

Pathologic nodal evaluation improves prognostic accuracy in Merkel cell carcinoma: Analysis of 5823 cases as the basis of the first consensus staging system

Bianca D. Lemos, MD,^{a*} Barry E. Storer, PhD,^{d*} Jayasri G. Iyer, MD,^{a*} Jerri Linn Phillips, MA, CTR,^c Christopher K. Bichakjian, MD,^f L. Christine Fang, MD,^b Timothy M. Johnson, MD,^f Nanette J. Liegeois-Kwon, MD, PhD,^h Clark C. Otley, MD,ⁱ Kelly G. Paulson, PhD,^a Merrick I. Ross, MD,^g Siegrid S. Yu, MD,^k Nathalie C. Zeitouni, MD,^l David R. Byrd, MD,^{c,n} Vernon K. Sondak, MD,^j Jeffrey E. Gershenwald, MD,^g Arthur J. Sober, MD,^m and Paul Nghiem, MD, PhD^{a,d,n}

Seattle, Washington; Chicago, Illinois; Ann Arbor, Michigan; Houston, Texas; Baltimore, Maryland; Rochester, Minnesota; Tampa, Florida; San Francisco, California; Buffalo, New York; and Boston, Massachusetts

Background: The management of Merkel cell carcinoma (MCC) has been complicated by a lack of detailed prognostic data and by the presence of conflicting staging systems.

Objective: We sought to determine the prognostic significance of tumor size, clinical versus pathologic nodal evaluation, and extent of disease at presentation and thereby derive the first consensus staging/prognostic system for MCC.

Methods: A total of 5823 prospectively enrolled MCC cases from the National Cancer Data Base had follow-up data (median 64 months) and were used for prognostic analyses.

Results: At 5 years, overall survival was 40% and relative survival (compared with age- and sex-matched population data) was 54%. Among all MCC cases, 66% presented with local, 27% with nodal, and 7% with distant metastatic disease. For cases presenting with local disease only, smaller tumor size was associated with better survival (stage I, ≤ 2 cm, 66% relative survival at 5 years; stage II, > 2 cm, 51%; $P < .0001$). Patients with clinically local-only disease and pathologically proven negative nodes had better outcome (76% at 5 years) than those who only underwent clinical nodal evaluation (59%, $P < .0001$).

Limitations: The National Cancer Data Base does not capture disease-specific survival. Overall survival for patients with MCC was therefore used to calculate relative survival based on matched population data.

Conclusion: Although the majority (68%) of patients with MCC in this nationwide cohort did not undergo pathologic nodal evaluation, this procedure may be indicated in many cases as it improves prognostic accuracy and has important treatment implications for those found to have microscopic nodal involvement. (J Am Acad Dermatol 10.1016/j.jaad.2010.02.056.)

From the Departments of Medicine/Dermatology,^a Radiation Oncology,^b and Surgery,^c University of Washington; Clinical Research Division, Fred Hutchinson Cancer Research Center, Seattle^d; Commission on Cancer of the American College of Surgeons, Chicago^e; Department of Dermatology, University of Michigan, Ann Arbor^f; University of Texas M. D. Anderson Cancer Center^g; Johns Hopkins Medicine, Baltimore^h; Department of Dermatology, Mayo Clinic, Rochesterⁱ; H. Lee Moffitt Cancer Center and Research Institute and the University of South Florida, Tampa^j; Department of Dermatology, University of California at San Francisco^k; University of Buffalo, Roswell Park Cancer Institute^l; Department of Dermatology, Massachusetts General Hospital^m; and Seattle Cancer Care Alliance.ⁿ

*These authors contributed equally to this study.

Dr Lemos is currently affiliated with the Department of Dermatology, Emory University, Atlanta, GA.

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Reprint requests: Paul Nghiem, MD, PhD, 815 Mercer St, Brotman 242, Seattle, WA 98109. E-mail: pnghiem@uw.edu.

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Merkel cell carcinoma (MCC) is a neuroendocrine cancer that arises most commonly on the sun-exposed skin of Caucasians who are older than 50 years. Over the past 20 years, the reported incidence of MCC has more than tripled¹ because of new pathologic techniques that diminish missed diagnoses (cytokeratin-20 stain introduced in 1994) and an increased population at risk because of ultraviolet exposure, advanced age, and immune suppression. As of 2008, there were approximately 1500 MCC cases per year in the United States.² MCC is challenging to control because of its propensity for locoregional recurrence and early microscopic spread to nodes and distant sites. A novel human polyomavirus was recently found to be integrated into the genome of the majority of MCCs.³ This virus helps to explain the epidemiologic association of MCC with immune suppression.⁴ The clinical features most commonly associated with primary MCC tumors have been summarized using an acronym “AEIOU”: asymptomatic or nontender; expanding rapidly; immune suppressed; older than 50 years; and ultraviolet-exposed fair skin. Among patients presenting with a primary cutaneous MCC, 89% had 3 or more of these 5 features.⁵

Five staging systems for MCC have been published over the past 17 years, all of which were based on cohorts of 251 or fewer cases derived from 3 or fewer institutions.⁶⁻¹⁰ Discrepancies among these 5 systems include: (1) 3-stage versus 4-stage systems; (2) regional nodal disease variably defined as stage II or stage III; and (3) different tumor size thresholds for determining the tumor (T) categories for primary lesions. Depending on which system was used, “stage III MCC” could refer to invasive local-only disease, regional nodal disease, or distant metastatic MCC. In addition, prior staging systems did not differentiate either whether: (1) nodal evaluation

was microscopic or clinical only; or (2) nodal involvement was clinically detectable or only microscopic in extent.

