VOLUME 23 · NUMBER 10 · APRIL 1 2005

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Merkel Cell Carcinoma: Prognosis and Treatment of Patients From a Single Institution

Peter J. Allen, Wilbur B. Bowne, David P. Jaques, Murray F. Brennan, Klaus Busam, and Daniel G. Coit

From the Departments of Surgery and Pathology, Memorial Sloan-Kettering Cancer Center, New York, NY.

Submitted December 9, 2004; accepted December 21, 2004.

Supported by the Kristen Ann Carr Fund, New York, NY (P.J.A.).

This report contains original material and analysis not previously reported. Previous reports from our group regarding management of Merkel cell carcinoma include: Allen PJ, Zhang ZF, Coit DG: The surgical management of Merkel cell carcinoma. Ann Surg 229:97-105, 1999; and Yiengpruksawan A, Coit DG, Thaler HT, et al: Merkel cell carcinoma: Prognosis and management. Arch Surg 126:1514-1519, 1991.

Authors' disclosures of potential conflicts of interest are found at the end of this article.

Address reprint requests to Daniel G. Coit, Department of Surgery, Memorial Sloan-Kettering Cancer Center, 1275 York Ave, New York, NY 10021; e-mail: coitd@mskcc.org.

0732-183X/05/2310-2300/$20.00

DOI: 10.1200/JCO.2005.02.329

ABSTRACT

Purpose
Merkel cell carcinoma (MCC) is an uncommon cutaneous malignancy. Most reports consist of single-institution experiences of fewer than 30 patients. The natural history of MCC is poorly defined.

Patients and Methods
A review was performed of Memorial Sloan-Kettering Cancer Center's MCC database, identifying 251 patients who had been treated between 1970 and 2002. Patient, tumor, and treatment-related factors were analyzed for their association with recurrence and survival.

Results
The average follow-up for all patients was 40 months and 46 months for patients alive at last follow-up. The 5-year disease-specific survival rate was 64%. Disease stage was the only independent predictor of survival (stage I, 81%; stage II, 67%; stage III, 52%; stage IV, 11%; $P = .001$). Pathologic staging of the draining nodal basin was performed in 71 (40%) of 177 patients who presented with clinically negative nodes, and 16 of these patients (23%) were found to have node-positive disease. Pathologic nodal staging was associated with improved stage-specific survival probabilities (clinical node-negative, 75% *v* pathologic node-negative disease, 97%; $P = .009$) and decreased nodal recurrence (44% *v* 11%, $P < .001$). The median time to recurrence was 9 months, and 102 patients (43%) recurred. Local recurrence developed in 8% of patients after margin-negative excision.

Conclusion
These data demonstrate that the natural history of MCC is variable and dependent on the stage of disease at presentation. Pathologic nodal staging identifies a group of patients with excellent long-term survival. After margin-negative excision and pathologic nodal staging, local and nodal recurrence rates are low.

J Clin Oncol 23:2300-2309. © 2005 by American Society of Clinical Oncology

INTRODUCTION

Merkel cell carcinoma (MCC) is an uncommon cutaneous malignancy with a natural history that has been poorly defined. Survival and recurrence rates for this disease have been reported from studies of fewer than 40 patients with limited follow-up, patients accrued over long periods of time, and variable methods used for staging; and often, stage-specific survival is not reported.[1-6] Because of these factors, widely disparate recurrence and survival data have been published. Local recurrence rates have been reported between 4% and 62%.[1,7-10] Overall recurrence rates have been reported between 45% and 75%.[1,2,7,8] Overall survival rates have been reported between 30% and 75%.[1,2,5,7-9]

The recommended treatment for patients with MCC has also been variable. Some authors have reported low recurrence rates and excellent survival after surgical excision in early-stage patients and have not found the use of adjuvant therapies to be associated with improved outcome.[7,8,10]

Others have reported high locoregional recurrence rates after surgical excision.[9,11,12] Many of these studies have found adjuvant radiotherapy and adjuvant chemotherapy to be associated with improved rates of recurrence and survival.[9,11,12] Others have recommended systemic chemotherapy and radiation, rather than excision, because of the high metastatic potential of MCC.[13,14] These authors have investigated the use of definitive chemoradiotherapy in patients with tumors more than 1 cm in size or with nodal metastases.

The purpose of this study was to review our prospectively maintained MCC database and to describe the natural history of this disease from a large single-institution experience. Patient, tumor, and treatment-related variables were assessed for their association with recurrence and survival. Stage-specific survival rates were calculated. Methods used for determining nodal status were assessed and evaluated for their influence on stage-specific survival probabilities.

PATIENTS AND METHODS

A review was performed of Memorial Sloan-Kettering Cancer Center's (MSKCC) MCC database. This database includes all patients identified in hospital and pathology records as having been treated at MSKCC for the diagnosis of MCC since 1970. The current study includes all patients who had been treated for MCC between January 1970 and December 2002. Approval for this study was obtained from the institutional review board before database review.

At MSKCC, a four-tiered staging system is used for patients with MCC. The staging of MCC was developed in the 1980s as a three-tiered system and was stratified by the presence or absence of nodal disease (node negative, stage I; and node positive, stage II) or by the presence of distant metastatic disease (stage III). A prior study from our institution in 1999[7] identified the diameter of the primary tumor (< 2 cm or ≥ 2 cm) as an additional predictor of survival in node-negative patients, and this was incorporated into the staging of the node-negative group. Our current four-tiered system separates patients with node-negative disease into stage I ($<$ 2-cm primary tumor) and stage II ($\geq$ 2-cm primary tumor). Patients with node-positive disease are categorized as having stage III disease, and the presence of distant metastatic disease is categorized as stage IV disease (Table 1). This system is more consistent with other American Joint Committee on Cancer staging systems. Stages I and II represent low- and high-risk primary disease, respectively, and stages III and IV represent the presence of nodal metastases and distant metastases, respectively.

