EXAMINATION OF INCOMPLETELY EXCISED NON-MELANOMA SKIN Cancers

Cathy Koger, DO,* Roxanne Rajaii, MS,** Vanessa Pazdernik, MS,*** Kelby Martens,**** Jonathan L. Cleaver, DO, FAOCD,***** Lloyd J. Cleaver, DO, FAOCD******

*Dermatology Resident, 3rd year, Northeast Regional Medical Center, Kirksville, MO
**Medical Student, 4th year, A.T. Still University, Kirksville, MO
***Biostatistician, Research Support, A.T. Still University, Mesa, AZ
****Histology Technician, Cleaver Dermatology, Kirksville, MO
*****Principal Investigator, Dermatologist, Northeast Regional Medical Center/Cleaver Dermatology, Kirksville, MO
******Program Director, Dermatology Residency Program, Northeast Regional Medical Center/Cleaver Dermatology, Kirksville, MO

Abstract
Wide-local excision is standard of treatment for non-invasive or non-aggressive basal cell carcinomas (BCCs) and squamous cell carcinomas (SCCs) (collectively “non-melanoma skin cancers,” or NMSCs) that do not meet the guidelines for Mohs micrographic surgery. Criteria for excisional margins used during NMSC removal have been suggested, but no absolute guidelines exist for specific margins. Although different surgical margins have been suggested, no consensus has been reached. Tumor start size, patient age and gender, tumor type and location have been examined in analyses of incomplete excision of NMSCs. Despite consideration of these factors and use of recommended margins, our clinic still has cases of incompletely excised NMSCs. Therefore, we retrospectively reviewed our surgical databases to determine whether a correlation existed between margins used and incomplete excisions of NMSCs. We also looked at other factors including patient age and gender, location of NMSC, and tumor type (BCC or SCC) that may have contributed to incomplete excision in these cases.

Introduction
Wide-local excision (WLE) has long been recognized and accepted as a standard treatment for non-melanoma skin cancers (NMSCs), specifically those not meeting the criteria for Mohs micrographic surgery.25 In WLE, the skin cancer and a small margin of healthy tissue around it is cut out, typically using a fusiform-shaped ellipse. The wound edges are closed, and the tissue is sent for processing and margin evaluation by a pathologist.17,25 Surgical failure, or incomplete excision, is often defined by pathologists as residual tumor within 1 mm of the lateral or deep margin of the excised specimen.2 Although clear surgical margins have not been shown to completely eliminate tumor recurrence, most studies advocate re-treatment of incompletely excised NMSCs, especially those that are defined as high-risk (deep-margin-involvement tumors, recurrent tumors, aggressive histological subtype tumors, or tumors in critical anatomic sites).3,6,8,15,16,24 This re-treatment can be very costly, time-consuming, and stressful for patients. Thus, eliminating the need for re-treatment through complete excision of NMSCs is important.

Since the 1970s, numerous studies have looked at optimal surgical margins for successful NMSC excision.2,4,6,9,15,16,19,20,26,27 Unlike in melanoma, where guidelines for excisional margins exist based on Breslow depth of the original tumor, NMSCs do not have set guidelines for margins, merely recommendations.1,3 The recommendations for NMSC surgical margins have been largely debated in numerous studies and range from 2 mm to 10 mm for basal cell carcinoma (BCC) excision and 4 mm to 15 mm for squamous cell carcinoma (SCC) excision, depending on tumor type, risk, size, location, and a number of other factors.2,4,6,9,15,16,19,20,26,27 Despite taking into account these recommendations for NMSC surgeries, our clinic has still had instances of incompletely excised NMSC tumors, which have led to additional procedures for the patients in order to completely eradicate their cancer.

