What Is the Best Surgical Margin for a Basal Cell Carcinoma: A Meta-Analysis of the Literature

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Background: Current management of basal cell carcinoma is surgical excision. Most resections use predetermined surgical margins. The basis of ideal resection margins is almost completely from retrospective data and mainly from small case series. This article presents a systematic analysis from a large pool of data to provide a better basis of determining ideal surgical margin.
Methods: A systematic analysis was performed on data from 89 articles from a larger group of 973 articles selected from the PubMed database. Relevant inclusion and exclusion criteria were applied to all articles reviewed and the data were entered into a database for statistical analysis.
Results: The total number of lesions analyzed was 16,066; size ranged from 3 to 30 mm (mean, 11.7 ± 5.9 mm). Surgical margins ranged from 1 to 10 mm (mean, 3.9 ± 1.4 mm). Negative surgical margins ranged 45 to 100 percent (mean, 86 ± 12 percent). Recurrence rates for 5-, 4-, 3-, and 2-mm surgical margins were 0.39, 1.62, 2.56, and 3.96 percent, respectively. Pooled data for incompletely excised margins have an average recurrence rate of 27 percent.
Conclusions: A 3-mm surgical margin can be safely used for nonmorpheaform basal cell carcinoma to attain 95 percent cure rates for lesions 2 cm or smaller. A positive pathologic margin has an average recurrence rate of 27 percent. (*Plast. Reconstr. Surg.* 126: 1222, 2010.)

Basal cell carcinoma is the most common cancer in humans.[1–3] Basal cell carcinoma is usually an indolent, locally invasive neoplasm that mostly—but not exclusively—afflicts fair-skinned people.[3] Reported incidence rates of basal cell carcinoma vary significantly based mainly on geographic factors such as latitude and sun exposure. Australia consistently reports the highest incidence rate of 788 for every 100,000 people annually.[4] In contrast, in the United States, the incidence rate is 146 for every 100,000 people annually.[5] Eighty-five percent of all basal cell carcinomas appear in the head and neck region.[6,7] The tumor may occur at any age, but the incidence of basal cell carcinoma increases markedly after the age of 40. The incidence in younger people is increasing, possibly as a result of increased sun exposure. Risk factors include fair skin, tendency to freckle,[8] degree of sun exposure,[9–11] excessive sun-bed use, radiotherapy, phototherapy, male gender, and a genetic predisposition.[12]

Basal cell carcinomas are usually slow-growing tumors that only rarely metastasize.[13] Growth of basal cell carcinomas is usually localized to the area of origin; however, some basal cell carcinomas tend to infiltrate tissues in a three-dimensional fashion through the irregular growth of finger-like projections, which may not be obvious on visual inspection.[2,14] If left untreated, or inadequately treated, the basal cell carcinoma can cause extensive tissue destruction, particularly on the face. The clinical course of basal cell carcinoma is unpredictable; it may remain small for years, or it may grow rapidly or proceed by successive spurts of extension of tumor and partial regression.[15] Thus, early prompt treatment is essential to minimize the morbidity of both cancer and its treatment.

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The treatment of choice for basal cell carcinoma is surgical excision, which can be accomplished in various ways, such as curettage where no margins are identified; surgical excision with predetermined margins of clinically normal tissue; excision under frozen section control; or Mohs' micrographic surgery. Costs, availability, and curative effectiveness of these methods vary. The ideal treatment should provide total tumor eradication with the lowest recurrence risk and use the most cost-effective method with acceptable cosmetic outcomes. Mohs' micrographic surgery offers the smallest overall defect size with the lowest recurrence rate for basal cell carcinoma and is the standard against which other treatments are compared.[16] However, it is very costly and time consuming, may require coordination between two separate physicians (one for excision and another for reconstruction), and is not universally available. In addition, Mohs' surgery is generally performed under local anesthesia and is therefore unavailable for some of the larger tumors that require general anesthesia. Excision under frozen section control is also time consuming and can be inaccurate. Any instance where the frozen section results are negative while the permanent pathology results are positive may lead to a treatment dilemma, especially if reconstruction was completed. Curettage is very rapid, but it does not allow for assessment of the resection margins.