To address these issues, a prognostic analysis of clinical factors in MCC was carried out using data from the National Cancer Data Base (NCDB) (established in 1989 as a joint project of the American College of Surgeons and the American Cancer Society). The NCDB is a national tumor registry maintained by the Commission on Cancer that captures approximately 70% of all cancer diagnoses in the United States¹¹ and has accumulated one of the largest known cohorts of patients with MCC. This analysis was used to derive a new MCC prognostic/staging system to be adopted worldwide in 2010.

METHODS

Cases from the NCDB were identified using MCC-specific histology code 8247. A flow diagram of the MCC cases used for the prognosis and staging analysis is shown in Fig 1. There were 10,020 patients with MCC captured in the NCDB between 1986 and 2004 who were used for basic demographic analyses (Table I). The NCDB policy is to collect follow-up data from the time of initial diagnosis at 5-year intervals. All patients given a diagnosis before the year 2000 (5823 patients) had follow-up data available and were used for this analysis. Median follow-up was 64.1 months for the 2282 patients who were alive at the time of last contact.

Among patients with follow-up, some have incomplete staging data because: (1) staging was not required by the Commission on Cancer/NCDB before 1990; (2) complete information may not have been available in the medical record; or (3) a cancer such as MCC that was uncommon and did not have a dedicated American Joint Committee on Cancer (AJCC) staging system may have been staged less frequently. Of the patients with follow-up data, 1119 were

CAPSULE SUMMARY

- Previous studies have shown that approximately 1 in 3 patients with clinically node-negative Merkel cell carcinoma have microscopic nodal disease.
- Analysis of national registry data demonstrated that pathologic node staging in Merkel cell carcinoma significantly improves prognostic accuracy.
- Determining the pathologic status of nodes in Merkel cell carcinoma is indicated in many cases for improved prognostic accuracy and therapeutic management of the involved node bed or beds.
- The new consensus staging system described herein replaces 5 conflicting systems and is based on a cohort that is more than 10 times larger than that used by any of the previous staging systems.

Abbreviations used:

AJCC:	American Joint Committee on Cancer
F/U:	follow-up
MCC:	Merkel cell carcinoma
NCDB:	National Cancer Data Base
TNM:	tumor node metastasis

excluded from staging analyses because they had no recorded data regarding tumor size, or regional nodal or distant metastatic disease status ($T_xN_xM_x$ in Fig 1). Thus, 4704 cases with data from at least one of the T, N, or M categories (any TNM) were further analyzed. Previously published principles^{12,13} for development of cancer staging systems were used.

For patients presenting with distant metastatic disease (M1; $n = 277$), nodal and primary tumor status are not relevant for staging and these cases were therefore removed from subsequent T and N substaging analyses. Patients for whom no distant metastatic data were recorded (Mx; $n = 1655$) were assumed to have negative metastatic disease status because their survival curves were essentially identical to those with no distant metastatic disease (M0; $n = 2772$; data not shown). Thus, patients who did not have documented distant metastatic disease (Mx + M0; $n = 4427$) were then analyzed for nodal status and prognosis (Fig 1). Patients with no nodal disease (N0; $n = 2356$) were further analyzed for the effect of primary tumor size on survival. Complete staging does not necessarily require all types of data (eg, local tumor data are not required to fully stage cases presenting with nodal or distant metastatic disease). The total number of cases with follow-up that could thus be staged was 2856.

Primary tumor size (maximum tumor dimension by pathologic or clinical report) was recorded by the NCDB in millimeters up to 70 (larger tumors were also recorded as 70 mm). In the NCDB, if both pathologic and clinical primary tumor size were present in the patient's chart, pathologic size superseded and was entered into the database. Patients were considered to have clinical evaluation only (clinically staged) for their lymph nodes if the number of nodes examined by pathology was zero or was not stated. Patients were considered to have pathologic evaluation (pathologically staged) for their lymph nodes if the number of nodes examined was one or greater.

The NCDB captures overall survival data but does not record information regarding the cause of death. Given the median age at diagnosis (76 years) (Table I), a large fraction of deaths in this cohort would therefore be expected to result from non-MCC causes. We therefore adjusted survival data using age- and sex-matched life expectancy information

from the National Center for Health Statistics. The fraction of MCC cohort survival relative to expected survival was calculated at each time point to determine percent relative survival. Statistical comparisons of relative survival were based on a proportional excess hazard model as previously described.¹⁴

For each patient, the associated population probability of surviving the next 1 to 5 years after diagnosis was determined using US life table data from the year 2000 census, matched to the patient's age and sex, and obtained from the National Center for Health Statistics World Wide Web site (http://www.cdc.gov/nchs/data/statab/lewk3_2003.pdf). For any cohort of patients, the "expected" survival probability at years 1 to 5 after diagnosis is calculated as the average of the population-based probabilities for each patient in the cohort, with linear interpolation between annual time points. The "observed" survival probability is the standard Kaplan-Meier estimate of overall survival for the cohort. "Relative" survival is the ratio of the "observed" and "expected" survival probabilities at each point in time.

