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Primary Treatment Selection for Clinically Node-Negative Merkel Cell Carcinoma of the Head and Neck

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Abstract

Objective. Merkel cell carcinoma practice guidelines recommend sentinel lymph node biopsy after wide local excision for the initial management of clinically node-negative disease without distant metastases (cN0M0). Despite guideline publication, treatment selection remains variable. We hypothesized that receipt of guideline-recommended care would be more common in patients evaluated at academic centers and institutions with high melanoma case volumes and that such therapy would be associated with improved overall survival.

Study Design. Retrospective cohort analysis.

Setting. The National Cancer Database from 2004 to 2015.

Methods. A total of 3500 patients were included. We utilized Kaplan-Meier analysis and logistic and Cox proportional hazard regressions. Survival analysis was performed on inverse probability–weighted cohorts.

Results. There has been a trend toward evaluation at academic programs at a rate of 1.58% of patients per year (95% CI, 1.06%-2.11%) since 2004. However, the percentage of patients receiving guideline-compliant primary tumor excision and lymph node evaluation has plateaued at approximately 50% since 2012. Guideline-compliant surgical management was more commonly provided to patients evaluated at academic programs than nonacademic programs but only when those institutions had a high melanoma case volume (odds ratio, 2.01; 95% CI, 1.62-2.48). Receipt of guideline-compliant primary tumor excision and lymph node evaluation was associated with improved overall survival (hazard ratio, 0.70; 95% CI, 0.64-0.76).

Conclusion. Facility factors affect rates of receipt of guideline-compliant initial surgical management for patients with node-negative Merkel cell carcinoma. Given the survival benefit of such treatment, patients may benefit from care at hospitals with high melanoma case volumes.

Keywords

Merkel cell carcinoma, survival, treatment selection, NCDB, surgical oncology, case volume

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Merkel cell carcinoma (MCC) is an aggressive cutaneous neuroendocrine tumor that is increasing in incidence in the United States and around the world.[1-9] Risk factors for MCC development include increased age, ultraviolet exposure, immunosuppressed status, and presence of Merkel cell polyomavirus.[10-14] Indeed, in the United States, Merkel cell polyomavirus DNA has been found in approximately 80% of MCC tumors.[12] The overall incidence of MCC in the United States increased 95.2% between 2000 and 2013 to 0.7 cases per 100,000.[5] This incidence rate increases to 9.8 cases per 100,000 in those aged $\geq$85 years.[5] In 2013, 2488 new cases were diagnosed, and the annual incidence is projected to reach 3284 in 2025 as the population ages.[5] Survival of MCC varies in patients with local, nodal, and distant disease, with 5-year survival rates of 78%, 52%, and 19%, respectively.[15]

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Consensus management guidelines for MCC are published by the National Comprehensive Cancer Network (NCCN) and were first released in 2004, with subsequent updates in 2006, 2009, 2014, 2018, 2019, and 2020.[16-22] Per current guidelines, patients with clinically node-negative status without distant metastatic disease (cN0M0) should receive sentinel lymph node biopsy (SLNB), followed by wide local excision or Mohs micrographic surgery of the primary tumor.[22] Guidelines for the initial management of cN0M0 disease have not changed since 2004 for all primary sites, except the head and neck.

For the head and neck, there was an alteration in the guidelines from 2009 to 2018, when patients were recommended to have wide local excision with either SLNB or radiation therapy (RT) to the lymph node (LN) drainage bed.[16,19] The recommendation in the 2018 guidelines reverted to SLNB without RT for all patients.[16] The 2009 alteration arose because head and neck lymphatic drainage was believed to be complex and aberrant, raising concern for false-negative SLNB results.[17,19,23] A recent systematic review revealed false-negative rates for the head and neck to be 19.2%, defined as a negative SLNB finding with subsequent regional nodal recurrence.[24] This result is similar to the 17.6% rate across all sites,[25] thus alleviating concern of aberrant lymphatic drainage.

