JAMA Dermatology | Original Investigation

# Recurrence and Mortality Risk of Merkel Cell Carcinoma by Cancer Stage and Time From Diagnosis

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**IMPORTANCE** Merkel cell carcinoma (MCC) often behaves aggressively; however, disease-recurrence data are not captured in national databases, and it is unclear what proportion of patients with MCC experience a recurrence (estimates vary from 27%-77%). Stage-specific recurrence data that includes time from diagnosis would provide more precise prognostic information and contribute to risk-appropriate clinical surveillance.

**OBJECTIVE** To estimate risk of stage-specific MCC recurrence and mortality over time since diagnosis.

**DESIGN, SETTING, AND PARTICIPANTS** This prospective cohort study included 618 patients with MCC who were prospectively enrolled in a Seattle-based data repository between 2003 and 2019. Of these patients, 223 experienced a recurrence of MCC. Data analysis was performed July 2019 to November 2021.

**MAIN OUTCOMES AND MEASURES** Stage-specific recurrence and survival, as well as cumulative incidence and Kaplan-Meier analyses.

**RESULTS** Among the 618 patients included in the analysis (median [range] age, 69 [11-98] years; 227 [37%] female), the 5-year recurrence rate for MCC was 40%. Risk of recurrence in the first year was high (11% for patients with pathologic stage I, 33% for pathologic stage IIA/IIB, 30% for pathologic stage IIIA, 45% for pathologic stage IIIB, and 58% for pathologic stage IV), with 95% of recurrences occurring within the first 3 years. Median follow-up among living patients was 4.3 years. Beyond stage, 4 factors were associated with increased recurrence risk in univariable analyses: immunosuppression (hazard ratio [HR], 2.4; 95% CI, 1.7-3.3; $P < .001$), male sex (HR, 1.9; 95% CI, 1.4-2.5; $P < .001$), known primary lesion among patients with clinically detectable nodal disease (HR, 2.3; 95% CI, 1.4-4.0; $P = .001$), and older age (HR, 1.1; 95% CI, 1.0-1.3; $P = .06$ for each 10-year increase). Among 187 deaths in the cohort, 121 (65%) were due to MCC. The MCC-specific survival rate was strongly stage dependent (95% at 5 years for patients with pathologic stage I vs 41% for pathologic stage IV). Among patients presenting with stage I to II MCC, a local recurrence (17 arising within/adjacent to the primary tumor scar) did not appreciably diminish survival compared with patients who had no recurrence (85% vs 88% MCC-specific survival at 5 years).

**CONCLUSIONS AND RELEVANCE** In this cohort study, the MCC recurrence rate (approximately 40%) was notably different than that reported for invasive melanoma (approximately 19%), squamous cell carcinoma (approximately 5%-9%), or basal cell carcinoma (approximately 1%-2%) following definitive therapy. Because more than 90% of MCC recurrences arise within 3 years, it is appropriate to adjust surveillance intensity accordingly. Stage- and time-specific recurrence data can assist in appropriately focusing surveillance resources on patients and time intervals in which recurrence risk is highest.

*JAMA Dermatol*. doi:10.1001/jamadermatol.2021.6096
Published online February 23, 2022.

Multimedia

Supplemental content

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Merkel cell carcinoma (MCC) is a rare but aggressive skin cancer. The incidence of MCC in the US is increasing, with 3284 cases projected for 2025.[1-3] Merkel cell carcinoma has a high propensity to recur after initial treatment and is associated with lower overall survival than melanoma.[4] However, recurrence data are not collected in national data sets such as the Surveillance, Epidemiology, and End Results database and the National Cancer Database (NCDB). Reported rates of MCC recurrence range from 27% to 77% depending on each cohort's patient and tumor characteristics.[5-8] The MCC-specific mortality and recurrence risk based on current staging[9] have not been reported.

The lack of stage-specific recurrence data makes it difficult to determine appropriate surveillance plans for individual patients based on their risk of developing a recurrence. As a result, current guidelines lack specificity and suggest imaging studies "as clinically indicated."[10] Furthermore, the rate at which recurrence risk decreases with time after diagnosis is unclear, making it difficult to appropriately de-escalate surveillance. Using a large repository of prospectively enrolled patients with MCC, we assessed risk factors associated with MCC recurrence, stage-specific and overall recurrence risk, the timing and type of MCC recurrences, and postrecurrence survival.

### Key Points

**Question** What is the risk that Merkel cell carcinoma (MCC) will recur based on a patient's cancer stage and time since diagnosis?

