Merkel cell carcinoma: Epidemiology, disease presentation, and current clinical practice outcomes

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Using the National Cancer Database, we introduce the findings of a retrospective investigation of the largest cohort of cases with Merkel cell carcinoma (N = 20,829). A decreasing proportion of stage I (P = .0004) and stage II (P = .0065) Merkel cell carcinoma among skin cancers was complemented by an increasing proportion of stage III disease (P < .0001). A predominance of non-Hispanic White (96.4%), male (62.6%) patients with a mean age of 74.5 ± 10.8 years and Medicare coverage (73.5%) was observed. Stage I was the most common presenting stage at diagnosis (29.2%), followed by stages II (12.7%), III (11.0%), and IV (3.8%). Most Merkel cell carcinoma tumors grew outside the head and neck (53.4%) and showed a nodular growth pattern (66.0%) but no extracapsular lymph node (90.5%) or lymphovascular involvement (63.8%). Narrow-margin excision and radiation therapy (RT) were used in 75.2% and 56.3% of tumors, respectively. Wide-margin excision lead to improved overall survival (P < .001) versus narrow-margin excision, particularly in stage III (difference in the median overall survival rate [ΔmOS], 23.7 months; P < .001). RT showed a significant OS benefit (P = .006), most pronounced in stage II (ΔmOS, 37.8 months) followed by stage I (ΔmOS, 16.1 months; P < .001). The survival benefit with primary-site RT (ΔmOS, 24.0 months) was higher than that with primary-site/lymph node RT (ΔmOS, 5.2 months; P < .001). Wide-margin excision independently predicted improved OS (hazard ratio, 0.577; 95% CI, 0.403-0.826; P = .003) versus narrow-margin excision and RT predicted better OS (hazard ratio, 0.608; 95% CI, 0.424-0.873; P = .007) versus no RT on multivariable analysis. (JAAD Int 2022;9:128-36.)

Key words: clinical research; epidemiology; medical dermatology; Merkel cell carcinoma; neuroendocrine tumors; oncology; radiation oncology; skin cancer; skin disease; surgery.

INTRODUCTION

Merkel cell carcinoma (MCC) is a rare neuroendocrine carcinoma highly prone to localized recurrence and metastasis. Despite its low incidence, the knowledge of MCC’s uncommon characteristics is valuable given the aggressive nature of this skin cancer, even compared with melanoma. Indeed, it has the second highest rate of death because of skin cancer after melanoma.1

As the population aged ≥65 years continues to grow driven by the aging of the baby boomer generation and the global solar UV index continues to rise, the incidence of skin cancer, notably MCC, is set to increase.2-6 The MCC incidence rate of 2488 cases/y in 2013 in the United States is projected to rise to 3284 cases/y in 2025.7 Thus, optimizing therapeutic options for MCC becomes a priority. Surgery remains the primary therapeutic modality, as recommended by the current National Comprehensive Cancer Network (NCCN) guidelines.8 Although chemotherapy, and most recently immunotherapy, are used in metastatic disease, jointly program of the Commission on Cancer of the American College of Surgeons and the American Cancer Society. Accepted for publication June 3, 2022. Correspondence to: Marita Yaghi, MD, Dr Philip Frost Department of Dermatology and Cutaneous Surgery, University of Miami, Miller School of Medicine, 1600 NW 10th Ave, Miami, FL 33136. E-mail: mxy537@miami.edu. 2666-3287 © 2022 Published by Elsevier Inc on behalf of the American Academy of Dermatology, Inc. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/). https://doi.org/10.1016/j.jdin.2022.06.004
adjuvant and definitive radiation therapy (RT) can be used in patients with nonmetastatic MCC. To our knowledge, no data on the national epidemiology and presentation of MCC have been published in the United States within the last 5 years. Using the National Cancer Database (NCDB) (2004-2018), we aimed to describe the current incidence, patient population, clinical presentation, and adopted treatment modalities nationwide. Additionally, we aimed to analyze the outcomes of surgical resection and RT on survival.

METHODS

The NCDB is a national registry jointly supported by the Commission on Cancer and the American College of Surgeons. It gathers information from >1500 medical institutions and includes the deidentified data of >70% of patients with cancer in the United States. The NCDB was sampled for all adult patients diagnosed with MCC (2004-2018). Only cases with a known primary site (PS) were included and stratified into cutaneous or mucosal MCC. The NCDB was also sampled for the number of adult patients diagnosed with any skin cancer (melanoma and nonmelanoma).