In consideration of the rising incidence of MCC, we aimed to evaluate trends in treatment selection in patients with cN0M0 MCC of the head and neck and to determine the effect of treatment selection on overall survival (OS). We hypothesized that receipt of guideline-compliant primary tumor excision and LN evaluation would be more common in academic centers. Furthermore, given the similarities in management between MCC and cutaneous melanoma,[26] we hypothesized that institutions with high melanoma case volumes would be more likely to follow NCCN practice guidelines. Finally, we hypothesized that receipt of surgical care compatible with current guidelines for the initial management of MCC would be associated with a survival benefit.

Methods

Inclusion Criteria

The National Cancer Database (NCDB) was queried from 2004 through 2015 for MCC with histology code 8247. Previous classifications of MCC were assessed and excluded (Supplemental Methods, available online).[27,28] Codes for the head and neck included C44.0 to C44.4 (*International Coding of Diseases for Oncology, Third Edition*). Patients who were <18 years of age, had all treatment decisions outside of the reporting facility, had unknown surgery type (<1% of patients), or had unknown LN surgery were excluded.

Variables

Per consensus guidelines, wide local excision of the primary tumor is preferred, but the option for Mohs micrographic surgery remains.[22] Due to ambiguity in the coding, the definition of ''guideline-compliant primary tumor excision'' was broadened to also capture surgery from gross excision after biopsy (code 30) through amputation (code 60). Mohs micrographic surgery was included as guideline-compliant primary tumor excision. Such inclusion increases the sensitivity of the analysis toward receipt of guideline-compliant care but may risk overestimating true parameters.[29] LN evaluation was defined by the NCDB as biopsy, aspiration, or surgical LN excision. Sensitivity analysis for this coding with more specific data from 2012 to 2015 was performed.

Statistical Analyses

Variable recoding was performed with SPSS version 25.0 or 26.0 (IBM Corp). Statistical analyses were performed with SAS version 9.4 (SAS Institute Inc). All statistical tests performed had a prespecified α value of 0.05, and 95% CIs are reported in the text and as error bars in figures. *P* values are obtained from 2-tailed tests when applicable.

Multivariable binary logistic regression models were run with a forward stepwise method. Race was not included in multivariable regression models due to the predominance of White individuals. Survival was assessed with inverse probability–weighted (IPW) Kaplan-Meier (KM) and Cox proportional hazard regression analyses. Probabilities were calculated from propensity scores (PSs). PSs were calculated by assessing odds for guideline-compliant excision plus LN evaluation (treatment group) versus other forms of treatment (control group; Supplemental Methods, available online). Patients who received no therapy (no surgery, no LN evaluation, and no RT) were excluded from the PS analysis. Variables included in the PS analysis can be found in the balance assessment (Supplemental Table S1). Survival analysis was limited to those who survived $\geq$3 months from diagnosis, to limit immortal time bias.[30] Statistical significance for IPW KM analysis was assessed with log-rank tests. IPW Cox regression was performed only with variables included in the PS calculation to ensure double robustness.

Ethics

This work was deemed exempt from Institutional Review Board committee review by the Yale Human Research Protection Program.

Results

Patient Characteristics

A total of 3500 patients with cN0M0 MCC of the head and neck were included for analysis (Supplemental Figure S1, available online). The median age at diagnosis was 79 years (interquartile range, 71-85), and disease was more common among men (61.1%), White patients (97.7%), and patients with a Charlson-Deyo comorbidity score of 0 (76.6%; Supplemental Table S2). Overall, 6.2% of patients were evaluated in community cancer programs, 38.0% in comprehensive community cancer programs, 47.9% in academic/research programs, and 7.9% in integrated network cancer programs. By melanoma case volume, 12.8% of patients were evaluated in hospitals in the bottom 2 quartiles ($\leq$50th

