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# Sentinel lymph node biopsy in Merkel cell carcinoma: The Mayo Clinic experience of 150 patients

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ABSTRACT

*Background:* Merkel cell carcinoma (MCC) is a rare cutaneous malignancy of neuroendocrine origin with a high propensity for lymph node metastasis. Sentinel lymph node (SLN) status is important for accurate staging; however, the optimal treatment following SLN biopsy, regardless of nodal status, remains unclear.

*Methods:* 150 patients with MCC who underwent SLN biopsy from 1995 to 2011 at 3 Mayo Clinic sites were reviewed.

*Results:* Of 150 patients with MCC who underwent SLN biopsy, 39 (26%) were positive and 111 (74%) were negative. There was no significant difference between the sex, age, tumor location, or size of primary in the positive and negative SLN groups. While there was no difference in the cumulative incidence of any regional recurrence between SLN groups, the rate of in-transit recurrences was significantly higher in patients with a positive SLN ($p = 0.022$). The disease-specific survival for MCC was 97.0%, 82.4%, and 82.4% at 1, 3, and 5 years with a positive SLN and 99.0%, 94.9%, and 86.8% with a negative SLN ($p = 0.31$). Among those alive at last follow up, the median follow up was 3.8 years (IQR, 2.1–8.4) and 2.9 years (IQR, 1.8–6.1) for positive and negative SLN cohorts respectively.

*Conclusions:* Occult nodal metastasis is common in MCC(26%). No tumor or patient characteristics were identified to predict SLN positivity. Patients with a positive SLN have a higher risk of in-transit recurrence and may benefit from adjuvant radiation with inclusion of the in-transit field in amenable cases. When patients with a positive SLN receive additional treatment to the at-risk nodal basin, both OS and DSS are similar to patients with a negative SLN.



## 1. Introduction

Merkel cell carcinoma (MCC) is a rare cutaneous malignancy of neuroendocrine origin. It most commonly affects males (56.3–70.0%) of advanced age with the majority of patients being over the age of 70 [1–4]. It occurs predominantly in the head and neck and other sun-exposed areas of skin, as ultraviolet (UV) light exposure is thought to be a significant risk factor with the incidence being 11 times higher in white patients compared to black patients [4]. Immunosuppression also seems to be a significant risk factor with higher incidence rates being found in patients with HIV infections and certain lymphoproliferative disorders [5,6].

Similar to other cutaneous malignancies, MCC is increasing in incidence. One study using the (SEER) database found a 360% increase in incidence from 1986 to 2011 in the United States, likely related to multiple factors including a higher life-expectancy (in a disease of the elderly), increase in diagnosis, continued UV exposure, and an aging population of immunosuppressed patients [7].

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Since it's initial description in 1972 [8], much has been learned about the clinical behavior of this aggressive malignancy; however, the optimal treatment regimen is still controversial, particularly with regard to the draining nodal basin of the primary lesion.

MCC has a high propensity for nodal metastasis with 27–31% presenting with clinical nodal disease [3,9]. In addition to this, another 16–38% [10–15] have occult nodal metastasis determined by sentinel lymph node (SLN) biopsy. Because of this high incidence of occult nodal disease, SLN biopsy has become the standard of care in patients without clinically apparent lymphadenopathy and is recommended by the National Comprehensive Care Network (NCCN) [6]. While factors such as tumor size [10,14,16], tumor depth [10,16], mitotic index [16], and the presence of lymphovascular invasion (LVI) [14] have been associated with positive sentinel node status, none of these factors are able to predict a low-risk subgroup in which nodal metastasis rates would be low enough to avoid SLN biopsy. Therefore, regional lymph node evaluation via SLN biopsy is recommended in all patients with MCC.

While most authors would agree that sentinel node status is important for accurate staging and treatment planning, its overall affect on prognosis is unclear. A few studies [17–20] have shown significantly higher recurrence rates in patients with a positive SLN; however, a large study [14] of 153 patients who underwent SLN biopsy found no difference in recurrence rates between positive and negative SLN groups. The data regarding the effect of SLN status on overall and disease-specific survival is also heterogeneous [13–15,20]. Because of this conflicting data, the optimal treatment following SLN biopsy, regardless of nodal status, remains unclear. Therefore, our aim was to examine our large cohort of patients with MCC and compare treatment regimens, recurrence rates, and survival outcomes between patients with positive and negative sentinel lymph nodes in hopes of outlining an effective treatment algorithm.

