Improved survival in women versus men with merkel cell carcinoma

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Background: Studies have observed that women have better outcomes than men in melanoma, but less is known about the influence of sex differences on outcomes for other aggressive cutaneous malignancies.

Objective: To investigate whether women and men have disparate outcomes in Merkel cell carcinoma (MCC).

Methods: Patients with nonmetastatic MCC undergoing surgery and lymph node evaluation were identified from the National Cancer Database (NCDB) and the Surveillance, Epidemiology, and End Results (SEER) database. Kaplan-Meier analysis and Cox proportional hazards regression models were used for overall survival, and competing-risks analysis and Fine-Gray models were used for cause-specific and other-cause mortality.

Results: The NCDB cohort (n = 4178) included 1516 (36%) women. Women had a consistent survival advantage compared with men in propensity score–matched analysis (66.0% vs 56.8% at 5 years, $P < .001$) and multivariable Cox regression (hazard ratio, 0.68; 95% confidence interval, 0.61-0.75; $P < .001$). Similarly, women had a survival advantage in the SEER validation cohort (n = 1202) with 457 (38.0%) women, which was entirely due to differences in MCC-specific mortality (5-year cumulative incidence: 16.4% vs 26.7%, $P = .002$), with no difference in other-cause mortality (16.8% vs 17.8%, $P = .43$) observed in propensity score–matched patients.

Limitations: Potential selection bias from a retrospective data set.

Conclusion: In MCC, women have improved survival compared with men, driven by MCC-related mortality. (J Am Acad Dermatol 2021;84:321-9.)

Key words: Merkel cell cancer; National Cancer Data Base; NCDB; SEER; sex.

Merkel cell carcinoma (MCC) is a primary cutaneous neuroendocrine malignancy that exhibits aggressive behavior, with high tropism for local, regional, and distant relapse.[1] MCC disproportionately affects patients older than 65 years,[2] is approximately 25 times more common in white individuals compared with other ethnic/racial groups, and is twice as common in men.

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Although still relatively rare, the incidence has dramatically increased over the last 3 decades in the United States[2,3] and other developed nations.[4-6] Because of the projected aging of the US population,[7] MCC is likely to represent an increasingly important disease facing health care providers in the near future.

Differences in cancer outcomes according to sex have been noted in multiple cancers, including melanoma.[8-13] The etiology for this interplay between sex and outcome is unclear, although possibilities include cultural sex differences (eg, behavior with early detection), hormonal differences,[14] and immunologic differences between men and women. Multiple studies of MCC have suggested similar trends of improved survival outcomes for women,[15-20] but this finding has not been explored comprehensively.

CAPSULE SUMMARY

- Women have improved survival compared with men in patients with Merkel cell carcinoma, driven by differences in Merkel cell carcinoma—related mortality.
- More research is needed to investigate the underlying biological and immunologic differences that may account for these survival differences.

Therefore, to further explore the impact of sex differences on survival outcomes in MCC, we analyzed the association between patient sex and overall survival in the National Cancer Database (NCDB), adjusting for other clinicopathologic, socioeconomic, and epidemiologic factors. We then validated our initial results by using the Surveillance, Epidemiology, and End Results (SEER) database, which also allowed the investigation of cancer-specific mortality.

MATERIALS AND METHODS

Data sources

Data were obtained from the NCDB and SEER databases. The NCDB is a tumor registry, maintained by the American Cancer Society and the Commission on Cancer of the American College of Surgeons, that records data from more than 1500 hospitals and captures approximately 70% of all cancers treated in the United States. The SEER-18 database is derived from 18 cancer registries across the United States and covers approximately 28% of incident cases in the United States (http://seer.cancer.gov). The data and analyses were kept separate, and no attempts were made to compare data between cohorts or to determine whether patients overlapped. This study was determined to be exempt by the Cedars-Sinai institutional review board (IRB) review because it is based on publicly available registry data. All analysis and data storage were performed exclusively at Cedars-Sinai Medical Center.