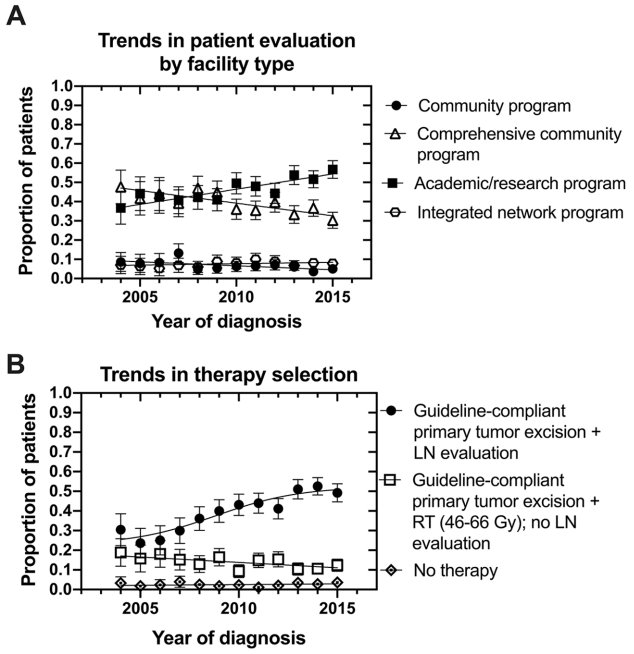

Figure 1. Evaluation of the changes in the trends in care by (A) facility type and (B) treatment selection. Error bars indicate 95% CI. LN, lymph node; RT, radiation therapy.

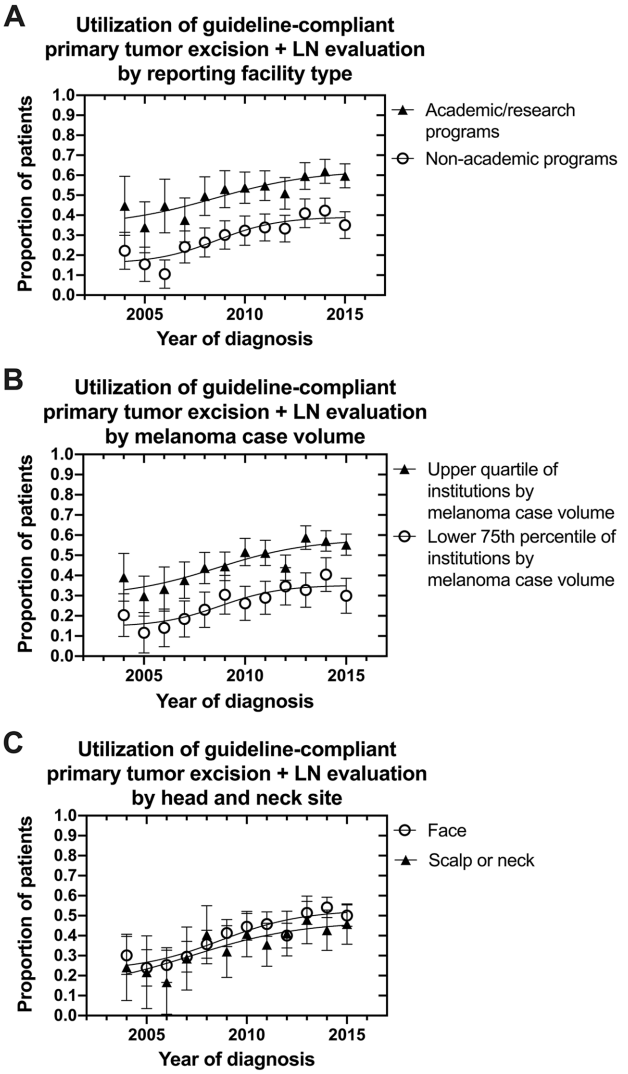

Figure 2. Trends in the utilization of guideline-compliant primary tumor excision in combination with lymph node (LN) evaluation by (A) facility type, (B) institutional melanoma case volume, and (C) primary site. Error bars indicate 95% CI.

percentile), 19.0% in the third quartile, and 68.1% in the upper quartile (>75th percentile). The correlation between treatment at an academic facility and treatment at a hospital in the upper quartile by melanoma case volume was 0.504 by Pearson correlation with a covariance of 0.117.

We assessed the sensitivity of our coding for LN evaluation on the basis of specific details included for patients diagnosed between 2012 and 2015. Of patients who received LN evaluation from 2012 to 2015, 69.5% received SLNB; 14.3% had excision of 1 to 3 LNs; 14.6% received more extensive LN evaluation (≥4 nodes excised); and 1.6% received LN aspiration or unspecified LN evaluation. From 2004 to 2015, of those who had LN evaluation, 22.3% had at least 1 LN positive on pathologic examination.

