Quantitative metastatic lymph node burden and survival in Merkel cell carcinoma

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Background: Current lymph node (LN) staging for Merkel cell carcinoma (MCC) does not account for the number of metastatic LNs, which is a primary driver of survival in multiple cancers.

Objective: To determine the impact of the number of metastatic LNs on survival in MCC.

Methods: Patients with MCC undergoing surgery were identified from the National Cancer Database (NCDB). The association between metastatic LN number and survival was modeled with restricted cubic splines. A novel nodal classification system was derived by using recursive partitioning analysis. MCC patients undergoing surgery in the Surveillance, Epidemiology, and End Results (SEER) Program were used as validation cohort.

Results: Among 3670 patients in the NCDB, increasing metastatic LN number was associated with decreased survival ($P < .001$). Mortality risk increased continuously with each additional positive LN when using multivariable, nonlinear modeling. According to a novel staging system derived via recursive partitioning analysis, the hazard ratio for death in multivariable regression compared with patients without LN involvement was 1.24 ($P = .049$), 2.08 ($P < .001$), 3.24 ($P < .001$), and 6.13 ($P < .001$) for the proposed N1a (1-3 metastatic LNs with microscopic detection), N1b (1-3 metastatic LNs with macroscopic detection), N2 (4-8 metastatic LNs), and N3 (≥9 metastatic LNs), respectively. This system was validated in the SEER cohort and showed improved concordance compared with the American Joint Committee on Cancer, Eighth Edition.

Limitations: Retrospective design.

Conclusions: Number of metastatic LNs is the dominant nodal factor driving survival in patients with MCC. (J Am Acad Dermatol 2021;84:312-20.)

Key words: immunotherapy; lymph node staging; Merkel cell carcinoma; National Cancer Database; radiation; SEER.

Merkel cell carcinoma (MCC) is a rare but aggressive cutaneous malignancy that is highly susceptible to local recurrence and metastatic spread.[1] Since MCC was first reported in 1972, its incidence has dramatically increased, according to populational studies in the United States

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and worldwide.[2-9] Moreover, MCC has the highest mortality rate of any cutaneous malignancy,[10,11] and MCC is the second most common cause of skin cancer death after melanoma. Immune checkpoint inhibitors were recently shown to produce high objective response rates in both treatment-naive advanced MCC and in chemotherapy-refractory MCC,[12-15] but their use is not standard of care for patients with curable, localized disease. Given the poor overall prognosis of MCC, there is a strong need for precise staging methods to guide treatment stratification for experimental treatment options.

The current American Joint Committee on Cancer's *AJCC Staging Manual*, Eighth Edition (AJCC 8E) TNM staging system considers only 2 lymph node (LN) factors: the location of metastatic LNs (regional vs in-transit) and method of metastasis detection (microscopic vs macroscopic).[16] However, it does not account for number of metastatic LNs, which has been shown to be a predominant and independent predictor of mortality in a variety of cancers.[17-26] Given that the relative importance of various LN factors has not been systemically investigated previously in MCC, we sought to determine whether quantitative nodal burden would be the dominant nodal factor driving survival in MCC and could produce a more accurate staging system.

CAPSULE SUMMARY

- Metastatic lymph node burden is the dominant predictor of survival in patients with Merkel cell carcinoma who undergo up-front surgery.
- Number of metastatic lymph nodes should be the foundation of nodal classification in this disease and may eventually drive adjuvant treatment decisions.

MATERIALS AND METHODS

Database information

Deidentified patient data were obtained from the National Cancer Database (NCDB), a clinical oncology database sponsored by the American College of Surgeons and the American Cancer Society as well as the Surveillance, Epidemiology, and End Results (SEER) 18 database. The NCDB contains clinical data from more than 1500 Commission on Cancer–accredited facilities and includes more than 70% of newly diagnosed cancer cases in the United States.[27] The SEER-18 database contains patient data from 18 cancer registries and includes approximately 28% of incident cancer cases in the United States.[28] This study was deemed exempt by the Cedars-Sinai institutional review board, and the requirement for patient consent was waived.

Patient selection

All patients 18 years or older undergoing up-front surgical resection for MCC (International Classification of Disease for Oncology, Third Edition, code 8247) with complete pathologic staging of LNs were assessed between 2004 and 2015 in the NCDB (Supplemental Fig 1; available via Mendeley at https://doi.org/10.17632/c2x4zk9gcm.1). Patients with clinical or pathologic distant metastasis were excluded. Patients with incomplete staging, treatment, or follow-up data were excluded. Finally, patients with positive metastatic LNs and with fewer than 5 LNs examined were excluded to ensure accurate nodal counts. In the SEER cohort, patients were excluded if they had unknown follow-up (n = 201), metastatic disease (n = 490), incomplete LN staging (n = 1526), and noncutaneous primary or T0 stage (n = 413).