Patient, tumor, and treatment characteristics were reviewed. Patient characteristics were sex and age at diagnosis. Tumor characteristics were tumor site, primary tumor size, clinical and pathologic stage at presentation, and disease status at the time of last follow-up. Treatment characteristics included management of the primary lesion, margin status of resected specimens, and management of the draining nodal basin. Sentinel lymph node biopsy (SLNBx) was first used at our institution for nodal staging in selected patients with MCC in 1996. Before 1996, pathologic staging for patients with clinically negative nodes was performed selectively by elective lymph node dissection (ELND).

Associations between disease recurrence and patient, tumor, and treatment variables were assessed using the χ^2 test. Means of continuous variables were compared using a two-sample t test. Disease-specific survival probabilities were estimated using the Kaplan-Meier method and compared by the log-rank test. Factors associated with survival by log-rank comparison were entered into a Cox regression analysis. All statistical tests were two-sided, with the type I error controlled at 5%.

RESULTS

Patient and Tumor Data

Two hundred fifty-one patients were treated at our institution between 1970 and 2002. Since 1990, 190 patients (81%) have been treated for MCC, and 161 (64%) of the 251 patients have been treated since 1995. The patient and tumor data is listed in Table 2.

One hundred seventy-seven patients (70%) presented with clinically negative regional nodes, 60 patients (24%) presented with clinically suspicious regional lymphadenopathy, and 14 patients (6%) presented with evidence of distant metastatic disease. The two most common sites for the primary lesion were the extremities (n = 95, 38%) and the head and neck (n = 73, 29%). Metastatic disease in the setting of an unknown primary tumor was diagnosed in 31 patients (12%). The median diameter of the primary tumor

Table 1. Current MSKCC Staging System for Patients With Merkel Cell Carcinoma

TNM Staging for Merkel Cell Carcinoma		
T	N	M
T1, primary tumor < 2 cm	N0, negative regional lymph nodes	M0, no evidence of distant metastatic disease
T2, primary tumor ≥ 2 cm	N1, positive regional lymph nodes	M1, distant metastatic disease present

Stage	Criteria
I	T1, N0, M0
II	T2, N0, M0
III	Any T, N1, M0
IV	Any T, Any N, M1

Abbreviation: TNM, tumor, node, metastasis.

Table 2. Patient and Tumor Characteristics of the 251 Patients Treated for Merkel Cell Carcinoma

Factor	No. of Patients	%
Age, years		
Median	69	
Range	36-95	
Sex		
Male	150	60
Female	101	40
Location of primary		
Extremity	95	38
Head and neck	73	29
Buttocks	36	14
Unknown	31	12
Trunk	16	7
Diameter of primary, cm		
Median	1.5	
Range	0.2-14.0	
Clinical stage at presentation		
I	111	44
II	66	26
III	60	24
IV	14	6
Recurrence of disease (n = 236)		
Yes	102	43
No	134	57
Relapse-free interval (n = 102), months		
Median	9	
Range	2-70	
Site of first recurrence (n = 102)		
Local	15	15
In transit	9	9
Nodal	55	55
Distant	29	29
Status at last follow-up		
NED	140	56
AWD	22	9
DOD	64	25
DOC	25	10

Abbreviations: NED, no evidence of disease; AWD, alive with disease; DOD, died of disease; DOC, died of other causes.

was 1.5 cm (range, 0.2 to 14.0 cm). Patients with tumors of the head and neck presented with lesions that were smaller in diameter than patients with tumors of other locations (mean, 1.3 *v* 2.6 cm, respectively; $P < .001$) and were less likely to present with clinically apparent regional nodal disease (16% *v* 38%, respectively; $P < .001$).

Treatment of the Primary Tumor and Draining Nodal Basin

A wide excision was attempted on all but two of the patients who presented with local or regional disease and a known primary (Table 3). The two patients who did not undergo wide excision received radiotherapy to the primary lesion. Margin status could be determined in 196 of 211 patients who underwent excision of the primary lesion. Negative margins were obtained in 185 (94%) of these 196 patients. The average width of the surgical margin was 1.1 cm.

At the time of presentation, 177 patients presented with clinically negative nodes and no evidence of distant metastatic disease. Operative nodal staging and treatment (ELND or SLNBx) was performed in 71 of these patients (40%), and 106 patients (60%) were clinically staged as node negative (Table 3). Adjuvant radiotherapy was delivered to the clinically negative nodal basin in four of the 106 clinically node-negative patients. Within the group of 71 patients who underwent pathologic staging, ELND was performed in 17 patients (24%), and 54 patients (76%) underwent SLNBx. Over the last 6 years of the study, patients who presented with clinically negative nodes were more likely to have undergone pathologic nodal staging (35%, 1970 to 1995 *v* 71%, 1996 to 2002; $P < .001$).

Histologically positive nodes were identified in 16 (23%) of the 71 patients who underwent pathologic staging of a clinically negative nodal basin. Positive nodes were identified in four (24%) of the 17 patients who underwent ELND and in 12 (22%) of the 54 patients who underwent SLNBx ($P = .81$). Completion lymphadenectomy was performed in eight (67%) of the 12 patients discovered to have node-positive disease by SLNBx, and additional positive nodes were identified in two (25%) of these eight patients. Positive nodes were discovered in 24% of patients with tumors less than 2 cm in diameter and in 20% of patients with tumors $\geq$ 2 cm in diameter ($P = .71$). A single positive lymph node (range, one to five positive nodes) was identified in 11 (69%) of the 16 patients who presented with clinically negative and pathologically positive nodes.