NCDB patient selection

Patients with nonmetastatic cutaneous MCC diagnosed between 2004 and 2014 undergoing surgical resection of the primary site and pathologic lymph node evaluation with or without adjuvant therapy were identified in the NCDB. Patients were excluded if they had distant metastatic disease (n = 979), no surgery to the primary site (n = 1369), unknown follow-up (n = 1294), unknown staging or unknown primary site (n = 4148), unknown chemotherapy and/or radiation (n = 175), unknown anatomic site (n = 44), or unknown sociodemographic information (n = 140); received chemotherapy before surgery (n = 18) or radiation before surgery (n = 19); or did not have regional lymph nodes examined pathologically (n = 924). Patients who did not have surgery, lymph node evaluation, preoperative radiotherapy, or preoperative chemotherapy were excluded to ensure that men and women would have valid, consistent pathologic staging that could be adjusted for in multivariable models.

SEER database patient selection

Patients with nonmetastatic cutaneous MCC diagnosed between 2004 and 2014 and undergoing surgical resection of the primary site and pathologic lymph node evaluation with or without adjuvant therapy were identified in the SEER-18 database. Patients were excluded if they had no surgery (n = 1048), noncutaneous primary site (n = 116), unknown primary (n = 1297), unknown stage (n = 68), metastatic disease (n = 170), unknown follow-up (n = 1018), radiotherapy before surgery or unknown sequence (n = 13), no pathologic lymph node evaluation (n = 743), and unknown marital status (n = 62).

Statistical methods

Differences in patient baseline characteristics were compared between men and women using the Pearson chi-square tests for categorical variables and Welch *t* test for continuous variables. Time to event was calculated from the date of diagnosis. Overall survival (OS) was calculated by using the Kaplan-Meier method, with survival curves compared by using the log-rank test. Cause-specific mortality and other-cause mortality were calculated

Abbreviations used:

CI:	confidence interval
HR:	hazard ratio
MCC:	Merkel cell carcinoma
NCDB:	National Cancer Database
OS:	Overall survival
SEER:	Surveillance, Epidemiology, and End Results

with the cumulative incidence method, and curves compared using the *k*-sample test.[21]

Univariate and multivariable analyses were performed with Cox proportional hazards regression to obtain hazard ratios (HRs) for OS. Multivariable analysis was performed by using Fine-Gray regression to obtain cause-specific hazards for MCC.[22,23] Covariate selection for the multivariable models were performed by using a backward stepwise selection based on the Akaike information criterion. Furthermore, the variable inflation factor and the scaled Schoenfeld residuals were used to assess multicollinearity and the proportional hazards assumption.[24]

To further adjust for the potential of underlying bias among our cohorts, propensity scores were estimated for each patient by using a multivariable logistic regression model, adjusting for all baseline factors and demographics such as age, race, marital status, T stage, N stage, radiation, chemotherapy, and primary site. A 1-to-1 propensity score–matched cohort was then created by using the nearest neighbor method with a caliper of 0.2.[25] The quality of the match was assessed visually by using comparative density figures of the pre- and postmatched propensity scores.

Multivariable subgroup analysis was performed in all subgroups for both OS and cause-specific survival to evaluate the impact of sex on survival according to tumor and patient characteristics. A test of interaction was performed to evaluate the differences between each level of the subgroup, with a Bonferroni correction for multiple hypothesis testing and a significant P value of less than .05/9 = 0.005 and .05/8 = 0.006 for OS and cause-specific survival, respectively.

A sensitivity analysis was performed to evaluate the generalizability of our findings by expanding the patient population in the NCDB and SEER data sets to include those with metastatic disease and those who underwent nonsurgical management. Univariate survival analyses were performed in all patients with follow-up (NCDB, n = 11,810; SEER, n = 3801). For multivariable models, to allow for adjustments in differences in baseline covariates, patients with unknown values for included covariates were excluded, leaving 9074 patients in the NCDB data set available for analysis (Supplemental Table I; available via Mendeley at https://doi.org/10.17632/4hm7n3b5d9.2). Multivariable analysis was performed with adjustment for surgical treatment and for overall stage (I/II/III/IV) instead of T and N stage, given that those variables are not routinely coded in patients with metastatic disease. All statistical analyses were performed using R software package, version 3.5.1 (R Core Team, Vienna, Austria), with a 2-sided test and a P value less than .05 considered significant.

