# Survival outcomes and epidemiology of Merkel cell carcinoma of the lower limb and hip: A Surveillance, Epidemiology, and End Results analysis 2000-2018

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***Background:*** Merkel cell carcinoma of lower limb and hip skin is a rare skin tumor that has a high recurrence rate.

***Objective:*** To assess epidemiology and survival outcomes of the lower limb and hip Merkel cell carcinoma, which are less addressed in the literature.

***Methods:*** The Surveillance, Epidemiology, and End Results database was searched for all cases of skin Merkel cell carcinoma between 2000 and 2018. Demographic and clinicopathologic features were compared between lower limb and other skin localizations using the *t* test or $\chi^2$ test. The overall survival (OS) of lower limb Merkel cell carcinoma was calculated using the Kaplan-Meier method. Subgroups were compared using the log rank test. Multivariate cox regression was used to identify independent prognostic factors.

***Results:*** In total, 976 patients were identified. The mean age was 72.7 years. The median OS was 68 months, better than that of other localizations. Older age, regional lymph node, and distant metastasis were associated with low OS. Surgery with >1-cm margins, when associated with radiotherapy, had the best OS. Age, tumor size, lymph node status, presence of metastasis, and treatment sequence were identified as independent prognostic factors.

***Conclusion:*** Lower limb and hip Merkel cell carcinomas have better OS than tumors in other skin localizations. In this dataset, the best OS was ensured using surgery with >1-cm margins and adjuvant radiotherapy. (JAAD Int 2022;7:13-21.)

***Key words:*** carcinoma; Merkel; population; SEER; survival; treatment.

## INTRODUCTION

Merkel cell carcinoma (MCC) is a rare skin tumor that has neuroendocrine attributes. With the incidence between 0.24 and 2.5 per 100,000 person-years, MCC remains less common than other skin tumors.[1-4] However, a trend toward an increasing incidence has been reported, although some studies have noted stabilization in the last years.[1,3-6] The head and neck regions have been reported as the most frequent localizations compared with other regions affected by MCC, with an incidence of around 40%.[4,6-8] Lower limb and hip skin, despite being the third-most frequent localization after upper limb and hand skin, is less addressed in the current literature.[4,6,8] UV exposure might explain the high incidence of head, neck, and upper limb tumors. The lower limbs and hip are less UV-exposed body areas that maintain a high MCC

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incidence. It might be explained by an alternative pathogenesis: immunosuppression and Merkel cell polyomavirus (MCPyV) activity.[9,10] Although UV-mutational MCC is known to be aggressive, with high regional invasion and metastasis rates, MCPyV-linked MCC might behave differently.[8,11,12]

MCC treatment requires close collaboration among dermatologists, oncologists, orthopedics, and plastic surgeons. Optimal treatment is determined according to initial staging, and procedures such as sentinel lymph node biopsy, allow the avoidance of more invasive surgeries that are associated with high morbidity.[13,14] Guidelines might differ slightly among centers, but surgery with wide margins, if feasible, seems to be a mainstay in treatment. Its association with radiation or molecular therapy is frequent.

**CAPSULE SUMMARY**

- No large demographic and survival study has focused on Merkel cell carcinoma of the lower limb and hip skin.
- Surgery with >1-cm margins with adjuvant radiotherapy appears to offer the best overall survival.

Large population analyses have been conducted on MCC, but these focused mainly on other anatomic locations.[2,3,5-7,15-21] Although institutional reviews have reported outcomes of MCC of the lower limb and hip, no large epidemiologic population study has been conducted to the best of our knowledge. Because lower limb MCC might have a different pathogenesis and less morbidity or aesthetic concerns with regard to surgical margins, the aim of this study was to determine whether its survival outcomes and patient characteristics differ from other localizations. By assessing epidemiology and unveiling differences in survival outcomes between different therapeutic strategies, this article aimed to help counsel patients and plan adequate therapies.

## MATERIALS AND METHODS

### Patient selection

The Surveillance, Epidemiology, and End Results (SEER) program is an incidence and survival database extracted from different US cancer registries under the supervision of the National Cancer Institute. It covers up to 35% of the population and is representative of the country's demographics.[22] It reports cancer data in a rigorous and comprehensive way, allowing demographic and survival analyses of tumors with a low incidence.