Statistical analysis

Missing values were imputed by using the multivariate imputation by chained equations algorithm.[29,30] Baseline characteristics between patients with no metastatic LNs and positive metastatic LNs were compared by using the Welch *t* test and the Pearson chi-square test for continuous and categorical covariates, respectively (Supplemental Table I; available via Mendeley at https://doi.org/10.17632/c2x4zk9gcm.1). The primary outcome was overall survival (OS), as calculated from date of diagnosis to date of death or censoring at last follow-up. Median follow-up was calculated with the reverse Kaplan-Meier method.[31] Survival functions were derived by using the Kaplan-Meier method and were compared with the log-rank test.[32] Univariate and multivariable survival analyses were constructed by using Cox proportional hazards models. The proportional hazards assumption was assessed with scaled Schoenfeld residuals, and multicollinearity was assessed by the variable inflation factor.

Restricted cubic spline functions were used to model the nonlinear relationship between number of positive LNs and OS. Optimal numbers of knots were selected based on the lowest Akaike information criterion. Three knots were placed at 0, 1, and 5 positive LNs corresponding to 10th, 50th, and 90th percentiles, respectively.[33] The association

Abbreviations used:

AJCC 8E:	American Joint Committee on Cancer, Eighth Edition
CI:	confidence interval
ENE:	extranodal extension
HR:	hazard ratio
LN:	lymph node
MCC:	Merkel cell carcinoma
NCDB:	National Cancer Database
OS:	overall survival
RPA:	recursive partitioning analysis
SD:	standard deviation
SEER:	Surveillance, Epidemiology, and End Results

of the number of positive LNs and OS was illustrated by plotting the log relative hazard by the continuous number of positive LNs, with 0 LNs as the reference level. The change point in number of positive LNs was estimated with piecewise linear regression modeling.[34]

Recursive partitioning analysis (RPA) was used to derive a novel MCC nodal classification system based on available nodal covariates (ie, number of positive LNs, microscopic vs macroscopic detection, and in-transit metastases).[35,36] A conditional inference tree was generated by using optimized binary recursive partitioning and a permutation test with a quadratic form of the standardized log-rank statistic with Bonferroni-adjusted *P* values for multiple comparisons. The performance of the RPA-derived and the AJCC 8E nodal classification systems were assessed with concordance indices (or *C* statistics) by using the bootstrap method with 1000 replicates.[37] Statistical analyses were performed with R statistical software, version 3.5.1 (R Foundation, Vienna, Austria).[38] Significance was determined with 2-sided tests and at the $P < .05$ level.

RESULTS

Patient cohort

Overall, 3670 patients (mean age ± standard deviation [SD], 71.8 ± 10.6 years; n = 2337 men [63.7%]) met the inclusion criteria (Supplemental Table I and Supplemental Fig 1; available via Mendeley at https://doi.org/10.17632/c2x4zk9gcm.1). Median follow-up was 50.8 months. Among patients with nodal involvement, the mean number of LNs examined was 21.8 (SD, ±14.9) and the mean number of positive metastatic LNs was 4.4 (SD, ±5.7). Of the 696 patients with positive metastatic LNs, 47.7% (n = 332) had macroscopic detection of metastases, and 10.2% (n = 71) had in-transit metastases. In patients with node-positive disease and known extranodal extension (ENE) status, 38.9% (n = 243) were ENE positive.

Number of positive metastatic LNs

An increasing number of positive metastatic LNs was associated with poorer OS in univariate analysis and multivariate analysis after controlling for factors such as location (nodal vs in-transit) and detection method (macroscopic vs microscopic) ($P < .001$) (Table I). We observed that risk of death continuously increased with each additional positive LN (Fig 1). The relationship between OS and positive LN number was nonlinear, with increasing hazard ratio (HR) per positive LN to a change point of 3 metastatic LNs (HR, 1.17; 95% confidence interval [CI], 1.04-1.31; $P = .007$). The risk of death continued to increase beyond 3 metastatic LNs, although at a decreased rate (HR, 1.03; 95% CI, 1.01-1.05; $P = .009$).

Metastatic LN features

Macroscopic detection of metastasis (HR, 1.40; 95% CI, 1.09-1.80; $P = .008$) and the presence of in-transit metastasis (HR, 1.73; 95% CI, 1.27-2.36; $P = .001$) were both independently associated with increased mortality risk in multivariable models. Because 10.3% (n = 72) of patients with positive LNs were missing ENE status, we performed a separate multivariate analysis excluding these patients. Consistent with the main analysis, LN number ($P < .001$), in-transit metastasis ($P < .001$), and macroscopic detection ($P = .006$) were associated with worse survival (Supplemental Table II; available via Mendeley at https://doi.org/10.17632/c2x4zk9gcm.1). However, ENE had no significant impact on survival (HR, 1.11; 95% CI, 0.82-1.41; $P = .365$) and was excluded from the primary and final multivariable models.