Trends in Care

We observed a linear trend toward being evaluated in academic programs, with 36.7% of patients receiving at least part of their treatment decisions at academic programs in 2004 as compared with 56.7% in 2015 (**Figure 1A**). The percentage of patients evaluated at academic programs increased at a rate of 1.58% per year (95% CI, 1.06%-2.11%). Evaluation at community programs and comprehensive community programs declined at a rate of −0.41% per year (95% CI, −0.67% to −0.16%) and −1.31% per year (95% CI, −1.82% to −0.80%), respectively.

There has also been a trend across all facilities toward providing guideline-compliant primary tumor excision and LN evaluation (**Figure 1B**), from 30.5% (95% CI, 22.4%-38.6%) in 2004 to 49.2% (95% CI, 44.6%-53.8%) in 2015. However, the trend deviates from linearity and appears to plateau starting in 2012. In patients who did not receive LN evaluation, there has been a decline in the utilization of guideline-compliant primary tumor excision plus RT. Furthermore, while utilization of guideline noncompliant therapies has declined (Supplemental Figure S2, available online), such therapies were more likely received by older patients in whom treatment of the neck was more commonly noncompliant than therapy to the primary site (Supplemental Table S3).

On subgroup analysis, utilization of wide local excision has remained largely unchanged, while gross excision after biopsy has increased (Supplemental Figure S3, available online). Furthermore, academic programs and institutions with high melanoma case volumes have been more likely to provide guideline-compliant primary tumor excision and LN evaluation (**Figure 2A** and **2B**) to approximately 20% more

patients per year than other institutions. There is no difference between the utilization of guideline-compliant primary tumor excision and LN in patients with MCC of the face or scalp/neck (**Figure 2C**).

We next assessed factors associated with receipt of guideline-compliant primary tumor excision and LN evaluation as compared with no therapy or other therapy types (**Table 1**). Patients were more likely to receive guideline-compliant primary tumor excision and LN evaluation at academic programs only if that academic program also had a high melanoma case volume (odds ratio [OR], 2.01; 95% CI, 1.62-2.48). There was no statistically significant difference at academic programs as compared with nonacademic programs in institutions with a low melanoma case volume (≤75th percentile; OR, 0.98; 95% CI, 0.60-1.61). High institutional melanoma case volume was associated with an increased likelihood for provision of guideline-compliant primary tumor excision and LN evaluation at nonacademic (OR, 1.45; 95% CI, 1.15-1.83) and academic (OR, 2.97; 95% CI, 1.83-4.80) programs. Patients who traveled farther for evaluation were more likely to receive guideline-compliant primary tumor excision and LN evaluation and were more likely to seek out academic facilities and institutions with high melanoma case volumes ($P < .001$; Supplemental Table S4, available online). Factors associated with a decreased likelihood for receipt of guideline-compliant primary tumor excision and LN evaluation were increasing age, higher clinical T stage, and evaluation in institutions in New England or the mid-Atlantic regions as compared with the central United States.

Survival Analysis

Based on IPW KM analysis (**Figure 3**), OS for patients who received guideline-compliant primary tumor excision and LN evaluation (median survival, 80.3 months; 95% CI, 70.4-100.5) was significantly improved (log rank, $P < .001$) as compared with patients who received other forms of treatment (median survival, 54.0 months; 95% CI, 46.0-65.3).

On multivariable IPW analysis, receipt of guideline-compliant primary tumor excision and LN evaluation was associated with improved OS (hazard ratio, 0.70; 95% CI, 0.64-0.76; **Table 2**). Factors associated with an increased risk for death included increasing age, male sex, increasing Charlson-Deyo score, increasing clinical T stage, MCC of the ear, and MCC of the scalp or neck. Geographic location of treatment was associated with survival. Treatment at an academic facility was associated with a decreased risk for death (hazard ratio, 0.88; 95% CI, 0.78-0.99), while there was no detectable difference in survival based on institutional melanoma case volume. On post hoc analysis, there was no clinically significant difference in OS when patients who received biopsy followed by ''gross excision'' were excluded or when patients who received LN evaluation other than SLNB were excluded from analyses (data not shown).

Table 1. Multivariable Binary Logistic Model: Factors Associated With Receipt of Guideline-Compliant Primary Tumor Excision and Lymph Node Evaluation vs No Therapy or Other Therapy.