Comparisons of relative survival among groups were based on a proportional excess hazards model, such that the overall hazard of mortality is expressed as $\lambda(t) = \lambda_e(t) + \lambda_d(t)$, where $\lambda_e(t)$ is the "expected" mortality hazard and $\lambda_d(t)$ is the excess mortality hazard as a result of a diagnosis of disease. Because survival is directly related to the (cumulative) hazard function as $S(t) = \exp\{-\Lambda(t)\}$, a proportional hazards model for $\lambda_d(t)$ is a model for the relative survival $S(t)/S_e(t)$. To implement this model we used the methods described in Dickman et al¹⁴ where the observed number of deaths (d_j) in an interval of follow-up time (y_j) is treated as a Poisson random variable and the expected number of deaths (e_j) in the interval is calculated from the US life table data based on individual patient sex and age at diagnosis. We used SAS (SAS Institute Inc, Cary, NC) to fit the model, with a user-specified link function $\ln(\mu_j - e_j)$ relating the Poisson mean (μ_j) to a covariate model offset by $\ln(y_j)$.

RESULTS

The clinical and demographic characteristics of 10,020 MCC cases captured by the NCDB are shown in Table I. Similar to smaller, previously reported cohorts,^{1,5,15,16} men comprised the majority of cases (61%). The age at diagnosis was 50 years or older in 94% of MCC cases and the median age was 76 years. Head/neck presentation was the most common primary site (45%). Non-Caucasian ethnicities were underrepresented in the MCC cohort (4%) as compared with their representation in the US population

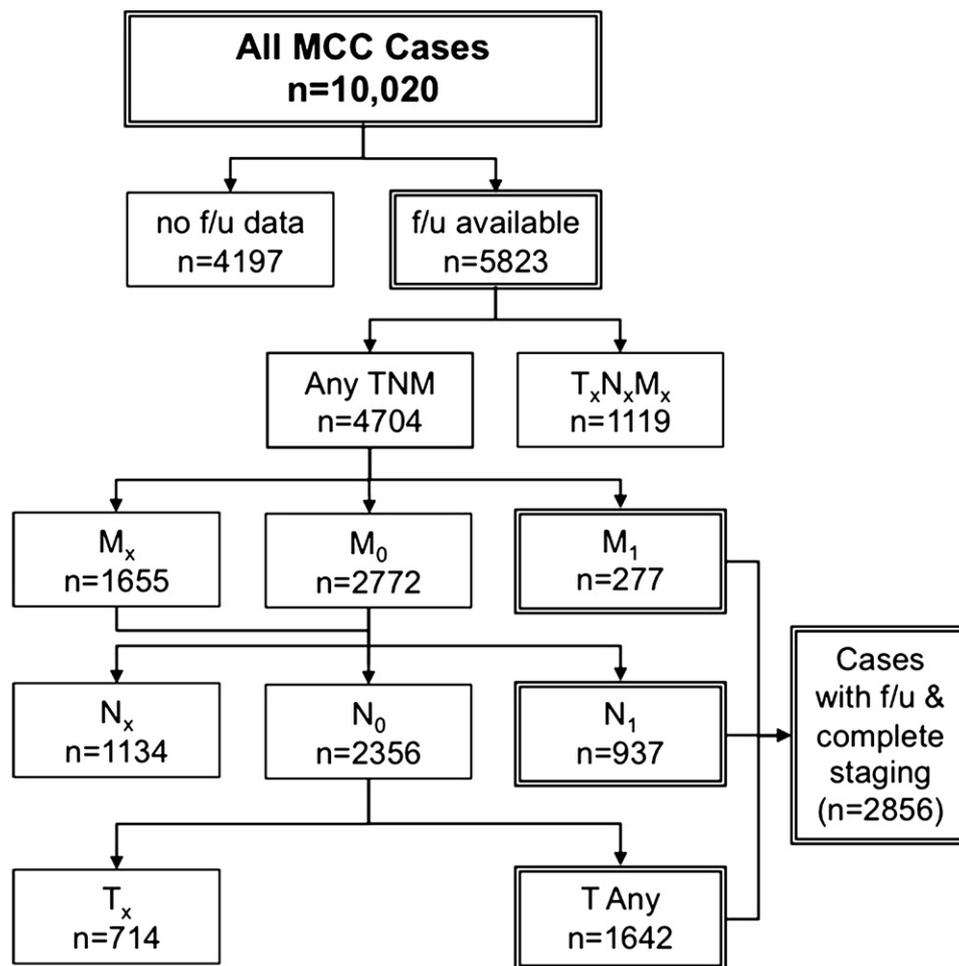


Fig 1. Flow diagram for Merkel cell carcinoma (MCC) cases prospectively captured by National Cancer Data Base (NCDB) and extent of available data. There were 10,020 MCC cases captured by NCDB during 1986 to 2004. Among those captured before year 2000, 5823 cases had available follow-up (*f/u*) data and served as basis for overall survival and staging analyses. *Double boxes* indicate groups used for analysis and discussed in this study. As detailed in “Methods” section, cases that had no data in any TNM categories ($T_xN_xM_x$) were eliminated from consideration beyond basic demographic characteristics (Table I). Effect of N and T status on prognosis was assessed using cases that were negative for distant metastatic disease; therefore, patients with distant metastasis (M_1) were excluded from analysis of nodal and primary tumor data. Similarly, cases presenting with pathologically confirmed nodal disease (pN1) were excluded from analysis of primary tumor data, as were those with unknown nodal status (N_x). In total, 2856 cases had available *f/u* and TNM data sufficient for stage assignment.

(18%), perhaps because of the protection afforded by increased skin pigmentation in these ethnicities. The majority of cases presented with local disease (66%) followed by nodal disease (27%) and distant metastatic disease (7%).