**Findings** In this cohort study of 618 patients from a large data repository, 40% of whom experienced a recurrence, stage was a powerful prognostic factor: at 5 years, 80% of patients with pathologic stage I were without MCC recurrence vs 28% of patients with stage IV. Approximately 95% of all MCC recurrences arose within 3 years of diagnosis.

**Meaning** Recurrence data can help clinicians determine which patients with MCC merit intensive surveillance and when de-escalation of surveillance is appropriate.

## Methods

### MCC Cohort

Patients with pathologically confirmed MCC were prospectively enrolled between January 2003 and April 2019 in an institutional review board–approved repository maintained at the University of Washington in Seattle with written informed consent provided by participants. After exclusions, the cohort (hereafter, the Seattle cohort) included 618 patients (eFigure 1 in the Supplement). In this cohort, the median duration of initial treatment (surgery, radiation, and systemic therapy) was approximately 90 days. Therefore, patients with fewer than 90 days of follow-up from the date of diagnosis (n = 49) were excluded because the goal of this study was to determine outcomes following completion of treatment. Data regarding disease presentation were collected at time of enrollment by medical record review. Data regarding recurrence(s) and survival were systematically collected at least annually via acquisition and review of interval medical records and/or direct outreach to patients and health care professionals.

### Classification of Recurrences

Merkel cell carcinoma recurrence was defined as reappearance of disease or considerable progression of existing disease after initial treatment. For the recurrence analyses, only the first recurrence was considered, which may have been local (within/adjacent to the primary tumor scar), in-transit, nodal, or distantly metastatic. If more than 1 recurrence location was detected simultaneously, that recurrence event was classified by the most advanced site involved (distant/metastatic > regional > in-transit > local-only MCC).

### Overall Recurrence Rate Calculation

Because each stage has a different risk of recurrence, the overall recurrence rate for a cohort depends in part on the proportion of patients presenting with each stage, and this distribution may differ between cohorts. To address this issue, we used a cumulative incidence function to calculate overall MCC recurrence risk using a stage distribution derived from (1) the Seattle cohort or (2) the largest national data set (NCDB)[9] to reweight risk of recurrence based on stage prevalence at the national level (eFigure 3 in the Supplement).

For the systematic summary of reports shown in **Figure 1**,[5-7,9,11-15] a search was performed using PubMed for all studies that included MCC recurrence data. Reports were excluded if the study cohort (1) was limited to 1 to 2 stages, (2) only included MCC of specific anatomic sites (eg, head and neck only), or (3) the sample size was fewer than 20.

### Statistical Analysis

Risk of recurrence and MCC-specific survival were estimated using cumulative incidence functions. Patients were treated as at risk starting at 90 days after diagnosis (end of initial treatment) or time of enrollment, whichever was later. Non-MCC–associated death was a competing event because the patient was no longer at risk for the primary event. Events were censored at the date of last follow-up. Univariable Fine and Gray competing risk regression models were used to assess the influence of individual patient and tumor characteristics (eg, immune suppression, sex) on recurrence risk. The MCC-specific mortality after first recurrence was estimated based on initial stage and site of recurrence (local vs nonlocal). Gray's test was performed to evaluate the equality of cause-specific cumulative incidence functions between groups. All statistical analyses were performed using Stata, version 14.2 (StataCorp), and R, version 3.6.1 (R Foundation). All tests were 2-sided, and $P < .05$ was considered statistically significant.

## Results

### MCC Cohort, Analysis of Recurrence Risk Factors, and Distantly Metastatic Recurrences

A total of 618 patients from the Seattle-based institutional MCC repository met inclusion criteria, and patient characteristics

**Figure 1. Comparison of Merkel Cell Carcinoma (MCC) Recurrence and Survival Rates Between the Present Cohort and Existing Literature**

Recurrence rates, all stages

| Source | Recurrence rate, % | Total patients | Follow-up time, mo | Patient enrollment years | Reporting institution or location |
|---|---|---|---|---|---|
| Santamaria-Barria,[7] 2013 | 48 | 161 | 36[a] | 1980-2010 | Massachusetts General Hospital |
| Allen,[5] 2005 | 43 | 251 | 40[b] | 1970-2002 | Memorial Sloan Kettering Cancer Center |
| Eng,[12] 2004 | 40 | 85 | 39.5[b] | 1988-2003 | San Antonio, Texas |
| Seattle (present cohort) | 40[c] | 618 | 38[a] | 2003-2018 | University of Washington and Fred Hutchinson Cancer Research Center |
| Liang,[14] 2015 | 31 | 87 | 17[a] | 1984-2014 | University of Wisconsin |
| Soult,[6] 2012 | 31 | 26[d] | 26[b] | 1998-2010 | Eastern Virginia Medical School |