Therefore, we performed a retrospective review of our surgical databases to determine whether the margins used during our NMSC surgeries were directly correlated to incomplete excision of NMSC tumors. We also looked at other variables that previous studies had cited as contributors to incomplete excisions, namely patient age, patient gender, tumor location, and tumor type (SCC or BCC).2,5,9,15,19,24 Our purpose was to identify any factors contributing to incomplete NMSC excision so that we could reduce the burden to patients of having multiple procedures performed to eliminate skin cancers.

Methods
We extracted surgical data for non-melanoma skin cancers over a four-year period, from February 2010 to October 2013. This surgical data was archived within our SOAPware database (2010-2011) and our EMA Dermatology database (2012-2013). We initially searched the pathology records for patients who had WLEs of NMSCs to find all incompletely excised tumors. Patients with incompletely excised NMSCs were considered positive-margin patients. Information regarding each patient’s age, gender, location of tumor (neck, trunk, upper extremity, lower extremity), tumor type (BCC or SCC), and margins used for excisions was also recorded. We noted, but did not include in our analyses, the date of excision. All patients within our study
were Caucasian with Fitzpatrick skin type II. As this is a case control study, we used all non-positive margin patients between February 2010 and October 2013 as controls for our study. Because our study was specifically related to BCC and SCC, exclusion criteria for both controls and positive-margin patients included patients who had melanoma excisions and dysplastic nevi excisions. One cellular blue nevus patient was also excluded. The current study was approved by the local institutional review board.

A random-intercepts multivariable logistic-regression model was used to test for potential risk factors for positive margins after return from surgery. The patient was treated as a random effect to allow for correlation of surgery results within an individual patient. The potential risk factors were age, gender, location of tumor (neck, trunk, upper extremity, lower extremity), tumor type (BCC or SCC), and size of margins used for excisions. Age was categorized into two groups determined by the median age. Size of margins was broadened into two categories: greater than or equal to 3 mm and less than or equal to 3 mm. Tukey-Kramer adjustments were used in pairwise comparisons of location types. Significance was set at .05. Analyses were conducted using SAS 9.3 (SAS Institute Inc, Cary, NC).

Results
Surgical data on 473 surgeries from 374 patients was collected. Of the 473 surgeries, 213 surgeries were for female patients. The average age of patients was 71 years (standard deviation, 13.6 years). Demographic information is presented in Table 1. Table 1. Demographics

<table>
<thead>
<tr>
<th>Variable</th>
<th>Summary*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>71 (13.6)</td>
</tr>
<tr>
<td>Sex, Female</td>
<td>213 (45%)</td>
</tr>
<tr>
<td>Margin (mm)</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>2 (.4%)</td>
</tr>
<tr>
<td>2</td>
<td>52 (11%)</td>
</tr>
<tr>
<td>3</td>
<td>285 (60%)</td>
</tr>
<tr>
<td>4</td>
<td>115 (24%)</td>
</tr>
<tr>
<td>5</td>
<td>8 (1.7%)</td>
</tr>
<tr>
<td>≥6</td>
<td>11 (2.3%)</td>
</tr>
</tbody>
</table>

The primary aim of the current study was to determine whether a correlation existed between surgical margins used and incompletely excised NMSCs. We also wanted to determine whether age, gender, location of tumor, or tumor type contributed to incompletely excised NMSCs, because previous studies of positive-margin NMSC excisions have also evaluated these factors.2,5,13,15,22-24 Our intention was to use any positive correlations found in the current study to appropriately adjust our WLEs and decrease incomplete excision rate for NMSCs.

Discussion
NMSC is the most common cancer worldwide, with BCCs comprising roughly 80% of all NMSCs.1 Various treatment options exist for NMSC; however, WLE and Mohs micrographic surgery have the highest potential cure rate and are the most widely accepted therapeutic options.4,5,16,19,21,26,28 WLE for NMSCs is commonly used when tumors do not meet the criteria for Mohs.21 Although the method for excising a tumor is well-defined, recommendations of surgical margins for NMSC are often debated and frequently revised.2,4,6,9,15,16,19,20,27-29 The multivariable logistic-regression model did not show a significant independent effect of potential risk factors (age, gender, tumor location, tumor type, or size of margins) on the probability of returning from surgery with positive margins (all P ≥ .05). Table 2 provides Tukey-Kramer adjusted p-values for pairwise comparisons of locations of tumors. There were no significant differences in rates of positive margins between tumor types (4.33% and 2.21%), surgical margins (3.22% and 2.98%), age ranges (3.09% and 3.11%) or genders (3.13% and 3.06%). After adjusting for multiple surgeries from an individual, the overall incomplete excision rate for NMSCs was 5.1% in our study (95% confidence interval [3.4%, 7.6%]).