Operative nodal treatment was performed on 57 of the 60 patients who presented with regional lymphadenopathy, two patients received radiotherapy alone to the nodal basin, and a single patient received systemic chemotherapy. A therapeutic nodal dissection was performed in 45 (79%) of the 57 patients who underwent operative nodal treatment, and 12 patients (21%) underwent excisional biopsy of the clinically suspicious node(s) (Table 3). All patients who underwent operative nodal treatment were found to have pathologically positive nodes. The average number of positive nodes in these 57 patients was four (range, one to 29 positive nodes).

Adjuvant radiotherapy was administered to 41 (17%) of the 237 patients who presented with local or regional disease. Adjuvant radiotherapy was delivered to the surgical bed in 17 patients, to the draining nodal basin in nine patients, and to both the surgical bed and nodal basin in 15 patients. The diameter of the primary tumor was associated with the use of adjuvant radiotherapy to the surgical bed ($<$ 2 cm, 10% *v* $\geq$ 2 cm, 23%; $P = .02$). Margin status was not associated with the use of adjuvant radiotherapy to the surgical bed (margin negative, 14% *v* margin positive, 27%; $P = .20$). The status of the draining nodal basin was

Table 3. Treatment of the Primary Lesion and Regional Nodal Basin in Patients Presenting With Local or Regional Disease

	Operative Treatment (No. of patients)	Adjuvant* Radiotherapy (No. of patients)
Treatment of the primary lesion		
Patients with local or regional disease and known primary (n = 211)		
Margin-negative excision	185	25
Margin-positive excision	11	3
Treatment of the nodal basin		
Patients with clinically negative nodes (n = 177)		
None	106	4
SLNBx (n = 54) or ELND (n = 17)	71	7
Patients with clinically positive nodes (n = 60)		
None	3	—
Therapeutic node dissection	45	11
Excisional biopsy	12	2

Abbreviations: SLNBx, sentinel lymph node biopsy; ELND, elective lymph node dissection.
*Two patients who had local or regional disease and a known primary did not undergo excision and, thus, received definitive radiotherapy to the primary lesion. Also, two patients with clinically positive nodes, who did not receive operative treatment, received definitive radiotherapy to the nodal basin.

associated with the use of adjuvant radiotherapy to the nodal basin (node positive, 22% *v* node negative, 5%; $P < .001$). Although they were more likely to present with smaller node-negative tumors, patients who presented with tumors of the head and neck were more likely to receive adjuvant radiotherapy to both the surgical bed (head and neck, 21% *v* other sites, 10%; $P = .02$) and to the draining nodal basin (head and neck, 15% *v* other sites, 8%; $P = .08$).

Adjuvant chemotherapy was administered to 28 (12%) of the 237 patients who presented with local or regional disease. Multiple different regimens were used; however, carboplatin and etoposide were the most common agents used. Nodal status was associated with the use of adjuvant chemotherapy (node positive, 30% *v* node negative, 2%; $P < .001$).

Recurrence

The 5-year relapse-free survival for the 237 patients who presented with local or regional disease was 48% (Fig 1). Disease recurred in 102 patients. The median time to recurrence was 9 months (range, 2 to 70 months), and 93 (91%) of the 102 patients experienced disease recurrence within 2 years of diagnosis. The most common site of first recurrence for all patients was the draining nodal basin (Table 2).

Local recurrence developed as a first or subsequent recurrence in 19 (8%) of the 237 patients who presented with local or regional disease. Local recurrence developed in 15 (8%) of the 185 patients who underwent a margin-negative excision and in two (18%) of the 11 patients who underwent a margin-positive excision ($P = .31$). Obtaining a surgical margin of more than 1 cm was not associated with decreased local recurrence (< 1 cm, 9% *v* ≥ 1 cm, 10%; $P = .83$). The use of adjuvant radiotherapy (surgical bed) was not associated with a decrease in local recurrence (radiotherapy, 10% *v* no radiotherapy, 8%; $P = .76$). In addition, no association was identified between adjuvant radiotherapy and local recurrence in the subgroup of patients (n = 185) who had undergone a margin-negative excision (Table 4).

Nodal recurrence developed as a first or subsequent recurrence in 59 (25%) of the 237 patients who presented with local or regional disease. Nodal recurrence developed in 15 (11%) of the 128 patients who presented with stage I to III disease and who underwent operative nodal staging and treatment (SLNBx, ELND, or therapeutic node dissection) and in 44 (44%) of the 102 patients who were clinically staged as node negative ($P < .001$). Distant metastatic disease, rather than nodal recurrence, was the most common

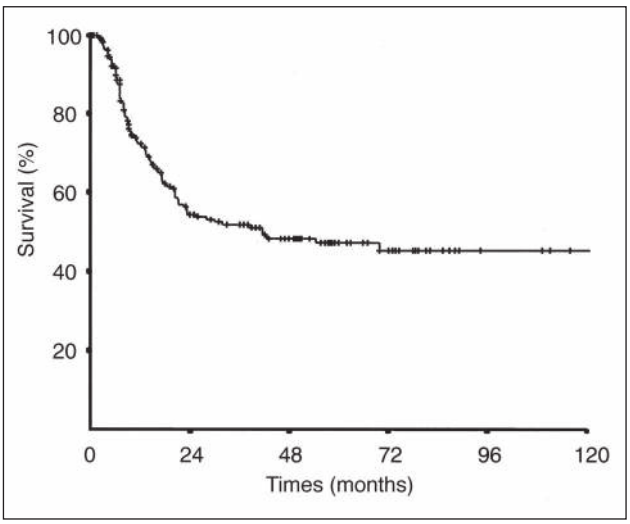

Fig 1. Relapse-free survival for the 237 patients who presented with local or regional disease.