The exact margin of normal tissue should be based first on oncologic safety and then on reduction of unnecessary resection of normal tissues. Such margin definitions are numerous in the literature, but the scientific basis usually relies on small numbers of patients and retrospective reviews. Recent studies proposing guidelines for standard margins of excision expose the discrepancy and lack of scientific proof in the literature. For instance, 4-mm margins have been recommended as standard surgical margins for primary nonmelanoma skin cancers.[17,18] However, some studies have shown that only 7 percent of small, well-circumscribed primary basal cell carcinomas infiltrate beyond 1 mm of their clinical margins.[19] Given the sensitive cosmetic and functional location of many basal cell carcinomas such as on the eyelid or nose, taking standard 4-mm surgical margins may not be desirable or necessary.[20] Therefore, excisions with narrower margins are often performed with the surgeon determining the appropriate margin depending on the clinical situation.

Although there are a variety of opinions as to what is the optimal size of basal cell carcinoma margin of resection, the vast majority of the tumors are treated successfully. As expected, there is an abundance of literature reporting various excision margins with excellent cure rates. Our goal is to systematically review the literature using a meta-analysis in an attempt obtain an ideal surgical excision margins by using aggregated data.

METHODS

Eighty-nine articles were selected from 973 scientific articles initially obtained from the PubMed database. Search was performed in a systematic fashion using the algorithm illustrated in Figure 1.

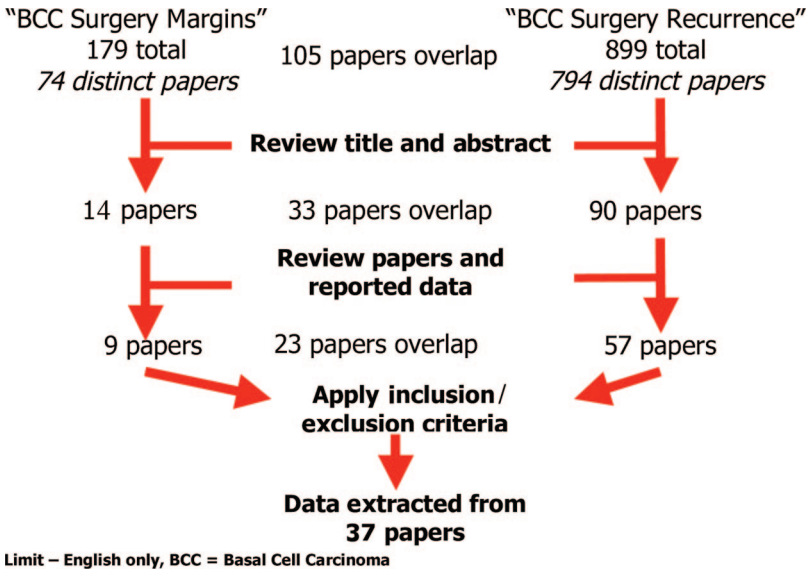

Fig. 1. The algorithm used to search for and select relevant articles for the review.

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Search terms used were "basal cell carcinoma surgery margins," which yielded 179 articles, and "basal cell carcinoma surgery recurrence," which yielded 899 articles. A limit of English language and human-only articles was applied. These two searches had an overlap of 105 articles.

A review of abstracts reduced the number of articles to 137. Further review of reported data, for quality and redundancy applied to these articles, resulted in a total of 89 articles that had usable data for this review with dates of publication ranging from 1966 to 2008.

Inclusion and exclusion criteria for data extraction were applied. Studies were selected based on study quality and existence of margin data, safety margin values, recurrence rates, and tumor size. Specific inclusion criteria included all articles with original surgical excision data, pathology data, case series of open resections, and/or Mohs' surgery. Exclusion criteria included articles with re-resection data, previously irradiated lesions, review series, and data involving morpheaform type lesions.