Data were extracted using the case listing option of the survival session in SEER*stat software (version 8.3.9). The study period between 2000 and 2018 was selected because it includes the largest population available, with data obtained from 18 different registries. Furthermore, it includes data regarding modern therapies and medical progress compared with those in a broader study period. Patients were selected using the International Classification of Diseases for Oncology, third edition, code 8247/3 (Merkel cell carcinoma) and International Classification of Diseases primary site code C44.0-C44.9 to include all cutaneous MCCs because other primary sites (mucosa or deep tissues) use different therapeutic classifications that cannot be analyzed using cutaneous ones. Intervals were defined in months.

### Variable selection

The following multiple variables were defined: age at diagnosis, sex, race, marital status, year of diagnosis, primary site, stage, TNM classification, SEER registry, type of surgery, global treatment, and chemotherapy. When available, SEER-defined variables were used. For analysis, we created "merged" variables using the SEER*stat merging tool, such as global treatment that combines the type of surgery with the use of radiotherapy. This variable has 5 different values: standard of care (SOC) with or without radiotherapy, no SOC with or without radiotherapy, and unknown. SOC was defined in our study as a surgical procedure with >1-cm surgical margin, as defined by the European Organisation for Research and Treatment of Cancer guidelines (>1-2 cm).[14] The term standard of care could not be used outside of this study because our analysis did not cover recommended treatments such as Mohs micrographic surgery or immunotherapy. The No SOC group included patients who did not benefit from any surgery to avoid numerous subcategories.

Variables with multiple values, such as marital status and type of surgery, were categorized into subgroups to ease interpretation and analysis.

Because age is a continuous variable, 3 categories were created for survival analysis: <65, 65-79, ≥80 years. These categories were randomly designed with the aim of separating young and fit patients (aged <65 years) from the elderly ones (aged ≥80 years), who are expected to have low survival because of their comorbidities. The group of patients aged 65-79 years is thought to be representative of patients aged close to the mean diagnostic age and sufficiently fit for curative treatment.

SEER registries correspond to regions for which we could extrapolate high or low UV exposure. Thirteen states were reported, some containing multiple registries. To define UV exposure, we used

*Abbreviations used:*

MCC: Merkel cell carcinoma
MCPyV: Merkel cell polyomavirus
OS: overall survival
SEER: Surveillance, Epidemiology, and End Results
SOC: standard of care

the National Weather Service 2017 UV index report.[23] Days with the UV index defined as "extreme," "very high," and "high" were cumulated. The cutoff was randomly assigned as ≥180 days. For the California registry, the UV index was available for 2 major cities: San Francisco and Los Angeles. We chose Los Angeles because it was the southernmost city. High sun exposure registries are California (219 days), Georgia (180 days), Hawaii (308 days), Louisiana (222 days), and New Mexico (213 days). Low sun exposure registries are Alaska (2 days), Connecticut (115 days), Detroit (103 days), Iowa (125 days), Kentucky (141 days), New Jersey (136 days), Seattle (101 days), and Utah (166 days).

The TNM classification allowed the extraction of data on tumor size, lymph node, and metastatic status. T0 subgroup of T variable was not included in the survival analysis because it contained only 1 patient with MCC in the lower limb and hip. The SEER summary stage variable was used to define the initial stage.

### Statistical analysis

Raw data were processed using IBM SPSS software (version 21). Demographic, clinicopathologic data were compared between the lower limb and hip skin and other cutaneous localizations (as a single category) using cross tables. The significance of differences was assessed using the $\chi^2$ test for categorical variables or Student $t$ test for continuous variables. Unknown values were considered as missing and not accounted for in the statistical analysis.

An overall survival (OS) analysis was then performed for the skin of lower limb and hip localizations using the Kaplan-Meier method. A univariate analysis of survival in subgroups was performed using the log-rank test.