Proposed nodal staging system

RPA based on number of metastasis-positive LNs, macroscopic versus microscopic nodal detection, and in-transit metastasis was used to generate a novel MCC nodal classification system (Supplemental Fig 2; available via Mendeley at https://doi.org/10.17632/c2x4zk9gcm.1). We identified 5 distinct clusters of patients, primarily based on number of LNs with metastasis, and used these to create a new nodal classification system (N0: 0 LNs; N1a: 1-3 positive LNs detected microscopically; N1b: 1-3 positive LNs detected macroscopically; N2: 4-8 positive LNs; N3: ≥9 positive LNs). Kaplan-Meier survival curves stratified by the novel nodal classification and AJCC 8E are

Table I. Univariable and multivariate Cox regression analyses of overall survival in Merkel cell carcinoma

	Univariate survival analysis		Multivariable survival analysis	
Characteristics	**HR (95% CI)**	***P***	**HR (95% CI)**	***P***
Age, year	1.058 (1.051-1.064)	<.001	1.054 (1.046-1.061)	<.001
Sex				
Male	1.000	—	1.000	—
Female	0.603 (0.533-0.682)	<.001	0.675 (0.594-0.766)	<.001
Race				
White	1.000	—	1.000	—
Black	0.49 (0.244-0.982)	.044	0.593 (0.294-1.196)	.144
Other	0.738 (0.436-1.25)	.259	0.98 (0.575-1.67)	.941
Anatomic site				
Head and neck	1.000	—	1.000	—
Trunk	1.052 (0.878-1.26)	.584	1.035 (0.855-1.252)	.724
Extremity	0.659 (0.585-0.742)	<.001	0.789 (0.696-0.894)	<.001
Facility type				
Nonacademic	1.000	—	1.000	—
Academic	0.793 (0.71-0.887)	<.001	0.81 (0.72-0.912)	<.001
Region of United States				
East	1.000	—	1.000	—
South	1.153 (0.991-1.342)	.066	1.019 (0.867-1.196)	.823
Midwest	1.09 (0.928-1.279)	.294	1.011 (0.858-1.191)	.895
West	1.107 (0.93-1.319)	.253	1.045 (0.873-1.25)	.632
Population density				
Rural	1.000	—	1.000	—
Urban	0.791 (0.708-0.885)	<.001	0.86 (0.764-0.968)	.012
Insurance				
Uninsured	1.000	—	1.000	—
Private	0.511 (0.241-1.085)	.081	0.764 (0.357-1.635)	.488
Medicaid	0.521 (0.194-1.398)	.195	0.639 (0.235-1.735)	.379
Medicare	1.129 (0.537-2.375)	.749	0.825 (0.388-1.751)	.616
Other government	0.545 (0.203-1.463)	.228	0.621 (0.229-1.683)	.349
Median household income				
<$48,000	1.000	—	1.000	—
≥$48,000	0.843 (0.75-0.947)	.004	0.986 (0.868-1.12)	.827
Charlson comorbidity score				
0	1.000	—	1.000	—
1	1.459 (1.276-1.667)	<.001	1.297 (1.131-1.488)	<.001
2	1.775 (1.411-2.233)	<.001	1.573 (1.248-1.984)	<.001
3+	1.977 (1.381-2.83)	<.001	1.636 (1.139-2.35)	.008
T classification				
T1	1.000	—	1.000	—
T2	1.493 (1.312-1.698)	<.001	1.341 (1.171-1.537)	<.001
T3	1.559 (1.192-2.041)	.001	1.364 (1.036-1.797)	.027
T4	2.445 (1.937-3.087)	<.001	1.454 (1.14-1.853)	.003
Number of metastatic lymph nodes*				
≤3	1.368 (1.261-1.485)	<.001	1.167 (1.042-1.307)	.007
>3	1.031 (1.013-1.049)	.001	1.027 (1.007-1.047)	.009
Extranodal extension				
Negative	1.000	—	†	
Positive	3.153 (2.649-3.753)	<.001		
In-transit metastases				
No	1.000	—	1.000	—
Yes	3.229 (2.478-4.206)	<.001	1.729 (1.265-2.364)	.001
Postoperative radiation				
No	1.000	—	1.000	—
Yes	0.862 (0.771-0.964)	.009	0.754 (0.67-0.848)	<.001

Continued

Table I. Cont'd

Characteristics	Univariate survival analysis		Multivariable survival analysis	
	HR (95% CI)	*P*	HR (95% CI)	*P*
Postoperative chemotherapy				
No	1.000	—	1.000	—
Yes	1.41 (1.141-1.743)	.001	1.106 (0.88-1.389)	.388
Nodal disease detection method				
Microscopic	1.000	—	1.000	—
Macroscopic	3.258 (2.794-3.801)	<.001	1.402 (1.093-1.797)	.008

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

*Number of positive metastatic lymph nodes was fitted as a restricted cubic spline function with 3 knots located at 0, 1, and 5 lymph nodes corresponding to the 10th, 50th, and 90th quantiles, respectively. HR is expressed in 1-unit increments.

