STUDY

Sentinel Lymph Node Biopsy for Evaluation and Treatment of Patients With Merkel Cell Carcinoma

The Dana-Farber Experience and Meta-analysis of the Literature

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Objective: To determine the diagnostic accuracy and usefulness of sentinel lymph node biopsy (SLNB) and computed tomographic scans in the initial evaluation and treatment of patients with Merkel cell carcinoma (MCC).

Design: Single-institution case series and literature-based case-level meta-analysis.

Setting: Academic cutaneous oncology clinic.

Patients: Sixty-one adults with biopsy-proven MCC (30 who had undergone SLNB) plus 92 cases from the literature of patients who had undergone SLNB.

Main Outcome Measures: Relapse-free survival.

Results: In 122 patients with no nodal disease found by physical examination, SLNB findings revealed nodal involvement in 39 cases (32%). At 3 years, the recurrence rate for those with a positive SLNB was 3 times (60%) higher than for those with a negative SLNB (20%; $P = .03$). Patients with a positive SLNB who received adjuvant nodal therapy had a relapse-free survival rate of 51% at 3 years (n = 26) compared with 0% for patients who did not receive nodal therapy (n = 3; $P < .01$). In contrast, among patients with a negative SLNB there was no significant difference in 3-year relapse-free survival rates for those who did (90%; n = 24) or did not (70%; n = 19; $P = .26$) receive adjuvant nodal therapy. Using SLNB plus clinical follow-up as a gold standard, computed tomographic scans had low sensitivity (20%) for detecting MCC that had spread to the lymph node basin and low specificity for distant disease (only 4 of 21 "positive" scans were confirmed during 6 months of follow-up).

Conclusions: Sentinel lymph node biopsy detects MCC spread in one third of patients whose tumors would have otherwise been clinically and radiologically understaged and who may not have received treatment to the involved node bed. There was a significant benefit of adjuvant nodal therapy, but only when the SLNB was positive. Thus, SLNB is important for both prognosis and therapy and should be performed routinely for patients with MCC. In contrast, computed tomographic scans have poor sensitivity in detecting nodal disease as well as poor specificity in detecting distant disease.

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MERKEL CELL CARCINOMA (MCC) is an aggressive neuroendocrine skin cancer[1,2] that is often compared with a thick or ulcerated melanoma, and patients with MCC have a 5-year survival rate of 65%. In the past 15 years, its age-adjusted incidence in the United States has

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increased 3-fold, to as many as 950 new cases per year.[3,4] A contributor to this increase is more accurate diagnosis of MCC by using cytokeratin-20 staining, a very specific histologic marker for MCC that has been available since 1992. In the past, many MCC tumors were likely misclassified as lymphoma or metastatic small cell lung cancer. Other reasons for a rise in the number of MCC cases in the United States are an aging population, increasing sun exposure, and increasing numbers of immunocompromised patients; older age, increased sun exposure, and an immunocompromised condition are all established risk factors.[1,5,6] Despite this marked increase in disease incidence, there is still great variability in evaluation and treatment practices. Optimal initial therapy has yet to be determined, and unfortunately, it is broadly agreed that no effective treatment exists for metastatic disease.

Merkel cell carcinoma is classified into 3 stages: I, local disease; stage II, nodal disease; and stage III, metastatic disease with survival being highly dependent on stage

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Table 1. Demographic and Tumor Characteristics of 61 Patients Presenting at the Dana-Farber Cancer Institute (DFCI), 1997-2004*

Characteristic	No. (%)
Age, median (range), y	69 (44-86)
Sex	
Men	33 (54)
Women	28 (46)
Race	
White	59 (97)
Black	1 (1.6)
Asian	1 (1.6)
Profound immunosuppression (solid organ transplant, CLL, HIV)	7 (11)
Follow-up, median (range), mo	16 (0-67)
Diameter, median (range), cm	1.5 (0.2-6.0)
Anatomic Site	
Head and neck	16 (26)
Leg	16 (26)
Arm	14 (23)
Occult†	8 (13)
Buttock	4 (7)
Trunk	3 (5)
Stage at diagnosis	
IA (<2 cm)	24 (39)
IB (≥2 cm)	9 (15)
II (nodal)	19 (31)
III (distant)	5 (8)
Unstaged	4 (7)

Abbreviations: CLL, chronic lymphocytic leukemia; HIV, human immunodeficiency virus.