Multivariate Cox regression was used to identify independent prognostic factors between age at diagnosis, sex, race, tumor size, lymph node status, metastasis, overall treatment, and the use of chemotherapy. The proportionality of hazards assumption was tested using the Schoenfeld residuals test. The variables of age at diagnosis and metastasis did not meet the assumption of the proportionality of hazards, and caution must be applied while interpreting results.

A $P$ value $<.05$ was considered statistically significant.

## RESULTS

We identified 976 patients with lower limb and hip skin MCCs (Table I). The mean age was 72.7 years, and the median age was 74 years. The mean age was significantly younger than those with MCC in other localizations (Fig 1). The population was predominantly White (93.7%), with 50.4% men and 49.6% women. Lower limb and hip MCCs were significantly more frequent (44.5%) in low UV exposure registries than MCCs of other skin localizations (40.4%). A diagnosis was made mainly at the localized stage (61.8%), with tumor size <2 cm (T1) in 49.8% of the cases. Tumors >2 cm (T2 and T3) were more frequent than those in other localizations, but adjacent tissue invasion (T4) was less frequent. Surgery with >1-cm surgical margins (SOC) was performed in 40.8% of the patients, more frequently than in those with MCCs in other localizations.

The median OS was 68 months (95% CI, 55.1-80.9), significantly better than that of other skin localizations: 51 months (95% CI, 47.4-54-6) (Fig 2). The 5-year OS rate was 52.5%, with 46.3% in other skin localizations. The OS was significantly different between the 3 age categories ($P < .05$). Age ≥80 years was associated with the lowest survival (median, 31 months; 95% CI, 26-36). No survival difference was noted between men (median, 70 months; 95% CI, 51.5-88.5) and women (median, 65 months; 95% CI, 47.7-82.3). Survival between different races did not differ significantly. Survival between married (median, 91 months; 95% CI, 67.4-114.6) and unmarried (median, 117 months; 95% CI, 88.3-145.7) individuals did not significantly differ, but both had better OS than widowed individuals (median, 31 months; 95% CI, 24.1-37.9) ($P < .05$). A tumor size of ≤2 cm (T1) had significantly better OS (median, 118 months; 95% CI, 85.1-150.9) than larger or locally invasive tumors (Fig 3). No significant difference was observed between T2, T3, and T4 OS ($P > .05$). Overall survival was significantly better for a negative lymph node status (median, 99 months; 95% CI, 76.1-121.9) than for a positive lymph node status (median, 36 months; 95% CI, 24.3-47.7). Metastasis was significantly associated with lower survival (median, 14 months; 95% CI, 6.4-21.6) compared with no metastasis (median, 80 months; 95% CI, 61.1-98.8). Localized (median, 108 months;

