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Optimal Resection Margin for Head and Neck Cutaneous Melanoma

Albert Y. Han, MD, PhD; Suraj Dhanjani; Kelly Pettijohn, MD; Pratik B. Patel, MD; Maie A. St. John, MD, PhD

**Objectives/Hypothesis:** The objective of this study was to examine the difference between a narrow (between 1 and 2 cm) and a wide (>2 cm) margin in the surgical resection of head and neck cutaneous melanoma.

**Study Design:** Population-based cohort analysis.

**Methods:** The Surveillance, Epidemiology, and End Results database was employed to identify patients who had cutaneous melanoma of the head and neck from 2004 to 2014. Outcome measures were overall survival (OS) and disease-specific survival (DSS).

**Results:** Among the total of 3,583 cases of cutaneous melanoma of the head and neck with known resection margins, 2,641 individuals had narrow resection margins, and 942 patients had wide margins. Most of the tumors presented in the skin of the scalp and neck, followed by the face, external ear, and other areas. The 5-year and 10-year Kaplan-Meier OS probabilities for narrow and wide margins were 65% and 66%, respectively, compared with 49% and 48%, respectively. The DSS probabilities exhibited similar trends between the two groups at these time points. In the Cox regression model, the patients who received narrow margins had similar OS (95% confidence interval [CI]: 0.918-1.217) and DSS (95% CI: 0.856-1.352) compared with the wide resection margin group, even when controlled for age, sex, T stage, and histology.

**Conclusions:** The survival of patients with cutaneous melanoma of the head and neck depends on age, depth of tumor invasion, and histology. Within the head and neck, a wider resection margin of >2 cm does not confer any additional survival benefit compared with a narrower margin. Future studies should examine whether wider surgical margins would confer survival benefit in local or recurrent melanoma.

**Key Words:** Melanoma, skin cancer, head and neck surgery, otolaryngology.

**Level of Evidence:** 4

INTRODUCTION
Melanoma is the fifth leading cancer diagnosis in men, and the seventh in women. The annual incidence exceeds 75,000 cases, and recent observations have determined that the incidence rate is rising rapidly. This neoplasm is most commonly found in white males, especially those in higher socioeconomic groups. Risk factors for melanoma include light skin, immunosuppression, and chronic sun exposure. The depth of invasion is also the most important prognosticator. The 10-year survival of lesions <0.5 mm thick is as high as 96%, but for those with tumors more than 4.0 mm thick, the rate decreases to 54%. For this reason, screening for and the early detection of melanoma is critical.

The location of the tumor creates a unique problem in the management of cutaneous melanoma. The first-line treatment for cutaneous melanoma is surgical management involving a wide excision. Positive pathological margins have been found to be associated with increased local recurrence and lower overall survival (OS). The importance of negative margin status was recognized early in history, and Hunter and colleagues initially proposed the wide excision of melanoma by “an inch” in the early 20th century. Although such a margin is relatively easy to achieve for most areas of the body, it is challenging to perform a wide-margin resection in the head and neck region due to the presence of structures vital to aesthetic, communicative, and sensory functions. Approximately one-third of melanoma diagnoses are found in the head and neck. Surgeons are often faced with the dilemma of balancing the need to attain negative margins with minimizing functional and cosmetic morbidity by preserving the eyelids, the eye, and the facial nerve.

Melanoma of the head and neck is distinct from that of the rest of the body in several ways. A rich lymphatic and blood supply to the face and the brain are located superficially in the neck. The resection of cutaneous lesions is frequently limited by their proximity to vital structures. Tumors of the head and neck are also often associated with a worse prognosis. Despite these differences, much of the literature regarding the management...
of melanoma has not emphasized differences by anatomical regions. Thus, a paucity of literature exists regarding the treatment of melanoma of the head and neck with regard to margins.

The objective of this study was to compare long-term survival in patients with head and neck cutaneous melanoma who had received wide local excisions with a 1- to 2-cm margins versus margins greater than 2 cm. Using the Surveillance, Epidemiology, and End Results (SEER) database, prognosticators for survival were assessed using a population-based analysis. The results of this study could be used to guide surgical planning in the resection of head and neck cutaneous melanoma.