Extent of disease at presentation and survival

As shown in Fig 2, A, observed survival for the MCC cohort (40% at 5 years) is lower than expected survival (75% at 5 years) based on age- and sex-matched US population data. To determine the increased mortality associated with an MCC

diagnosis, we calculated percent relative survival as described above (Fig 2, B). As shown in Fig 2, C, patients with MCC presenting with local disease had 64% relative survival at 5 years, those with regional nodal disease had 39%, and those with distant metastatic disease had 18%. Fig 2, D, shows relative survival data for patients with local-only disease grouped by size using the existing AJCC T stages: less than or equal to 2.0 cm (T1), 2.1 to 5.0 cm (T2), and greater than 5.0 cm (T3). Five-year relative survival was 66% among patients with local-only disease and primary tumor less than or equal to 2.0 cm versus

Table I. Demographics of 10,020 patients with Merkel cell carcinoma in National Cancer Data Base (1986-2004)

	No.	Percent
Sex		
Male	6144	61.3
Female	3876	38.7
Age, y (median = 76)		
<40	93	0.9
40-49	297	3.0
50-59	848	8.5
60-69	1796	17.9
70-79	3543	35.4
80-89	2835	28.3
≥ 90	608	6.1
Body site		
Lip	249	2.5
Eyelid	249	2.5
External ear	398	4.0
Other unspecified part of face	2787	27.8
Scalp and neck	973	9.7
Trunk	1176	11.7
Upper limb and shoulder	2100	21.0
Lower limb and hip	1534	15.3
Overlapping lesion of skin	38	0.4
Skin, NOS	516	5.2
Extent of disease*		
Local	4437	65.6
Nodal	1836	27.1
Metastatic	491	7.3
Race		
Caucasian [†]	9640	96.2
Black	126	1.3
American Indian, Aleutian, or Eskimo	13	0.1
Asian, Pacific Islander	77	0.8
Other/unknown	164	1.6

NOS, Not otherwise specified.*Extent-of-disease data were only available for 6764 patients.[†]Of those classified as Caucasian, 1.8% (n = 181) are of Spanish/Hispanic ethnicity.

51% for those with primary tumor 2.1 to 5.0 cm (excess hazard ratio 1.77; 95% confidence interval 1.4-2.2; $P < .0001$). It is noteworthy that patients presenting with the smallest tumors (primary tumor diameter ≤ 1 cm, n = 511) had a 5-year relative survival of 69% that was only modestly better than the 61% 5-year relative survival of patients with tumors in the 1.1- to 2.0-cm range (n = 509). There was no survival difference between AJCC tumor categories of 2.1 to 5.0 cm and greater than 5.0 cm. Fig 2, E, shows 5-year relative survival data for all patients with local-only disease grouped by 1-cm increments in size. Primary tumor size in the local-only disease category affected relative survival only for tumors less than or equal to 4.0 cm. For larger

tumors, correlation between size and survival was likely lost because patients presenting with regional nodal and distant metastasis were censored from this analysis and disproportionately presented with large primary tumors.

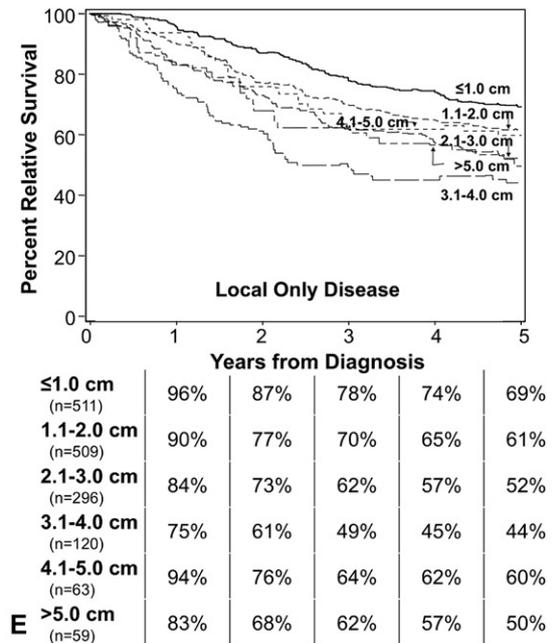
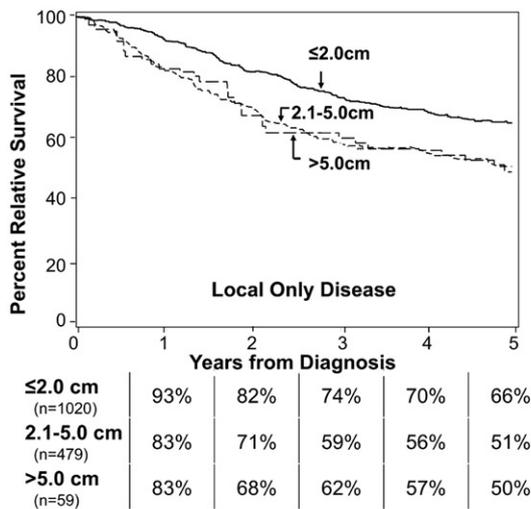
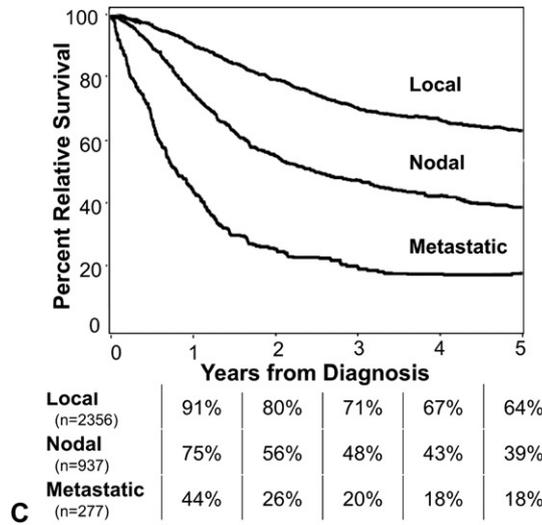
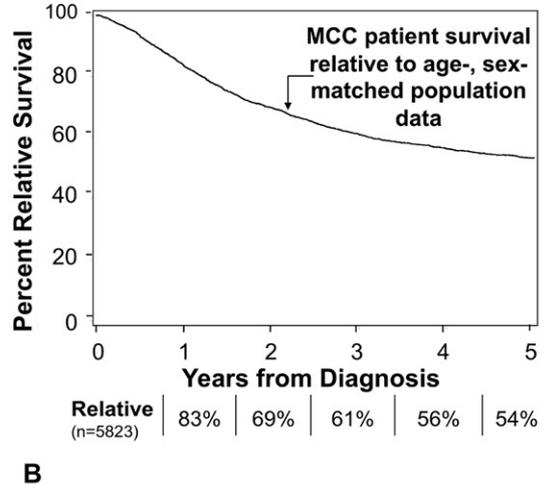
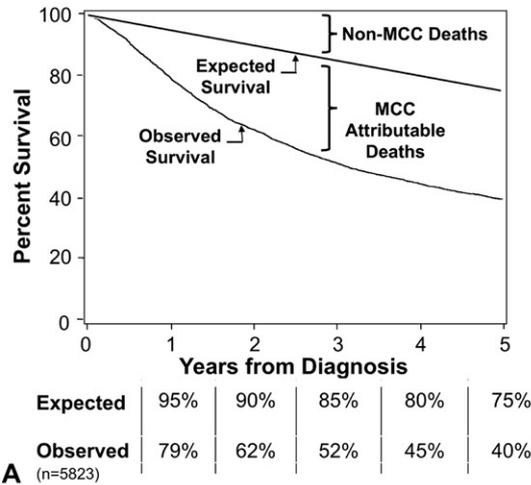
Clinical versus pathologic lymph node staging