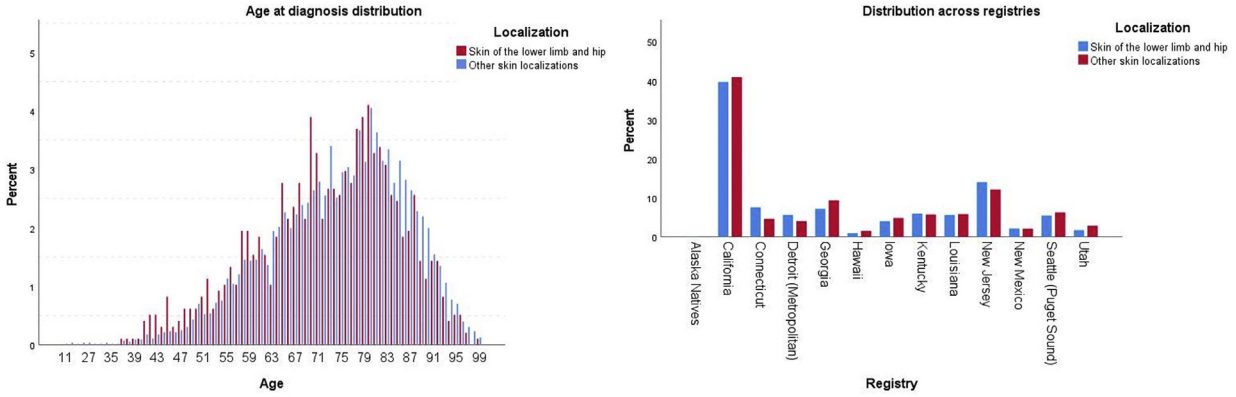


**Fig 1.** Age and registry distribution.

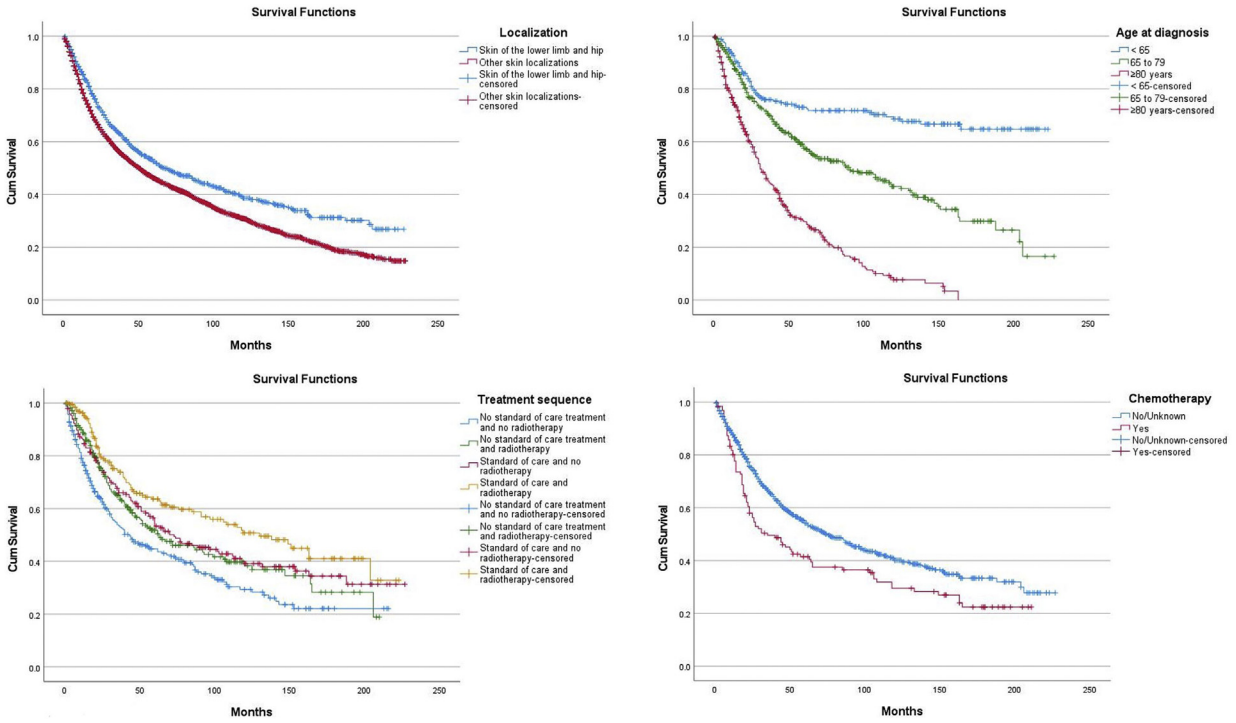


**Fig 2.** Localization, age, and treatment survival curves.

95% CI, 87.3-128.7), regional (median, 49 months; 95% CI, 34-64), and distant (median, 18 months; 95% CI, 11-25) disease at diagnosis had significantly different survival between them ($P < .05$). SOC surgery with radiotherapy (median, 130 months; 95% CI, 87.5-172.5) was significantly associated with better OS compared with other treatment modalities. No significant difference in terms of survival was observed in the case of SOC surgery without radiotherapy (median, 73 months; 95% CI, 49.3-96.7) and no SOC with radiotherapy (median, 63 months; 95% CI, 40.4-85.6). No SOC without radiotherapy (median, 43 months; 95% CI, 28.5-57.5) showed worse OS than other treatment sequences ($P < .05$). The use of chemotherapy (median, 35 months; 95% CI, 16.6-53.4) was associated with lower survival compared with no chemotherapy (median, 75 months; 95% CI, 61.2-88.8) ($P < .05$).