RESULTS

NCDB discovery data set

In total, 4178 patients met the inclusion criteria, including 2662 (64%) men and 1516 (36%) women (Table I). Compared with men, women were more likely to be of non-white race (3.6% vs 1.8%; $P < .001$), have pT1 (68.5% vs 61.9%; $P < .001$) and pN0 (63.4% vs 57.6%; $P < .001$) disease, and have disease located on the extremities (56.9% vs 49.6%; $P < .001$) than men, although the absolute differences were relatively small. Among all patients, the median follow-up was 53.3 months.

In univariate Cox regression, female sex was associated with significantly longer OS (HR, 0.65; 95% confidence interval [CI], 0.59-0.73; $P < .001$) (Table II). After adjustment for patient and tumor characteristics in multivariable regression, female sex remained significantly associated with better OS, with a similar magnitude (HR, 0.68; 95% CI, 0.61-0.75; $P < .001$) (Table II). In a propensity score–matched cohort, the 5-year OS was 66.0% versus 56.8% for women and men, respectively ($P < .001$) (Fig 1).

When stratifying patients into subgroups, women had better OS compared with men across essentially all subgroups. Tests of interaction showed a borderline significant interaction with anatomic site after correcting for multiple hypothesis testing (interaction $P = .005$), with somewhat larger effect of female sex on survival seen in head and neck primaries versus other sites.

Immunosuppression data were available for 1359 patients (32.5%), with 166 (12.2%) patients having documented immunosuppression. There was a trend toward increased rates of immunosuppression in men (13.8% vs 9.8%; $P = .06$). In multivariable Cox regression accounting for immunosuppression status in this subgroup, female sex remained associated with improved survival (HR, 0.78; 95% CI, 0.63-0.96; $P = .02$).

Table I. Baseline characteristics of male versus female patients with Merkel cell carcinoma in the National Cancer Data Base undergoing curative intent surgery*

Characteristics	Overall (N = 4178)	Male (n = 2662)	Female (n = 1516)	*P*
Age, y, mean (SD)	72.02 (10.82)	72.15 (10.50)	71.80 (11.36)	.321
Race, n (%)				
White	4077 (97.6)	2615 (98.2)	1462 (96.4)	<.001
Non-white	101 (2.4)	47 (1.8)	54 (3.6)	
T-classification, n (%)				
T1	2686 (64.3)	1648 (61.9)	1038 (68.5)	<.001
T2	1090 (26.1)	746 (28.0)	344 (22.7)	
T3	210 (5.0)	147 (5.5)	63 (4.2)	
T4	192 (4.6)	121 (4.5)	71 (4.7)	
N-classification, n (%)				
N0	2494 (59.7)	1533 (57.6)	961 (63.4)	<.001
N1	1603 (38.4)	1065 (40.0)	538 (35.5)	
N2	81 (1.9)	64 (2.4)	17 (1.1)	
Comorbidity score, n (%)				
0	3178 (76.1)	2009 (75.5)	1169 (77.1)	.485
1	792 (19.0)	518 (19.5)	274 (18.1)	
≥2	208 (5.0)	135 (5.1)	73 (4.8)	
Facility type, n (%)				
Non-academic center	2149 (51.4)	1366 (51.3)	783 (51.6)	.861
Academic center	2029 (48.6)	1296 (48.7)	733 (48.4)	
Facility volume, n (%)				
Low	3431 (82.1)	2185 (82.1)	1246 (82.2)	.963
High	747 (17.9)	477 (17.9)	270 (17.8)	
Radiation, n (%)				
No	1767 (42.3)	1097 (41.2)	670 (44.2)	.065
Yes	2411 (57.7)	1565 (58.8)	846 (55.8)	
Chemotherapy, n (%)				
No	3706 (88.7)	2340 (87.9)	1366 (90.1)	.035
Yes	472 (11.3)	322 (12.1)	150 (9.9)	
Anatomic site, n (%)				
Head and neck	1538 (36.8)	990 (37.2)	548 (36.1)	<.001
Trunk	456 (10.9)	351 (13.2)	105 (6.9)	
Extremity	2184 (52.3)	1321 (49.6)	863 (56.9)	
Insurance status, n (%)				
Private	1170 (28.0)	755 (28.4)	415 (27.4)	.139
Medicare	2847 (68.1)	1816 (68.2)	1031 (68.0)	
Other	161 (3.9)	91 (3.4)	70 (4.6)	
Zip code median income, n (%)				
<$48,000	1391 (33.3)	877 (32.9)	514 (33.9)	.549
≥$48,000	2787 (66.7)	1785 (67.1)	1002 (66.1)	
Zip code education status, n (%)				
≥20% without high school diploma	427 (10.2)	264 (9.9)	163 (10.8)	.422
<20% without high school diploma	3751 (89.8)	2398 (90.1)	1353 (89.2)	
Regional population, n (%)				
<1 million	1964 (47.0)	1266 (47.6)	698 (46.0)	.362
≥1 million	2214 (53.0)	1396 (52.4)	818 (54.0)	