*For variables that could be compared, the patient population from the literature was similar in demographics to the DFCI group. Thirty patients underwent sentinel lymph node biopsy; the tumors of others were staged clinically. Data are given as number (percentage) except where indicated.

†Occult indicates that no primary tumor was identified.

at presentation.[2,7,8] Identification of disease in the sentinel lymph node basin provides information about prognosis and identifies the draining lymph node bed for surgery and adjuvant radiation therapy.[1,2,7] Because sentinel lymph node biopsy (SLNB) is a relatively new technique in the staging of MCC, there are few published studies on this topic, many of which report fewer than 10 cases. Over the past 7 years we have collected data on 61 patients with MCC, 30 of whom underwent an SLNB as part of their initial workup. By pooling our data with those from other published reports,[4,9-19] we have collected data on the largest population (n=122) of such patients and have examined the impact of SLNB on the tumor staging of and the disease-free survival for patients with MCC. In addition, to our knowledge, we provide the first data on the relative usefulness of SLNB vs computed tomographic (CT) imaging for staging and initial evaluation of the spread of MCC.

METHODS

SINGLE-INSTITUTION CASE SERIES

The institutional review board of the Dana-Farber/Harvard Cancer Center, Boston, Mass, approved this study. Consent was obtained for telephone interviews as needed. All adult patients with MCC seen at the Dana-Farber Cancer Institute (DFCI) Cutaneous Oncology Clinic from October 1997 to November 2004 were included. In most cases, patients were referred to our center after undergoing initial biopsy by referring physicians. Data were collected based on retrospective chart reviews, and prospective follow-up was conducted by telephone interviews and clinic visits.

EVALUATION OF CT IMAGING FINDINGS

This analysis included 35 patients seen in our clinic who underwent CT imaging (34 cases) or positron emission tomographic imaging (1 case). Imaging data were classified as true positive or true negative if the imaging result was confirmed using as the gold standard SLNB, further radiologic tests, or clinical follow-up within 6 months. Results were classified as false positive or false negative if the imaging reading was refuted by SLNB, further radiologic tests, or clinical follow-up within 6 months. A 6-month follow-up period was adopted based on the rapid spread of MCC to lymph nodes and the standard end point used in similar imaging analyses in patients with melanoma.[20] Sensitivity was calculated as the number of cases identified as positive according to the scan divided by the number of cases found to be positive according to the gold standard. Specificity was calculated as the number of cases identified as negative according to the scan divided by the number of cases found to be negative according to the gold standard.

CASE-LEVEL META-ANALYSIS AND STATISTICAL ANALYSIS

A PubMed search of English language literature involving human subjects from January 1976 to April 2005, using the key words "Merkel" and "sentinel," yielded 45 articles. All case series involving patients with MCC who underwent SLNB were examined for case details and outcome. We excluded any series that failed to report the status of recurrence (to the lymph node basin or distant sites) with a minimum of 1-month follow-up. Single case reports were also excluded to avoid the inherent reporting bias toward positive findings from an SLNB. Care was taken to count only once those patients whose cases were reported in multiple publications. We accomplished this by comparing dates of publication and specific patient characteristics of articles from the same institution.

We used SAS statistical software (SAS Institute Inc, Cary, NC) for data analysis, and *t* test and Fisher exact test were used as appropriate. Prism 4 (Graphpad Software Inc, San Diego, Calif) was used for Kaplan-Meier survival analysis with the log rank; *P* values smaller than .05 were considered significant.