Table 4. Influence of Adjuvant Radiotherapy (surgical bed) on Local Recurrence After Margin-Negative Excision (n = 185)*

Recurrence	Received Radiotherapy	Did Not Receive Radiotherapy
No local recurrence, No.	148	22
Local recurrence, No.	12	3
Local recurrence rate, %	8	14

*P = .45.

site of first recurrence (n = 18) in the 128 patients who had undergone operative nodal staging and treatment at the time of presentation. Patients who presented with clinically positive nodes experienced a similar rate of nodal recurrence as those who presented with clinically negative and pathologically positive nodes (15% *v* 8%, respectively; P = .19). The use of adjuvant radiotherapy (nodal basin) was not associated with decreased nodal recurrence (radiotherapy, 13% *v* no radiotherapy, 26%; P = .13). In addition, no association between the use of adjuvant radiotherapy and nodal recurrence was identified in the subgroup of patients who presented with pathologically positive nodes (Table 5).

Distant metastatic disease developed as a first or subsequent recurrence in 49 (21%) of the 237 patients who presented with local or regional disease. The development of distant metastases was associated with the stage of disease at presentation (stage I, 13%; stage II, 25%; and stage III, 29%; P = .04). The use of adjuvant chemotherapy was not associated with the development of distant recurrence in patients who presented with local or regional disease (adjuvant chemotherapy, 32% *v* no adjuvant chemotherapy, 19%; P = .11).

Survival

The average length of follow-up for all patients in this study was 40 months. Patients who were alive at the time of last follow-up (n = 162) had an average follow-up of 46 months. The 5-year disease-specific survival rate for all patients was 64% (Fig 2). At the time of last follow-up, 140 (56%) of 251 patients were without evidence of disease, 64 patients (25%) had died from disease, 25 patients (10%) had died from other causes, and 22 patients (9%) were alive with disease.

Table 5. Influence of Adjuvant Radiotherapy (nodal basin) on Nodal Recurrence in Patients Found to Have Pathologically Positive Nodes (n = 73)*

Recurrence	Received Radiotherapy	Did Not Receive Radiotherapy
No nodal recurrence, No.	49	14
Nodal recurrence, No.	8	2
Nodal recurrence rate, %	14	13

*P = .83

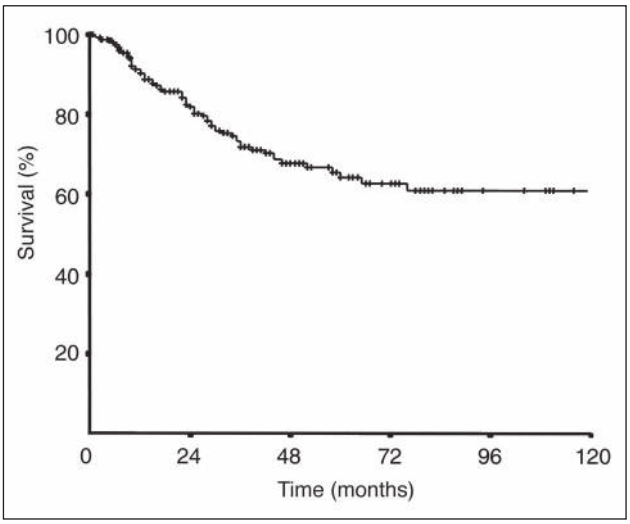

Fig 2. Disease-specific survival for the 251 patients treated for Merkel cell carcinoma.

Patient, tumor, and treatment-related variables and their association with survival in patients who presented with local or regional disease (n = 237) are presented in Table 6. Sex, tumor location (head and neck *v* other), tumor size, clinical nodal status, and pathologic nodal status were factors associated with survival by univariate analysis. The use of adjuvant chemotherapy was associated with decreased survival by univariate analysis. The use of adjuvant chemotherapy was not associated with survival in the subgroup of 76 patients identified as having node-positive disease (Fig 3).

When factors associated with survival were analyzed by Cox regression, the only independent predictor of survival was the pathologic nodal status. Stage of disease at presentation was also an independent predictor of survival when substituted for pathologic nodal status and size of primary tumor and placed into the regression analysis. The stage-specific survival probabilities for the 251 patients in this study are presented in Figure 4.

The stage-specific survival probabilities for patients with locoregional disease who underwent clinical nodal staging (n = 166) and pathologic nodal staging (n = 131) are presented in Figure 5. None of the 35 patients with pathologic stage I disease (< 2 cm, node negative) had died from disease at the time of the last follow-up (Fig 5B). The median length of follow-up for this group of patients was 33 months. One of the 20 patients who were identified as having pathologic stage II disease (≥ 2 cm, node negative) had died of disease at the time of last follow-up (Fig 5B).