Recurrence rates, stages I-III

| Source | Recurrence rate, % | Total patients | Follow-up time, mo | Patient enrollment years | Reporting institution or location |
|---|---|---|---|---|---|
| Seattle (present cohort) | 38 | 578 | 40[a] | 2003-2018 | University of Washington and Fred Hutchinson Cancer Research Center |
| Fields,[10] 2012 | 30 | 364 | 43[a,e] | 1969-2010 | Memorial Sloan Kettering Cancer Center |
| Farley,[13] 2020 | 27 | 209 | 16[a] | 2005-2017 | Emory University and Moffitt Cancer Center |
| Mattavelli,[11] 2017 | 27 | 64 | 78[a] | 2002-2014 | Milan, Italy |

5-y Outcomes

| Source | Overall survival | | Disease-specific survival | | Recurrence-free survival | |
|---|---|---|---|---|---|---|
| | Local-only MCC, % | Nodal MCC, % | Local-only MCC, % | Nodal MCC, % | Local-only MCC, % | Nodal MCC, % |
| Seattle (present cohort) | 75 | 60 | 89 | 69 | 59 | 44 |
| Farley,[13] 2020 | 73 | 63 | 90 | 77 | 65 | 48 |
| Harms,[8] 2016 | 51 | 35 | NA | NA | NA | NA |

Recurrence and survival rates were similar across studies, with the Seattle cohort (shaded in gray) having a larger sample size and more recent data. NA indicates not available.

[a] Median follow-up time.

[b] Mean follow-up time.

[c] 95% CI, 36%-43%.

[d] One patient presented with stage IV cancer.

[e] Calculated from available data.

are shown in **Table 1**; 498 patients had pathologically staged cancer, and 120 had clinically staged cancer (eFigure 1 in the Supplement). A total of 223 patients experienced a recurrence. At the time of analysis, median follow-up for all patients was 3.1 years (range, 3 days to 13 years), with the median follow-up of patients still alive at their last visit being 4.3 years. After adjusting for stage, immunosuppression was strongly associated with an increased risk of recurrence (hazard ratio [HR], 2.4; 95% CI, 1.7-3.3; $P < .001$), while female sex (HR, 0.5; 95% CI, 0.4-0.7; $P < .001$) and unknown primary tumor (HR, 0.4; 95% CI, 0.3-0.7; $P = .001$) were associated with decreased risk of recurrence (Table 1). Older age was associated with increased risk of recurrence (HR, 1.1; 95% CI, 1.0-1.3; $P = .06$ per 10-year increase), while site of primary tumor was not statistically significantly associated with increased risk of recurrence ($P = .44$; Table 1). Merkel cell carcinoma was likely to recur distantly. Among the 223 patients who experienced a recurrence, 133 (60%) developed distant metastatic disease. The proportion of recurrences that were distantly metastatic increased with higher stage at presentation (eg, 5% for patients with pathologic stage I at presentation, 26% for pathologic stage IIIA, 58% for pathologic stage IV; see eFigure 2 in the Supplement for details of all 9 substages).

## Overall Recurrence Rate

The overall 5-year recurrence rate of the total cohort was 40% (95% CI, 36%-43%) with all stages combined. When the Seattle cohort was reweighted to have the same distribution of *AJCC Cancer Staging Manual*, 8th edition (*AJCC-8*), stage as the largest national cohort,[9] the overall 5-year recurrence risk estimate was 41% (95% CI, 37%-47%). Before reweighting, compared with the NCDB cohort, the Seattle cohort included a higher proportion of patients with stage I (41% vs 38%; $P = .15$) and pathologic stage III cancers (42% vs 33%; $P < .001$), and a lower proportion of stage II (13% vs 18%; $P = .001$) and pathologic stage IV cancers (4% vs 11%; $P < .001$; eFigure 3 in the Supplement). Review of the MCC recurrence literature demonstrated that overall recurrence risk was 31% to 48% when studies included stages I through IV (Figure 1).[5-7] For studies that included stages I through III, overall recurrence risk was 27% to 30%.[11,12,14] Additionally, for a head and neck MCC cohort, a recurrence rate as high as 77% has been reported.[8]

## MCC Recurrence Risk and Survival by Stage

Risk of recurrence in the first year after diagnosis was high and related to stage: 11% for pathologic stage I, 33% for pathologic stage IIA/IIB, 30% for stage IIIA, 45% for pathologic stage IIIB, and 58% for pathologic stage IV (**Table 2**). At 5 years, 80% of patients with pathologic stage I cancer were without recurrence vs 28% of patients with stage IV (Table 2). Pathologic stage IIIA consists of patients with (1) nodal disease and an unknown primary tumor or (2) clinically apparent primary tumor and positive sentinel lymph node biopsy. These distinct clinical subsets were combined in the most current staging system because of similar overall survival data.[9] In the Seattle cohort, the recurrence rate for patients with pathologic stage IIIA