	Odds ratio (95% CI)	*P* value
Demographic factors		
Age, y		
≤64	Reference	
65-74	0.79 (0.60-1.04)	.098
75-84	0.53 (0.41-0.68)	<.001
≥85	0.23 (0.17-0.31)	<.001
Charlson-Deyo score		
0	Reference	
1	0.92 (0.75-1.15)	.47
≥2	0.83 (0.59-1.16)	.27
Geographic location		
Central	Reference	
New England	0.68 (0.49-0.95)	.023
Mid-Atlantic	0.66 (0.51-0.86)	.002
South Atlantic	0.93 (0.75-1.15)	.49
Mountain	1.45 (0.98-2.16)	.065
Pacific	0.91 (0.70-1.18)	.48
Distance traveled for evaluation, mi		
≤10	Reference	
10-25	1.26 (1.03-1.55)	.025
25-50	1.46 (1.15-1.86)	.002
>50	1.56 (1.21-2.00)	<.001
Clinical factors		
Tumor clinical T stage		
T1	Reference	
T2 or T3	0.73 (0.60-0.90)	.002
T4	0.47 (0.27-0.80)	.006
Primary site		
Face	Reference	
Ear	1.20 (0.89-1.63)	.24
Scalp or neck	0.86 (0.70-1.05)	.14
Reporting facility type [a]		
Low melanoma case volume		
Nonacademic program	Reference	
Academic program	0.98 (0.60-1.61)	.94
High melanoma case volume		
Nonacademic program	Reference	
Academic program	2.01 (1.62-2.48)	<.001
Institutional melanoma case volume [a]		
At nonacademic programs		
Low	Reference	
High	1.45 (1.15-1.83)	.002
At academic programs		
Low	Reference	
High	2.97 (1.83-4.80)	<.001

[a]Low and high melanoma case volumes were defined as ≤75th and >75th percentiles, respectively. Sex was not included (*P* = .25 on univariate analysis).

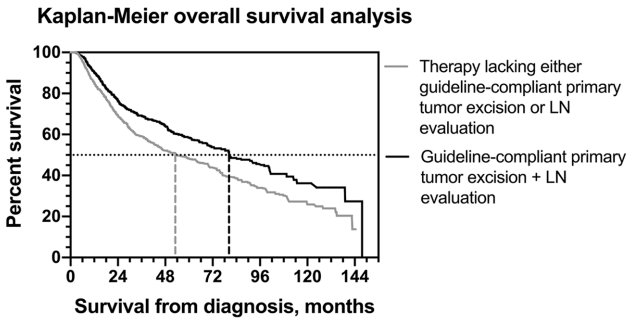

Figure 3. Inverse probability–weighted Kaplan-Meier analysis for overall survival. Treatment lacking either guideline-compliant primary tumor excision or lymph node (LN) evaluation had at least some form of surgery or radiation therapy.

Discussion

NCCN guidelines are formulated by expert consensus to optimize patient care based on current literature.[31] We described that since NCCN guidelines for MCC were introduced in 2004, there has been an increase in provision of guideline-compliant primary tumor excision plus LN evaluation for the initial care in patients with cN0M0 disease. However, momentum in the utilization of this treatment approach has slowed in recent years. This slowdown cannot be attributed to a change in utilization of RT in place of LN evaluation, as recommended by 2009-2018 guidelines. Furthermore, a large discrepancy in the provision of guideline-compliant primary tumor excision and LN evaluation exists: patients evaluated at institutions with high melanoma case volumes are up to 4.8 times more likely to receive such care. However, this finding is mitigated by the fact that in 2015 only around 60% of patients received guideline-compliant surgical management to the primary site and neck, even at institutions with high melanoma case volumes. Finally, we describe a survival benefit associated with guideline-compliant primary tumor excision and LN evaluation as compared with other therapies.

The first major finding is that patients evaluated at institutions with high melanoma case volumes have been more likely to receive NCCN guideline-compliant primary tumor excision plus LN evaluation. One potential reason for this finding is that, given MCC's rarity,[5] institutions with a high melanoma case volume may have clinicians more familiar with uncommon cutaneous diseases. Furthermore, multidisciplinary care through tumor board discussions may be more widely utilized at academic programs and centers with high institutional melanoma case volumes, which may affect subsequent care. The importance of multidisciplinary care has been shown to be beneficial in management of MCC and in related cancers.[31-35] Finally, there are major similarities in the approach to treatment for MCC and melanoma,[26] so standards for the ''default'' management of patients institutionally may be important. While patients evaluated at institutions with high melanoma volumes and at academic programs have

Table 2. Inverse Probability–Weighted Multivariable Cox Regression Assessing Factors Associated With Overall Survival.