The American Joint Committee on Cancer pathological staging was used, and only cases with staging information were further included in the analyses. Information on patient and tumor characteristics and indicators of socioeconomic demographics and care accessibility-related factors were collected. Treatment modalities and overall survival (OS) information were also collected.

The proportion of MCC of the skin among all skin cancers by year was trended using a Cochran-Armitage test for the overall patient population and for every stage. We conducted a descriptive analysis of the baseline clinicopathologic features of the included patients. This was followed by a similar descriptive analysis focusing on localized and regional MCC of the skin, stratified by stage, and the use of the \( \chi^2 \) test to compare the tumor characteristics by subgroup.

We stratified patients into subgroups based on tumor histologic growth pattern (nodular vs infiltrative), surgical excision margin (narrow-margin excision [NME] vs wide-margin excision [WME], defined as \(<1.0 \text{ cm vs } \geq 1.0 \text{ cm})\), RT administration, and RT target (PS vs PS and draining lymph node [LN]). The OS rates and median OS (mOS) of localized and regional MCC within each subgroup were estimated using the Kaplan-Meier survival analysis. Hazard ratios (HRs) were calculated for each comparison using the Cox proportional hazards model with backward elimination to analyze the factors that impact survival.

RESULTS

Disease burden

A total of 20,829 cases with MCC were reported in the NCDB between 2004 and 2018, summarized in the case schema in Figure 1. Focusing on MCC of the skin (\( N = 19,020 \)), the overall proportion of MCC among skin cancers showed an increasing trend over the years (\( P < .0001 \)). Only cases with staging information (\( N = 10,808 \)) were stratified by stage. The proportion of MCC among skin cancers showed a decreasing trend by years in patients with stage I (\( P = .0004 \)) and stage II (\( P = .0065 \)) disease and increasing trend by years in patients with stage III disease (\( P < .0001 \)). The proportion did not significantly change over the years in patients with stage IV disease (\( P = .2390 \)) (Fig 2).

Baseline characteristics of patients with MCC

Most patients diagnosed with MCC were non-Hispanic White (96.4%) and were aged \( >65 \) years (82.1%), with a mean age of 74.5 ± 10.8 years at diagnosis. Male predominance was observed (62.6%). Most patients had Medicare coverage (73.5%) and had a comorbidity score of 0 (73.1%) or 1 (17.9%).

Treating facilities were mostly located in metropolitan settings (80.4%) and classified as academic centers (43.5%) or Comprehensive Community Cancer Programs (33.9%). Among cases with MCC, stage I was the most common presenting stage at diagnosis (5555 [29.2%]), followed by stages II (2424 [12.7%]) and III (2086 [11.0%]). Only 715 (3.8%) patients presented with distant metastases at diagnosis (Table 1).

Clinicopathologic characteristics of localized and regional MCC

The analysis of localized and regional disease (\( N = 10,065 \)) showed that most tumors developed outside the head and neck (53.4%) and showed a

### CAPSULE SUMMARY

- Merkel cell carcinoma of the skin continues to be associated with high mortality. Advanced disease is associated with a worse prognosis, warranting early recognition and prompt treatment initiation.
- A positive association exists between survival and wide-margin excision or radiation therapy in all invasive nonmetastatic MCC, regardless of patient or tumor characteristics.
nodular histologic growth pattern (66.0%). Most tumors showed no involvement of the extracapsular LNs (90.5%) or lymphovascular involvement (63.8%). The mean tumor depth was 10.5 ± 18.9 mm. Most tumors received NME (75.2%), had their base transected during surgery (54.4%), and were treated with RT (56.3%). Most patients did not receive immunotherapy (99.0%) or systemic chemotherapy (90.5%). Most patients were not immunosuppressed (89.0%), with chronic lymphocytic leukemia (3.2%) and HIV (3.1%) being the most common underlying causes of immunosuppression.

Stage I tumors were more likely to be located in the head and neck (51.2%) and have no lymphovascular involvement (73.1%) \((P < .001)\). Interestingly, stage I tumors were most likely to receive WME (26.0%) compared with stage II (24.3%) or III (21.8%) \((P = .002)\) tumors. Stage II tumors had the highest mean tumor depth of 16.0 ± 23.8 mm compared with stage I (8.2 ± 16.2 mm) and stage III (11.1 ± 18.7 mm, \(P < .001\)) tumors. Stage III tumors

![Fig 1. Case schema for all Merkel cell carcinoma subtypes for years 2004-2018 National Cancer Database.](image_url)
were the most likely to be treated with RT (71.5%, \( P < .001 \)), immunotherapy (2.8%, \( P < .001 \)), or systemic chemotherapy (28.5%, \( P < .001 \)). Immunosuppression was also most common with stage III tumors, particularly among solid organ transplant patients (5.5%) or patients with chronic lymphocytic leukemia (4.8%) (\( P < .001 \)) (Table 2).