Table 1. Prevalence of Clinical Characteristics and Association With Recurrence Risk Among the Study Cohort

| Characteristic | No. (%) (n = 618) | Univariable analysis of recurrence risk | |
|---|---|---|---|
| | | HR (95% CI) | *P* value |
| Sex | | | |
| Female | 227 (37) | 0.5 (0.4-0.7) | <.001 |
| Male | 391 (63) | 1 [Reference] | |
| Age, median (range), y[a] | 69 (11-98) | 1.1 (1.0-1.3) | .06 |
| Immunosuppressed | 82 (13) | 2.4 (1.7-3.3) | <.001 |
| Unknown primary tumor | | | |
| Among patients with clinically detectable lymph nodes (n = 138)[b] | 75 (54) | 0.4 (0.3-0.7) | .001 |
| Among patients with stage IV cancer (n = 40) | 23 (57) | 0.9 (0.4-2.0) | .78 |
| Site of primary tumor (n = 520)[c] | | | |
| Extremity | 243 (47) | 1 [Reference] | .44 |
| Chest/abdomen/pelvis | 73 (14) | 1.3 (0.8-1.9) | |
| Head/neck | 204 (39) | 1.0 (0.7-1.3) | |
| *AJCC Cancer Staging Manual*, 8th edition, stage | | | |
| p-I | 183 (30) | 1 [Reference] | <.001 |
| c-I | 52 (8) | 1.9 (1.0-3.5) | |
| p-II | 47 (8) | 2.8 (1.6-4.9) | |
| c-II | 28 (5) | 2.9 (1.5-5.6) | |
| p-IIIA | 179 (29) | 2.6 (1.7-4.0) | |
| Positive on SLNB | 104 (17) | 3.3 (2.1-5.2) | |
| Unknown primary tumor | 75 (12) | 1.9 (1.1-3.2) | |
| p-IIIB | 63 (10) | 4.5 (2.8-7.4) | |
| c-III | 26 (4) | 6.7 (3.8-12.0) | |
| c/p-IV | 40 (6) | 6.1 (3.6-10.3) | |

Abbreviations: HR, hazard ratio; NA, not applicable; SLNB, sentinel lymph node biopsy.

[a] The HR is expressed as the change per 10-year increase in age.

[b] Patients with stage IIIA cancer and unknown primary tumor or patients with stage IIIB cancer.

[c] Includes only patients with a known primary tumor.

cancer with known vs unknown primary tumor were statistically significantly different (eFigure 5 in the Supplement). In the first year, recurrence rate was 37% for patients with stage IIIA cancer with known primary tumor and 21% for patients with stage IIIA cancer with unknown primary tumor ($P = .03$). Interestingly, MCC-specific survival trends for patients with stage IIIA cancer with known vs unknown primary tumor were not statistically significantly different ($P = .12$; eFigure 5 in the Supplement). For all stages, the highest risk of recurrence occurred 1 to 3 years after initial treatment (Table 2), and 94% of recurrences occurred within the first 3 years after initial treatment. This proportion ranged from 70% to 100% across stages. All initial recurrences in the Seattle cohort occurred within 6 years after treatment (eFigure 6 in the Supplement).

For patients who presented with local-only disease, MCC-specific survival was excellent (95% at 5 years for those with pathologic stage I). In contrast, patients who presented with distantly metastatic disease had a poor prognosis (41% 5-year MCC-specific survival for patients with pathologic stage IV; **Figure 2** and Table 2). Overall survival by stage in the Seattle cohort can be found in Table 2 and eFigure 4 in the Supplement.

### Postrecurrence MCC-Specific Survival

Disease-specific survival after first MCC recurrence is shown in **Figure 3**. Of note, among patients who originally presented with stage I to II disease and experienced a local recurrence, MCC-specific survival was minimally affected and remained high (85% at 5 years). In contrast, MCC-specific survival was relatively low and not statistically significantly different between patients with stage III cancer with local recurrence, patients with stage III cancer with nonlocal recurrence, and patients with stage IV cancer with any recurrence ($P = .89$; Figure 3). It is important to note that these results largely reflect the clinical course of MCC before the era of immunotherapy.