Age at diagnosis, tumor size, lymph node status, presence of metastasis, and treatment sequence were identified as independent prognostic factors in the multivariate cox regression analysis (Table II). No SOC with radiotherapy was the treatment that offered the best prognosis compared with no SOC without radiotherapy (hazard ratio, 0.515; 95% CI, 0.364-0.728).

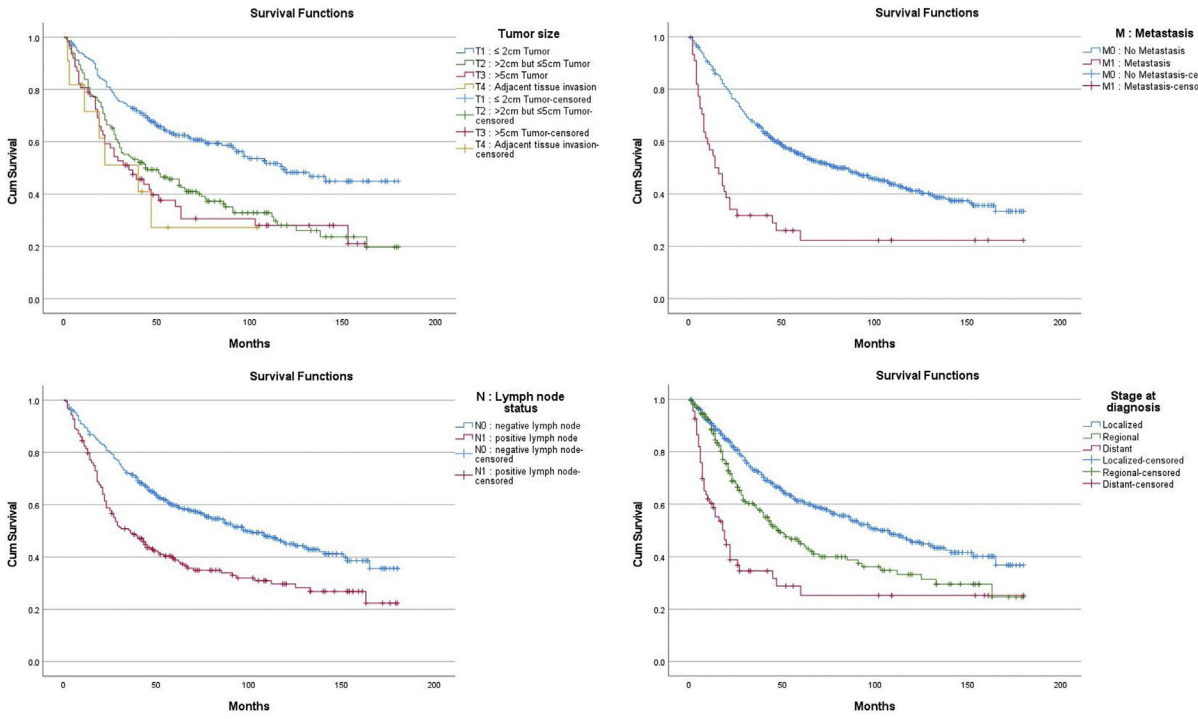


**Fig 3.** Staging survival curves.

## DISCUSSION

The demographic and clinicopathologic results confirmed the current literature results, supporting that MCC affects the overall elderly White population. This can be explained by light skin phototypes, more sensitive to UV exposure, and is supported by worldwide distribution of MCC cases, with a high incidence in Nordic and Austral countries.[24] The differences in the distribution of MCC localization according to UV exposure were significant, with lower limb and hip MCCs being represented more often in low UV exposure registries. It can be explained by the less UV exposure in the lower limb and hip areas, suggesting that carcinogenesis is not linked to UV exposure. The lower limb and hip MCCs had a male-to-female ratio of close to 1 compared with other skin MCC localizations, with men being more affected. The male and female distribution seems to vary among countries (more women than men in Denmark and Japan).[3,19]

No statistical difference in stage at diagnosis distribution was seen between the localizations. Despite delays in diagnosis due to paucisymptomatic evolution, MCC continues to be mainly diagnosed at the localized stage.[2-5,7,15,17-19,25]

Compared with the upper limb and hand, the mean age is younger, and the male-to-female ratio is close to 1 in the lower limb and hip. The tumor size seemed bigger in the lower limb and hip, which have less nodal involvement but more distant metastasis.[20] These differences might suggest another pathophysiology between upper and lower limb MCCs.