Each of the 89 selected articles was reviewed for specific data on basal cell carcinoma excision results. Of the 89 articles[16–102] reviewed, 37[17–55] provided adequate patient demographics, lesion size, and surgical margin data that were extracted, aggregated, and analyzed. All articles were reviewed by one investigator and the data were entered into the SPSS (SPSS, Inc., Chicago, Ill.) database for statistical analysis. SPSS software was used to obtain descriptive statistics and perform parametric and nonparametric tests.

RESULTS

Patients

The total number of patients analyzed was 10,261. Approximately half of the reviewed articles involving 5376 patients reported demographic information. Average age was 67.7 ± 3.7 years (range, 60 to 77 years), 2754 patients were male, and 2622 were female. Demographic data are limited to articles that have included that information as primary data.

Lesions

The total number of lesions studied was 16,066. Size of the lesions ranges from 3 to 30 mm, with a mean size of 11.7 ± 5.9 mm. Surgical margins varied from 1 to 10 mm, with an average of 3.9 ± 1.4 mm. Rates of negative surgical margins ranged from 45 to 100 percent, with an average of 86 ± 12 percent. Overall recurrence rates ranged from 0 to 9.7 percent, with a mean of 2.0 ± 2.1 percent. Descriptive statistics of lesions included in this review are listed in Table 1.

Table 1. Descriptive Statistics of the Lesions Analyzed Including the Total Number of Lesions, Size, Surgical Margins, Negative Margins, and Recurrence Rates

	No.	Mean ± SD	Range
No. of lesions	16,066		
Size	3590	11.7 ± 5.9 mm	3–30 mm
Surgical margin	15,253	3.9 ± 1.4 mm	1–10 mm
Percentage of surgical margins with clear pathology findings	10,257	86 ± 12%	45–100%
Recurrence	8936	2.0 ± 2.1%	0–9.7%

Margins

Surgical margins were found to generally increase with the size of the lesion. This trend is summarized by plot of the mean surgical margins of resection plotted against lesion size in Figure 2. Lesion sizes are clustered in 5-mm increments. These clusters show a significant statistical difference by the Kruskal-Wallis test.

Among the lesions reviewed, a total of 8936 lesions had recurrence data. There is a statistically significant inverse relationship between recurrence and surgical resection margins: 5-mm margins of resection (n = 1459) have a mean ± SD recurrence rate of 0.39 ± 0.26 percent, 4-mm resection margins (n = 4957) have a mean recurrence rate of 1.62 ±1.8 percent, 3-mm resection margins (n = 1264) have a mean recurrence rate of 2.56 ± 1.6 percent, and 2-mm margins (n = 1459) have a mean recurrence rate of 3.96 ± 1.9 percent. Thus, our data reveal that a decrease in resection margin increases the recurrence rate. Relative risk of recurrence increases steadily. The relative risks (hazard ratio) for 4-, 3-, and 2-mm margins are 4.2, 6.5, and 10, respectively (Tables 2 and 3).

A number of articles reviewed also reported the rates of clear surgical margins. In our review, 6807 lesions had surgical margin clearance data, which are summarized in Table 4. We observe that lesions with 5-mm margins (n = 340) had an average clearance rate of 85 ± 8.5 percent; 4-mm margins (n = 4231) also had a clearance rate of 85 ± 12 percent, and 2-mm margins (n = 2236) had a slightly lower clearance rate of 82 ± 15 percent. The difference in surgical margin clearance rate is significant for the 2-mm margin compared with 3-, 4-, and 5-mm margins.