## Discussion

Using a uniquely large, prospectively enrolled MCC cohort, this study details the risk of MCC recurrence and mortality by cancer stage to a greater degree than was previously available. The current paucity of data regarding MCC recurrence risk is largely because national databases collect survival, but not disease recurrence, data. Beyond factors included in *AJCC-8* staging, we found several patient characteristics that were independently predictive of MCC recurrence, including age, sex, immune suppression, and unknown site of primary tumor for patients with stage III disease. These stage-specific recurrence data, combined with details regarding how rapidly risk decreases after diagnosis, will contribute to patient education and surveillance management of this cancer that we conclude recurs at an overall rate of approximately 40%.





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Table 2. Patients With Merkel Cell Carcinoma (MCC) Without Recurrence or Death by Year After Diagnosis[a]

| | Year | | | | | |
|---|---|---|---|---|---|---|
| Cancer stage | 1 | 2 | 3 | 4 | 5 | 6 |
| **Patients without any MCC recurrence** | | | | | | |
| p-I | 141 (89) | 120 (86) | 102 (82) | 77 (81) | 58 (80) | 44 (80) |
| p-IIA/IIB | 29 (67) | 25 (62) | 21 (60) | 18 (60) | 10 (54) | 7 (54) |
| p-IIIA | 115 (70) | 98 (63) | 79 (61) | 69 (58) | 53 (58) | 44 (58) |
| p-IIIB | 32 (55) | 23 (49) | 18 (40) | 15 (40) | 13 (40) | 8 (40) |
| p-IV | 9 (42) | 6 (37) | 2 (28) | NA[b] | NA[b] | NA[b] |
| c-I | 33 (76) | 30 (74) | 20 (69) | 15 (69) | 12 (69) | 10 (69) |
| c-IIA/IIB | 16 (68) | 9 (64) | 8 (64) | 6 (64) | 4 (58) | 2 (49) |
| c-III | 7 (45) | 4 (31) | 2 (26) | 2 (26) | 2 (26) | 2 (26) |
| c-IV | 3 (34) | 3 (34) | 3 (34) | 3 (34) | NA[b] | NA[b] |
| **MCC-specific survival** | | | | | | |
| p-I | 159 (99) | 135 (97) | 118 (96) | 89 (95) | 68 (95) | 51 (95) |
| p-IIA/IIB | 40 (93) | 33 (84) | 29 (84) | 24 (84) | 15 (80) | 11 (80) |
| p-IIIA | 154 (96) | 122 (83) | 97 (81) | 86 (80) | 63 (78) | 47 (76) |
| p-IIIB | 47 (80) | 35 (69) | 29 (63) | 21 (58) | 15 (56) | 9 (52) |
| p-IV | 14 (71) | 9 (60) | 5 (51) | 3 (41) | NA[b] | NA[b] |
| c-I | 40 (92) | 35 (90) | 25 (90) | 20 (90) | 16 (86) | 12 (86) |
| c-IIA/IIB | 19 (82) | 11 (73) | 10 (73) | 7 (73) | 6 (73) | 5 (73) |
| c-III | 14 (75) | 4 (35) | 2 (35) | 2 (35) | 2 (35) | 2 (35) |
| c-IV | 4 (48) | 3 (38) | 3 (38) | 3 (38) | NA[b] | NA[b] |
| **Overall survival** | | | | | | |
| p-I | 159 (99) | 135 (96) | 118 (94) | 89 (91) | 68 (88) | 51 (88) |
| p-IIA/IIB | 40 (91) | 33 (79) | 29 (79) | 24 (73) | 15 (66) | 11 (66) |
| p-IIIA | 154 (94) | 122 (80) | 97 (78) | 86 (76) | 63 (68) | 47 (67) |
| p-IIIB | 47 (80) | 35 (68) | 29 (62) | 21 (57) | 15 (54) | 9 (43) |
| p-IV | 14 (71) | 9 (60) | 5 (51) | 3 (41) | NA[b] | NA[b] |
| c-I | 40 (82) | 35 (76) | 25 (69) | 20 (66) | 16 (59) | 12 (59) |
| c-IIA/IIB | 19 (68) | 11 (49) | 10 (44) | 7 (40) | 6 (40) | 5 (40) |
| c-III | 14 (60) | 4 (19) | 2 (15) | 2 (15) | 2 (15) | 2 (15) |
| c-IV | 4 (40) | 3 (30) | 3 (30) | 3 (30) | NA[b] | NA[b] |

Abbreviation: NA, not applicable.

[a] All data are reported as number (%) of patients. Risk of MCC recurrence or death was estimated using cumulative incidence functions. Death from non-MCC cause was a competing risk for MCC recurrence and MCC-specific survival. The number at risk at the end of each year is shown and calculated as the number of patients who did not experience an MCC recurrence (MCC recurrence outcome only), did not die (regardless of cause), and were not lost to follow-up at that time following initial diagnosis and treatment. Staging was determined according to *AJCC Cancer Staging Manual*, 8th edition.