Wide or radical excision was more frequent in the lower limb and hip skin than that in other localizations. This can be explained by the lesser morbidity and aesthetic concerns with regard to the lower limb and hip. Our analysis found that SOC surgery with radiotherapy offers the best OS. These findings support our results in which lower limb and hip localizations were associated with better OS compared with other skin localizations because wide surgical margins can be made more easily. Another possible explanation for better OS in this localization is the high MCPvY-positive MCC prevalence in the lower extremities than that in other regions. MCPyV-positive MCC is associated with a less mutational charge than MCPvY-negative tumors and might offer a better prognosis.[26] In a Finnish cohort, it was found that leg and buttock MCCs have a high rate of MCPyV infection, with better overall outcomes.[27] Comparing the proportion of MCPvY tumors in our study was not feasible because viral status was not reported in the database. When the 5-year OS was compared with that in other studies, including all MCC sites, we found a variable proportion of 5-year OS, with results such as 45% and 53.5%.[4,7]

SOC surgery with radiotherapy offered the best OS, as determined using the univariate analysis.

**Table I.** Demographic and clinicopathologic characteristics

| Variable | Lower limb and hip MCCs (n = 976) | Other skin localization MCCs (n = 5562) | Statistical difference | All cutaneous MCCs (n = 6538) |
|---|---|---|---|---|
| Age at diagnosis | | | $P < .05$ | |
| Mean (SD) | 72.7 (12.3) | 74.4 (11.9) | | 74.2 (12) |
| Median (min-max) | 74 (37-99) | 76 (11-99) | | 76 (11-99) |
| Sex | | | $P < .05$ | |
| Male | 492 (50.4%) | 3434 (61.7%) | | 3926 (60%) |
| Female | 484 (49.6%) | 2128 (38.3%) | | 2612 (40%) |
| Race | | | $P < .05$ | |
| White | 908 (93.7%) | 5277 (95.6%) | | 6185 (95.3%) |
| Asian/Pacific Islander | 29 (3.0%) | 142 (2.6%) | | 171 (2.6%) |
| Black | 27 (2.8%) | 77 (1.4%) | | 104 (1.6%) |
| American Indian/Alaska Native | 5 (0.5%) | 22 (0.4%) | | 27 (0.4%) |
| Registry | | | $P < .05$ | |
| High UV exposure registries | 542 (55.5%) | 3317 (59.6%) | | 3859 (59%) |
| Low UV exposure registries | 434 (44.5%) | 2245 (40.4%) | | 2679 (41%) |
| Stage | | | $P = .164$ | |
| Localized | 483 (61.8%) | 2645 (62.3%) | | 3128 (62.2%) |
| Regional | 232 (29.7%) | 1160 (27.3%) | | 1392 (27.8%) |
| Distant | 67 (8.6%) | 443 (10.4%) | | 510 (10.1%) |
| TNM | | | | |
| T | | | $P < .05$ | |
| T0 | 1 (0.2%) | 196 (8.1%) | | 197 (6.9%) |
| T1 | 233 (49.8%) | 1335 (55.5%) | | 1568 (54.5%) |
| T2 | 161 (34.4%) | 574 (23.8%) | | 735 (25.6%) |
| T3 | 62 (13.2%) | 152 (6.3%) | | 214 (7.4%) |
| T4 | 11 (2.4%) | 150 (6.2%) | | 161 (5.6%) |
| N | | | $P = .434$ | |
| N0 | 412 (68.1%) | 2231 (69.7%) | | 2643 (69.4%) |
| N1 | 193 (31.9%) | 970 (30.3%) | | 1163 (30.6%) |
| M | | | $P = .106$ | |
| M0 | 585 (93%) | 3105 (91%) | | 3690 (91.3%) |
| M1 | 44 (7%) | 306 (9%) | | 350 (8.7%) |