RESULTS

SINGLE-INSTITUTION CASE SERIES

Sixty-one adult patients with MCC were enrolled during a 7-year period. The demographic and tumor characteristics of the patients are shown in **Table 1**. The population had a median age of 69 years and was 97% white (n=59) and 54% male (n=33). Thirty patients underwent SLNB, and the tumors of 31 had been staged only clinically. Because some of the patients whose tumors were clinically staged likely had microscopic nodal involvement that was not detected, the percentage of patients presenting with stage II disease is likely somewhat higher than 31% (n=19). Seven patients (11%) had profound

Table 2. Detection of Metastases by Computed Tomographic Imaging*

Characteristic	LN Basin Scans (n = 35)	Distant Site Scans (n = 37)
Sensitivity	4/20 (20)	4/4 (100)
Specificity	13/15 (87)	16/33 (48)

Abbreviation: LN, lymph node.
*The ability of radiologic imaging to detect nodal and distant spread was compared with a gold standard of 6 months of clinical follow-up including sentinel lymph node biopsy and subsequent scans. Sensitivity and specificity are defined in the "Methods" section. Data are given as number (percentage).

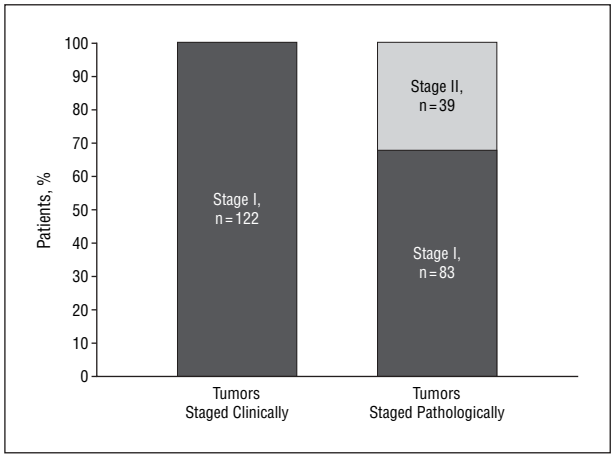

Figure 1. Effect of sentinel lymph node biopsy (SLNB) on staging. The tumors of 122 patients were staged as only local disease according to clinical examination at the time of SLNB. The SLNB findings revealed that 39 patients (32%) actually had lymph node disease (stage II). Data are from 122 patients (30 from the Dana-Farber Cancer Institute and 92 from the literature) for whom SLNB status was reported.

immunosuppression defined as those with solid organ transplantation, chronic lymphocytic leukemia, or human immunodeficiency virus infection. The tumors of 33 patients (54%) were stage IA or IB (local disease), as shown in Table 1. Seventy percent of the patients lived within 100 miles of Boston, which suggests that these data were not skewed by a major referral bias to a tertiary care center. The most common sites of primary lesion were the extremities (49% [30]) and the head and neck (26% [16]), with 13% (8) presenting as occult disease (nodal or visceral disease with no primary identified). Most cases reported in the literature did not have sufficient demographic data to make comparisons at all points. For those variables that could be compared, the demographic characteristics of the 2 groups were similar. The median age was 73 years (range, 39-90 years), slightly more than half (54%) were male, and the 2 most common tumor sites were the head and neck and the upper extremities. The median tumor diameter was 2.0 cm (range, 1.0-4.9 cm). In the DFCI population, only 5 (45%) of the 11 SLNB procedures performed in the head and neck region were successful in isolating 1 or more lymph nodes with dye or radiotracer uptake. All SLNB procedures (n=25) attempted in other locations were successful.