**Localized and regional MCC treatment modalities outcomes**

The Kaplan-Meier modeling showed a decreasing OS associated with MCC stage progression. The 5-year OS was 36.1% for stage III, 45.7% for stage II, and 60.4% for stage I (\( P < .001 \)) tumors (Supplementary Fig 1, available via Mendeley at https://data.mendeley.com/datasets/vb47jyyv6h/1). Similarly, the mOS was 28.2 months for stage III, 47.4 months for stage II, and 92.9 months for stage I (\( P < .001 \)) tumors (Supplementary Table I, available via Mendeley at https://data.mendeley.com/datasets/vb47jyyv6h/1).

Focusing on the histopathologic growth pattern of MCC and potential implications on survival, the Kaplan-Meier analysis revealed similar OS when comparing tumors with nodular growth pattern to those with an infiltrative growth pattern, in the overall sample (\( P = .50 \)) and stratifying per stage (\( P = .109 \)) (Supplementary Fig 2). There was no significant difference in mOS rates (\( \Delta \mbox{mOS} \)) between patients who had tumors with a nodular versus infiltrative growth pattern (Supplementary Table II).

A significant survival benefit was observed with WME versus NME in the overall sample (\( P < .001 \)) and upon stage stratification (\( P < .001 \)) (Supplementary Fig 3). Overall, WME led to a 19.0-month improvement in the mOS (\( P < .001 \)). On subgroup analysis, the survival benefit was highest in stage III (\( \Delta \mbox{mOS}, 23.7 \) months) followed by stage I (\( \Delta \mbox{mOS}, 17.0 \) months), with stage II benefiting the least (\( \Delta \mbox{mOS}, 15.4 \) months) (\( P < .001 \)) (Supplementary Table III).

A significant benefit in OS was observed with RT overall (\( P = .006 \)) and upon stage subgroup stratification (\( P < .001 \)) (Supplementary Fig 4). The difference in the mOS was most pronounced with stage II tumors (\( \Delta \mbox{mOS}, 37.8 \) months) followed by stage I tumors (\( \Delta \mbox{mOS}, 16.1 \) months) and was least in stage III tumors (\( \Delta \mbox{mOS}, 6.1 \) months) (\( P < .001 \)) (Supplementary Table IV).

RT to either PS or PS+LN yielded a survival benefit for the overall sample (\( P < .001 \)), which was also observed on subgroup analysis by stage (\( P < .001 \)) (Supplementary Fig 5). Survival benefit with PS radiation (\( \Delta \mbox{mOS}, 24.0 \) months) was higher than with PS+LN radiation (\( \Delta \mbox{mOS}, 5.2 \) months) in the overall sample compared with no RT (\( P < .001 \)). In stage I, only PS RT yielded a survival benefit compared with no RT (\( \Delta \mbox{mOS}, 13.4 \) months). Stage II
The highest survival benefit with either PS RT (ΔmOS, 31.4 months) or PS 1 LN RT (ΔmOS, 12.1 months) compared with no RT. PS RT also showed a higher survival in stage III (ΔmOS, 11.1 months) than PS 1 LN RT (ΔmOS, 1.3 months) compared with no RT (P < .001) (Supplementary Table V).

On multivariable analysis, female sex (HR, 0.581; 95% CI, 0.419-0.805; P < .001) was a predictor of improved OS compared with the male sex. An increase in the number of co-morbidities was associated with decreased OS, as seen with a Charlson/Deyo score of ≥3 (HR, 4.831; 95% CI, 2.334-9.996; P < .001), compared with a score of 0. Immune-compromise was another independent predictor of worse OS (HR, 2.831; 95% CI, 1.949-4.111; P < .001). The tumor stage independently predicted worse OS: stage III was associated with the worst OS rate (HR, 2.891; 95% CI, 1.975-4.231; P < .001), whereas stages I and II showed similar OS rates (HR, 1.219; 95% CI, 0.835-1.780; P = .305). Lymphovascular invasion independently correlated with worse OS (HR, 1.683; 95% CI, 1.234-2.297; P = .001). Focusing on therapeutic approaches, WME independently predicted improved OS (HR, 0.577; 95% CI, 0.403-0.826; P = .003) compared with NME, and RT predicted better OS (HR, 0.608; 95% CI, 0.424-0.873; P = .007) than no RT. All other variables used in the model were not independent predictors of OS (Table 3).