The relationship between surgical margin size and the rates of recurrence is described in Figure

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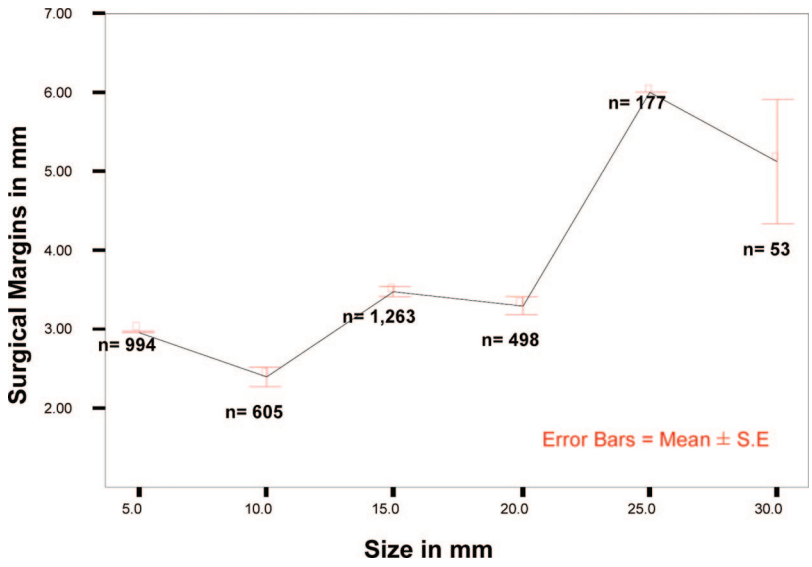

Fig. 2. Relationship of size to margin size. On average, there is an increase in the margin size with increasing size of the lesion.

Table 2. Comparison of the Mean Recurrence Rates for 2-, 3-, 4-, and 5-mm Margins*

Surgical Margin	No.	Recurrence Rate (%)	Relative Risk	χ^2	Asymptote Significance
5 mm	1459	0.39 ± 0.26	1	3541	0.0001
4 mm	4957	1.62 ± 1.8	4.2		
3 mm	1264	2.56 ± 1.6	6.5		
2 mm	1246	3.96 ± 1.9	10		

*In this analysis, the raw relative risk of recurrence with a 2-mm margin is approximately 10 times that of a 5-mm margin. Median rank comparisons by using the Kruskal-Wallis test show a statistically significant difference.

Table 3. Comparison of Risk Ratios of 3-mm and 2-mm Margins with 4-mm as a Standard*

Surgical Margin	No.	Recurrence Rate (%)	Relative Risk	χ^2	Asymptote Significance
4 mm	4957	1.62 ± 1.8	1	3262	0.0001
3 mm	1264	2.56 ± 1.6	1.6		
2 mm	1246	3.96 ± 1.9	2.4		

*Median rank comparison by using the Kruskal-Wallis test shows a statistically significant difference.

Table 4. Comparison of Means of Percentage Negative Surgical Margins of 2, 4, and 5 mm*

Surgical Margin	No.	Negative Pathologic Margin Rate (% cleared)	χ^2	Asymptote Significance
2 mm	2236	82 ± 15	56.3	0.0001
3 mm	1958	85 ± 12		
4 mm	4231	85 ± 12		
5 mm	340	85 ± 8.5		

*Median rank comparison by using the Kruskal-Wallis test shows a statistically significant difference.

3. We observe a consistent decrease in recurrence rates with increasing surgical margin size from 2 to 5 mm. On lesions with larger than 5-mm surgical margins, the recurrence increases significantly. Of note, the majority of the lesions (87 percent, n = 8926) in our data pool have reported surgical margins of 5 mm or less. As can be seen in Figure 2, all reported margins larger than 5 mm are obtained from lesions larger than 2.5 cm, which constitute a very small fraction sample analyzed. In Figure 3, we observe that the majority of data suggest a trend of decreasing recurrence with the increase of the size of the surgical margin for lesions up to 2.5 cm.

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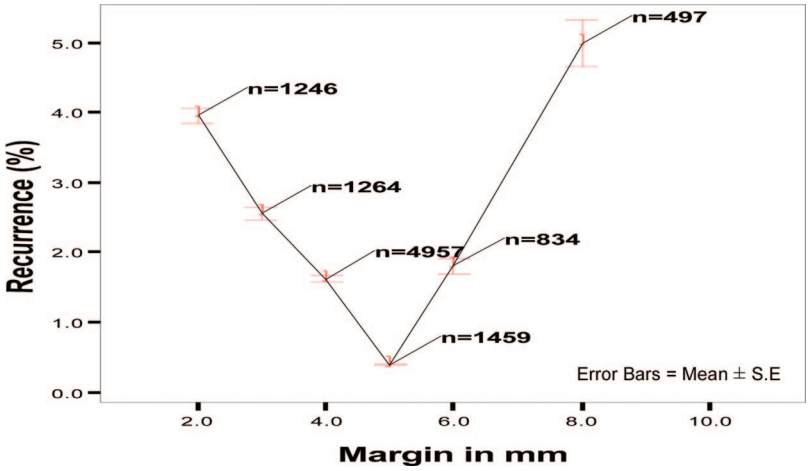