†Dropped from multivariable model.

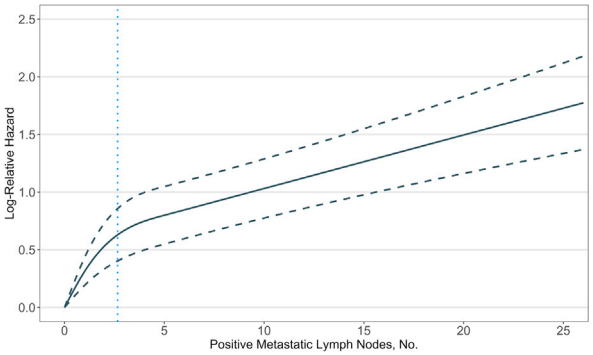

Fig 1. Increasing mortality risk with increasing number of positive lymph nodes (LNs) in Merkel cell carcinoma. The black solid line represents the multivariable smoothed restricted cubic spline plot of the natural logarithm of adjusted hazard ratio (HR) versus the number of positive metastatic LNs, with a reference value of 0. The gray dashed line represents estimated 95% confidence intervals of the predicted HRs. The blue vertical line represents the estimated change point, at 3 positive LNs, of the impact of number of LNs on survival.

shown in Fig 2 and showed significant differences in survival ($P < .001$). The 3-year OS rates for the proposed nodal staging system are 78.2%, 66.1%, 56.7%, 35.3%, and 13.6% for the proposed N0, N1a, N1b, N2, and N3, respectively (Table II).

In multivariate analysis (Supplemental Table III; available via Mendeley at https://doi.org/10.17632/c2x4zk9gcm.1), the RPA-derived nodal classification predicted outcomes across a greater risk spectrum than the current AJCC system. Compared with patients without nodal involvement, the HR for death for the proposed N1a, N1b, N2, and N3 was 1.24 ($P = .049$), 2.08 ($P < .001$), 3.24 ($P < .001$), and 6.13 ($P < .001$), respectively (Table II). Finally, in subgroup analysis, metastatic LN number was significantly associated with survival within each individual AJCC 8E nodal stage (N1a, N1b, and N2) (Supplemental Fig 3; available via Mendeley at https://doi.org/10.17632/c2x4zk9gcm.1).

Our proposed RPA-derived system was confirmed by independent analysis of the SEER database. Of the 2624 patients who met inclusion criteria in the SEER database, the proposed nodal classification system showed significant differences in both overall survival and cause-specific survival on Kaplan-Meier analysis (Supplemental Fig 4; available via Mendeley at https://doi.org/10.17632/c2x4zk9gcm.1). Predictive ability of survival was improved with the RPA-derived staging system (optimism-corrected *C* statistic, 0.734; 95% CI, 0.719-0.748) over the AJCC 8E TNM system (*C* statistic, 0.731; 95% CI, 0.716-0.745).

DISCUSSION

The presence of LN involvement has been previously shown to adversely affect survival in MCC.[39,40] Although it is plausible that the risk of death would increase with increasing number of metastatic LNs, there have been no studies to our knowledge that systemically measured the impact of number of metastatic lymph nodes in MCC as a continuous nonlinear function. Here, we quantified the cumulative effect of increasing metastatic LN burden on overall survival in this disease. We showed that each additional metastatic node conferred an increased risk of death, even after adjusting for a variety of tumor- and patient-associated factors. This effect was most pronounced for the first 3 metastatic LNs, with an added 17% risk of death for each metastasis-positive LN. Beyond 3 LNs, the risk of death continued to increase at a reduced rate of 3% per each additional LN.

Although extranodal extension is a critical nodal factor in other cancers, such as breast and head and neck, we observed that ENE was not significantly associated with survival in our cohort, and it was