DETECTION OF METASTASES BY CT IMAGING

Imaging studies that included the regional lymph node basin were performed at the time of presentation in 35 patients (34 CT scans and 1 positron emission tomographic scan). Scans of the lymph node basin had a low sensitivity (20% [4]) and a high specificity (87% [13]) for the detection of nodal disease (**Table 2**). Sixteen patients had false-negative scans with evidence of lymph node disease apparent at presentation or within 6 months. Imaging studies failed to detect nodal disease in all 7 patients who had a positive SLNB. There were 4 true-positive results for imaging of the lymph node basin. In 3 of these cases, clinically apparent nodal involvement had already been found on initial physical examination. The fourth patient had lymph node disease identified solely by imaging because an attempted SLNB was unsuccessful. Thirteen patients had true-negative scans of the lymph node basin with no evidence of nodal disease after a median follow-up period of 17 months (range, 10-60 months). Two patients had false-positive scans with no evidence of disease observed during a minimum 6-month follow-up period.

In the detection of distant spread of MCC, 36 CT scans and 1 positron emission tomographic scan were evaluated (Table 2). Suspicious findings were detected in 21 patients, but further studies and follow-up confirmed only 4 cases (19%). Of the 4 true-positive imaging studies, 3 were of patients with clinically advanced disease at presentation. The other 17 positive scans were of patients who did not develop evidence of disease during the follow-up period, and the findings were thus classified as false positive. Sixteen patients had negative scans for distant disease at diagnosis. Two of them developed metastases at 7 and 8 months after the initial scan, but because this was more than 6 months after the initial scan, these scans were classified as true negative. There were no false-negative scans for the detection of distant spread. Distant spread was detected only in patients with a positive SLNB. One hundred percent of the positive findings among patients with a negative SLNB were false in both the lymph node basin and distant sites.

CASE-LEVEL META-ANALYSIS FOR SLNB, TREATMENT, AND RECURRENCES

Our literature search found 12 publications reporting a total of 92 patients who fit our inclusion criteria.[4,9-19] Selecting only patients with individual follow-up allowed a case-level analysis to be performed, which meant that each patient could be considered independently. When combined with our own series (30 patients who underwent SLNB), a total of 122 patients met the criteria for inclusion. Overall, the characteristics of the 2 groups were similar. Our patients from the DFCI and the cases from the literature are listed in the eTable (available at www.archdermatol.com).

Among these 122 patients, SLNBs were positive in 39 patients (32%) whose tumors would otherwise have been classified as stage I (local disease) according to clinical criteria (**Figure 1**). The incidence of positive SLNBs