MATERIALS AND METHODS

A population-based cohort analysis was performed using patient information in the case-listing session of the SEER 18 database (www.seer.cancer.gov), which is a widely used cancer registry that covers an estimated 27.8% of the US population. The geographic regions covered include California, Connecticut, Metropolitan Detroit, Hawaii, Iowa, New Mexico, Seattle (Puget Sound), Utah, Metropolitan Atlanta, San Jose–Monterey, Los Angeles, Alaska (Natives), rural Georgia, Kentucky, Louisiana, New Jersey, and Greater Georgia. No internal review board approval was required, because the database uses publicly available information with no personal identifiers.

Patients with cutaneous melanoma from 2004 to 2014, the widest date range available in the latest version of the SEER software with staging and treatment information, were identified using the histologic codes 8720 (malignant melanoma), 8721 (nodular melanoma), 8722 (balloon cell melanoma), 8723 (malignant melanoma, regressing), 8730 (amelanotic melanoma), 8740 (malignant melanoma in junctional nevus), 8741 (precancerous melanoma, not otherwise specified [NOS]), 8742 (lentigo melanoma), 8743 (superficial spreading melanoma), 8744 (acral lentiginous melanoma, malignant), 8745 (desmoplastic melanoma), 8761 (malignant melanoma in giant pigmented nevus), and 8770 (mixed epithelial and spindle cell melanoma). Site codes 8722, 8723, 8730, 8740, 8741, 8744, 8761, and 8770 were grouped as “other” category in subsequent analyses.

The primary site codes were C44.0 (skin of lip, NOS), C44.1 (eyelid), C44.2 (external ear), C44.3 (skin other/unspecified parts of face), and C44.4 (skin of scalp and neck). The following primary data were extracted from the database for analysis: age at diagnosis; sex; race; primary site; tumor T stage, N stage, and M stage; site-specific surgery of primary site; scope of regional lymph node surgery; number of regional nodes positive; and OS and disease-specific survival (DSS) in months. The T stage was retroactively determined where possible using the extent of disease and collaborative stage staging codes for tumor sizes and locations, following the classification protocol developed by the American Joint Committee on Cancer.10 Stage IV cases were excluded, as these patients would typically not receive surgery with curative intent. Tumors were staged as T1 for melanoma ≤1.0 mm in thickness with or without ulceration. T2 was for melanoma 1.01 to 2 mm in thickness with or without ulceration. T3 was for melanoma 2.01 to 4.0 mm in thickness with or without ulceration. T4 was for melanoma >4.0 mm in thickness with or without ulceration.10 Only cases with surgical codes that reported the sizes of margins taken (wide local excision with 1–2 cm margins, code 46; wide local excision >2 cm, code 47) were included in the study. To evaluate the effect of margins on the survival of patients with sentinel lymph node (SLN) biopsies, we isolated patients with only SLN biopsies and no other neck dissections or extra lymph nodes removed (RX Summ–Scope Reg LN Sur [2003+], code 2 Sentinel lymph node biopsy [only]).

The primary outcome was defined as the time in months from diagnosis to death from any cause for OS and as the time from diagnosis to death specific to the cancer-related diagnosis for DSS. Descriptive statistics were calculated for all variables. The OS and DSS curves were calculated using the Kaplan-Meier method, and the absolute difference in the mean survival and 95% confidence interval (CI) around the difference were formally tested using the log-rank test. Covariates were assessed for predictive performance with univariate and multivariate Cox proportional hazards regression models concerning OS and DSS. The comparisons between groups were deemed statistically significant at the $P < .05$ threshold. Covariates were chosen for multivariate analysis on the basis of the factors identified as significant or with log-rank $P < .25$ on univariate analysis. This method was selected to minimize the total number of covariates, thus improving the generalizability of the findings and minimizing instability within the model.11 As a default, age and sex were included in all of the multivariate models. Using this methodology, there were no fewer than 10 events per covariate for each model. The statistical analyses were performed with SPSS version 23 (IBM Corp., Armonk, NY).

RESULTS

The SEER database search retrieved 3,583 patients with cutaneous melanoma of the head and neck region with margin information from 2004 to 2014 (Table I). These patients were categorized into two groups based on the resection margin information.