**P* values are calculated by Pearson chi-square test for categorical variables and Student *t* test for continuous variables.

SEER database validation data set

To validate these results in a separate data set and evaluate cancer-specific survival, the SEER data set was used. In total, 1202 patients met the inclusion criteria, including 745 (62.0%) men and 457 (38.0%) women. Compared with men, women more often were unmarried (47.5% vs 24.4%; $P < .001$), had stage T1 disease (65.0% vs 58.0%; $P = .04$), did not receive radiotherapy (46.2% vs 38.9%; $P = .02$), and had disease located on the extremities (59.1% vs 52.9%; $P = .001$). Among all patients, the median follow-up was 48.0 months.

Table II. Univariate and multivariable Cox regression for predictors of overall survival in patients with Merkel cell carcinoma undergoing curative intent surgery in the National Cancer Data Base

	Univariate survival analysis				Multivariable survival analysis			
Characteristics	**HR**	**95% CI**		***P***	**HR**	**95% CI**		***P***
Sex								
Male	1.000	—	—	—	1.000	—	—	—
Female	0.653	0.587	0.726	<.001	0.677	0.609	0.754	<.001
Age (continuous years)	1.051	1.046	1.057	<.001	1.048	1.043	1.054	<.001
Race								
White	1.000	—	—	—	1.000	—	—	—
Nonwhite	0.609	0.416	0.890	.011	0.675	0.460	0.992	.045
T classification								
T1	1.000	—	—	—	1.000	—	—	—
T2	1.665	1.493	1.856	<.001	1.388	1.240	1.555	<.001
T3	2.168	1.793	2.622	<.001	1.719	1.414	2.088	<.001
T4	2.753	2.278	3.327	<.001	1.816	1.491	2.211	<.001
N classification								
N0	1.000	—	—	—	1.000	—	—	—
N1	2.621	2.374	2.894	<.001	2.339	2.107	2.596	<.001
N2	3.577	2.659	4.811	<.001	2.767	2.048	3.739	<.001
Comorbidity score								
0	1.000	—	—	—	1.000	—	—	—
1	1.379	1.226	1.552	<.001	1.341	1.191	1.511	<.001
≥2	1.946	1.603	2.361	<.001	1.750	1.441	2.126	<.001
Facility type								
Nonacademic center	1.000	—	—	—	1.000	—	—	—
Academic center	0.804	0.729	0.886	<.001	0.897	0.804	1.000	.051
Facility volume								
Low	1.000	—	—	—	1.000	—	—	—
High	0.702	0.608	0.809	<.001	0.772	0.659	0.905	.001
Radiation								
No	1.000	—	—	—	1.000	—	—	—
Yes	0.928	0.842	1.023	.135	0.803	0.726	0.887	<.001
Chemotherapy								
No	1.000	—	—	—	*			
Yes	1.272	1.109	1.460	.001				
Anatomic site								
Head and neck	1.000	—	—	—	1.000	—	—	—
Trunk	0.982	0.840	1.147	.815	0.970	0.825	1.141	.716
Extremity	0.683	0.616	0.758	<.001	0.780	0.699	0.869	<.001
Insurance status								
Private	1.000	—	—	—	*			
Medicare	2.142	1.889	2.429	<.001				
Other	1.730	1.294	2.311	<.001				
Zip code median income								
<$48,000	1.000	—	—	—	1.000	—	—	—
≥$48,000	0.774	0.701	0.856	<.001	0.906	0.814	1.008	.070
Zip code education								
≥20% without high school diploma	1.000	—	—	—	*			
<20% without high school diploma	0.876	0.751	1.023	.094				
Regional population								
<1 million	1.000	—	—	—	1.000	—	—	—
≥1 million	0.743	0.675	0.819	<.001	0.812	0.733	0.901	<.001