Among patients without distant metastatic disease, we determined whether there was a survival difference between those whose nodal status was determined by clinical evaluation (Fig 3, A) and those whose nodal status was determined by pathologic examination (Fig 3, B). Among patients with negative nodal disease, relative survival was worse for those who had only clinical nodal evaluation (cN0 in Fig 3, A) compared with those who had pathologic confirmation of node negativity (pN0 in Fig 3, B) (excess hazard ratio 1.80; 95% confidence interval 1.4-2.4; $P < .0001$). For patients with nodal disease, relative survival was worse for those who had clinically apparent nodal involvement (cN1 in Fig 3, A) as compared with those who had pathologically proven nodal disease (pN1 in Fig 3, B) (both clinically apparent and occult nodal disease cases) (excess hazard ratio 1.48; 95% confidence interval 1.1-1.9; $P = .004$). Of patients with MCC in this cohort, 68% did not have pathologic nodal evaluation as this was performed infrequently for MCC between 1986 and 1999.

Components of the new staging system

The final TNM category and stage groupings for MCC as to be used by tumor registrars¹⁷ are shown in Table II. Whenever possible, TNM terminology was preserved from the 6th edition of the AJCC staging manual chapter on carcinoma of the skin¹⁸ or adapted for use in MCC from the AJCC melanoma staging system.¹⁹ Although there was no survival difference for T2 (2.1-5.0 cm) versus T3 (>5.0 cm) tumors (Fig 2, D), these categories were preserved to allow the T4 category to represent tumors that invade deep structures as in other AJCC staging systems.

The regional N categories are in part defined by the method of nodal evaluation: pathologic versus clinical. For example, “nodes not clinically detectable” is designated as cN0, whereas “nodes positive by pathologic examination” is designated as either N1a (micrometastatic) or N1b (macrometastatic) as appropriate (Table II). Similar to other AJCC staging systems, patients with nodal disease detected by pathologic examination but not detectable clinically have “micrometastatic” or N1a nodal disease. Those who have clinically apparent regional lymph node disease, confirmed by pathologic evaluation, have “macrometastatic” or N1b nodal disease. In-transit