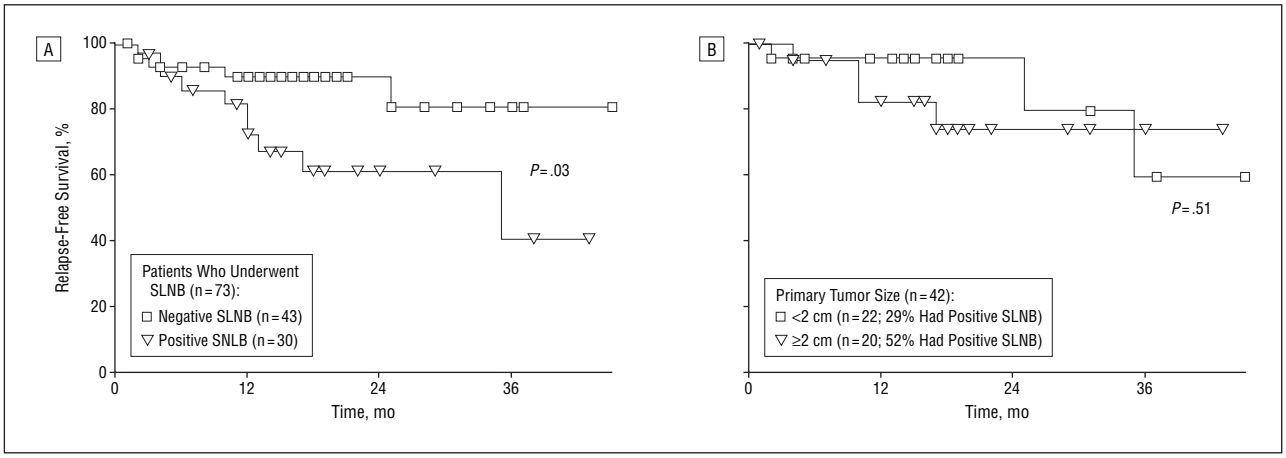

Figure 2. Influence of sentinel lymph node biopsy (SLNB) status and tumor size on relapse-free survival rate. A, Patients with a negative SLNB had an 80% 3-year relapse-free survival rate vs 40% for those with a positive SLNB ($P=.03$). Median follow-up was 15 months (range, 1-46 months) for patients with a negative SLNB and 12 months (range, 2-43 months) for those with a positive SLNB. Data are from 73 patients (29 from the Dana-Farber Cancer Institute [DFCI] and 44 from the literature) who underwent SLNB and for whom follow-up was reported. B, There was no significant difference in relapse-free survival based on size of primary lesion at presentation in this cohort ($P=.51$). Data are from 42 patients (25 from the DFCI and 17 from the literature) who underwent SLNB and for whom size and follow-up were reported.

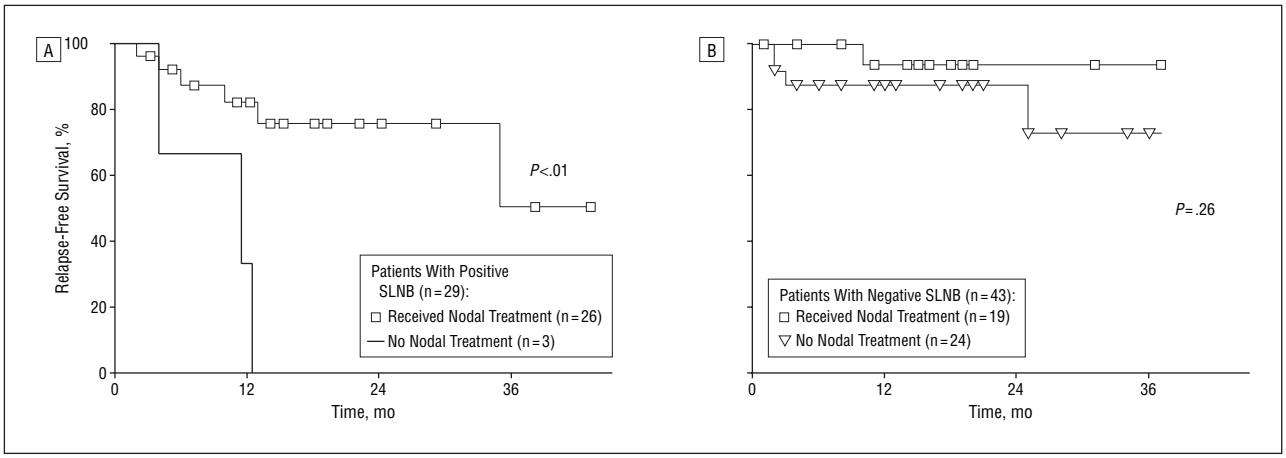

Figure 3. Influence of adjuvant lymph node therapy on relapse-free survival in patients with a positive sentinel lymph node biopsy (SLNB) and those with a negative SLNB. A, Patients with a positive SLNB who did not receive adjuvant therapy had a 0% 3-year relapse-free survival rate vs 51% for those who received therapy ($P<.01$). Data are from 29 patients who had a positive SLNB and for whom follow-up was reported. B, Patients with a negative SLNB who did not receive adjuvant therapy had a 70% 3-year relapse-free survival rate vs 90% for those who received therapy ($P=.26$). Data are from 43 patients who had a negative SLNB and for whom follow-up was reported.

tended to increase with the increasing size of the primary lesion; among patients with tumors 2 cm or larger, 52% of SLNBs were positive compared with 29% of SLNBs that were positive among patients with tumors smaller than 2 cm ($P=.23$; data not shown).