CI, Confidence interval; *HR*, hazard ratio.
*Dropped from model.

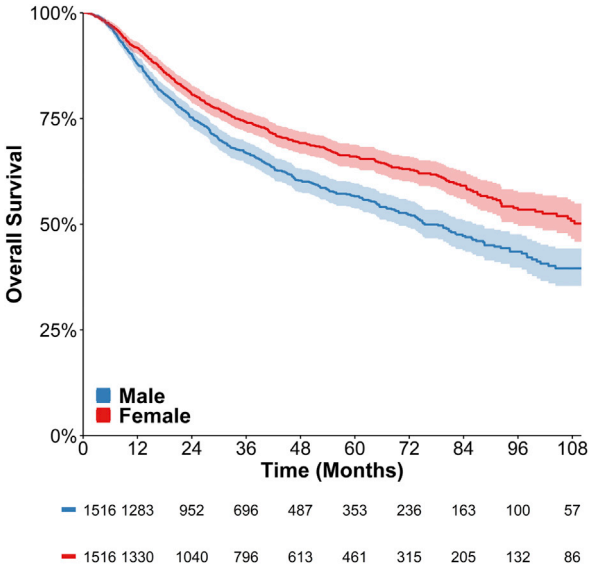

Fig 1. Overall survival of men versus women with Merkel cell carcinoma undergoing surgery in the National Cancer Data Base among propensity score–matched cohorts.

In multivariable regression (Table III), female sex was associated with both improved OS (HR, 0.68; 95% CI, 0.55-0.85; $P < .001$), and improved cancer-specific survival (HR, 0.67; 95% CI, 0.50-0.91; $P = .01$), with nearly identical magnitude. In propensity-score matched cohorts, 5-year OS was 66.9% versus 55.5% ($P = .001$) in women and men, respectively (Fig 2). Because MCC occurs in an elderly population with relatively high non-cancer mortality, we also evaluated cancer-specific mortality and other-cause mortality using competing risks analysis. In the propensity score–matched cohorts, the cumulative incidence of MCC-related mortality was 16.4% versus 26.7% at 5 years in women and men, respectively ($P < .001$) (Fig 2). Other-cause mortality was similar (16.8% vs 17.8%; $P = .810$).

In subgroup analysis, women had improved OS and cause-specific survival in virtually all subgroups. Although there were no significant interactions after correcting for multiple hypothesis testing, as in the NCDB data set, there was a trend toward greater OS (interaction $P = .007$) and cause-specific survival (interaction $P = .008$) differences between men and women in patients with head and neck primary tumors.