	Hazard ratio (95% CI)	*P* value
Demographic factors		
Age, y		
≤64	Reference	
65-74	1.70 (1.37-2.11)	<.001
75-84	2.72 (2.23-3.31)	<.001
≥85	4.91 (4.01-6.02)	<.001
Sex		
Male	Reference	
Female	0.55 (0.50-0.61)	<.001
Hispanic origin		
No	Reference	
Yes	0.61 (0.36-1.04)	.071
Charlson-Deyo score		
0	Reference	
1	1.29 (1.14-1.46)	<.001
≥2	1.91 (1.62-2.26)	<.001
Geographic location		
Central	Reference	
New England	0.85 (0.71-1.01)	.061
Mid-Atlantic	0.81 (0.69-0.94)	.006
South Atlantic	0.78 (0.69-0.88)	<.001
Mountain	1.04 (0.85-1.28)	.68
Pacific	0.71 (0.61-0.84)	<.001
Distance traveled for evaluation, mi		
≤10	Reference	
10-25	1.05 (0.93-1.17)	.44
25-50	1.07 (0.93-1.23)	.36
>50	0.95 (0.81-1.12)	.54
Clinical factors		
Facility type		
Nonacademic	Reference	
Academic	0.88 (0.78-0.99)	.031
Melanoma case volume, percentile		
≤75th	Reference	
>75th	0.93 (0.83-1.04)	.18
Tumor clinical T stage		
T1	Reference	
T2 or T3	1.35 (1.21-1.50)	<.001
T4	1.31 (0.95-1.80)	.099
Primary site		
Face	Reference	
Ear	1.27 (1.08-1.49)	.005
Scalp or neck	1.69 (1.51-1.89)	<.001
Radiation dose, cGy		
0	Reference	
1-4599	1.38 (1.19-1.61)	<.001
4600-6600	0.86 (0.78-0.95)	.003
Receipt of chemotherapy		
No	Reference	

(continued)

been more likely to receive guideline-compliant care, such care is still being provided to fewer than two-thirds of patients. Therefore, while nonacademic programs and institutions with low melanoma case volumes may have more room for improvement, all facilities may warrant increased adherence to guidelines.

Potential areas for improvement may lie where disparities in care exist. Interestingly, while age was the most important patient-specific factor associated with receipt of recommended surgical excision and LN evaluation, there was no association with Charlson-Deyo comorbidity score. This is likely because comorbidity score is a crude estimate of morbidity, as highlighted by only 6.2% of patients having a score $\geq$2 despite a median age of 79 years in our study. Potential age bias should be acknowledged and addressed when selecting appropriate surgical candidates for initial treatment. However, further studies are needed to understand the nuanced degree to which clinical and social factors, not purposeful nonadherence, affect guideline compliance. Finally, patients should be provided resources and encouragement to seek out evaluation at academic institutions with high melanoma case volumes. This is likely achievable since approximately 80% of our study population lived within 50 miles of a high-volume melanoma center.

The second association described is that of a survival benefit in those receiving guideline-adherent treatment. This finding is consistent with literature assessing the impact of SLNB for MCC irrespective of primary site.[36] It should be made clear that we do not necessarily believe that the event of receiving guideline-compliant surgery and LN evaluation improves OS. Rather, we believe that receipt of such therapy is more likely to be an indicator and proxy for receipt of subsequent guideline-adherent care throughout the course of a patient's treatment. That is, results from pathologic examination of LN specimens and surgical margins undoubtedly aid in selection of risk-based adjuvant therapy[22] and clinical trial eligibility for potential immune-based therapy (eg, NCT03712605).[37] Given that 22.3% of the cases in our study will be up-staged pathologically after LN evaluation (a number consistent with the literature),[24,38] appropriate adjuvant therapy may be needed in a substantial proportion of this clinically node-negative cohort.