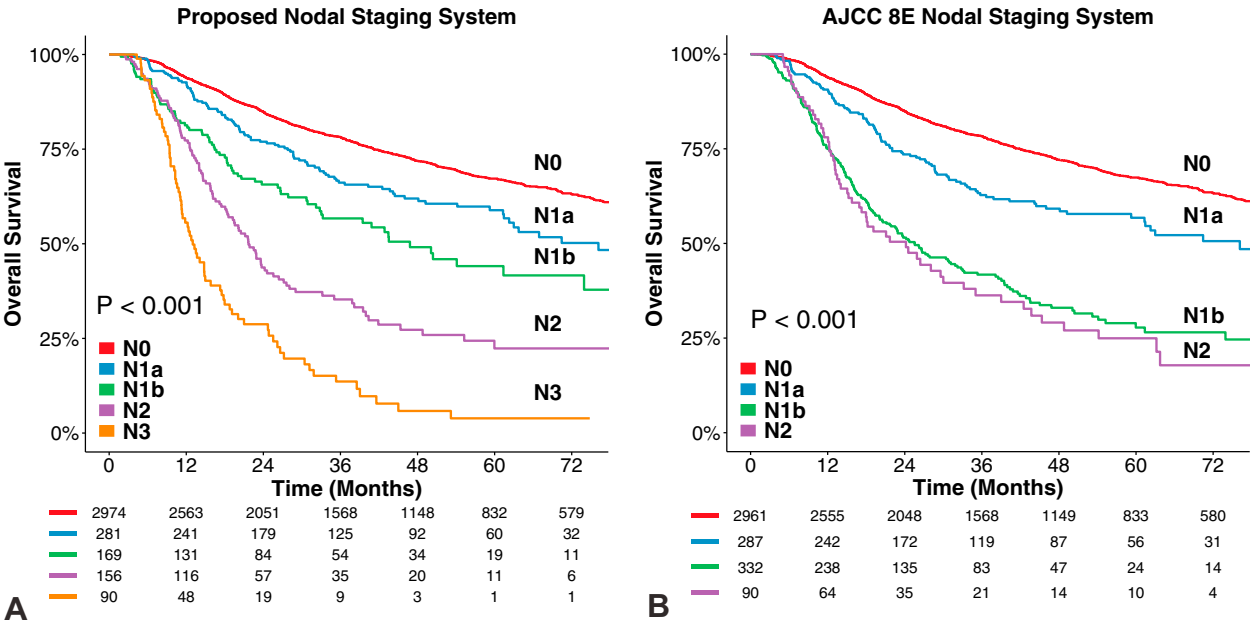

Fig 2. Overall survival for the proposed and American Joint Commission on Cancer, Eighth Edition (AJCC 8E) TNM nodal classification systems. **A**, Kaplan-Meier estimate for the proposed nodal classification system. **B**, Kaplan-Meier estimate for the AJCC 8E TNM staging system. Below each figure are the number of patients at risk for each nodal stage group at their respective time points. Of note, 19 patients with AJCC 8E N2 disease had 0 metastasis-positive LNs and were reclassified as N0 in the RPA-derived system. Conversely, 6 patients with metastasis-positive LNs were incorrectly coded as having AJCC 8E N0 disease, leading to minor differences in the number of patients with N0 disease in the AJCC 8E and RPA-derived systems. *AJCC 8E,* American Joint Committee on Cancer, Eighth Edition; *LN,* lymph node; *LN*$^+$, metastatic lymph node; *RPA,* recursive partitioning analysis.

excluded from our RPA. Moreover, although traditional nodal factors for MCC like nodal detection method (macroscopic vs microscopic) and in-transit metastasis were individually associated with survival, their impact in RPA was limited compared with the number of metastatic LNs, which drove the RPA-derived staging system. Thus, the impact of metastatic LN number overwhelms the impact of traditional nodal factors in MCC.

Given that the AJCC 8E nodal classification does not account for number of metastasis-positive LNs, each individual AJCC 8E nodal classification is highly heterogeneous. For example, in our study, patients with AJCC 8E N1a disease and 10 metastasis-positive LNs had much poorer survival than patients with N1a disease with 1 metastasis-positive node. As a result, we found that our proposed RPA-derived nodal classification system had improved predictive capability compared with the AJCC 8E system. In addition to improved predictive capability, the RPA-derived system also distributes patients across a wider spectrum of mortality risk. For example, the highest risk category in the RPA-derived system had more than double the risk of mortality as the highest risk category in the AJCC system (6.1 vs 2.9 times the risk of death in comparison to patients with N0 disease, respectively). Moreover, the proposed system distributes patients across distinct groups without overlapping prognoses as observed with AJCC 8E staging for N1b and N2 disease. Finally, AJCC 8E N3 disease (in-transit metastasis with LN metastasis) is virtually nonexistent (10 patients out of more than 15,000 total MCC cases in the NCDB, none meeting inclusion criteria for this analysis because they either had distant metastases or did not have LNs removed surgically). We further validated our proposed nodal staging system in an independent cohort of patients from the SEER database, which was predictive for overall survival and cause-specific survival.

