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https://doi.org/10.1016/j.jaad.2020.08.012

Sites of distant metastasis in Merkel cell carcinoma differ by primary tumor site and are of prognostic significance: A population-based study in the Surveillance, Epidemiology, and End Results database from 2010 to 2016

To the Editor: Merkel cell carcinoma (MCC) is highly aggressive, with a propensity for recurrence and distant metastasis. Sentinel lymph node biopsy is critical for workup; however, optimal use of imaging is unclear.[1] A large institutional registry recently identified that liver metastases were more common with a head/neck primary compared with other sites, which could guide workup and surveillance strategies.[2] Thus, we sought to investigate the effect of the primary tumor site on metastasis patterns in a national cohort, hypothesizing that a relationship would exist.

We identified patients with MCC (code 8247/3) in the Surveillance, Epidemiology, and End Results (SEER)-18 registries. Our inclusion criteria consisted of patients with metastatic disease upon initial presentation based on American Joint Committee on Cancer 8th Edition staging, diagnosed between 2010 and 2016. Our cohort was stratified by primary lesion site, which consisted of the trunk, head/neck, upper/lower extremities, and other disease sites encompassing visceral or primary nodal disease.

We used χ^2 tests and Student t tests (2-tailed P values) to assess for differences in clinical and pathologic characteristics and metastatic disease distributions based on primary site and performed Kaplan-Meier analysis to analyze overall survival and disease-specific survival (DSS). We performed multivariate Cox proportional hazards analysis to assess for independent prognosticators of DSS.

Our cohort of 331 patients with M1 disease was predominantly male and White (Table I). Patients with a head/neck primary site had a higher proportion of liver metastasis (42.3%, $P = .0003$) relative to other primary sites, and patients with a trunk primary site had a higher proportion of bone metastasis (36.9%, $P = .0049$). Overall 5-year overall survival was 11.2%, and DSS was 16.2%. Increasing age and liver and brain metastases were independent prognosticators of poorer DSS by Cox proportional hazards analysis (Table II).

Our analysis corroborates findings by Lewis et al,[2] also suggesting that in metastatic MCC, a head/neck primary is associated with increased propensity for liver metastasis, generalizing this finding in a national cohort. Additionally, we demonstrate that a trunk primary is associated with bone metastasis compared with other primary sites and in our multivariate analysis that liver and brain metastases (although rare), but not lung or bone, are associated with poorer DSS.

These findings may guide further research regarding imaging in MCC. Current guidelines suggest whole-body positron emission tomography (PET)/computed tomography (CT) or PET/magnetic resonance imaging (MRI), or CT imaging of the chest, abdomen, and pelvis with contrast, with or without neck CT or brain MRI, for evaluation of regional or distant disease, when clinically indicated.[1] Guidelines however do not suggest that all clinically node-negative patients should be screened with PET/CT at the initial diagnosis, because PET/CT is more likely to change staging or management in those with features suggesting potential for advanced disease (large tumor size, lymphovascular invasion, immunosuppression).

Considering our findings, unexplained liver function abnormalities in head/neck primary MCC may particularly raise clinical suspicion for distant disease and guide imaging decisions. Furthermore, imaging methods differ in sensitivity and specificity for metastasis detection, and limited data suggest greater utility of PET/CT for detection of bone metastases in MCC and for liver metastases (although studied on other malignancies) compared with CT.[3] In addition, an area of potential interest is whole-body PET/MRI, which has shown better detection of liver metastases compared with PET/CT, although these data are not in MCC.[4] This may be particularly relevant for patients with a head/neck primary, but cost-effectiveness would be important to consider. In addition, given the rarity of brain metastasis, further studies could focus on optimal selection of patients for brain MRI. Ultimately, future prospective studies

Table I. Cohort characteristics stratified by Merkel cell carcinoma primary site

Variable*	Head/neck	Trunk	Upper/lower extremities	Other†	*P* value
Number (% of cohort)	97 (29.3)	38 (11.5)	91 (27.5)	105 (31.7)	.0039
Age at diagnosis, mean (SD), y	78.5 (9.7)	71.7 (11.2)	77.3 (11.6)	70.8 (13.5)	
Sex					.003
Male	82 (84.5)	26 (68.4)	56 (61.5)	77 (73.3)	
Female	15 (15.5)	12 (31.6)	35 (38.5)	28 (26.7)	
Race					.107
White	95 (98.0)	33 (86.8)	85 (93.4)	98 (93.3)	
African American	1 (1.0)	2 (5.3)	5 (5.5)	1 (1.0)	
Other/unknown	1 (1.0)	3 (7.9)	1 (1.1)	6 (4.7)	
Tumor size					<.0001
0-10 mm	9 (9.3)	1 (2.6)	4 (4.4)	35 (33.3)	
11-20 mm	14 (14.4)	0	11 (12.1)	1 (1.0)	
21-30 mm	16 (16.5)	7 (18.4)	8 (8.8)	2 (1.9)	
31-40 mm	6 (6.2)	5 (13.2)	9 (9.9)	0	
41-50 mm	3 (3.1)	2 (5.3)	8 (8.8)	2 (1.9)	
>50 mm	3 (3.1)	10 (26.3)	17 (18.7)	1 (1.0)	
Unknown	46 (47.4)	13 (34.2)	34 (37.3)	64 (60.9)	
Bone metastasis					.0049
Yes	24 (24.7)	14 (36.9)	15 (16.5)	15 (14.3)	
No	70 (72.2)	23 (60.5)	73 (80.2)	77 (73.3)	
Unknown	3 (3.1)	1 (2.6)	3 (3.3)	13 (12.4)	
Brain metastasis					.0315
Yes	3 (3.1)	1 (2.6)	0	2 (1.9)	
No	89 (91.7)	36 (94.8)	88 (96.7)	89 (84.8)	
Unknown	5 (5.2)	1 (2.6)	3 (3.3)	14 (13.3)	
Liver metastasis					.0003
Yes	41 (42.3)	5 (13.2)	21 (23.1)	22 (20.9)	
No	52 (53.6)	32 (84.2)	67 (73.6)	70 (66.7)	
Unknown	4 (4.1)	1 (2.6)	3 (3.3)	13 (12.4)	
Lung metastasis					.272
Yes	13 (13.4)	7 (18.4)	18 (19.8)	13 (12.4)	
No	79 (81.4)	30 (79.0)	70 (76.9)	81 (77.1)	
Unknown	5 (5.2)	1 (2.6)	3 (3.3)	11 (10.5)	