**DISCUSSION**

In this assessment of the national data, we introduce the results of a retrospective analysis.
| Variable                                      | Overall | Stage I | Stage II | Stage III | $\chi^2$ P value |
|-----------------------------------------------|---------|---------|----------|-----------|-----------------|
| **Primary site**                              |         |         |          |           |                 |
| Head and neck                                 | 4680 (46.6%) | 2843 (51.2%) | 893 (36.9%) | 944 (45.3%) | <.001           |
| Other                                         | 5373 (53.4%) | 2705 (48.8%) | 1526 (63.1%) | 1142 (54.7%) |                 |
| **Growth pattern**                            |         |         |          |           |                 |
| Circumscribed/nodular                         | 1189 (66.0%) | 695 (67.1%) | 295 (67.5%) | 199 (60.5%) | .066            |
| Diffusely infiltrative                        | 613 (34.0%) | 341 (32.9%) | 142 (32.5%) | 130 (39.5%) |                 |
| **Extracapsular LN involvement**              |         |         |          |           |                 |
| None seen                                     | 6420 (90.5%) | 3979 (96.8%) | 1621 (96.1%) | 820 (63.4%) | <.001           |
| Clinical only                                 | 39 (0.5%) | 0 (0.0%) | 0 (0.0%) | 39 (3.0%) |                 |
| Pathologic only                               | 593 (8.4%) | 132 (3.2%) | 66 (3.9%) | 395 (30.5%) |                 |
| Clinical and pathologic                       | 39 (0.5%) | 0 (0.0%) | 0 (0.0%) | 39 (3.0%) |                 |
| **Lymphovascular involvement**                |         |         |          |           |                 |
| No                                            | 3151 (63.8%) | 2062 (73.1%) | 673 (57.4%) | 416 (43.9%) | <.001           |
| Yes                                           | 1790 (36.2%) | 759 (26.9%) | 500 (42.6%) | 531 (56.1%) |                 |
| **Tumor depth (mm)**                          |         |         |          |           |                 |
| Mean ± SD                                     | 10.5 ± 18.9 | 8.2 ± 16.2 | 16.0 ± 23.8 | 11.1 ± 18.7 | <.001           |
| <10                                           | 2871 (75.5%) | 1852 (83.9%) | 494 (57.2%) | 525 (71.5%) |                 |
| ≥10                                           | 934 (24.5%) | 356 (16.1%) | 369 (42.8%) | 209 (28.5%) |                 |
| **Excision margins**                          |         |         |          |           |                 |
| Narrow (<1 cm)                                | 6999 (75.2%) | 3996 (74.0%) | 1687 (57.2%) | 1316 (78.2%) | .002            |
| Wide (>1 cm)                                  | 2311 (24.8%) | 1402 (26.0%) | 542 (42.8%) | 367 (21.8%) |                 |
| **Sentinel LN biopsy**                        |         |         |          |           |                 |
| Not performed                                 | 3548 (35.3%) | 3544 (63.9%) | 1277 (52.8%) | 429 (20.6%) | <.001           |
| Performed                                     | 6465 (64.3%) | 1992 (35.9%) | 1127 (46.6%) | 1644 (78.8%) |                 |
| **Margin status after surgery**               |         |         |          |           |                 |
| Negative                                      | 8128 (82.4%) | 4982 (91.1%) | 1816 (76.8%) | 1330 (65.5%) | <.001           |
| Positive                                      | 1020 (10.3%) | 347 (6.3%) | 357 (15.1%) | 316 (15.6%) |                 |
| Unable to assess                              | 713 (7.2%) | 137 (2.5%) | 191 (8.1%) | 385 (19.0%) |                 |
| **Tumor base transection**                    |         |         |          |           |                 |
| No                                            | 1209 (45.6%) | 688 (45.1%) | 281 (44.9%) | 240 (48.2%) | .445            |
| Yes                                           | 1440 (54.4%) | 837 (54.9%) | 345 (55.1%) | 258 (51.8%) |                 |
| **Radiation**                                 |         |         |          |           |                 |
| No                                            | 4321 (43.7%) | 2743 (50.2%) | 995 (41.8%) | 583 (28.5%) | <.001           |
| Yes                                           | 5563 (56.3%) | 2720 (49.8%) | 1383 (58.2%) | 1460 (71.5%) |                 |
| **Radiation site**                            |         |         |          |           |                 |
| None                                          | 4833 (55.2%) | 2995 (59.0%) | 1137 (54.1%) | 701 (44.6%) | <.001           |
| PS only                                       | 2680 (30.6%) | 1507 (29.7%) | 726 (34.5%) | 447 (28.4%) |                 |
| PS+LN                                         | 1234 (14.1%) | 571 (11.3%) | 239 (11.4%) | 424 (27.0%) |                 |
| **Immunotherapy**                             |         |         |          |           |                 |
| No                                            | 9916 (99.0%) | 5518 (99.7%) | 2386 (99.1%) | 2012 (97.2%) | <.001           |
| Yes                                           | 96 (1.0%) | 17 (0.3%) | 21 (0.9%) | 58 (2.8%) |                 |
| **Chemotherapy**                              |         |         |          |           |                 |
| No                                            | 8938 (90.5%) | 5314 (97.2%) | 2169 (91.3%) | 1455 (71.5%) | <.001           |
| Yes                                           | 939 (9.5%) | 154 (2.8%) | 206 (8.7%) | 579 (28.5%) |                 |
| **Vital status**                              |         |         |          |           |                 |
| Dead                                          | 5005 (49.8%) | 2345 (42.3%) | 1347 (55.7%) | 1313 (62.9%) | <.001           |
| Alive                                         | 5048 (50.2%) | 3203 (57.7%) | 1072 (44.3%) | 773 (37.1%) |                 |
| **Immunosuppression**                         |         |         |          |           |                 |
| No                                            | 4005 (89.0%) | 2341 (90.6%) | 896 (88.9%) | 768 (84.5%) | <.001           |
| HIV                                           | 17 (0.4%) | 8 (0.3%) | 2 (0.2%) | 7 (0.8%) |                 |
| Solid organ transplant                        | 139 (3.1%) | 63 (2.4%) | 26 (2.6%) | 50 (5.5%) |                 |
| CLL                                           | 146 (3.2%) | 70 (2.7%) | 32 (3.2%) | 44 (4.8%) |                 |
| Lymphoma                                      | 72 (1.6%) | 33 (1.3%) | 20 (2.0%) | 19 (2.1%) |                 |
| >1                                            | 4 (0.1%) | 2 (0.1%) | 1 (0.1%) | 1 (0.1%) |                 |
| Other                                         | 117 (2.6%) | 66 (2.6%) | 31 (3.1%) | 20 (2.2%) |                 |