Because patients with high nodal burden harbor a much higher risk of death than those with limited nodal disease, these patients may potentially benefit from treatment intensification of adjuvant therapy, such as immune checkpoint inhibitors or other novel systemic therapies. Both pembrolizumab and

Table II. Survival for proposed and AJCC 8E TNM nodal classification systems for Merkel cell carcinoma*

N classification	Criteria	3-Year OS, %	HR (95% CI)
AJCC Eighth Edition TNM nodal staging system			
N0	0 LN^+	78.3	1.00 (ref)
N1a	Clinically occult LN metastasis	62.8	1.51 (1.23-1.86)
N1b	Clinically and/or radiographically detected LN metastasis	41.8	2.94 (2.48-3.48)
N2	In-transit metastasis without LN metastasis	36.3	2.90 (2.20-3.83)
N3	In-transit metastasis with LN metastasis	N/A	N/A
Proposed nodal staging system			
N0	0 LN^+	78.2	1.00 (ref)
N1a	1-3 LNs^+ with microscopic detection	66.1	1.24 (1.00-1.54)
N1b	1-3 LNs^+ with macroscopic detection	56.7	2.08 (1.63-2.65)
N2	4-8 LNs^+	35.3	3.24 (2.58-4.07)
N3	$\geq$9 LNs^+	13.6	6.13 (4.74-7.93)

AJCC 8E, American Joint Committee on Cancer, Eighth Edition; *CI,* confidence interval; *HR,* hazard ratio; *LN,* lymph node; *N/A,* not applicable; *OS,* overall survival; *ref,* reference.

*HRs and 95% CIs are the result of multivariable Cox regression. Only 10 out of more than 15,000 cases of Merkel cell carcinoma were classified as AJCC 8E stage N3, with none meeting the inclusion criteria for this analysis because of distant metastases or incomplete nodal staging.

avelumab have relatively high response rates in patients with treatment-naive advanced MCC and chemotherapy-refractory, metastatic MCC, respectively.[12-15] Given these promising results with immunotherapy in advanced MCC, patients with high metastatic LN burden are excellent candidates for receiving immune checkpoint inhibitors in the adjuvant setting. Several clinical trials are investigating the use of immunotherapy in the adjuvant (NCT02196961, NCT03271372) and neoadjuvant settings (NCT02488759).[41,42] It is plausible that the patients with the most to gain from adjuvant therapy and systemic therapy are the high-risk patients identified based on number of metastatic LNs, and this should be an avenue of future investigation.

The current National Comprehensive Center Network guidelines recommend sentinel LN biopsy as a first step in the management of MCC.[43] For those with a positive sentinel LN biopsy result, the current recommendations are for radiation therapy to the nodal basin and/or nodal dissection. The fact that not all patients undergo completion LN dissection, and therefore may not have an accurate count of the number of metastasis-positive LNs, is a potential limitation of implementing our proposed staging system. Similar issues have been noted in other aggressive cutaneous malignancies, such as in melanoma, where staging is based predominantly on LN number, even though not all patients receive completion LN dissection.[44] Nonetheless, we included patients with node-positive disease and as few as 5 LNs examined, suggesting that our results are still applicable to those with limited dissection. In addition, our staging system may be particularly applicable to MCC of the head and neck (~40% of patients in this study) because the morbidity of a limited neck dissection is lower in this region versus that of other nodal basins.[45,46] Given that, in the future, it is conceivable that number of metastatic LNs, the dominant prognostic factor in this disease, could drive adjuvant systemic therapy recommendations, it is possible that completion LN dissection for patients with node-positive disease could become more widespread.

Limitations

Of the 15,137 patients with MCC registered in the NCDB, only 3670 met the inclusion criteria of this study. Approximately 7300 patients were excluded because of incomplete pathologic staging. Nevertheless, we believe these results are generalizable given the relatively large cohort and our validation in the SEER dataset. Additionally, although we included a broad range of disease- and node-specific factors in our multivariate analysis, factors such as Merkel cell polyomavirus positivity, smoking history, performance status, and sun-exposure history were not available in the NCDB, and immunosuppression status had large amounts of missing data and could not be imputed. Finally, our results are specific to pathologic staging and may not translate to clinically staged patients, given that precisely determining metastatic LN number is more difficult via imaging.[47] Nonetheless, our findings provide strong quantitative evidence to guide pathologic nodal staging in MCC.

CONCLUSIONS

The number of metastatic LNs is the dominant predictor of survival in patients with MCC, having substantially more impact on survival than traditional nodal factors such as in-transit metastases, microscopic versus macroscopic metastasis, and ENE. We showed that each metastatic LN continuously increases the risk of death in MCC. Using unbiased RPA, we developed a novel nodal classification system based predominantly on number of positive LNs that outperforms the current AJCC 8E staging system across multiple domains. In total, these data strongly support the inclusion of metastatic LN number as the primary component of MCC nodal classification and may redefine adjuvant treatment escalation.