The first group of 2,641 patients had resection margins between 1 and 2 cm (defined as the narrow-margin group). This group had a mean age of diagnosis of 65.4 years (minimum 18 years, maximum 103 years). Males comprised 76.0% (n = 2,008), and whites comprised 98.8% (n = 2,609) of the patients. The most common primary site was the scalp and neck (51.5%, n = 1,350), followed by the face (36.0%, n = 950), external ear (11.9%, n = 315), eyelid (0.5%, n = 13), and cutaneous lip (0.5%, n = 13). Histologic diagnosis of malignant melanoma was the most common by 38.7% (1021). Histologic diagnoses included superficial spreading melanoma (25.1%, n = 662), nodular melanoma (16.0%, n = 423), lentigo melanoma (12.4%, n = 327), desmoplastic melanoma (6.0%, n = 158), and others (1.9%, n = 50) (Table I).

In the narrow-margin group, about 55.6% (n = 1,469) patients had stage I disease, whereas 32.4% (n = 855) had stage II disease, and 12.0% (n = 317) had stage III disease. No patients had Stage IV disease given patients with metastatic disease were excluded, as they do not typically undergo surgical resection for achieving a cure. Regarding T staging, 38.2% (n = 1,009) had T1, 26.1% (n = 689) had T2, 20.8% (n = 55) had T3, and 14.9% (n = 393) had T4 stage tumor. Most patients (88.0%, n = 2,324) did not have lymph node involvement (i.e., N0 stage). Only 5.5% (n = 144) had N1 disease, 4.5% (n = 118) had N2, and 2.1% (n = 55) had N3 (Table I). Of the narrow-margin group, 38.6% (n = 1,021) of patients underwent SLN biopsies in addition to resection. Of these patients, 4.8% (n = 49) had positive SLNs and 95.2% (n = 972) had negative SLNs (Table II).
The second group, comprised of patients with resection margin of >2 cm; these individuals similar demographic information (the wide-margin group). The mean age of diagnosis was 65.2 years (minimum 18 years, maximum 97 years). Most of the patients in this group were also male (76.8%, n = 723) and white (98.4%, n = 927). More than half of the patients in this group presented with lesions on the scalp and neck (52.0%, n = 490). The remaining patients had lesions on the face (35.7%, n = 336), external ear (10.4%, n = 98), eyelid (1.5%, n = 14), and external lip (0.4%, n = 4). Similar to the narrow-margin group, patients most frequently had malignant melanoma (42.1%, n = 397), followed by superficial spreading melanoma (23.6%, n = 222), nodular melanoma (14.6%, n = 138), lentigo melanoma (13.0%, n = 122), desmoplastic melanoma (5.1%, n = 48), and others (1.6%, n = 15). These other types are the same as the types for the narrow-margin group (Table I).

Stage I disease (59.6%, n = 561) was most common for the wide-margin patients as well. Of the remaining patients, 28.5% (n = 268) had stage II and 12.0% (n = 113) had stage III cancer. Again, there were no stage IV cases, as metastatic disease was excluded from the study. When analyzed by T stage, 44.3% (n = 417) had T1, 21.0% (n = 198) had T2, 17.3% (n = 163) had T3, and 17.4% (n = 164) had T4. In terms of N stage, the majority of patients (88.0%, n = 829) had N0 disease, 5.8% (n = 55) had N1; 3.3% (n = 31) had N2, and 2.9% (n = 27) had N3 disease (Table I). Of the wide-margin patients, 29.8% (n = 281) underwent SLN biopsies in addition to resection. Of these patients, 5.0% (n = 14) had positive SLNs and 95.0% (n = 267) had negative SLNs (Table II).

The Kaplan-Meier survival probabilities were similar between the narrow- and wide-margin resection groups for all stages (Table III). Univariate analysis revealed that age (P < .001), histology (P < .001), OS (P < .001), T stage (P < .001), and N stage (P < .001) were significant determinants of OS and DSS. Sex was a determinant of OS (P < .001), but not DSS (P = .500). The primary site was a significant prognosticator for DSS (P < .001), but not OS (P = .096) (Table IV). Of note, the eyelid was the only primary site that had significantly more narrow-margin cases, perhaps due to the potential comorbidity that might result from a wide resection.