We also show that patients evaluated at academic programs had a survival benefit over patients evaluated at nonacademic programs, after adjusting for the same level of care (ie, treatment selection) and institutional melanoma case volume. It may be that academic institutions have more access to clinic trials or that some unmeasured confounders unique to academic centers, such as care dynamics, explain this association. Interestingly, melanoma case volume in this survival analysis was not statistically significant, despite previous work demonstrating that MCC-specific case volume to be associated with outcomes after surgery.[39,40] Therefore, it appears as though assessment at an institution with a high melanoma case volume positively affects receipt of care, but once that care has been delivered, institutional factors at these melanoma centers, apart from being academic institutions or not, are less important. This is corroborated by the observation that distance traveled to care affected receipt of guideline-compliant primary tumor excision and LN evaluation but did not affect OS. Since node-negative MCC accounts for approximate 66% of cases,[41] our findings strongly support the need to adopt current NCCN guidelines in the initial management of these patients.

Table 2. (continued)

	Hazard ratio (95% CI)	*P* value
Yes	0.98 (0.76-1.26)	.86
Guideline-compliant primary tumor excision and lymph node evaluation		
No	Reference	
Yes	0.70 (0.64-0.76)	<.001

Limitations

First, the NCDB is not a population-based database, so generalizability of the study findings must be considered. However, since the NCDB covers approximately 70% of new cancer cases[42] and the demographics of those affected by MCC are relatively homogenous, we believe the results to be largely generalizable.

Second, therapy coding in the NCDB can be ambiguous. To address the problem, sensitivity analysis was performed to determine the method of LN evaluation. While we report that 69.5% of patients received SLNB, the number is likely higher, since a proportion of those who had excisional biopsy of 1 to 3 LNs likely had SLNB. Furthermore, while patients who had $\geq$4 LNs removed likely had neck dissections, it is possible that a minority of MCCs, especially in the midline, might have drained to $\geq$4 sentinel LNs. For surgical therapy, coding in our analysis was designed to increase sensitivity to capture all possible cases in which the correct surgery was done. Likewise, we were unable to distinguish whether RT targeted the primary site, LN drainage bed, or both. More granular detail on these factors and specific comorbidities and systemic therapy agents would have improved our models.

Third, to address the likelihood of selection bias in therapy selection, survival analysis was performed on IPW cohorts. While there may still be unmeasured functional status differences between the cohorts that influence survival, this influence should be substantially reduced by weighting based on age and comorbidity status and by including only patients who received some form of therapy. We also advise caution in assigning clinical meaning to exact survival times shown in the KM analysis, since the cohorts are artificially weighted to ''pseudo-randomize'' the cohorts.

Finally, the NCDB does not provide disease-specific survival. Given the tendency of the cancer to affect older

individuals, it would be important in the future to analyze how disease-specific survival is affected by facility type and primary tumor site.

Conclusions

This study demonstrates that guideline-compliant primary tumor excision with LN evaluation is provided more frequently to patients evaluated at institutions with high melanoma case volumes but that such care may be underutilized across all facility types. Efforts should be made, where possible, to increase utilization of guideline-compliant primary tumor excision with LN evaluation, especially since such therapy may convey a survival advantage over other therapies and help guide appropriate adjuvant therapy selection.

Author Contributions

Daniel Jacobs, conceptualization, data curation, formal analysis, funding acquisition, investigation, methodology, software, validation, visualization, writing–original draft, and writing–review and editing; **Kelly Olino**, conceptualization, methodology, funding acquisition, visualization, and writing–review and editing; **Henry S. Park**, conceptualization, interpretation, and writing–review and editing; **James Clune**, conceptualization, interpretation, and writing–review and editing; **Shayan Cheraghlou**, methodology, data curation, and writing–review and editing; **Michael Girardi**, resources (data acquisition), interpretation, and writing–review and editing; **Barbara Burtness**, conceptualization, interpretation, and writing–review and editing; **Harriet Kluger**, conceptualization, interpretation, and writing–review and editing; **Benjamin L. Judson**, conceptualization, methodology, project administration, resources, software, visualization, writing–original draft, and writing–review and editing.

Disclosures

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Supplemental Material

Additional supporting information is available in the online version of the article.

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