REFERENCES

1. Coggshall K, Tello TL, North JP, Yu SS. Merkel cell carcinoma: an update and review: pathogenesis, diagnosis, and staging. *J Am Acad Dermatol*. 2018;78:433-442.
2. Agelli M, Clegg LX. Epidemiology of primary Merkel cell carcinoma in the United States. *J Am Acad Dermatol*. 2003; 49:832-841.
3. Hodgson NC. Merkel cell carcinoma: changing incidence trends. *J Surg Oncol*. 2005;89:1-4.
4. Fitzgerald TL, Dennis S, Kachare SD, Vohra NA, Wong JH, Zervos EE. Dramatic increase in the incidence and mortality from Merkel cell carcinoma in the United States. *Am Surg*. 2015;81:802-806.
5. Youlden DR, Soyer HP, Youl PH, Fritschi L, Baade PD. Incidence and survival for Merkel cell carcinoma in Queensland, Australia, 1993-2010. *JAMA Dermatol*. 2014;150:864-872.
6. Fondain M, Du Thanh A, Bessaoud F, Dereure O, Tretarre B, Guillot B. Epidemiological trends in Merkel cell carcinoma in southern France: a registry-based study. *Br J Dermatol*. 2017; 176:1379-1381.
7. Zaar O, Gillstedt M, Lindelof B, Wennberg-Larko AM, Paoli J. Merkel cell carcinoma incidence is increasing in Sweden. *J Eur Acad Dermatol Venereol*. 2016;30:1708-1713.
8. Reichgelt BA, Visser O. Epidemiology and survival of Merkel cell carcinoma in the Netherlands. A population-based study of 808 cases in 1993-2007. *Eur J Cancer*. 2011;47:579-585.
9. Girschik J, Thorn K, Beer TW, Heenan PJ, Fritschi L. Merkel cell carcinoma in Western Australia: a population-based study of incidence and survival. *Br J Dermatol*. 2011;165:1051-1057.
10. Becker JC. Merkel cell carcinoma. *Ann Oncol*. 2010;21(Suppl 7): vii81-vii85.
11. Albores-Saavedra J, Batich K, Chable-Montero F, Sagy N, Schwartz AM, Henson DE. Merkel cell carcinoma demographics, morphology, and survival based on 3870 cases: a population based study. *J Cutan Pathol*. 2010;37:20-27.
12. Nghiem PT, Bhatia S, Lipson EJ, et al. PD-1 blockade with pembrolizumab in advanced Merkel cell carcinoma. *N Engl J Med*. 2016;374:2542-2552.
13. Kaufman HL, Russell J, Hamid O, et al. Avelumab in patients with chemotherapy-refractory metastatic Merkel cell carcinoma: a multicentre, single-group, open-label, phase 2 trial. *Lancet Oncol*. 2016;17:1374-1385.
14. Nghiem P, Bhatia S, Lipson EJ, et al. Durable tumor regression and overall survival in patients with advanced Merkel cell carcinoma receiving pembrolizumab as first-line therapy. *J Clin Oncol*. 2019;37:693-702.
15. D'Angelo SP, Russell J, Lebbe C, et al. Efficacy and safety of first-line avelumab treatment in patients with stage IV metastatic Merkel cell carcinoma: a preplanned interim analysis of a clinical trial. *JAMA Oncol*. 2018;4:e180077.
16. Amin MB. *American Joint Committee on Cancer, American Cancer Society. AJCC Cancer Staging Manual*. Chicago, IL: Springer; 2017.
17. Ho AS, Kim S, Tighiouart M, et al. Association of quantitative metastatic lymph node burden with survival in hypopharyngeal and laryngeal cancer. *JAMA Oncol*. 2018;4: 985-989.
18. Ho AS, Kim S, Tighiouart M, et al. Metastatic lymph node burden and survival in oral cavity cancer. *J Clin Oncol*. 2017;35: 3601-3609.
19. Roberts TJ, Colevas AD, Hara W, Holsinger FC, Oakley-Girvan I, Divi V. Number of positive nodes is superior to the lymph node ratio and American Joint Committee on Cancer N staging for the prognosis of surgically treated head and neck squamous cell carcinomas. *Cancer*. 2016;122:1388-1397.
20. Sinha P, Kallogjeri D, Gay H, et al. High metastatic node number, not extracapsular spread or N-classification is a node-related prognosticator in transorally-resected, neck-dissected p16-positive oropharynx cancer. *Oral Oncol*. 2015; 51:514-520.
21. O'Sullivan B, Huang SH, Su J, et al. Development and validation of a staging system for HPV-related oropharyngeal cancer by the International Collaboration on Oropharyngeal Cancer Network for Staging (ICON-S): a multicentre cohort study. *Lancet Oncol*. 2016;17:440-451.
22. Schiavina R, Borghesi M, Brunocilla E, et al. Differing risk of cancer death among patients with lymph node metastasis after radical prostatectomy and pelvic lymph node dissection: identification of risk categories according to number of positive nodes and Gleason score. *BJU Int*. 2013; 111:1237-1244.
23. Ditto A, Martinelli F, Lo Vullo S, et al. The role of lymphadenectomy in cervical cancer patients: the significance of the number and the status of lymph nodes removed in 526 cases treated in a single institution. *Ann Surg Oncol*. 2013;20: 3948-3954.
24. Rajeev P, Ahmed S, Ezzat TM, Sadler GP, Mihai R. The number of positive lymph nodes in the central compartment has prognostic impact in papillary thyroid cancer. *Langenbecks Arch Surg*. 2013;398:377-382.
25. Esfandiari NH, Hughes DT, Yin H, Banerjee M, Haymart MR. The effect of extent of surgery and number of lymph node metastases on overall survival in patients with medullary thyroid cancer. *J Clin Endocrinol Metab*. 2014;99:448-454.
26. Aro K, Ho AS, Luu M, et al. Development of a novel salivary gland cancer lymph node staging system. *Cancer*. 2018;124: 3171-3180.
27. Bilimoria KY, Stewart AK, Winchester DP, Ko CY. The National Cancer Data Base: a powerful initiative to improve cancer care in the United States. *Ann Surg Oncol*. 2008;15:683-690.
28. National Cancer Institute. Surveillance, epidemiology, and end results program. Available at: http://seer.cancer.gov. Accessed November 2, 2019.
29. van Buuren S. Multiple imputation of discrete and continuous data by fully conditional specification. *Stat Methods Med Res*. 2007;16:219-242.
30. Van Buuren S, Brand JPL, Groothuis-Oudshoorn CGM, Rubin DB. Fully conditional specification in multivariate imputation. *J Stat Comput Sim*. 2006;76:1049-1064.