*Data are presented as number (%) unless indicated otherwise.
†Owing to the nature of coding in the Surveillance, Epidemiology, and End Results database, the "other" category contains patients with overlapping primary skin sites and those with an unknown primary where Merkel cell carcinoma was first discovered in a lymph node or visceral location.

will be needed to clarify imaging strategies in MCC with the consideration that patterns of metastasis can guide future research.

Limitations include the retrospective nature and lack of details on immune status or metastatic location beyond bone, liver, lung, and brain. In addition, data from this study largely predate immune checkpoint inhibitors for advanced MCC, but optimizing surveillance and early detection of metastases may be increasingly relevant because metastatic tumor burden in melanoma has been shown to influence treatment response and progression-free survival with checkpoint blockade, which could also be the case for MCC.[5] Ultimately, our findings provide further insight into patterns of metastasis of MCC and may help guide future studies.

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Funding sources: None.

Conflicts of interest: None disclosed.

IRB approval status: Not required.

Reprints not available from the authors.

Table II. Cox proportional hazards analysis for disease-specific survival (*DSS*) in patients with metastatic Merkel cell carcinoma

Variable	DSS hazard ratio (95% CI)	*P* value
Age at diagnosis	1.03 (1.02-1.05)	<.0001
Sex		
Female (Ref)	1.0	
Male	1.14 (0.83-1.56)	.417
Race		
White (Ref)	1.0	
African American	1.82 (0.78-3.73)	.155
Primary site		
Head and neck (Ref)	1.0	
Trunk	1.39 (0.86-2.27)	.181
Upper and lower extremities		
Other	1.05 (0.72-1.53)	.805
Other*	1.53 (1.01-2.32)	.044
Tumor size		
0-10 mm (Ref)	1.0	
11-20 mm	1.48 (0.79-2.78)	.222
21-30 mm	1.07 (0.60-1.92)	.818
31-40 mm	0.84 (0.42-1.68)	.627
41-50 mm	1.63 (0.82-3.25)	.166
>50 mm	1.61 (0.86-3.02)	.136
Bone metastasis		
No (Ref)	1.0	
Yes	1.18 (0.84-1.67)	.083
Brain metastasis		
No (Ref)	1.0	
Yes	3.85 (1.58-9.38)	.0030
Liver metastasis		
No (Ref)	1.0	
Yes	1.86 (1.37-2.52)	<.0001
Lung metastasis		
No (Ref)	1.0	
Yes	1.12 (0.77-1.64)	.555

CI, Confidence interval; *Ref*, reference.

*Owing to the nature of coding in the Surveillance, Epidemiology, and End Results database, the "other" category contains patients with overlapping primary skin sites and those with an unknown primary where Merkel cell carcinoma was first discovered in a lymph node or visceral location.

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https://doi.org/10.1016/j.jaad.2020.08.023

A retrospective cohort study of comprehensive peripheral and deep margin assessment in Merkel cell carcinoma: Standard margins may be unreliable

To the Editor: The National Comprehensive Cancer Network (NCCN) guidelines recommend wide excision with 1- to 2-cm margins to investing muscular fascia or pericranium for Merkel cell carcinoma (MCC) treatment. The ideal method of excision and surgical margin assessment has not been established. The goal of this study was to assess the adequacy of currently recommended surgical margins using complete histopathologic margin evaluation methods: Mohs micrographic surgery (MMS) or wide local excision with complete circumferential peripheral and deep margin assessment with intraoperative en face frozen sections.

An Institutional Review Board-approved retrospective review was performed of patients with MCC treated by MMS or wide local excision with complete circumferential peripheral and deep margin assessment (MMS-assessment) from January 2012 through May 2018. The initial and subsequent surgical margin and stages required for complete tumor extirpation were recorded. If a variable depth or width was noted in operative notes, the narrowest or most superficial dimensions were recorded. The Clark level of residual tumor was noted. Any residual margin positivity was graded in quartiles as the percentage of a ×2 microscopic field filled by tumor, designated as mild, 0% to 25%; mild-moderate, 26% to 50%; moderate, 51 to 75%; and high, 76% to 100%. All patients and slides were independently reviewed by A.V., T.K., and E.W. Summary statistics pertaining to positive margins were calculated to evaluate the sufficiency of standard margins.

There were 22 patients with MCC, mean tumor size 1.8 cm (SD, 1.3 cm), treated during the 6-year period.