Table 2. Patient distribution by number and type of surgery

<table>
<thead>
<tr>
<th># of Surgeries for Positive Margin Cases</th>
<th># of Surgeries for Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>1</td>
<td>16</td>
</tr>
<tr>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Total</td>
<td>17</td>
</tr>
</tbody>
</table>

The multivariable logistic-regression model did not show a significant independent effect of potential risk factors (age, gender, tumor location, tumor type, or size of margins) on the probability of returning from surgery with positive margins (all P ≥ .05) (Table 2). The test for location of tumor trended toward significance (P = .09), with the upper extremity having the highest rate of positive margins at 7.5%, the lower extremity at 5.8%, the neck at 1.7%, and the trunk at 0.9%. Table 3 provides Tukey-Kramer adjusted p-values for pairwise comparisons of locations of tumors. There were no significant differences in rates of positive margins between tumor types (4.33% and 2.21%), surgical margins (3.22% and 2.98%), age ranges (3.09% and 3.11%) or genders (3.13% and 3.06%). After adjusting for multiple surgeries from an individual, the overall incomplete excision rate for NMSCs was 5.1% in our study (95% confidence interval [3.4%, 7.6%]).

Discussion
NMSC is the most common cancer worldwide, with BCCs comprising roughly 80% of all NMSCs.1 Various treatment options exist for NMSC; however, WLE and Mohs micrographic surgery have the highest potential cure rate and are the most widely accepted therapeutic options.4,5,16,19,21,26,28 WLE for NMSCs is commonly used when tumors do not meet the criteria for Mohs.21 Although the method for excising a tumor is well-defined, recommendations of surgical margins for NMSC are often debated and frequently revised.2,4,6,9,15,16,19,20,27-29 The primary aim of the current study was to determine whether a correlation existed between surgical margins used and incompletely excised NMSCs. We also wanted to determine whether age, gender, location of tumor, or tumor type contributed to incompletely excised NMSCs, because previous studies of positive-margin NMSC excisions have also evaluated these factors.2,5,13,15,22-24 Our intention was to use any positive correlations found in the current study to appropriately adjust our WLEs and decrease incomplete excision rates.

Table 3. Multivariable logistic-regression analyses

<table>
<thead>
<tr>
<th>Covariable</th>
<th>Rate</th>
<th>Odds Ratio</th>
<th>P Values (95% CI)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tumor Type</td>
<td>BCC vs. SCC</td>
<td>4.33% vs. 2.21%</td>
<td>2.01</td>
</tr>
<tr>
<td>Surgical Margin</td>
<td>≤3mm vs. &gt;3mm</td>
<td>3.22% vs. 2.98%</td>
<td>1.08</td>
</tr>
<tr>
<td>Location</td>
<td>Neck</td>
<td>1.70%</td>
<td>0.21</td>
</tr>
<tr>
<td></td>
<td>Trunk</td>
<td>1.20%</td>
<td>0.15</td>
</tr>
<tr>
<td></td>
<td>Lower Extremity</td>
<td>5.81%</td>
<td>0.76</td>
</tr>
<tr>
<td></td>
<td>Upper Extremity</td>
<td>7.48%</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>≤73 vs. &gt;73</td>
<td>3.09% vs. 3.11%</td>
<td>1.01</td>
</tr>
<tr>
<td>Gender</td>
<td>Female vs. Male</td>
<td>3.13% vs. 3.06%</td>
<td>1.03</td>
</tr>
</tbody>
</table>