The method used (clinical *v* pathologic) for nodal staging was associated with stage-specific survival. Patients with clinically negative nodes (clinical stage I and II) had a 5-year

Table 6. Patient, Tumor, and Treatment-Related Variables and Their Association With DSS in Patients Presenting With Stage I to III Disease (n = 237)

Factor	No. of Patients	5-Year DSS (%)	*P* (log-rank)
Sex			
Male	140	62	.09
Female	97	78	
Age < 69 years			
Yes	114	64	.82
No	123	69	
Primary site of head and neck			
Yes	73	87	.02
No	164	62	
Size of primary			
< 2 cm	117	77	.02
≥ 2 cm	84	59	
Clinical nodal status			
Negative	177	75	.002
Positive	60	49	
Pathologic nodal status			
Negative	55	97	< .001*
Positive	73	52	
Margin-negative excision			
Yes	185	73	.11
No	11	33	
Adjuvant chemotherapy			
Yes	28	28	.001
No	209	73	

Abbreviation: DSS, disease-specific survival.
*Only factor independently predictive (Cox regression) of DSS.

survival rate of 75%, and patients with pathologically negative nodes (pathologic stage I and II) had a 5-year survival rate of 97% ($P = .009$). Patients with clinically negative and pathologically positive nodes had a 5-year survival rate of

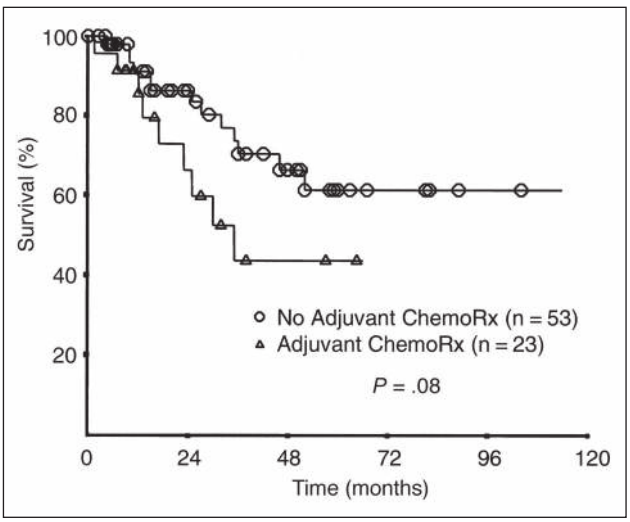

Fig 3. Comparison of disease-specific survival in node-positive patients who either received (n = 23) or did not receive (n = 53) adjuvant chemotherapy (ChemoRx).

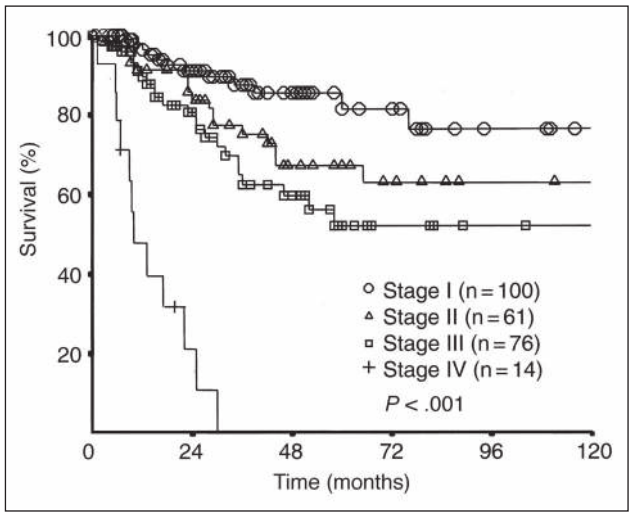

Fig 4. Disease-specific survival for the 251 patients treated for Merkel cell carcinoma by stage of disease at presentation.

62%, and patients who presented with clinically positive nodes had a 5-year survival rate of 49% ($P = .19$). In addition, patients with one positive lymph node (n = 40) had a 5-year survival rate of 66%, patients with two to four positive lymph nodes (n = 21) had a 5-year survival rate of 62%, and patients with more than four positive lymph nodes (n = 16) had a 5-year survival rate of 30% ($P < .001$, log-rank test).

The 2-year disease-specific survival rate for the 14 patients who presented with distant metastatic disease was 11%, and the median survival time was 9 months. At the time of last follow-up, two of these 14 patients were alive with disease. The length of follow-up for these two patients was 7 months and 20 months.

DISCUSSION

Staging systems have been developed to better define prognosis in patients with malignancy and are determined by the presence or absence of specific factors that are predictive of survival. As with all other malignancies, the prognosis of patients presenting with MCC is variable. Specific survival probabilities for MCC patients are dependent on the stage of disease at the time of presentation. Factors used in the staging system for MCC include the size of the primary tumor, the status of the regional nodal basin, and whether distant metastatic disease is present.[7,8,15] Identification of these factors in any given patient allows a more accurate assessment of prognosis and should be used to guide patients and physicians in balancing the benefits and risks of specific treatment modalities.

The 5-year disease-specific survival for the 251 patients in this study was 64%. The stage of disease at the time of