Sensitivity analysis

To ensure that our results were generalizable and not a result of our inclusion criteria, we performed sensitivity analyses in a broader population. First, we analyzed overall survival in all 11,810 patients with Merkel cell carcinoma with known follow-up in the NCDB, including those with distant metastasis and those not undergoing surgery (Supplemental Figure 1, *A*; available via Mendeley at https://doi.org/10.17632/4hm7n3b5d9.2). Similar to the narrower data set of patients with localized disease undergoing surgery, women had significantly improved overall survival (54.3% vs 42.0% at 5 years; $P < .001$). In a multivariable model of 9074 of these patients with treatment and staging information, replacing pathologic T/N classification with overall stage and adjusting for surgical or nonsurgical management (Supplemental Table II; available via Mendeley at https://doi.org/10.17632/4hm7n3b5d9.2), we found that female sex continued to be associated with improved survival in this broader population (HR, 0.69; 95% CI, 0.65-0.73; $P < .001$). We also analyzed cause-specific and other-cause mortality in the all 3801 patients with survival data in the SEER data set, including those with distant metastasis and those not undergoing surgery (Supplemental Figure 1, *B* and *C*) and found that women had lower cause-specific mortality (22.6% vs 33.5% at 5 years; $P < .001$) but no difference in other-cause mortality (24.1% vs 23.4%; $P = .26$).

DISCUSSION

In this study, we showed that women with MCC have a 32% lower rate of mortality than men in both the SEER and the NCDB data sets, corresponding to an approximately 10% absolute difference in 5-year survival, after adjusting for a variety of patient-, treatment-, and tumor-related variables. Remarkably, the magnitude of the effect was nearly identical in both the NCDB and SEER-18 databases. This difference in survival appeared to be driven entirely by difference in cancer-specific mortality, with men and women with MCC having similar other-cause mortality in the SEER-18 database. Similar results were also seen after adjusting for immunosuppression status in the subgroup of patients with this information available in the NCDB, although the magnitude of the survival difference was reduced. The relevance of these findings is strengthened by the consistent female survival advantage seen in every subgroup, making it unlikely that factors such as earlier diagnosis, socioeconomic differences, or disparate treatments are driving these results. The effect did appear more pronounced in patients with head and neck primaries, although tests of interaction between primary site and sex were not strictly significant when accounting for multiple hypothesis testing.

The underlying cause of the improved survival observed in women with MCC is unclear. One possibility is that inherent immunologic differences

Table III. Multivariable Fine-Gray regression for cause-specific survival and multivariable Cox regression for overall survival in patients with Merkel cell carcinoma undergoing surgery in the Surveillance, Epidemiology, and End Results database

	Cause-specific survival				Overall survival			
Characteristics	**HR**	**95% CI**		***P***	**HR**	**95% CI**		***P***
Sex								
Male	1.000	—	—	—	1.000	—	—	—
Female	0.673	0.499	0.908	.010	0.683	0.551	0.846	<.001
Age (continuous years)	1.018	1.005	1.031	.006	1.049	1.038	1.060	<.001
Race	*							
White					*			
Black/other								
Marital status	*							
Married					*			
Unmarried								
Year of diagnosis (continuous)	*				0.964	0.928	1.001	.054
T classification								
T1	1.000	—	—	—	1.000	—	—	—
T2	1.084	0.783	1.501	.630	1.231	0.975	1.556	.081
T3	1.238	0.770	1.990	.380	1.554	1.071	2.253	.020
T4	1.991	1.181	3.355	.010	1.518	1.034	2.229	.033
N classification								
N0	1.000	—	—	—	1.000	—	—	—
N1-2	3.446	2.532	4.689	<.001	3.039	2.452	3.767	<.001
Radiation	*							
No					1.000	—	—	—
Yes					0.673	0.545	0.830	<.001
Chemotherapy								
No	1.000	—	—	—	*			
Yes	1.526	1.053	2.213	.026				
Anatomic site	*							
Head and neck					1.000	—	—	—
Trunk					0.568	0.404	0.799	.001
Extremity					0.711	0.566	0.895	.004

CI, Confidence interval; *HR*, hazard ratio.
*Dropped from the model.