*Confidence interval
**The category reference is listed last. For example, the odds for positive margins on neck tumors are 0.21 times the odds on upper extremity tumors.
Surgical margins used in our NMSC excisions followed literature recommendations, but given the variability of these recommendations, we hypothesized that surgical margins would be our main contributor to incompletely excised NMSCs. However, surgical margins were not a statistically significant contributor to incompletely excised NMSCs in our study. Similarly, age, gender, and tumor type were not statistically significant contributors. Location of tumor had the closest positive correlation to incompletely excised NMSCs, with the upper extremity having the highest rate of positive margins, but this correlation was not statistically significant.

WLE with adequate surgical margins is one of the most commonly used treatments for all types of skin cancer, including NMSCs that do not meet Mohs criteria as well as melanomas of all subtypes.1,4,6,9,15,19,21,28 Over the last few decades, considerable research has been performed that has established appropriate and effective margin sizes for melanoma excisions based on the depth of the tumor, defined as the Breslow depth. Currently accepted guidelines for melanoma margins include the following: 5-mm margin for melanoma in situ; 1-cm margin for melanomas less than 1.0 mm Breslow depth; 1-cm to 2-cm margins for melanomas of 1.0 mm to 4.0 mm Breslow depth; and 2-cm margins for melanomas greater than 4.0 mm Breslow depth.14,3 While surgical margins for melanoma skin cancers have been well-studied and categorized, surgical margins for non-melanoma skin cancers have not. Hence there is a greater discrepancy in margins used for excision of BCCs and SCCs. While some have endeavored to propose guidelines to standardize NMSC margins, variability in the literature has highlighted discrepancies and a lack of consensus.2,4,6,9,15,19,20,26,27

A study by Thomas et al. claimed that advisable surgical margins for BCC excisions ranged from 2 mm to 10 mm, and for SCC excisions from 4 mm to 15 mm.19 Other authors have recommended a 4-mm surgical margin for primary NMSCs less than 2 cm in diameter that can be safely classified as low-risk. Low-risk NMSCs are defined as tumors that are less than 2 cm in diameter; are primary, well-defined, slow growing, and well-differentiated; occur in non-immunocompromised patients; and are without neurological symptoms and without perineural or vascular involvement.2,4,9,15,20,28

This 4-mm margin recommendation has been shown to increase the peripheral clearance rate of NMSC tumors to approximately 95%, compared with an 85% rate using a margin of 3 mm, and has thus decreased the number of incompletely excised NMSCs.6,9,16,27 In contrast, Gulleth et al. demonstrated that for low-risk BCCs, similar tumor clearance was observed using 3-mm, 4-mm, and 5-mm margins.4 For low-risk SCCs, both Motley et al. and Pua et al. agreed that a 4-mm surgical margin was adequate, but a 6-mm margin was necessary for high-risk SCCs.5,9,14

Most recently, Weinstein et al. used clinical and histologic correlations to stratify BCCs and SCCs into high- or low-risk groups.20 They suggested 4-mm margins for low-risk BCCs or SCCs and Mohs or complete peripheral/deep resection using 10-mm margins for high-risk BCCs or SCCs larger than 2 cm on the trunk or extremities.

In the current study, location of tumor contributed most to incomplete excision, specifically in the upper extremity, although the association was not significant. Other studies have also assessed location of the tumor and incomplete excision.5,15,24 Unlike our results, these studies reported the head and neck as the locations most significantly associated with incompletely excised NMSCs. However, these studies used WLE for both head and neck tumors with smaller than recommended margins, thus increasing their rates of incompletely excised NMSCs.5,15,19 Our clinic uses Mohs surgery where appropriate for head and neck tumors, and we excluded Mohs surgeries from our data analyses.15,19,21