Fig. 3. Relationship between surgical margin size and recurrence rates. Mean recurrence for a certain margin size generally decreases with increasing margin size up to 5 mm. For surgical margins larger than 5 mm, there is an increase in mean recurrence rates with the increase in margin size.

There is a notable variance in the margins of resection depending on the site of the lesion and the surgeon's choice. For example, Laloo and Sood reported adequately resecting 63 well-demarcated head and neck basal cell carcinoma lesions with 2-mm margins. All lesions were less than 2 cm, with 5 percent incomplete resection and no recurrence in 2 years.[41] We used these data to evaluate the risk ratios if a surgeon were to decrease their margins of resection from 4 mm to 3 mm or 2 mm. Again, the absolute change in recurrence was miniscule and the relative risk is still statistically significant, but clinically they will all have above a 95 percent cure rate. Similar findings are obtained when the surgeon would theoretically decrease their desired margin of resection from the assumed standard of 3 mm to 2 mm.

Pathologic Margins

A negative pathologic margin, although generally assumed to imply a complete resection, simply means that there were no tumor cells at the margin in the specific sections checked by the pathologist. The amount of sections and the confidence that a proclaimed negative margin is truly negative can vary depending on the pathologist and the dimensions of the tumor. This lack of certainty with margins using standard histologic sections is one of the major arguments favoring Mohs' resection and is also the reason that recurrence rates decrease with larger margins. In contrast, a positive margin may simply mean that the edge of the tumor is exactly where the surgeon made the cut. This point is illustrated by the many instances where the tumor does not recur despite a positive margin. One of the issues we are trying to address is how the status of pathologic margins, positive or negative, affects the surgical cure. Which is more important in predicting cure rates: the status of pathologic margins or the size of the surgical margins?

In most common clinical scenarios, basal cell carcinoma lesions are resected with a preplanned size of surgical margin depending on the surgeon preference, the location, and the size of the lesion. The goal is to clear disease with a minimum acceptable surgical margin, that is, to obtain a negative pathologic margin with the smallest surgical margin. In this series, the rate of negative pathologic margin (i.e., clear surgical margins) does not vary significantly with size of the surgical margin. The most commonly used margin was 4 mm. In our case, the rates of obtaining a negative pathologic margin for surgical margins of 3, 4, and 5 mm was the same at 85 percent. Negative pathologic margins decreased slightly to 82 percent for 2-mm surgical margins. As far as these data are concerned, negative pathologic margins remain relatively unchanged with decreasing the size of the surgical margin from 5 mm to 3 mm.

The role of positive pathologic margins in predicting recurrence has been widely studied.[57,62–64,68–73,77–78,100–104] We reviewed all studies that have reported, using primary data, the significance of incompletely excised lesions treated with observation alone and prognosis of disease. Table 5 lists all studies since 1965 reporting recurrence rates for basal cell carcinoma excisions that were

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Table 5. List of Raw Data from All Articles That Have Reported Recurrence Data on Incompletely Excised Basal Cell Carcinoma*