Using Kaplan-Meier analysis, we found that at 3 years' follow-up, the recurrence rate for those with a positive SLNB was 3 times higher (60%) than for those with a negative SLNB (20%). The 3-year relapse-free survival rate for patients with a negative SLNB was 80% compared with 40% ($P=.03$) for patients with a positive SLNB (**Figure 2**A). In contrast, tumor size at the time of diagnosis was not significantly associated with relapse-free survival ($P=.51$) (Figure 2B). In addition, relapse-free survival was not related to the age or sex of the patient (data not shown).

In patients with a positive SLNB, the frequency of those who received adjuvant treatment (total lymph node dissection, radiation therapy, or chemotherapy) to the lymph node bed was significantly higher (91% vs 36% for patients with a negative SLNB; $P<.001$), indicating that SLNB status likely affected subsequent clinical decisions quite often. Regardless of nodal status, those who received adjuvant nodal therapy were younger (median age, 67 years) than those who did not receive adjuvant therapy (median age, 73 years; $P=.02$), indicating that the patient's age may have biased the clinical decision to treat with adjuvant nodal therapy. We found no significant effect of sex or size of primary tumor on the likelihood of receiving adjuvant treatment to the node bed (data not shown).

At 3-years' follow-up, patients with a positive SLNB who received adjuvant nodal therapy (n=26) had a relapse-free survival rate of 60% compared with 0% (n=3; $P<.01$) for patients who did not receive nodal therapy (**Figure 3**A). Among patients with a negative SLNB there was a trend for adjuvant treatment to the lymph node to influence the relapse-free survival rate (Figure 3B). The 3-year relapse-free survival rate for patients with a negative SLNB who did receive adjuvant nodal therapy was

90% (n=24) compared with 70% for those who did not (n=19; $P=.26$).

COMMENT

The standard of care for evaluating patients with MCC has been a complete physical examination, usually with radiological imaging to detect spread of the disease. We have analyzed the largest cohort of patients with MCC who have undergone SLNB to date and have found evidence that suggests that an SLNB should be routinely included in the evaluation of patients diagnosed with MCC who seem to have no nodal involvement based on clinical examination findings. Indeed, 39 of 122 patients initially presumed to have only local (stage I) disease in fact had lymph node disease (stage II) detected by SLNB. This 32% frequency rate of pathologic lymph node involvement in patients with MCC is far higher than in patients with invasive melanoma (an approximately 5% incidence rate of positive SLNBs,[21] assuming an average tumor depth of about 0.8 mm[22]). There were significant prognostic and therapeutic implications for this cohort: (1) the risk of relapse was 3 times higher in those with a positive SLNB relative to those with a negative SLNB, (2) the clinical decision regarding adjuvant nodal therapy was highly affected by SLNB status (36% of patients with a negative SLNB received adjuvant therapy to the node bed vs 91% of patients with a positive SLNB), and (3) in individuals with a positive SLNB, adjuvant nodal treatment was associated with a relapse-free survival rate of 51% at 3 years compared with 0% for those who did not receive adjuvant nodal therapy. In patients with a negative SLNB, the benefit of adjuvant nodal therapy was not statistically significant, which suggests that the benefit for these patients may be more modest and would require a larger cohort to reach statistical significance. In contrast with SLNB, we found that primary tumor size and CT scans had relatively little prognostic or therapy-guiding value.

Similar to populations in previous studies,[5,6,23,24] our population was mostly older than 65 years, fair skinned, and had tumors presenting on sun-exposed surfaces. Eleven percent (7) of our patients had chronic immune suppression, a higher percentage than would be expected in the general population, which likely reflects the known association of MCC with human immunodeficiency virus infection and solid organ transplantation.