The assessment of survival by T stage demonstrated the expected decrease in survival with increasing T stage (P < .001) (Fig. 1). To clarify whether margin status had any influence on survival, univariate analysis on surgical margin was repeated for each T stage. All T stages demonstrated no significant difference in OS between patients who had 1- to 2-cm margins taken intraoperatively and those who had >2-cm margins taken. This was specifically evaluated in less than 1 mm depth of invasion (T1, P = .0705).
and T stage (HR: 1.888, 95% CI: 1.716-2.076) were significant covariates. The resection margin was not found to be a significant variable for determining OS (HR: 1.057, 95% CI: 0.918-1.217) and DSS (HR: 1.076, 95% CI: 0.856-1.352) (Table V). Because the primary site was determined to be a significant prognosticator, we compared OS between the narrow-margin and wide-margin groups by primary site. From this analysis we found that OS was similar between the narrow-margin and wide-margin groups when stratified by primary site. This was specifically evaluated in the cutaneous lip (P = .752), eyelid (P = .585), external ear (P = .268), scalp and neck (P = .999), and face (P = .269) (Fig. 4). Furthermore, DSS followed a similar trend for the eyelid (P = .163), external ear (P = .815), scalp and neck (P = .962), and face (P = .305) (Fig. 5). The number of deaths for the cutaneous lip was too small to calculate a valid P value for DSS.

**DISCUSSION**

Similar to previous studies, advanced stage and older age were found to be a determinant of survival in cutaneous melanoma. Sex was a significant covariate for OS but not DSS, perhaps due to comorbidities associated with male patients. The relationship between the surgical margin and overall patient survival is critical; as much as one quarter of melanoma mortality is attributed to suboptimal excision margins. However, the exact surgical margin necessary to achieve a cancer-free state has been the subject of debate. There is surprisingly scarce literature focusing on surgical margins for cutaneous melanoma of the head and neck.

The salient finding of the present study was to demonstrate that there was no significant difference in survival for patients who had 1.0- to 2.0-cm resection margins as compared with those who had a >2.0-cm margins for all T stages of head and neck cutaneous melanoma (Fig. 1). The 2014 National Comprehensive Cancer Network (NCCN) guidelines on surgical resection margins for malignant melanoma are based on the thickness of the lesions. For melanoma in situ (equivalent to Clark level I), margins of 0.5 to 1.0 cm are generally considered to be adequate. For lesions <1.0 mm in thickness (T1 lesions), a surgical margin of 1.0 cm is recommended. However, for lesions that have thicker than 1.0mm, no surgical consensus exists. The NCCN
recommends a 2.0-cm margin for tumors with thickness >2.0 mm. In the currently available guidelines, the maximum recommended resection margin is 3.0 cm.

For surgeons to have confidence about implementing narrower margins, our findings must be generalizable to a variety of primary sites in the head and neck. Our study demonstrates no survival benefit for wider margins in all primary sites of head and neck cutaneous melanoma in the SEER database. More importantly, this study lends evidence with large statistical power to what other smaller-scale studies have already found with regard to narrow margins in specific head and neck primary sites. This study also refutes older, smaller studies that advocated for the use of up to 3-cm margins in some primary sites, such as the scalp.

SLN status has been shown to be a significant prognosticator for head and neck cutaneous melanoma. Our study found that both wide- and narrow-margin groups had lower survival for positive-SLN patients compared with negative-SLN patients. In both positive- and negative-SLN patients, there was no difference in survival between the narrow- and wide-margin groups. Therefore, the use of wider margins does not confer any survival benefit in patients with positive SLNs compared with patients with negative SLNs. Although our study found no significant difference in OS between patients of positive and negative SLNs with narrow margins, this counterintuitive finding could be due to the small sample size we

Fig. 1. Overall survival (A) and disease-specific survival (B) stratified by T stage of head and neck cutaneous melanoma.

Fig. 2. Disease-specific survival stratified by surgical margins for each T stage (A-D; T1-4) of head and neck cutaneous melanoma.
had for positive-SLN biopsies. Even with this finding, however, our study does not support the use of wider margins.

Decades of clinical research involving melanoma patients have led to the current guidelines for melanoma resection margins. An early prospective randomized trial by the World Health Organization Melanoma Collaborating Centers found no difference in survival by the size of the margin.22 Subsequent prospective randomized control trials revealed that a 1.0-cm margin is adequate for primary melanoma <1.0 mm.14 For between 0.8- and 2.0-mm thickness, the 2-cm-margin cohort had a similar recurrence rate and survival compared with the 5-cm-margin cohort.23 Similar results were found for melanoma with <2.1-mm thickness by the French Melanoma Group.24 For high-risk malignant melanoma (defined as >2.0 mm in thickness), a 1.0-cm margin of excision had a higher combined recurrence rate (local, regional, and nodal recurrence) compared with 3.0-cm margin, but OS was similar between the two groups.25 Combining all of the results, the meta-analysis of five randomized prospective trials failed to show differences in overall survival as well as locoregional and local recurrence.26 Furthermore, a Cochrane review revisited more recent randomized control trials comparing wide (3–5 cm) to narrow margins (1–2 cm), and it did not find any significant difference in survival as well.27 Of note, only one of the classic clinical trials focused on primary melanoma of the head and neck region.28 Similar to our study, this report noted that the use of narrower margins was not associated with poorer survival.29