| Type of surgery | | | $P < .05$ | |
| No surgery | 107 (11%) | 1019 (18.4%) | | 1126 (17.3%) |
| Local destruction (No margin) | 194 (19.9%) | 1110 (20.1%) | | 1304 (20%) |
| Gross excision (<1-cm margin) | 268 (27.5%) | 1626 (29.4%) | | 1894 (29.1%) |
| Wide + radical excision (>1-cm margin) | 397 (40.8%) | 1724 (31.2%) | | 2121 (32.6%) |
| Surgery (NOS) | 7 (0.7%) | 55 (1%) | | 62 (1%) |
| Global treatment* | | | $P < .05$ | |
| No SOC and no radiotherapy | 282 (29.5%) | 1956 (36.1%) | | 2238 (35.1%) |
| No SOC with radiotherapy | 281 (29.4%) | 1766 (32.6%) | | 2047 (32.1%) |
| SOC surgery and no radiotherapy | 196 (20.5%) | 851 (15.7%) | | 1047 (16.4%) |
| SOC surgery with radiotherapy | 196 (20.5%) | 849 (15.7%) | | 1045 (16.4%) |
| Chemotherapy | | | $P = .723$ | |
| Yes | 127 (13%) | 701 (12.6%) | | 828 (12.7%) |
| No/unknown | 849 (87%) | 4861 (87.4%) | | 5710 (87.3%) |
| Localization | | | | |
| C44.0: Skin of the lip, NOS | | | | 123 (1.9%) |
| C44.1: Eyelid | | | | 132 (2%) |
| C44.2: External ear | | | | 211 (3.2%) |
| C44.3: Skin of other/unspecified parts of the face | | | | 1690 (25.8%) |
| C44.4: Skin of the scalp and neck | | | | 594 (9.1%) |
| C44.5: Skin of the trunk | | | | 621 (9.5%) |
| C44.6: Skin of the upper limb and shoulder | | | | 1631 (24.9%) |
| C44.7: Skin of the lower limb and hip | | | | 976 (14.9%) |
| C44.8: Overlapping lesion of the skin | | | | 10 (0.2%) |
| C44.9: Skin, NOS | | | | 550 (8.4%) |

*max*, Maximum; *min*, minimum; *NOS*, not otherwise specified; *SOC*, standard of care.
*SOC was defined as surgical resection with a surgical margin of >1 cm.

**Table II.** Multivariate cox regression

| Variable | B | *P* value | Exp (B) | 95% CI for Exp (B) Lower/upper |
|---|---|---|---|---|
| Age, y | | | | |
| <65 | | .000 | | |
| 65-79 | 0.396 | .046 | 1.486 | 1.007/2.192 |
| ≥80 | 1.432 | .000 | 4.188 | 2.846/6.161 |
| Sex | | | | |
| Male | | | | |
| Female | −0.048 | .736 | 0.953 | 0.723/1.258 |
| Race | | | | |
| White | | .393 | | |
| Black | −0.092 | .803 | 0.912 | 0.444/1.876 |
| Asian or Pacific Islander | −0.495 | .190 | 0.610 | 0.291/1.279 |
| American Indian/Alaska Native | 1.068 | .298 | 2.910 | 0.389/21.769 |
| Tumor size | | | | |
| T1: ≤2 cm | | .000 | | |
| T2: >2 cm but ≤5 cm | 0.614 | .000 | 1.849 | 1.385/2.468 |
| T3: >5 cm | 0.616 | .002 | 1.852 | 1.256/2.730 |
| T4: Adjacent tissue invasion | 0.865 | .045 | 2.375 | 1.021/5.523 |
| Lymph node status | | | | |
| N0: Negative lymph node | | | | |
| N1: Positive lymph node(s) | 0.719 | .000 | 2.052 | 1.540/2.735 |
| Metastasis | | | | |
| M0: No metastasis | | | | |
| M1: Metastasis | 0.619 | .007 | 1.857 | 1.182/2.918 |
| Treatment | | | | |
| No SOC/no radiotherapy | | .001 | | |
| No SOC and radiotherapy | −0.664 | .000 | 0.515 | 0.364/0.728 |
| SOC surgery and no radiotherapy | −0.432 | .019 | 0.649 | 0.452/0.931 |
| SOC surgery and radiotherapy | −0.657 | .001 | 0.518 | 0.351/0.765 |
| Chemotherapy | | | | |
| No/unknown | | | | |
| Yes | 0.293 | .122 | 1.340 | 0.925/1.941 |

