through III Merkel cell carcinoma

Characteristic	Univariate OR (95% CI)	*P* value	Multivariable OR (95% CI)	*P* value
AJCC stage at presentation				
Stage I	Reference		Reference	
Stage II	1.19 (0.33–4.28)	0.79	0.99 (0.27–3.67)	0.99
Stage III	2.15 (0.99–4.68)	0.055	4.87 (1.84–12.9)	0.001
Age, per year	1.04 (1.00–1.08)	0.026	1.05 (1.01–1.09)	0.018
Sex				
Female	Reference			
Male	2.12 (0.90–4.99)	0.084		
Immunosuppression	1.33 (0.46–3.84)	0.59		
Previous malignancy	1.43 (0.67–3.02)	0.35		
Primary tumor location				
Head/neck	Reference		Reference	
Upper extremity	0.32 (0.09–1.10)	0.070	0.68 (0.18–2.49)	0.56
Lower extremity	0.97 (0.39–2.41)	0.95	1.14 (0.44–2.95)	0.79
Trunk	1.03 (0.30–3.59)	0.96	1.11 (0.30–4.08)	0.88
Unknown primary/not reported	0.66 (0.15–2.90)	0.58	0.18 (0.04–0.91)	0.038
Presence of lymphovascular invasion				
Absent	Reference			
Present	1.84 (0.70–4.84)	0.094		
Unknown primary/not reported	1.84 (0.70–4.84)	0.22		
Primary tumor depth (mm)				
≤ 6.0	Reference			
> 6.0	1.70 (0.73–3.99)	0.22		
Unknown primary/not reported	0.80 (0.30–2.14)	0.65		
Primary tumor excision margin (cm)				
No excision	Reference			
≤ 0.5	0.32 (0.06–1.76)	0.19		
> 0.5–1.0	0.83 (0.22–3.12)	0.79		
> 1.0–2.0	0.71 (0.22–2.30)	0.56		
> 2.0	0.89 (0.10–8.01)	0.92		
Not reported	1.20 (0.36–4.01)	0.76		
Complete lymph node dissection				
Not performed	Reference			
Performed	3.73 (1.73–8.05)	< 0.001		
Primary tumor radiation	0.43 (0.18–1.02)	0.054	0.24 (0.09–0.65)	0.005
Regional nodal basin radiation	0.91 (0.40–2.06)	0.83		
Chemotherapy				
None	Reference			
Neoadjuvant	3.90 (0.51–29.9)	0.19		
Adjuvant	0.66 (0.16–2.79)	0.57		

OR odds ratio, *CI* confidence interval

MCC.[34] All distant metastases in the present study occurred within the first 5 years. Similarly, Lewis et al. found that 99% of distant disease spread occurred within 5 years of initial MCC diagnosis.[13] These data support active surveillance during the early years following MCC diagnosis.[12]