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**TABLE V.**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>OS (Log-Rank P)</th>
<th>DSS (Log-Rank P)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age group</td>
<td>1.049 &lt;0.001</td>
<td>1.026 &lt;0.001</td>
</tr>
<tr>
<td>Sex</td>
<td>0.838 0.015</td>
<td>0.856 0.221</td>
</tr>
<tr>
<td>Primary site</td>
<td>1.098 0.037</td>
<td>1.392 &lt;0.001</td>
</tr>
<tr>
<td>Histology</td>
<td>0.997 0.307</td>
<td>0.995 .269</td>
</tr>
<tr>
<td>T</td>
<td>1.422 &lt;0.001</td>
<td>1.884 &lt;0.001</td>
</tr>
<tr>
<td>Margin (1–2 cm vs. &gt;2 cm)</td>
<td>1.080 0.286</td>
<td>1.083 0.493</td>
</tr>
</tbody>
</table>

**DSS = disease-specific survival; HR = hazard ratio; OS = overall survival.**

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**Fig. 3.** Disease-specific survival stratified by surgical margins for each T stage (A-D, T1-4) of head and neck cutaneous melanoma
In their retrospective analysis of 37 head and neck melanoma patients who received reduced margins (0.5 cm for ≤1.0-mm thickness, 0.5–1.0 cm for 1- to 2-mm thickness, 1.0 cm for >2.0-mm thickness), this group found a similar rate of local recurrence-free survival between patients treated with reduced versus wide margins. Given that the head and neck is unique from other sites of the body with regard to the importance of aesthetics, proximity to critical structures, and prognosis profiles often distinct from tumors of other sites of the body, there is a need for separate guidelines for melanoma of the head and neck region.

Looking to the future, innovations in microsurgery, such as Mohs micrographic surgery, have allowed for the intraoperative examination of specimens for the determination of an adequate margin at the time of resection in cutaneous malignancies other than melanoma. In the case of melanoma, preliminary studies have begun to investigate cases of melanoma treated with Mohs. Moyer and colleagues found that the mean margin required for histologic clearance was 9.3 mm for melanoma in situ and 13.7 mm for invasive melanoma. For this reason, at least a 15-mm margin has been proposed for a more complete margin. A newer, contoured marginal excision technique also provides an even tighter margin (2 mm of visually normal skin 5 mm from cancer). These innovations are exciting frontiers in the treatment of melanoma of the head and neck, but they are far from the standard of care at this time, and will require additional investigation.

A population-level study using the SEER database allows for the capturing of epidemiology with greater statistical power and minimal sampling error. Studies involving large-scale databases include some inherent limitations related to the study design, including a lack of detailed pathologic data, such as the depth of invasion and pathological margin status, comorbid conditions, the extent of surgery, and the administration of chemotherapy. Most importantly, the SEER database entry does not
distinguish primary from recurrent cases, thereby limiting our analysis of local and regional control. Furthermore, the absence of a centralized review by a head and neck pathologist raises concerns of misclassification. Nevertheless, the analysis of this database study provides an important contribution for optimal surgical planning in the resection of cutaneous melanoma. To our knowledge, this report represents the first large-scale effort to analyze differences in survival according to surgical margins from an epidemiological perspective at the population level.

**CONCLUSION**

The survival of patients with melanoma of the head and neck depends on age, depth of tumor invasion, histology, and status of locoregional metastasis. Within the head and neck, a wider resection margin greater than 2 cm does not confer any additional survival benefit compared with a narrower margin (between 1 and 2 cm). This trend held for the cutaneous lip, scalp and neck, external ear, eyelid, and face. Furthermore, the use of wider margins did not confer a survival benefit to patients with more advanced disease, such as SLN spread. This is of particular importance in the head and neck region, where the use of smaller margins allows for the preservation of aesthetics and facial/sensory function. Future studies should aim to incorporate local and regional recurrence that is not available in the SEER study for a more complete understanding of the best management for head and neck cutaneous melanoma.

**BIBLIOGRAPHY**