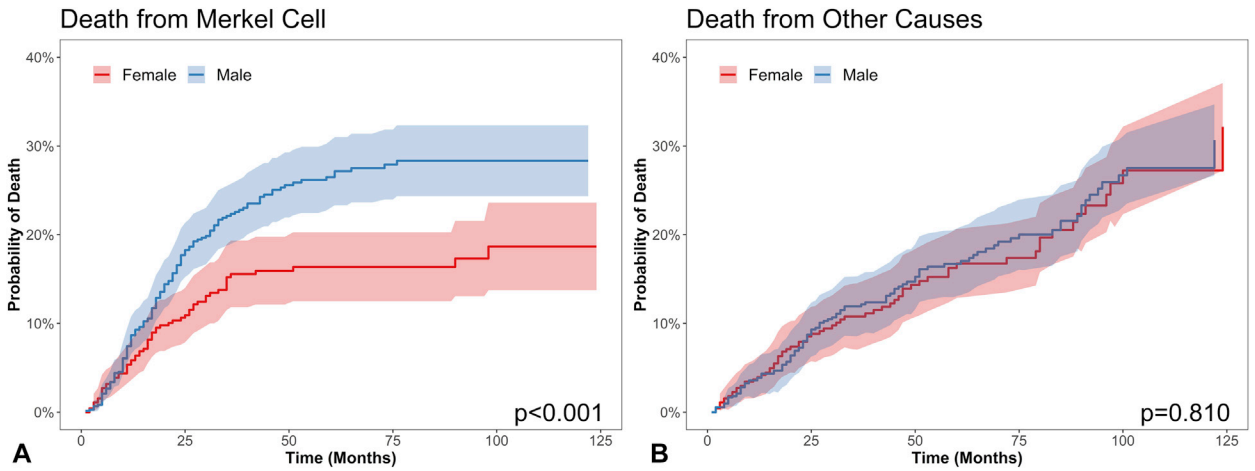

Fig 2. Estimated cumulative incidence of cancer-specific mortality and other-cause mortality of men versus women in propensity score–matched cohorts of patients with Merkel cell carcinoma undergoing surgery in the Surveillance, Epidemiology, and End Results database.

in men and women could play a role. Women have been shown to generally have stronger innate and adaptive immune responses than men[26] and have approximately 2 to 4 times higher rates of systemic autoimmune diseases.[26,27] A recent meta-analysis of patients with cancer enrolled in immune checkpoint inhibition trials found that these immunologic agents seemed to have a smaller survival benefit in women, further supporting the idea that there may be intrinsic sex differences in anticancer immune responses. It is well established that MCC is immunogenic and that the immune system plays a critical role in controlling and eradicating this disease. For example, immunocompromised patients are known to have an earlier onset and more aggressive course of MCC, with poorer outcomes.[28-31] Additionally, response rates with PD-1/PD-L1 immune checkpoint inhibitors are among the highest observed in any solid tumor.[32-34] Increased $CD3^+$ and $CD8^+$ T-cell density at the tumor periphery is a favorable prognostic indicator in MCC.[35] Given the emerging understanding of immunologic differences between men and women and the impact of the immune system on outcomes in MCC, it is plausible that the interplay between sex and immunity could account for at least some of the survival differences observed in our study.[14]

A major strength of our study is the use of 2 large databases with standardized abstraction and coding methods and substantial clinical and demographic information for discovery and validation. However, our study is limited by unmeasured confounders, which occurs with any retrospective database analysis. For instance, we are not able to adjust for immunosuppression in all patients, which is a known key determinant of survival in Merkel cell carcinoma, or degree of immune infiltration.[35] However, we did perform an analysis in a subgroup of patients with known immunosuppression status and found similar results when accounting for this variable. Data on Merkel cell polyomavirus were also not available, although it is not clear that this has a major impact on survival in MCC. Although SEER provides information on cause-specific survival, the SEER and NCDB databases do not provide additional important endpoints, such as the rates of local-regional recurrence or distant metastasis. SEER also is somewhat unreliable with respect to reporting radiation and chemotherapy delivery. Finally, it is possible that there is some overlap between the patients within the SEER database and those in the NCDB, which is not possible to account for.

In conclusion, we found that women with MCC have a survival advantage over men that is independent of other prognostic factors and was seen in all subgroups. The female survival advantage is entirely driven by MCC-related mortality and not by competing causes of mortality. More research is needed to investigate the underlying biological and immunologic differences that may account for this survival difference.

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