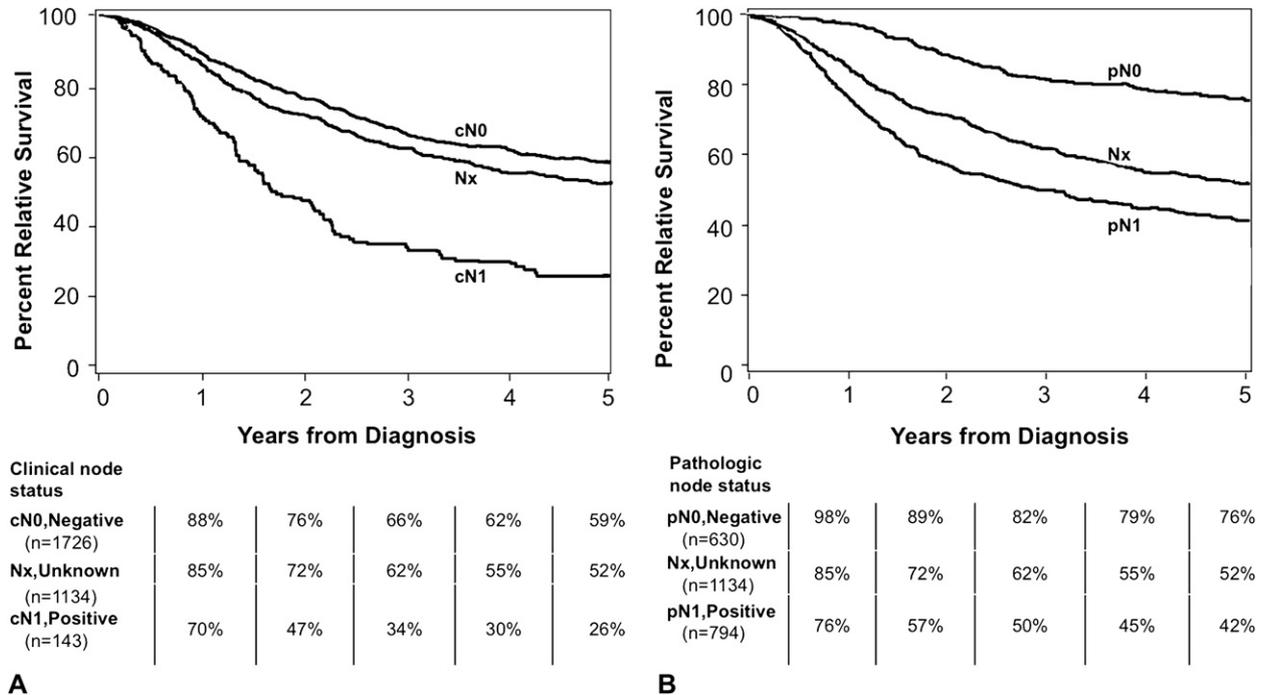


Fig 3. Relative survival by nodal status: clinical versus pathologic evaluation. Age- and sex-adjusted percent relative survival curves are shown for all patients with Merkel cell carcinoma who had follow-up data and did not have distant metastatic disease ($n = 4427$). Patients for whom no regional nodal data were available (1134 cases) are represented by same curve (Nx). Pathologic node-negative status ($pN0$) was established either by elective lymphadenectomy or by sentinel lymph node biopsy (SLNB). Pathologic node-positive status ($pN1$) was established by elective or therapeutic lymphadenectomy, fine needle aspirate, SLNB, or other biopsy technique. Age- and sex-adjusted excess hazard ratio comparing clinical node-negative with pathologic node-negative (*top lines*) is 1.80 (95% confidence interval 1.4-2.4; $P < .0001$). The age- and sex-adjusted excess hazard ratio comparing clinical node positive with pathologic node positive (*bottom lines*) is 1.48 (95% confidence interval 1.1-1.9; $P = .004$). There was very little overlap in data in this cohort for method of nodal evaluation because patients had only clinical or pathologic nodal data recorded in majority of cases. Specifically, 240 (5%) of 4427 cases included in this analysis had both pathologic and clinical nodal data recorded. These cases are included in pathologic category (**B**) and excluded from clinical nodal analysis (**A**) because pathologic data were considered to be more accurate.

Fig 2. Merkel cell carcinoma (MCC) 5-year survival. Below each panel, the number of patients considered and percent survival at each time point are listed in the associated table. **A**, Observed vs expected survival. Observed survival is shown for the National Cancer Database (NCDB) cohort of patients with MCC and follow-up data. Expected survival was calculated using age- and sex-matched population data from the US census. **B**, Relative survival (ratio of observed to expected survival) for all MCC cases. **C**, Relative survival by extent of MCC. Local = node-negative by clinical or pathologic examination and no distant metastasis. Regional = macroscopic/microscopic nodal disease but no distant metastasis. Distant = distant metastatic disease. **D** and **E**, Relative survival by primary tumor size. Only patients with local disease, known primary tumor size, and a lack of extracutaneous invasion were included in this analysis. **D** is plotted based on the existing AJCC T1 to T3 stage categories as indicated. Patients with primary tumors ≤ 2.0 cm (T1) fared better than those with tumors >2.0 cm (excess hazard ratio 1.8; 95% confidence interval 1.4-2.2; $P = .0001$). However, there was no survival difference between the 2.1-5.0 cm (T2) and >5.0 cm (T3) groups. **E** represents the same patients as in **D**, grouped by 1 cm size increments.

Table II. TNM criteria and stage groupings of new American Joint Committee on Cancer staging system for Merkel cell carcinoma

T		N		M	
Tx , Primary tumor cannot be assessed		Nx , Regional nodes cannot be assessed		Mx , Distant metastasis cannot be assessed	
T0 , No primary tumor		N0 , No regional node metastasis*		M0 , No distant metastasis	
Tis , In situ primary tumor		cN0 , Nodes not clinically detectable*		M1 , Distant metastasis ^{//}	
T1 , Primary tumor ≤ 2 cm		cN1 , Nodes clinically detectable*		-M1a , distant skin, distant subcutaneous tissues, or distant lymph nodes	
T2 , Primary tumor >2 but ≤ 5 cm		pN0 , Nodes negative by pathologic examination		-M1b , lung	
T3 , Primary tumor >5 cm		pNx , Nodes not examined pathologically		-M1c , all other visceral sites	
T4 , Primary tumor invades bone, muscle, fascia, or cartilage		N1a , Micrometastasis [†]			
		N1b , Macrometastasis [‡]			
		N2 , In-transit metastasis [§]			
Stage	Stage grouping				
0	Tis	N0		M0	
IA	T1	pN0		M0	
IB	T1	cN0		M0	
IIA	T2/T3	pN0		M0	
IIB	T2/T3	cN0		M0	
IIC	T4	N0		M0	
IIIA	Any T	N1a		M0	
IIIB	Any T	N1b/N2		M0	
IV	Any T	Any N		M1	

*"N0" denotes negative nodes by clinical, pathologic, or both types of examination. Clinical detection of nodal disease may be via inspection, palpation, and/or imaging; cN0 is used only for patients who did not undergo pathologic node staging.