Previous studies have reported a difference in rates of incomplete excision between BCCs and SCCs. Therefore, we investigated tumor type as a potential risk factor. Pua et al. reported an overall incomplete excision rate of 2.20% for NMSCs, a 1.54% rate for BCCs, and a 3.90% rate for SCCs.9 We had a similar incomplete excision rate of 5.1% for NMSCs but saw a slightly higher rate for BCCs vs. SCCs (4.3% vs. 2.2%). Thomas et al. reported incomplete excision rates for BCCs ranging from 4.5% to 13.7% and for SCCs ranging from 5.2% to 7.0%, slightly higher than previous studies or our current study.9,19 Most studies did find SCCs specifically to have a higher incomplete excision rate than BCCs. We found the reverse, but our difference was not statistically significant. The reported incomplete excision rates in the literature remain low, and our data concurred with this.

A possible association between incomplete excision of NMSCs and gender has not been extensively studied. Tan et al. and Bogdanov-Berezovsky et al. both reported that gender was not a statistically significant factor for incomplete excision of SCCs.15,23 Hansen et al. had similar results, but found that female patients had a 28% increased risk of an incomplete excision for SCCs.15 In contrast, Farhi et al. failed to find gender as a predictor of incomplete excisions for BCCs.24 The results of the current study supported previous findings that suggested gender was not a statistically significant factor for incomplete excision of NMSCs.

In the current study, age contributed least to incomplete NMSC excision. A possible association between age and risk of incomplete excision has been previously studied. As in our study, Tan et al. found that age was related to prevalence of NMSCs, specifically SCCs, but not to the risk of incomplete excision.15 Other studies have found no statistically significant association between incomplete excision of SCCs and age.22,23 Hansen et al., however, reported a significantly higher risk of incomplete BCC excisions among patients older than 70 years compared with those younger than 50 years.21

The current study had several limitations. Chart records were primarily created for purposes of clinical care, rather than for study objectives, so the data was not always comprehensive. For example, we did not look at start size of NMSCs, because it was not available for all records. This factor has been shown to be important in other studies of incompletely excised NMSCs and perhaps should be taken into account in future analyses.2,4,6,9,15,17,26,29 A second consequence is the possibility of erroneous data recording for each surgery. For example, the size of margins used for NMSCs was sometimes reported in our database using units of cm and in other instances using units of mm. The patient population used in our study was obtained from one hospital, which not only limited the sample size of data available (N=25 in our case) but also limited generalizability to other hospitals or larger patient populations. The patient data was recorded over a four-year time period for accuracy, which also limited our sample size. The small sample size inevitably decreased the power of the study and contributed to the lack of statistical significance.

Although the study has the aforementioned limitations, the fact that we used a consecutive four-year time period for retrieving surgical data did reduce selection bias. Also, the retrospective analysis prevented physicians’ knowledge of the study, eliminating the potential for influencing performance. The retrospective analysis done in the current study has helped us elucidate specific variables and data-collection methods for future prospective studies, thus allowing for more accurate data reporting.

**Conclusion**

The use of adequate surgical margins for complete excision of NMSCs continues to be controversial in the published literature.4,9,15,19,20,26,27 The most accepted and consistent recommendations suggest 4-mm margins in low-risk NMSCs and 10-mm margins or Mohs micrographic surgery in high-risk NMSCs.2,4,9,15,20,28 Other factors, such as age, gender, location of tumor, and tumor type show inconsistent relationships to incompletely excised NMSCs, results that were supported by our study findings. The percentage of incompletely excised NMSCs remains low in many studies, including ours. Because recurrence rates of NMSCs also vary, the recommendation is to re-treat these incompletely excised areas.4,9,16 Although re-treatment of an incompletely excised NMSC adds the burden of a second procedure to the patient, it minimizes tumor recurrence, which is better for overall patient well-being. Efforts should continue to determine the most optimal ways to minimize incomplete excision of NMSCs.

**References**


Correspondence: Cathy L. Koger, DO, kittykoger@yahoo.com