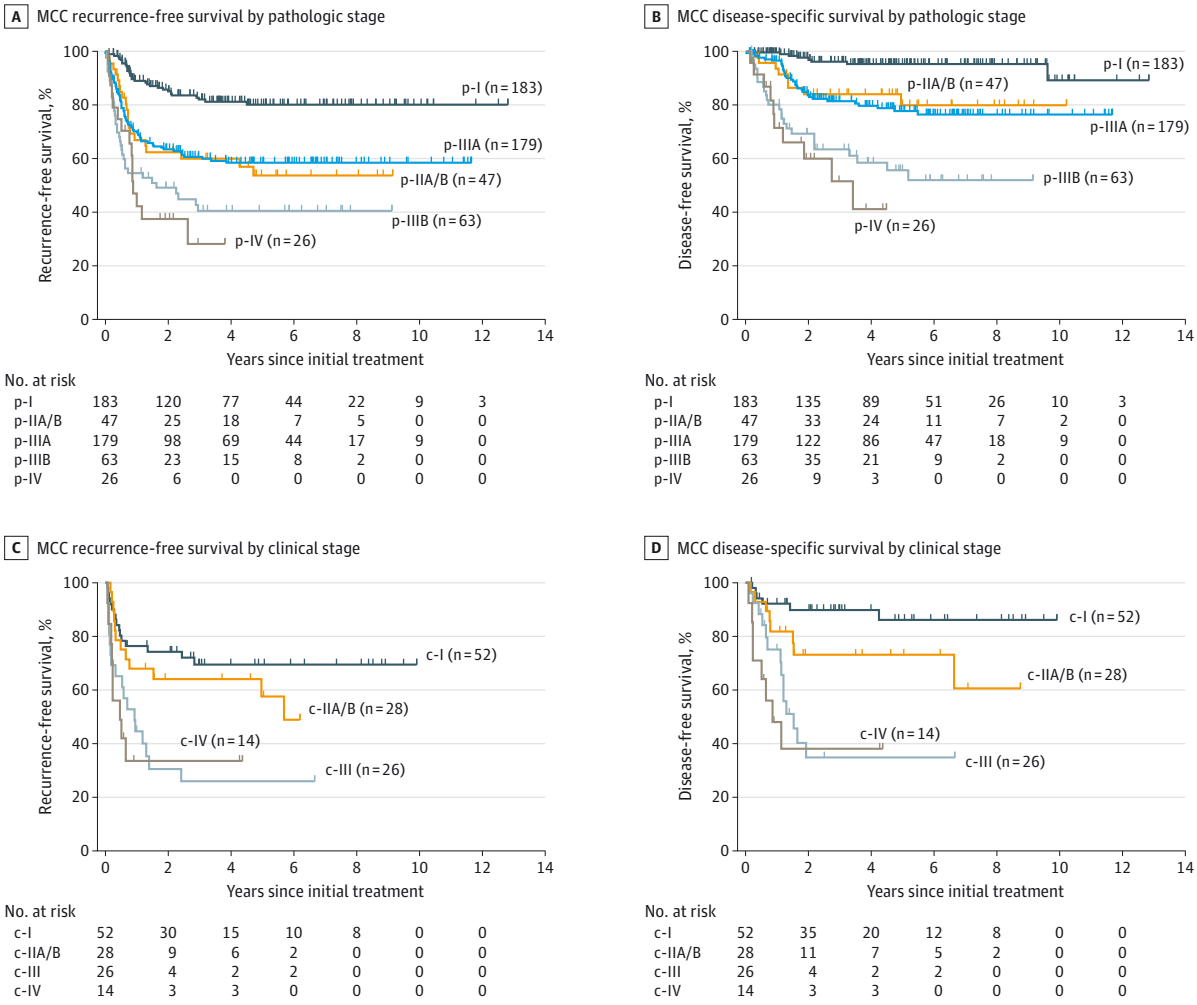
[b] Results are not shown once the number at risk is fewer than 2.