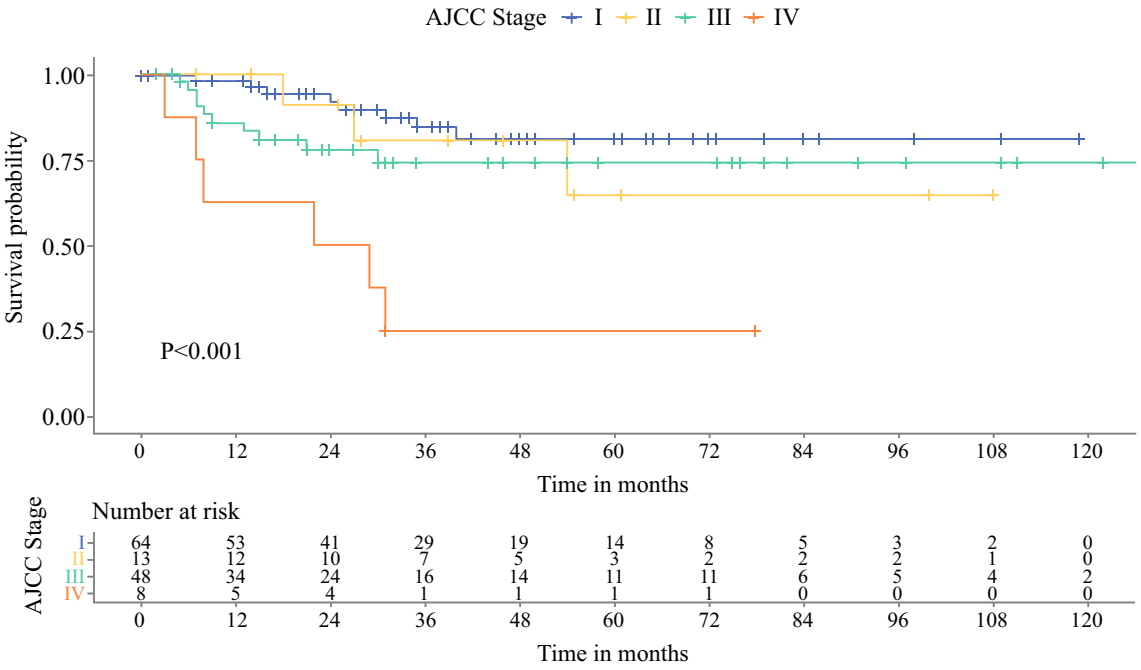

FIG. 4 Kaplan–Meier estimates of Merkel cell-specific survival

With respect to baseline and follow-up imaging modalities, PET/CT may be superior to CT in identifying distant involvement in MCC. PET/CT was the most common baseline imaging modality utilized in 68% of our study patients. In a small study of 18 patients with MCC, Concannon et al. found that PET/CT altered staging for 7 (33%) and changed management for 9 (43%) patients. Hawryluk et al. reported that PET/CT upstaged 16% of patients who underwent baseline scans at presentation of MCC.[12] In contrast, CT appears to have high sensitivity for distant MCC spread (100%), but very poor specificity (48%).[10]

Limitations of the current study include its retrospective nature and moderately sized cohort. While multivariable analyses adjusted for some covariates, these could not account for unobserved or unrecorded differences between patient groups. Patients classified as stage I and II may have represented a relatively heterogeneous population, because not all of these patients were pathologically staged, which could partially explain the absence of a significant difference in DMFS and MSS between these groups. Preliminary subgroup analyses of disease recurrence patterns among patients who were pathologically staged were presented here and will be further validated in a multicenter study. Additionally, patients received variable treatments, the heterogeneity of which may not be fully accounted for in the analyses of recurrence and survival outcomes. Finally, there may be a referral bias to an academic center of patients with more advanced disease or complex comorbidities, which could affect the generalizability of our findings.

CONCLUSIONS

The regional LN basin is the most common first metastatic site in MCC, confirming the importance of nodal evaluation at the time of diagnosis. Certain sites, including the abdominal viscera and distant LNs, are frequently involved early in distant metastatic disease, whereas the lung and brain were rarely the first distant sites. Recognizing these patterns of metastasis could help to guide surveillance strategies, which may focus on nodal disease for patients confirmed to have stage I and II MCC and include routine cross-sectional imaging for those who have had regional disease spread. A multicenter, retrospective study is planned to further validate these patterns of metastasis and to identify optimal surveillance strategies for patients diagnosed with MCC.

TABLE 3 Characteristics associated with Merkel cell-specific survival

Characteristic	Univariate OR (95% CI)	*P* value	Multivariable OR (95% CI)	*P* value
American Joint Committee on Cancer stage at presentation				
Stage I	Reference		Reference	
Stage II	1.65 (0.44–6.21)	0.46	1.26 (0.33–4.85)	0.74
Stage III	1.93 (0.76–4.88)	0.17	2.27 (0.80–6.42)	0.12
Stage IV	7.71 (2.66–22.3)	< 0.001	6.30 (1.93–20.5)	0.002
Age, per year	1.03 (0.99–1.06)	0.15		
Sex				
Female	Reference			
Male	1.47 (0.64–3.37)	0.36		
Immunosuppression	2.35 (0.94–5.82)	0.066	2.70 (0.98–7.44)	0.056
Previous malignancy	0.65 (0.26–1.62)	0.36		
Primary tumor location				
Head/neck	Reference			
Upper extremity	0.38 (0.08–1.79)	0.22		
Lower extremity	2.07 (0.80–5.38)	0.13		
Trunk	1.61 (0.43–6.07)	0.48		
Unknown primary/not reported	2.38 (0.78–7.29)	0.13		
Primary tumor depth (mm)				
≤ 6.0	Reference			
> 6.0	1.46 (0.57–3.70)	0.43		
Unknown primary/not reported	1.06 (0.41–2.74)	0.91		
Presence of lymphovascular invasion				
Absent	Reference		Reference	
Present	2.59 (0.97–6.91)	0.058	2.55 (0.92–7.04)	0.072
Unknown primary/not reported	1.70 (0.60–4.77)	0.32	0.96 (0.29–3.15)	0.95
Primary tumor excision margin (cm)				
No excision	Reference			
≤ 0.5	0.11 (0.01–0.86)	0.035		
> 0.5–1.0	0.58 (0.19–1.75)	0.34		
> 1.0–2.0	0.31 (0.11–0.86)	0.025		
> 2.0	0.54 (0.07–4.28)	0.56		
Not reported	0.51 (0.17–1.54)	0.23		
Complete lymph node dissection				
Not performed	Reference			
Performed	1.77 (0.83–3.77)	0.14		
Primary tumor radiation	0.27 (0.09–0.79)	0.017	0.23 (0.08–0.71)	0.011
Regional nodal basin radiation	0.71 (0.28–1.75)	0.45		
Chemotherapy				
None	Reference			
Neoadjuvant	4.39 (0.57–33.5)	0.15		
Adjuvant	0.41 (0.06–3.03)	0.38		
Definitive treatment[a]	1.71 (0.40–7.28)	0.47		

OR odds ratio, *CI* confidence interval

[a]Patients did not undergo surgical resection

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