## 2. Methods

A multi-institutional retrospective review was performed of all patients with MCC that underwent SLN biopsy between May 1995 and December 2011 at one of the three main Mayo Clinic campuses (Rochester, MN; Scottsdale, AZ; Jacksonville, FL). Institutional Review Board approval was attained prior to beginning the study. Multiple data points were collected on each patient including patient demographics, clinical and pathologic tumor characteristics, primary and adjuvant treatments, SLN status, and follow-up status. Dates and locations for recurrences were recorded, and each recurrence was defined as local, regional, or distant. Regional recurrences were further stratified as in-transit and nodal recurrences.

All patients underwent SLN biopsy at the time of their definitive wide local excision. Technetium-99m (99mTc)-radiolabeled sulfur colloid injection was followed by lymphoscintigraphy for visualization of the sentinel node. In some cases where the primary lesion was directly superficial to the draining nodal basin, Single-Photon Emission Computed Tomography (SPECT) was also used to better visualize the SLN. Methylene-blue was utilized for intraoperative visualization at the performing surgeon's discretion. Wide local excision of the primary tumor with 1–2 cm margins was performed on all patients except some head and neck cases in which smaller margins were necessary to prevent significant cosmetic or functional deformity.

Statistical analysis was performed by a biostatistician using SAS statistical software (SAS Institute, Cary, NC). Comparisons between positive and negative SLN groups were evaluated using the two-sample *t*-test for age, the Wilcoxon rank sum test for tumor size, and the chi-square test for remaining variables. The cumulative incidence (CI) function was used to estimate the cumulative proportion of patients by time who had a recurrence (separately for regional and distant) after accounting for the competing risk of death. The CI estimates were compared between subgroups using the methods developed by Gray [21]. Overall and disease-specific survival was estimated using the Kaplan-Meier method and comparisons between subgroups were evaluated using the logrank test. All calculated p-values were two-sided and p-values less than 0.05 were considered statistically significant.

## 3. Results

A total of 150 patients met criteria for the study. Thirty-nine (26.0%) patients had a positive SLN, and the remaining 111 (74.0%)were negative. The majority of patients in the cohort were males (70.0%) over the age of 70 (mean 71.4). The most common primary location was the extremities (54.0%) followed by the head and neck (36.0%). The median tumor size, measured by maximum dimension, was 1.5 cm (interquartile range (IQR), 1.0–2.3). Table 1 summarizes and compares patient and tumor characteristics between positive and negative SLN groups. There was no statistically significant difference between the two groups in any of the examined characteristics.

### 3.1. Primary and adjuvant treatment

All patients underwent wide local excision or Mohs surgery and had pathologically confirmed negative margins. Following SLN biopsy, 31 (79.5%) of the 39 patients with a positive SLN underwent completion lymphadenectomy. Twenty-four (61.5%) had only 1 positive lymph node, 11 (28.2%) had 2 positive nodes, and the

**Table 1**
Comparison of patient and tumor characteristics between positive and negative SLN groups.

| Characteristic | Negative SLNB (N = 111) | Positive SLNB (N = 39) | Total (N = 150) | p value[a] |
|---|---|---|---|---|
| Male gender, n (%) | 77 (69.4%) | 28 (71.8%) | 105 (70.0%) | 0.78 |
| Age at surgery (years), mean (SD) | 71.6 (10.8) | 70.9 (11.0) | 71.4 (10.9) | 0.71 |
| History of immunosuppression, n (%) | 11 (9.9%) | 4 (10.3%) | 15 (10.0%) | 0.95 |
| Location, n (%) | | | | 0.13 |
| Head or neck | 45 (40.5%) | 9 (23.1%) | 54 (36.0%) | |
| Extremities | 55 (49.5%) | 26 (66.7%) | 81 (54.0%) | |
| Trunk or buttock | 11 (9.9%) | 4 (10.3%) | 15 (10.0%) | |
| Tumor size (cm), median (IQR) | 1.5 (0.8, 2.2) | 1.8 (1.2, 3.0) | 1.5 (1.0, 2.3) | 0.12 |

[a] Comparisons between groups were evaluated using the two-sample *t*-test for age, the Wilcoxon rank sum test for tumor size and the chi-square test for all other variables.