## Findings in Context

There is wide variability in previously reported rates of overall MCC recurrence (27%-77%), and the rate in this cohort (40%) is near the median of results reported in prior, comparable studies (Figure 1). Merkel cell carcinoma thus recurs at a higher rate than melanoma (approximately 19% of patients with melanoma experience a recurrence).[16,17] Recurrence rates of squamous cell carcinoma (SCC; approximately 5%-9% of patients with SCC experience a recurrence)[18-20] and basal cell carcinoma (BCC; approximately 1%-10% of patients with BCC experience a recurrence) are lower,[21-24] meaning that there are different implications for the diagnosis of MCC, melanoma, SCC, or BCC. Compared with melanoma, MCC is associated with a higher risk of distant metastatic recurrence after initial treatment. In one study of patients with stage I to III melanoma, approximately 24% of first recurrences were distant[25] compared with MCC, in which 55% of first recurrences were distant (eFigure 2 in the Supplement). The high rates of distant metastatic recurrence emphasize the importance of surveillance imaging and serology testing (for patients who produce Merkel cell polyomavirus oncoprotein antibodies) because these recurrences are usually not detectable via clinical examination.[26]

The influence on survival of sex, immune suppression status, and an unknown primary lesion has been demonstrated in prior reports,[1,27,28] and the present results confirm the prognostic value of these factors in predicting recurrence risk, in addition to stage. Contrary to reports in the literature of a poorer prognosis for MCC arising on the head and neck,[29] anatomical site of MCC was not a statistically significant predictor of recurrence risk in this cohort. This may be attributable to the frequent use of radiation therapy (known to improve local control) in the Seattle cohort, in which 78% of patients received local or regional radiation therapy.[8,30] Unknown primary tu-

Figure 2. Merkel Cell Carcinoma (MCC) Recurrence-Free Survival and Disease-Specific Survival by Pathologic and Clinical Stage




Staging was determined according to the *AJCC Cancer Staging Manual*, 8th edition. Curves were estimated using cumulative incidence functions with death from a non-MCC cause as a competing risk. Curves were truncated when the number at risk was fewer than 2.

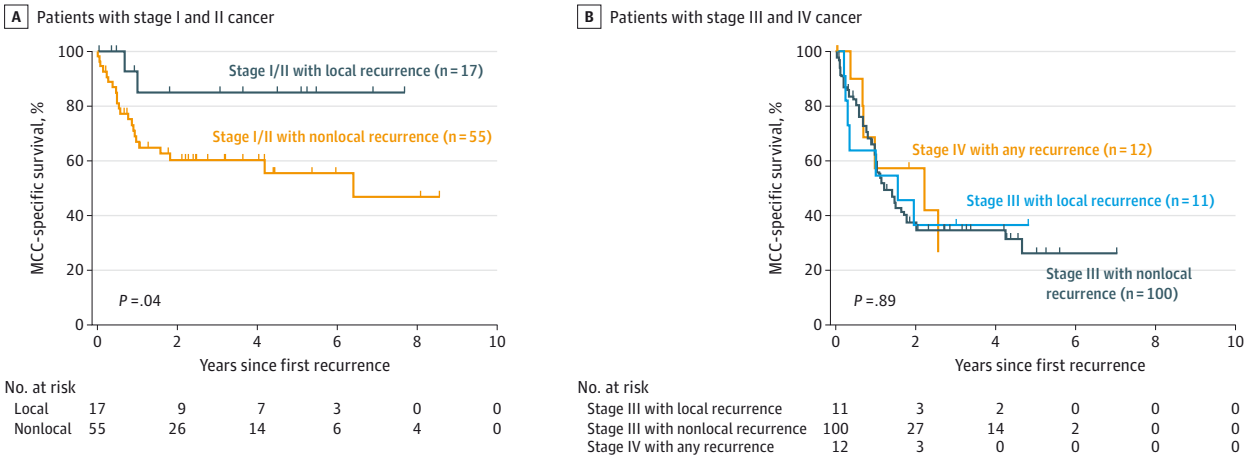
mor status has been linked to improved survival in multiple other cohorts and likely represents elimination of the primary tumor by an effective immune response that may be associated with better control of microscopic disease.[9,28,31-33] The present study identifies a statistically significantly decreased recurrence risk for patients with stage IIIA cancer with unknown primary tumor compared with patients with stage IIIA cancer and a known primary lesion. This suggests that patients with stage IIIA disease represent a heterogeneous group in terms of recurrence risk and underlines the importance of other nonstage factors when estimating prognosis.