[†]Micrometastases are diagnosed after sentinel or elective lymphadenectomy.

[‡]Macrometastases are defined as clinically detectable nodal metastases confirmed pathologically by biopsy or therapeutic lymphadenectomy.

[§]In-transit metastasis is tumor distinct from primary lesion and located either: (1) between primary lesion and draining regional lymph nodes; or (2) distal to primary lesion.

^{//}Because there are no data to suggest significant effect of M categories on survival in Merkel cell carcinoma, M1a-c are included in same stage grouping.

lymphatic disease was not included in any prior MCC staging system and is referred to as N2 in the new system (Table II). Although not occurring in lymph nodes per se, as this represents clinically detectable lymphatic disease, it is included in stage IIIB together with macrometastatic nodal disease.

Distant metastatic disease (M status), was divided into 3 categories as in the staging of melanoma,^{19,20} based on the site of metastasis: M1a—distant skin, distant subcutaneous tissues, or distant lymph nodes; M1b—lung; and M1c—all other visceral sites.

The final stage groupings and their relationship with percent relative survival over 5 years are summarized in Table II and Fig 4. The NCDB data show that the existing (if arbitrary) delineation of tumor sizes in the AJCC staging system is a significant predictor for survival at 5 years (≤ 2 cm, 66%; > 2 cm, 51%; $P < .0001$). Substages were created for stage I and stage II local disease based on the strong predictive effect of method of determining node negativity (59% survival for clinical staging vs 76% for pathologic staging at 5 years; $P < .0001$). These

substages specify whether node-negative status was established by pathologic examination (IA and IIA) or only by clinical evaluation (IB and IIB). We attempted to determine whether there was a subset of MCC cases with significantly higher survival based on TNM criteria. Even among patients with the smallest primary tumors (≤ 1 cm) who had pathologically negative lymph nodes, 5-year relative survival was 81% ($n = 128$), nearly identical to all patients at stage Ia who presented with a primary tumor 2.0 cm or smaller in diameter and pathologically negative nodes (79% relative survival, $n = 266$).

Stage IIC disease is a new substage that includes patients with a deeply invasive primary (Table II) whose nodal status was negative by either clinical or pathologic evaluation. As shown in Fig 4, A, patients at stage IIC had a worse relative survival compared with those patients whose tumors did not invade deep structures. Stage III includes patients with either micrometastatic nodal disease or macrometastatic/in-transit disease (5-year relative survival, 42% vs 26%, respectively; $P = .004$).