*SOC*, Standard of care.

Retrospective studies have supported our results by suggesting that adjuvant radiotherapy could have a positive impact on survival by controlling micrometastasis at the tumor resection margin.[28,29] These results support the current recommendations: wide excision should be done if feasible, and lymph node dissection or/and radiotherapy should be proposed depending on the sentinel lymph node status or estimated risk of regional lymph node metastasis.[13,14]

Radiotherapy maintains a primordial role when SOC surgery cannot be performed because of the morbidity associated with wide surgical margins. This observation can be extrapolated to our results as the absence of a significant difference in survival between the use of SOC surgery without radiotherapy and no SOC with radiotherapy. Current recommendations suggest the use of radiotherapy as a sole or adjuvant treatment in patients not eligible for SOC surgery.[30,31]

In our study, chemotherapy was associated with low survival. It can be explained by an indication bias, which resulted because chemotherapy is reserved for unfit patients or patients with systemic disease.[13,32] However, the use of modern checkpoint inhibitors, such as avelumab, could offer an alternative to chemotherapy in systemic disease management with promising results compared with standard chemotherapy.[33,34]

Independent prognostic factor interpretation must be done carefully because the proportional hazard assumption was not met for age at diagnosis and metastasis status variables. Despite this limitation, the results might show a valid trend because the age at diagnosis, tumor size, lymph node status, presence of metastasis, and treatment sequence have been identified as independent prognostic factors in other studies.[4,16,17,20,35] However, in our study, sex was not identified as an independent prognostic factor.[16]

The limitations of this study are attributed to the way the data are reported in the SEER program. A variable's coding can differ through years and between localizations. One example is the use of the combined summary stage variable that accounts only for cases after 2004 and codes them using other SEER variables. Furthermore, this classification cannot be compared with the American Joint Committee on Cancer classification, which is the current reference.[36] The use of different site-specific surgery codes limits comparison between different localizations, motivating our choice to include only cutaneous MCCs. The survival analysis with the merged category comparing SOC with no SOC constitutes another possible bias because patients who did not benefit from surgery were accounted in the no-SOC category. Distinction between radiotherapy without surgery and radiotherapy with no SOC surgery was not feasible. Comparison of treatment modalities in the SEER database is known to be subject to a possible bias.[37] Result interpretation should be done cautiously, and possible confounders should be taken into account before drawing conclusions.

Another limitation is that tumor thickness and the count of positive lymph nodes were not assessed because these 2 variables have an impact on OS.[21,35]

Despite these limitations, this study suggests demographic, clinical, and outcome differences with other MCC localizations. They might be explained because of different carcinogenesis mechanisms and differences in MCPvY infection. Despite these differences, SOC surgery with wide surgical margins associated with radiotherapy remains the mainstay of oncologic treatment with the highest OS. This study offers tools to better understand the demographic characteristics of the population affected by lower limb and hip MCCs and can help identify prognostic factors to guide patient counsel and therapeutic planning.

## CONCLUSION

MCC of the lower limb and hip skin is a rare neoplasm affecting the elderly, with low OS. Lower limb and hip localizations have better OS than other cutaneous localizations because of different carcinogenesis mechanisms with MCPvY infection. These data suggest that the best OS is ensured by SOC surgery with >1-cm surgical margin with adjuvant radiotherapy. Treatment outcomes should be interpreted cautiously because of a possible bias.

### Conflicts of interest

None disclosed.

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