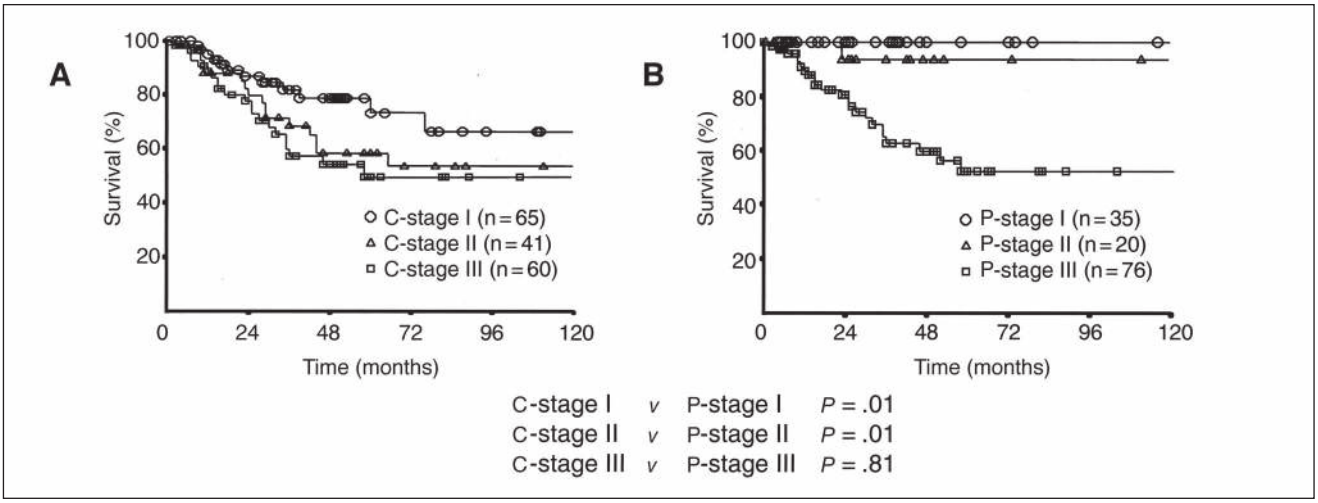

Fig 5. Disease-specific survival for patients who underwent (A) clinical nodal staging and (B) pathologic nodal staging by sentinel lymph node biopsy, elective lymph node disection, or therapeutic nodal staging (clinical stage I *v* pathologic stage I, $P = .01$; clinical stage II *v* pathologic stage II, $P = .01$; and clinical stage III *v* pathologic stage III, $P = .81$).

presentation was the only patient, tumor, or treatment-related factor found to be predictive of survival. The use of pathologic nodal staging identified a group of patients with excellent 5-year survival. The 5-year survival rate of pathologically staged node-negative patients was 97% (Fig 5B). Patients with pathologically positive nodes had a 5-year survival rate of 52%.

Because MCC is an uncommon malignancy, the majority of studies that describe the natural history of this disease consist of single-institution experiences of fewer than 40 patients.[1-3,5,6,16] In these studies, the inclusion of just a few patients with advanced disease can significantly decrease overall survival estimates and result in the labeling of this tumor as aggressive or highly malignant. However, even in these instances, when stage-specific survival is reported, patients who present with early-stage tumors experience prolonged survival. In a recent study from the University of Alabama, the 3-year actuarial survival rate for 16 patients treated for MCC was 31%.[1] Adenopathy was present in four patients, and two patients were found to be node positive after undergoing SLNBx. The median survival time for the node-positive patients (n = 6) was 15 months, and for patients who were clinically node negative (n = 10), the median survival time was 97 months.

The methods used for determining the stage of disease are important when survival rates are being reported. When staging is determined by the presence of nodal and distant metastatic disease, stage-specific survival probabilities will improve as techniques improve for determining the presence or absence of these factors. This concept of stage migration has been recently demonstrated with the use of SLNBx and immunohistochemistry for nodal staging in patients with melanoma and breast cancer.[17,18] When the more sensitive techniques of SLNBx and immunohistochemistry are used to determine nodal status, patients with lesser amounts of nodal disease are recategorized from node negative to node positive. The removal of these patients from the node-negative group and their addition to the node-positive group improves the probability of survival for both stages.

The data from this study further demonstrate this concept. In this study, clinically node-negative patients (clinical stage I or II) had a 5-year survival rate of 75%, and pathologically node-negative patients (pathologic stage I or II) had a 5-year survival rate of 97%. The addition of the clinically negative and pathologically positive patients (n = 16) to the 60 patients who presented with adenopathy (clinical stage III) increased stage III survival from 49% to 52%. Pathologic staging of the nodal basin resulted in an improvement in stage-specific survival probabilities and identified a group of patients with excellent long-term survival.

Pathologic staging of the regional lymph nodes is important in MCC patients who present with clinically localized disease. In the current study, approximately 25% of patients with clinically negative nodes were found to have nodal disease after pathologic evaluation. This incidence of clinically occult nodal disease was not associated with the size of the tumor. The extent of disease within the nodal basin was also associated with survival. Patients with a single positive lymph node had a 66% 5-year survival rate, patients with two to four positive nodes had a 62% 5-year survival rate, and patients with more than four positive nodes had a 30% 5-year survival rate ($P < .001$).

We currently recommend that all patients presenting with localized MCC undergo pathologic nodal staging with SLNBx. Prior studies from our institution and others have demonstrated the efficacy of SLNBx for MCC.[19,20] Many institutions did not recommend pathologic nodal staging

before the development of SLNBx because of the potential morbidity and unclear benefit of ELND. At our institution, 35% of patients underwent pathologic nodal staging before the development of SLNBx, and 71% have undergone pathologic staging since its initial use for MCC at our institution in 1996. The data from this study demonstrate that pathologic nodal staging provides a more accurate representation of stage-specific survival, identifies a group of patients who experience excellent long-term survival, and decreases regional nodal recurrence.

Our recommended treatment for the primary lesion consists of margin-negative surgical excision. This treatment can be achieved in the majority of patients and results in low rates of local recurrence. In the current study, patients who had undergone a margin-negative excision had a local recurrence rate of 8%, and patients with a positive histologic margin had a local recurrence rate of 18% ($P = .31$).