Report	Year	No. of Lesions	Lesions with Positive Margins	Reexcised	BCC Positive on Reexcision	Observation Only	Recurrence of Lesions with Positive Margins (%)
Gooding et al.	1965	1197	66	5	4	61	23 (37.7)
Pascal et al.	1968	361	42	6	3	36	14 (38.9)
Doxannas et al.	1981	165	34	7	5	16	7 (43.8)
Hauben et al.	1982	188	39	17	13		
Emmett et al.	1981	1411	10	10	6	0	
Dellon et al.	1985	?	57			57	24 (42.1)
Richmond et al.	1987	850	67	6	5	60	23 (38.3)
Sussman et al.	1996	723	82	8		70	21 (30.0)
Griffiths et al.	1999	1392	99	74	40	25	0 (0)
Kumar et al.	2000	879	41	16	2	25	
Hallock et al.	2001	309	50	25	7	25	0 (0)
Dieu et al.	2002	3558	223	125	74	88	7 (8.0)
Nagore et al.	2003	151	61			61	26 (42.6)
Wilson et al.	2004	3795	235	84	38	140	29 (20.7)
Total		14,979	906	375	197	664	174 (27)

BCC, basal cell carcinoma.
*These reports have accompanying follow-up data on the lesions such as reexcision outcomes and/or subsequent recurrence data.

found to have positive pathologic margins. The recurrence rate for basal cell carcinoma lesions with positive margins calculated from the aggregated data is 27 percent. With that in mind, we can roughly estimate the chances of getting a recurrence from 3- or 4-mm surgical margins that have an estimated 15 percent positive pathologic margin rate (Table 4) to range from 1 to 7 percent. This is estimated using the formula $0.27 \times (15 \pm 12)$, assuming that these patients are treated with observation alone.

DISCUSSION

This study attempts to answer three important questions for a surgeon taking care of a patient with a primary basal cell carcinoma lesion:

1. What is a reasonable treatment goal for a patient with a small, well-demarcated basal cell carcinoma lesion up to 2 cm?
2. What are appropriate surgical margins that will provide that treatment objective to the patients?
3. What is the appropriate management of the patient with a positive pathologic margin postoperatively?

Appropriate Treatment Goal

Reported cure rates for basal cell carcinoma by various modalities range from 90 to 100 percent.[19,24,98,105,106] A goal of 5 percent or less recurrence over 2 to 5 years is considered reasonable for surgical management of basal cell carcinoma.[17,22,41] We will use that standard in this review to analyze recurrence data. Aggregate data from this review indicate that 3360 lesions that were 2 cm or less with corresponding resection margins ranging from 2 to 4 mm have clearance rates of 82 to 85 percent. Two- to 5-year recurrence rate for these lesions was an excellent 3 percent or less.

Optimal Surgical Margins

Our data provide a basic relationship between size of surgical margins for basal cell carcinomas and recurrence risk. The goal is to safely predict appropriate margins of resection of basal cell carcinoma lesions while sacrificing a minimum amount of healthy surrounding skin. In guiding the surgeon on the choice of surgical margins, we used the relative advantages of different margin sizes by estimating the average recurrence rates and the relative risk of recurrence compared with established practice. In this case, margins ranging from 1 to 4 mm are compared with 5-mm margins of resection, which is a common size of margin of resection without frozen section control.

The following observation can be drawn from the data. Relative risk of recurrence for 2-mm, 3-mm, and 4-mm margins when compared with 5-mm margins of resection increases linearly. The statistical implications from these data indicate that the chances of getting a recurrence within 2 years for a basal cell carcinoma lesion with a 2-mm, 3-mm, or 4-mm resection margin are 10, 6.5, or 4.2 times, respectively, that of a lesion with a 5-mm resection margin. It is clear that smaller margins are inherently riskier than larger ones, even if the difference is 1 mm. However, the actual average recurrence rates are very low. From these data for all surgical margins from 1 to 5 mm, the observed

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mean recurrence is less than 5 percent, as seen in Tables 2 and 3. Thus, clinically, absolute difference in the risk of recurrence is not as large as the relative risk estimates would indicate.