Although overall survival data from the NCDB is the largest source of outcomes data for MCC and was used to establish both the *AJCC* 7th and 8th edition staging systems, overall survival data have important prognostic limitations. The MCC-specific survival is a more accurate measure of disease risk than overall survival. This is because patients with MCC are at considerable risk of mortality from non-MCC causes based on a median age at diagnosis of approximately 70 years. In this older population with comorbidities, overall survival can be a misleading metric when estimating MCC-specific survival.[1,34-38] This discrepancy is particularly prominent in lower-stage MCC where the proportional risk of death from MCC is far lower than other causes. For patients with stage I to II cancer in the Seattle cohort, only 53% of 57 deaths were caused by MCC compared with 90% of 20 deaths in patients with stage IV cancer. However, national data sets do not typically collect disease-specific death data owing to challenges with determining cause of death. Disease-specific survival by *AJCC* 7th edition stage was published in 2011 based on a single institution; however, this data set has not been updated using *AJCC-8* staging, nor have these findings been independently validated.[39]

## Limitations

The recurrence rates, disease-specific survival, and overall survival in this study may differ from national rates for multiple reasons. This study was performed using data from an aca-

Figure 3. Merkel Cell Carcinoma (MCC)-Specific Survival After First MCC Recurrence




Results largely reflect outcomes in the preimmunotherapy era. Analysis was performed using cumulative incidence functions and censored when number at risk was 1. Non-MCC death was a competing risk for MCC-specific survival. Staging was determined based on the *AJCC Cancer Staging Manual,* 8th edition.

demic center with a focus on MCC; thus, referral bias may exist such that some patients are more or less likely to be seen. Referral bias to the center based on stage did not considerably influence the observed overall recurrence rate, although there were modest differences in stage distribution between the Seattle cohort and the nationally representative NCDB cohort (eFigure 3 in the Supplement). Patients often incur considerable travel burden to visit a specialty center, and longer travel distances are associated with young age, more advanced stage at study entry, and fewer in-clinic visits.[40] Indeed, the median age of this cohort (69 years) is younger than that seen in national data sets such as NCDB (76 years).[9] Lastly, a greater proportion of patients in the Seattle cohort (>75%) received radiation therapy compared with the national population of patients with MCC (approximately 50%).[41] Because radiation therapy improves local control of MCC, it is plausible that recurrence rates would be higher in a population with less use or access to adjuvant radiation.[30]

## Conclusions

This cohort study indicates that the highest yield (and likely most cost-effective) time period for detecting MCC recurrence is 1 to 3 years after diagnosis. The frequency of scans, examinations, and blood tests should be relatively high for patients with stage III and IV cancer. For patients with MCC who have not experienced recurrence within 3 years from diagnosis, clinicians may discuss de-escalating surveillance. Nonstage factors should be considered when planning surveillance. In addition to patients with more advanced stage, those with 1 or more of the following high-risk features should be followed more closely: male sex, immune suppression, known primary tumor (within stage III and IV), and advanced age. Postrecurrence survival data will help clinicians inform patients about their prognosis after an MCC recurrence. Patients with stage I to II cancer may be relieved to know that their prognosis after a local recurrence is still relatively good. Patients with stage III cancer with any recurrence type should be strongly considered for immune therapy trials given their poor prognosis.

To our knowledge, prior to this study MCC recurrence data that considered a patient's stage and time since diagnosis were not available. These data should assist in appropriately focusing surveillance resources on patients and time ranges in which MCC recurrence risk is highest (within the first 3 years after diagnosis) and potentially de-escalated after that time frame. The present study demonstrates that while stage is meaningful, it is not the only important factor in predicting recurrence risk. A multivariate tool combining stage, age, sex, immune suppression, and unknown primary status would offer a more accurate recurrence risk estimate and is in development. Optimizing surveillance intensity is an important goal because it would minimize unnecessary costs, capture recurrences earlier, and improve the chance that immune/systemic therapy would work because it tends to be more effective in the setting of low disease burden.

ARTICLE INFORMATION

**Accepted for Publication:** December 30, 2021.

**Published Online:** February 23, 2022. doi:10.1001/jamadermatol.2021.6096

**Author Contributions**: Prof Nghiem had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
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**Conflict of Interest Disclosures:** Mr Hippe reported grants from GE Healthcare, Philips Healthcare, and Canon Medical Systems USA outside the submitted work. Dr Nghiem reported personal fees from Rain Therapeutics, EMD Serono, Pfizer, Sanofi/Regeneron, 4SC, and Merck; grants from EMD Serono and Bristol Myers Squibb to his institution outside the submitted work; and a patent for Merkel cell polyomavirus T antigen–specific T-cell receptors and uses thereof pending (University of Washington), as well as a patent for novel epitopes as T-cell targets in Merkel cell carcinoma pending (University of Denmark and University of Washington). No other disclosures were reported.

**Funding/Support:** This research was made possible by funding from the National Institutes of Health/National Cancer Institute (P01 CA225517 and Cancer Center Support Grant P30 CA015704), the MCC Patient Gift Fund, and the Kelsey Dickson Team Science Courage Research Team Award from the Prostate Cancer Foundation.

**Role of the Funder/Sponsor:** The funders had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

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