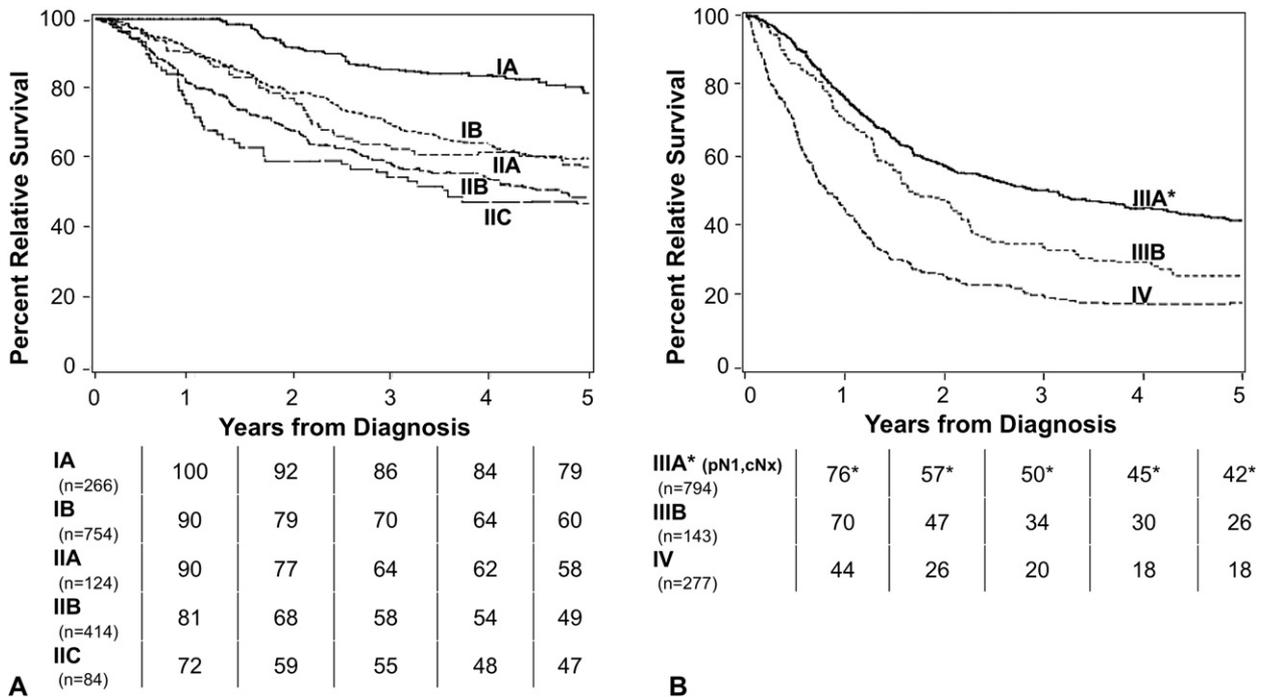


Fig 4. Relative survival for Merkel cell carcinoma (MCC) by stage at presentation in 2856 patients. Sufficient local, nodal, and distant data were available for stage classification of 2856 patients with MCC as summarized in Fig 1. Cases presenting with local (**A**) or regional nodal/distant metastatic (**B**) disease are shown by substages with annual percent relative survival below each panel. Stages are as indicated directly on survival curves except for stage IIIA (microscopic node positive, clinical node negative), which could not be derived using National Cancer Data Base as described in the “Discussion” section. Curve IIIA* represents pathologically node-positive patients whose clinical node status was unknown (*pN1, cNx*). It is anticipated that patients at true stage IIIA with known clinically negative node status (*pN1, cN0*) may have better survival than line marked IIIA* (*pN1, cNx*).

DISCUSSION

Here we present the prognostic analysis used to derive the first unified staging system for MCC. It is anticipated that this staging system, along with the recent introduction of 7 new MCC-specific diagnostic codes (*International Classification of Diseases, Ninth Revision, Clinical Modification*),²¹ will aid in standardizing language used to describe MCC and its prognosis among patients, clinicians, and researchers. This staging system is the result of multidisciplinary consensus meetings that analyzed NCDB data from more than 10 times as many patients as any of the prior MCC staging systems.

Analysis of this data set verified that primary tumor size (≤ 2 vs >2 cm) is predictive of survival and identified two aspects of nodal involvement that are highly significant for prognosis and are thus incorporated into the new staging system. These relevant characteristics of nodal disease are the method by which negative lymph node status was determined and whether involved lymph nodes were clinically apparent or only microscopically

detectable. Pathologic staging of clinically uninvolved lymph nodes (eg, via sentinel lymph node biopsy) is important to accurately determine prognosis in patients with MCC who present with local-only disease.

There are numerous differences among the 5 prior MCC staging systems and the new consensus system. Inclusion of 2.0-cm lesions with smaller tumors in stage I is consistent with the earlier AJCC system but differs from some of the prior staging systems that included 2.0-cm lesions with larger tumors. The new staging system now explicitly includes a stage IIC, for deeply invasive tumors (T4; invasion of bone, muscle, fascia, or cartilage) that carry a poorer prognosis than other localized disease categories (Fig 4, A). In-transit metastases are now included as N2 (stage IIIB disease).

The most significant difference between the new system and the prior systems is that the method of determining negative node status will now be included. Overall, approximately one third of patients with MCC who only undergo clinical nodal evaluation

are understaged as they in fact have occult microscopic nodal involvement.²² This difference is both clinically and statistically significant. It is clear, however, that many patients will not be staged pathologically for diverse reasons. Because the new staging system takes into account the best information available for each patient, it provides the most accurate possible prognostic data by not including patients whose nodes were negative by pathology together with patients who only had clinical node examination.

There are several limitations to the NCDB data set. The NCDB does not collect disease-specific survival data. Therefore, relative survival was calculated (see "Methods" section). A limitation of this type of calculation is that it would overestimate MCC-associated mortality if patients with MCC have coexisting comorbidities (eg, profound immunosuppression) that can themselves augment mortality.

A further limitation of the data set is that clinical lymph node data were often not recorded in the past if pathologic lymph node data were available. This means that the NCDB does not provide a direct source of data for patients at stage IIIA (micrometastatic nodal disease). Specifically, the survival of patients at true stage IIIA is predicted to be somewhat better than the stage IIIA* curve presented in Fig 4, B, as there was likely some inclusion of clinically node-positive patients in this group. Nonetheless, survival of patients in the IIIA* group (42% at 5 years) is markedly better than the clinically node-positive IIIB group (26% at 5 years). This suggests that many of the patients in the IIIA* group likely had only microscopic nodal disease although this was not explicitly captured. This limitation will be less significant in future analyses as both clinical and pathologic node data are now being collected by the NCDB.

An additional limitation of the data set is that information on tumor recurrence was not available, meaning that disease-free survival could not be calculated. Prior study has indicated that the vast majority of MCC recurrences happen within the first 3 years after diagnosis.⁸ Although NCDB did not provide information on MCC recurrences for this analysis, MCC-associated mortality in the current study becomes much less prominent in years 4 and 5 (Fig 4).

Future refinement of this new staging system will be dependent on the availability of additional parameters for analysis. Tumor registrars in the United States are already collecting more specific and detailed data on patients with MCC than in the past. This information includes both clinical and pathologic data on regional lymph node status and the presence or absence of profound immune suppression. Additional new parameters planned to be captured for later analysis include tumor thickness, lymphovascular invasion,²³

tumor-infiltrating lymphocytes,²³ growth pattern of the tumor (circumscribed or infiltrative),²³ and extracapsular extension/size of nodal tumor nests. A set of guidelines for pathologic evaluation of MCC has been developed by the College of American Pathologists and recommends capture of many of these features.²⁴

In addition to traditional TNM-type staging, other prognostic systems may be useful in the future. These would include nomograms^{25,26} that allow weighted integration of continuous variables based on their significance in multivariate analyses. Histologic or molecular features of MCC that are prognostically validated in the future could thus be incorporated. Such tools will likely exist in parallel with traditional TNM staging as their functions are complementary.

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