The rates of obtaining a clear pathologic margin using a resection margin of 2, 3, 4, and 5 mm are 82, 85, 85, and 85 percent, respectively. These clearance rates are essentially the same for these surgical margins even though they have significantly different relative risks of recurrence. The clinical implication of this finding is that although a larger surgical margin lowers the relative risk of recurrence, achieving a clear surgical margin does not correlate with lower recurrence risk. This empiric fact is supported by the biology of the basal cell carcinomas whereby the lesion expands beyond the visible margin in fingerlike projections in an uneven fashion.[2,14] Conversely, the rate of having positive pathologic margins as extrapolated from the data in Table 4 using either a 2-, 3-, 4-, or 5-mm surgical margin is estimated at 18, 15, 15, and 15 percent, respectively. This reinforces the previous point that our data do not indicate any significant improvement in pathologic margin clearance with the increase in size of surgical margins of resection.

Findings in Figure 3 also demonstrate an interesting relationship between margin size and recurrence. Here, the reported mean recurrence rates decrease linearly with increasing size of margins until it reaches 5 mm, where observed mean recurrence is lowest, then mean recurrence increases with increasing margin size. Theoretically, that indicates the optimal resection margin in terms of recurrence is 5 mm. Another view is that these are two different groups of lesions, whereby lesions with larger than 5-mm margins are most likely to be in the parts of the body where margins of resection are not restricted (i.e., away from the head and neck region). In addition, these lesions also tend to be larger. In this review, we consistently observe that lesions larger than 25 mm have on average had significantly larger surgical margins used, compared with lesions less than or equal to 20 mm. This is demonstrated in Figure 3. This might likely be attributable to the fact that these "larger lesions" are also more likely to be located in areas of the body other than the face where patients do not notice or complain about them as early. This explains, then, why in Figure 3, for surgical margins larger than 5 mm there is no decrease in relative risk with increased margin size as seen in margins less or equal to 5 mm.

Postoperative Management of Basal Cell Carcinoma Lesions with Positive Pathologic Margins

The outcomes for excised basal cell carcinomas that were found to have a positive pathologic margin have been reported with varying results by several investigators.[57,62–64,68–73,77–78,100–103] As described in Table 5, recurrence rates for lesions with positive pathologic margins that were treated with observation only ranges from 0 to 44 percent, with a mean of 27 percent.[57,62–64,68–73,77–78,100–103] Most of the lesions described are in the head and neck region. Most of these studies did not report on the size of the surgical margins used. However, we do know that the majority of the lesions excised were smaller than 2 cm.[57,62–64,68–73,77–78,100–103] A subsequent analysis of the factors affecting recurrence for these series have indicated that histologic features of the lesions and location of the lesion were the best predictors for chances of recurrence.

A recent prospective trial of incompletely excised basal cell carcinomas by Robinson et al. provides robust analysis and recurrence outcomes.[65] Over a period of 20 years, 962 patients with incomplete excision who eventually underwent Mohs' resection of recurrent lesions were followed. Important findings in this study were age at presentation and male gender. As in other studies, location and histologic characteristics were also important. For instance, lesions with positive margins on the scalp are the most likely to recur, followed by lesions on the nose, cheek, and then the rest of the body.

These data suggest that disease in the majority of patients with basal cell carcinoma found to have a positive margin after resection would not recur. However, a recurrence rate of 27 percent is certainly too high for recommending observation in all patients. A frank discussion between the surgeon and the patient, weighing the risks of observation alone versus the morbidity of a re-resection, is warranted, and in some select patients, observation may be appropriate.

CONCLUSIONS

It is clear that larger surgical margins and a negative margin on pathologic examination ensure better curative outcomes. Consistently, relative risk is inversely proportional to the size of the surgical margin. Using this criterion alone, the best margin in terms of relative recurrence is a 5-mm margin. However, the anatomical constraints require prejudice in choosing the resection margins, especially for lesions of the face. Thus, for those surgeons who desire a minimum 95 percent cure rate, these data indicate that a

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3-mm surgical margin can be safely used for basal cell carcinoma lesions 2 cm or smaller. Furthermore, a positive pathologic margin has a mean recurrence rate of 27 percent and thus does not necessarily indicate that a basal cell carcinoma will recur. Thus, when faced with a positive surgical margin, a case-by-case consideration of the risks of observation versus re-resection should be applied when determining the next step in management.

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