CLL, Chronic lymphocytic leukemia; LN, lymph node; PS, primary site.
(2004-2018) of the largest-to-date cohort of cases with MCC (N = 20,829). Cutaneous MCC accounted for 91.3% of all cases, followed by mucosal MCC of the genitourinary tract and then of the gastrointestinal tract. The most common anatomic site of involvement in mucosal MCC was the vulva.

Focusing on cutaneous MCC, the proportion of cases with MCC diagnosed per year compared with all skin cancers significantly increased during this 14-year period. Importantly, the proportion of stage I and II cancers dropped, whereas the proportion of stage III cancers increased over time. Conversely, the proportion of de novo metastatic disease did not change considerably during the study period. Conclusions regarding the increasing incidence of MCC could not be made from this data set, given that the NCDB collects only absolute numbers of cases and is not matched to population data. Although we cannot draw conclusions on the rising trends observed in our data, the high mean age of the patient population allows us to infer that most of them experienced an elevated degree of lifetime sun exposure and consequent UV-induced damage, an established risk factor for the development of MCC.9 In addition, it is important to note that the US Food and Drug Administration regulation of sunscreen protection came into effect in 1978,11 which supports the hypothesis of heavy UV-induced damage in the generations involved.

The demographics of our patient population support the previous data.12-14 Most of our patients were non-Hispanic White, males, and aged ≥65 years. Caucasians constituted an overpowering majority of patients. Although most patients were generally healthy, a significant portion had at least 1 comorbidity. Most had Medicare coverage, which might be explained by the advanced age of the patient population. Patients with cutaneous MCC were from all levels of education but resided in zip codes with a higher median household income. A significant portion of patients were diagnosed in facilities located in the South Atlantic (23.6%), an area with a high UV index.15 There was considerable variation in the extent of disease at diagnosis, with most tumors being localized. It is important to keep in mind that up to 30% of patients with localized MCC have micrometastatic LN involvement, diagnosed during sentinel LN biopsy, despite clinically negative LN involvement.