31. Schemper M, Smith TL. A note on quantifying follow-up in studies of failure time. *Control Clin Trials*. 1996;17:343-346.
32. Kalbfleisch JD, Prentice RL. *The Statistical Analysis of Failure Time Data*. Hoboken, NJ: Wiley; 2002.
33. Harrell FE Jr. *Regression modeling strategies: with applications to linear models, logistic and ordinal regression, and survival analysis*. New York: Springer; 2015.
34. Muggeo VMR. Estimating regression models with unknown break-points. *Stat Med*. 2003;22:3055-3071.
35. Hothorn T, Hornik K, Zeileis A. Unbiased recursive partitioning: a conditional inference framework. *J Comput Graph Stat*. 2006; 15:651-674.
36. Segal MR. Regression trees for censored data. *Biometrics*. 1988; 44:35-47.
37. Harrell FE, Lee KL, Mark DB. Multivariable prognostic models: issues in developing models, evaluating assumptions and adequacy, and measuring and reducing errors. *Stat Med*. 1996; 15:361-387.
38. Team RC. *R: A Language and Environment for Statistical Computing*. Vienna, Austria: R Foundation for Statistical Computing; 2013.
39. Harms KL, Healy MA, Nghiem P, et al. Analysis of prognostic factors from 9387 Merkel cell carcinoma cases forms the basis for the new 8th edition AJCC staging system. *Ann Surg Oncol*. 2016;23:3564-3571.
40. Allen PJ, Bowne WB, Jaques DP, Brennan MF, Busam K, Coit DG. Merkel cell carcinoma: prognosis and treatment of patients from a single institution. *J Clin Oncol*. 2005;23: 2300-2309.
41. Hollebecque A, Meyer T, Moore KN, et al. An open-label, multicohort, phase I/II study of nivolumab in patients with virus-associated tumors (CheckMate 358): efficacy and safety in recurrent or metastatic (R/M) cervical, vaginal, and vulvar cancers. *J Clin Oncol*. 2017;35:5504.
42. Topalian SL, Bhatia S, Kudchadkar RR, et al. Nivolumab (Nivo) as neoadjuvant therapy in patients with resectable Merkel cell carcinoma (MCC) in CheckMate 358. *J Clin Oncol*. 2018;36:9505.
43. Bichakjian CK, Olencki T, Aasi SZ, et al. Merkel cell carcinoma, version 1.2018, NCCN clinical practice guidelines in oncology. *J Natl Compr Canc Netw*. 2018;16:742-774.
44. Faries MB, Thompson JF, Cochran AJ, et al. Completion dissection or observation for sentinel-node metastasis in melanoma. *N Engl J Med*. 2017;376:2211-2222.
45. Geltzeiler M, Monroe M, Givi B, Vetto J, Andersen P, Gross N. Regional control of head and neck melanoma with selective neck dissection. *JAMA Otolaryngol Head Neck Surg*. 2014;140: 1014-1018.
46. Beitsch P, Balch C. Operative morbidity and risk factor assessment in melanoma patients undergoing inguinal lymph node dissection. *Am J Surg*. 1992;164:462-465.
47. Lemos BD, Storer BE, Iyer JG, et al. Pathologic nodal evaluation improves prognostic accuracy in Merkel cell carcinoma: analysis of 5823 cases as the basis of the first consensus staging system. *J Am Acad Dermatol*. 2010;63:751-761.