Local recurrence rates have been reported as high as 62% in other studies.[1,7-10] This wide variation in local recurrence may be attributed to an inconsistency in the methods of reporting. Many studies have not reported local recurrence, but rather, they have reported the combination of local and regional recurrence, reported as locoregional recurrence. Because these studies have often relied on clinical nodal staging, regional nodal recurrence is frequent, and therefore, locoregional recurrence may be significantly more regional than local. This method of reporting allows the misconception that many patients experience failure at the surgical site after complete excision. When local recurrence rates have been reported separately, many studies have reported rates similar to those in this study.[1,13,16] Local recurrence was reported in one (16%) of 16 patients treated at the University of Alabama, in four (16%) of 25 patients treated in Sydney, and in one (2%) of 45 patients treated with Mohs surgery by the United States Naval Medical Department.[1,13,16]

We do not recommend the routine use of adjuvant radiotherapy to the surgical bed. In this study, there was no association between the use of adjuvant radiotherapy and local recurrence. Also, in the subgroup of patients who received adjuvant radiotherapy after a margin-negative excision, there was no association between local recurrence and the use of adjuvant radiotherapy. The trend towards higher local recurrence rates after a margin-positive excision may warrant the use of adjuvant radiotherapy in selected patients in which a margin-negative excision cannot be obtained. However, because of the limited data, any recommendations regarding the use of this treatment for margin-positive patients must be considered speculative. In this study, the number of patients with positive histologic margins was low (n = 11), and local recurrence developed in two patients who had undergone a margin-positive excision (18%).

Regional nodal recurrence rates have been reported between 23% and 61%.[8,13,21] In this study, the overall nodal recurrence rate was 25%. Patients who had undergone pathologic nodal staging (ELND or SLNBx) experienced a nodal recurrence rate of 11%, and patients who were clinically staged had a nodal recurrence rate of 44%. The high variability in reported regional nodal recurrence rates may also be attributed in part to the predominance of clinical nodal staging before the mid 1990s. In a report by Boyle et al[16] of 34 patients treated between 1979 and 1990, 20 patients presented with clinically negative nodes and were clinically staged as node negative, 10 patients presented with palpable adenopathy, and four patients presented with distant metastatic disease. Nodal recurrence developed in 12 (60%) of the 20 patients who had been clinically staged as node negative. None of the 10 patients who underwent lymphadenectomy for palpable nodes experienced a nodal recurrence. These results suggest that clinical nodal staging results in the understaging of many patients with MCC and has resulted in the reporting of clinically occult nodal disease as regional nodal recurrence.

MCC has been shown to be radiosensitive in selected patients.[3,13] Thus, many have recommended the use of adjuvant nodal radiotherapy as a means for reducing the reported high rate of regional nodal recurrence.[1,9,11,12] Our data do not support the routine use of adjuvant nodal radiotherapy. In the current study, patients who underwent pathologic nodal staging had a nodal recurrence rate of 11%. The use of adjuvant radiotherapy was not associated with recurrence in patients who presented with localized disease or in the subgroup of patients who presented with pathologically positive nodes (14% without RT *v* 13% with RT; $P = .81$). Advocates of this treatment may argue that this lack of association between treatment and outcome is secondary to the potential selection bias inherent in a retrospective study. However, even if bias exists, the data demonstrate that nodal recurrence is low when pathologic staging has been performed. Thus, any potential benefit from adjuvant radiotherapy after pathologic staging must be balanced against the toxicity of the therapy, which will be delivered for no benefit in 90% of the patients.

Defining a subgroup of patients at high risk for nodal recurrence after pathologic staging would identify a group of patients in which the potential benefits of RT could be balanced by the risk. Current consensus guidelines from the National Comprehensive Cancer Network recommend the routine use of adjuvant nodal radiotherapy when SLNBx has not been performed or when patients present with clinically positive regional nodes.[22] Our data suggest that when SLNBx or ELND has not been performed, nodal disease will become clinically apparent in approximately 45% of patients, and therefore, the use of radiotherapy may be warranted. Patients with clinically positive nodes would seem to be at higher risk for nodal recurrence than those

with lower volume nodal disease; however, the data from the current study were unable to identify this association.

The use of systemic agents for the treatment of MCC has been investigated in both the adjuvant setting and in the setting of advanced disease.[4,14,22,23] Multiple agents have been used to treat MCC, including carboplatin, etoposide, and vincristine. Retrospective data of patients treated with nonstandardized regimens for advanced disease have documented initial response rates between 57% and 75%.[4,22] Despite these high response rates, many studies, as well as ours, report a median survival of approximately 9 months for patients with distant metastatic disease.

A variety of toxicities have been reported from the currently used chemotherapeutic treatment regimens. The toxic death rate has been reported to be as high as 3% to 7%.[4,22] Poulsen et al[23] published a prospective study of 53 patients evaluating definitive chemotherapy and local radiation for patients with tumors more than 1 cm in size or with node-positive disease. Reported toxicities included grade 3 and 4 neutropenia in 60% of patients and fever and sepsis in 35% of patients. Grade 3 and 4 skin toxicity, secondary to radiation, was reported in 63% of patients. Furthermore, grade 3 skin toxicity was present in 15% of patients 3 years after treatment, and a single patient required lower extremity amputation after grade 4 skin and subcutaneous tissue toxicity.

Currently, we do not recommend the routine use of adjuvant chemotherapy in patients with MCC. In this study, patients who presented with pathologically staged node-negative disease had a 5-year survival rate of 97%. The use of adjuvant chemotherapy in this group cannot be justified given the current unproven benefit and known toxicities of these regimens. Patients who present with node-positive disease experience a high rate of relapse, and approximately half of these patients will die from disease within 5 years. Our data did not find an association between the use of adjuvant chemotherapy and survival in this subgroup of patients. The use of adjuvant chemotherapy in node-positive MCC patients requires further study in a prospective setting with agents that have an improved toxicity profile.