Radiological imaging is routinely performed as part of the workup for patients with MCC. In our cohort, however, it had a limited role in the diagnosis of regional nodal spread owing to a high false-negative rate of 80%. The positive and negative predictive values of nodal imaging were 67% and 45%, respectively, which implies that a positive finding will be false in a third of cases and that a negative finding does not rule out lymph node involvement. Note that imaging failed to detect disease in any of the 7 patients with a positive SLNB. Moreover, of the 4 patients with lymph node involvement found by imaging, disease was clinically apparent in 3 and the SLNB of the remaining patient was a technical failure. Although further studies are needed to determine the efficacy and cost-effectiveness of routine imaging in asymptomatic patients with localized disease, our study suggests that baseline imaging of patients with MCC is likely to yield a large number of false-positive findings requiring further studies and is likely to miss nodal involvement in about 80% of cases. Accordingly, CT scans may be best reserved for evaluating distant metastatic disease in the presence of lymph node involvement or other high-risk disease.

Note that in the DFCI cohort our general surgical oncologists had only a 45% success rate in isolating a lymph node in the head and neck region. An oncologic surgeon who specializes in the head and neck region may well have a higher success rate. Even such technically unsuccessful SLNBs do, however, effectively map the draining node bed, allowing adjuvant nodal radiation therapy or other treatment if desired based on the risks and benefits for a given patient.

A recent study[2] of 54 patients who underwent SLNB found a far higher rate of disease-specific survival in patients with a negative SLNB at 5 years' follow-up (97%) compared with patients with a positive SLNB (52%), which is similar to our findings. This group also found that 22% of 54 patients whose nodes were clinically negative for disease and who underwent SLNB in fact had lymph node involvement. Although earlier studies[7] found differences in relapse-free and overall survival rates between those with primary tumors smaller than 2 cm (stage IA) and those with tumors 2 cm or larger (stage IB), more recent and larger studies[2,25,26] have not observed this association. Among those in our cohort, there was no effect of primary tumor size on the relapse-free survival rate, which suggests that this parameter (and thus classification as stage 1A vs stage 1B) is at best a weak predictor of outcome.

A limitation of this study is that we report relapse-free survival rather than disease-specific survival because we do not have sufficient follow-up data at this time. Our median follow-up period of about 12 to 15 months is reasonable, however, because about 60% of MCC recurrences happened by 1 year after diagnosis and about 90% by 2 years.[2] However, it is likely that some of the patients we report as having relapsed may ultimately be cured after further treatment because locoregional relapses are far more curable than distant disease. Therefore, the importance of SLNB-guided therapeutic decisions on overall survival rates remains to be characterized.

Optimal treatment of patients with MCC is a controversial issue. Surgery, radiation therapy, and chemotherapy have been used.[2,27,28] It is generally agreed that the primary tumor should be excised with clear margins, but lymph node dissection, radiation therapy, and the role of adjuvant chemotherapy are not agreed on. Merkel cell carcinoma is radiation sensitive, and some authors use radiation therapy on both the area of the primary tumor and the draining node bed.[25,26,28] According to increasingly good data, the addition of adjuvant chemotherapy is not beneficial[29] and has been associated with a worse prognosis among patients with nodal involvement (stage II).[2] In contrast, palliative chemotherapy is routinely used to treat advanced disease with a high response rate but short duration of response.[30] Our study found that patients with a positive SLNB were given nodal adjuvant treatment far more often than did those with a

negative SLNB and that this is likely appropriate. That is, only a minimal benefit was found in terms of recurrence rates of MCC if nodal adjuvant therapy was given to patients with a negative SLNB. In contrast, among patients with a positive SLNB, the relapse rate was profoundly affected by whether adjuvant therapy was administered: a 100% relapse rate by 1 year after diagnosis among the 3 patients who did not receive further therapy vs a 21% relapse rate in patients with MCC at 2 years if they received nodal therapy. For these reasons we recommend SLNB be performed routinely on patients presenting with MCC that does not clinically involve lymph nodes. Cooperative multicenter prospective studies to evaluate the effect of adjuvant treatments in patients with MCC are warranted.

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