Higher odds of regionally metastatic disease (stage III) at presentation were associated with tumor location not in the head and neck, lymphovascular involvement, and patient immunosuppression. Hidden location and decreased rates of thorough medical follow-up in nonimmunosuppressed patients might be the reason behind these differences. As expected, therapeutic modalities varied based on the stage. Despite receiving lower rates of WME, stage III tumors received more RT, immunotherapy, or chemotherapy. The current NCCN guidelines consider NME sufficient if adjuvant radiation is planned but recommend WME otherwise. Per the NCCN, the following features are indications for adjuvant RT: tumor size of >1 cm, lymphovascular invasion, head and neck as the primary location, or immunosuppressed patients.8 Given the higher prevalence of these baseline characteristics in patients with stage III MCC, this could explain the lower rates of WME in these tumors.

The stage-specific survival rates for localized and regional disease were lower than those reported in the literature. According to a recent study examining the OS rates for MCC using data from the Surveillance, Epidemiology, and End Results database from 2010 to 2016, the 5-year OS in patients with either stage I/II and stage III disease are, respectively, 76% and 53%,16 whereas our data showed 60.4% and 45.7% OS, respectively, in patients with stage I/II disease and 36.1% OS in patients with stage III disease. It is important to keep in mind that our data set is larger and examines a longer period of time.

Although the tumor growth pattern did not affect survival, mortality greatly varied based on the administered treatment modality. Our investigation revealed a significant improvement in mOS with WME, notably when the tumor had invaded the LN. WME remained an independent predictor of OS on multivariable analysis, suggesting that the NCCN guidelines regarding NME in high-risk patients need to be investigated and reconsidered.

Similar benefit in OS was observed with RT, with the largest benefit observed in patients with stage II disease. Adjuvant RT showed the highest survival benefit when targeting the PS as opposed to the PS+LN, notably in stage I and II disease. We postulate that a high prevalence of local micrometastasis or in-transit metastases targeted by “wide margin” RT likely explains the survival benefits seen with adjuvant radiation in our study. This is consistent with the NCCN guidelines recommending a 5-cm margin around the PS when planning RT treatment volumes.8 Nonetheless, only RT administration was an independent predictor of OS on multivariable analysis. This present study refutes the lack of benefit of RT in stage III MCC.17,18 Additionally, it demonstrates the survival benefit of WME and RT in all localized and regional MCC, highlighting the need for prospective trials
investigating the benefit of these therapeutic modalities compared with current treatment guidelines.8 Despite showing survival benefit on univariate analysis, RT site showed similar survival outcome with targeting PS or the PS+LN on multivariate analysis. This may reflect an underpowered analysis for this variable specifically, as only 14.1% of patients received PS+LN radiation.

Female sex was an independent predictor of survival on multivariate analysis, a finding supporting the previously published reports.19 Immunosuppression increased the mortality by 3.2 fold, most likely because of the incapacity of the patient’s immune system to stop disease progression and additional comorbidities.20 Our analysis is strengthened by the high NCDB coverage of cases with cancer in the United States and the reliability of the data.21 Additionally, the NCDB reflects real-world practices on a national level. However, only patients from participating institutions are captured; thus, this may not be an accurate representation of the entirety of cases with MCC nationwide. The limitations of this study also lie in the unavailability of data such as Merkel cell polyomavirus seroprevalence, histochemical biomarkers, disease-specific mortality, or progression-free survival.

**CONCLUSION**

Our data are the largest population-based report on MCC in the United States. Cutaneous MCC continues to be associated with high mortality. The rising incidence of tumors with local dissemination underlines the urgent need for a high degree of suspicion in the clinical setting, but also more public awareness on the matter, to drive patients to seek care. Advanced disease is associated with a worse prognosis, warranting early recognition and prompt treatment initiation. Prospective trials investigating the survival benefit of WME in all tumor stages and regardless of patient characteristics against the standard of care treatment are needed. The positive association between survival and RT also needs to be prospectively analyzed in all localized and regional MCC, with a focus on the RT site. Recent advances and guideline changes incorporating immunotherapy need to be assessed for efficacy on a national level in the years to come. Additional investigation into the prevention and therapeutics of MCC is needed to undertake the increasing trends and poorer survival rates observed.

**Conflicts of interest**

None disclosed.
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