In conclusion, the data from this study demonstrate that the natural history of MCC is variable and dependent on the stage of disease at the time of presentation. In this study, patients with histologically node-negative tumors experienced excellent long-term survival. Approximately half of patients with node-positive disease survived 5 years, and the median survival for patients with metastatic disease was 9 months. Local recurrence rates were approximately 10% after margin-negative excision, and regional nodal recurrence rates were approximately 10% after operative nodal staging. Adjuvant radiotherapy was not associated with decreased local or regional nodal recurrence. Adjuvant chemotherapy was not associated with decreased recurrence or survival. We currently recommend complete surgical excision and pathologic nodal staging in all patients presenting with local or locoregional disease. Adjuvant radiotherapy to the surgical bed is not warranted after a margin-negative excision. Adjuvant radiotherapy to the regional nodal basin is not warranted in patients who have undergone operative nodal staging. Adjuvant chemotherapy should be further investigated with newer agents in patients with node-positive disease.

Authors' Disclosures of Potential Conflicts of Interest

The authors indicated no potential conflicts of interest.

REFERENCES

1. Medina-Franco H, Urist MM, Fiveash J, et al: Multimodality treatment of Merkel cell carcinoma: Case series and literature review of 1024 cases. Ann Surg Oncol 8:204-208, 2001
2. Muller A, Keus R, Neumann N, et al: Management of Merkel cell carcinoma: Case series of 36 patients. Oncol Rep 10:577-585, 2003
3. Mortier L, Mirabel X, Fournier C, et al: Radiotherapy alone for primary Merkel cell carcinoma. Arch Dermatol 139:1587-1590, 2003
4. Tai PT, Yu E, Winquist E, et al: Chemotherapy in neuroendocrine/Merkel cell carcinoma of the skin: A case series and review of 204 cases. J Clin Oncol 18:2493-2499, 2000
5. Smith DE, Bielamowicz S, Kagan AR, et al: Cutaneous neuroendocrine (Merkel cell) carcinoma: A report of 35 cases. Am J Clin Oncol 18:199-203, 1995
6. Raaf JH, Urmacher C, Knapper WK, et al: Trabecular (Merkel cell) carcinoma of the skin. Cancer 57:178-182, 1986
7. Allen PJ, Zahan ZF, Coit DG: The surgical management of Merkel cell carcinoma. Ann Surg 229:97-105, 1999
8. Yiengpruksawan A, Coit DG, Thaler HT, et al: Merkel cell carcinoma: Prognosis and management. Arch Surg 126:1514-1519, 1991
9. Gillenwater AM, Hessel AC, Morrison WH, et al: Merkel cell carcinoma of the head and neck: Effect of surgical excision and radiation on recurrence and survival. Arch Otolaryngol Head Neck Surg 127:149-154, 2001
10. Boyer JD, Zitelli JA, Brodland DG, et al: Local control of primary Merkel cell carcinoma: Review of 45 cases treated with Mohs micrographic surgery with and without adjuvant radiation. J Am Acad Dermatol 47:885-892, 2002
11. Meeuwissen JA, Bourne RG, Kearsley JH: The importance of postoperative radiation therapy in the treatment of Merkel cell carcinoma. Int J Radiat Oncol Biol Phys 31:325-331, 1995
12. Morrison WH, Peters LJ, Silva EG, et al: The essential role of radiation therapy in securing locoregional control of Merkel cell carcinoma. Int J Radiat Oncol Biol Phys 19:583-591, 1990
13. Poulsen M, Harvey J: Is there a diminishing role for surgery for Merkel cell carcinoma of the skin? A review of current management. ANZ J Surg 72:142-146, 2003
14. Poulsen M, Rischin D, Walpole E, et al: High-risk Merkel cell carcinoma of the skin treated with synchronous carboplatin/etoposide and radiation: A Trans-Tasman Radiation Oncology Group study–TROG 96:07. J Clin Oncol 21:4371-4376, 2003
15. Miller SJ, Andersen J, Beenken SW, et al: Merkel cell carcinoma: Clinical Practice Guidelines in Oncology. J Natl Comprehensive Cancer Network 2:80-87, 2004
16. Boyle F, Pendlebury S, Bell D: Further insights into the natural history and management of primary cutaneous neuroendocrine (Merkel

cell) carcinoma. Int J Radiat Oncol Biol Phys 31:315-323, 2005

17. Schlag PM: The "sentinel node" concept: More questions raised than answers provided. Oncologist 3:6-7, 1998

18. Noguchi M: Therapeutic relevance of breast cancer micrometastases in sentinel lymph nodes. Br J Surg 89:1505-1515, 2002

19. Hill ADK, Brady MS, Coit DG: Intraoperative lymphatic mapping and sentinel lymph node biopsy for Merkel cell carcinoma. Br J Surg 86:518-521, 1999

20. Messina JL, Reintgen DS, Cruse CW, et al: Selective lymphadenectomy in patients with Merkel cell (cutaneous neuroendocrine) carcinoma. Ann Surg Oncol 4:389-395, 1997

21. Kokoska ER, Kokoska MS, Collins BT, et al: Early aggressive treatment for Merkel cell carcinoma improves outcome. Am J Surg 174: 688-693, 1997

22. Voog E, Biron P, Martin JP, et al: Chemotherapy for patients with locally advanced or metastatic Merkel cell carcinoma. Cancer 15: 2589-2595, 1999

23. Poulsen M, Rischin D, Walpole E, et al: Analysis of toxicity of Merkel cell carcinoma of the skin treated with synchronous carboplatin/etoposide and radiation: A Trans-Tasman Radiation Oncology Group study. Int J Radiat Oncol Biol Phys 1:156-163, 2001