

## Investigation of factors affecting postoperative recurrence of basal cell carcinomas

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**Objective:** The purpose of this study was to evaluate treatment outcomes of patients with basal cell carcinomas (BCCs) who underwent surgery.

**Methods:** A total of 126 patients with BCCs, that we had treated, were investigated in relation to the following characteristics: age, gender, site of onset, major axis length of the tumor, assessment of excision and surgical margins from the initial surgery, recurrence, histopathological type, and diagnostic inconsistencies between pathological frozen and permanent sections.

**Results:** The face was the most common site of onset. Most cases with positive surgical margins detected during surgery in the region around the eyelid were on the nasal side and particularly common inside the inferior punctum. A high rate of positivity for margins was determined in the nasal region, with higher positivity rates observed for deep margins compared with those in other sites. Postoperative recurrence was observed in 3 of 126 cases. Histological examination indicated that all 3 cases exhibited aggressive histological subtypes.

**Conclusion:** These results suggested that risk factors for positive surgical margins after excision include tumor sites at the inner portion of the eyelids or the alar groove region. The results also suggested that histological features indicated an aggressive subtype.

**Key words:** basal cell carcinoma, surgical excision margin, risk factor, aggressive subtype

### Introduction

Basal cell carcinoma (BCC) is a malignant skin tumor with rare metastasis and relatively favorable prognosis. The first line of treatment is surgical excision. Nonpigmented BCC often occurs in Caucasian patients and is usually treated in Europe and the United States using Mohs micrographic surgery (MMS) because BCC lesions pathologically classified as high risk are common. MMS is microscopically controlled surgery used to treat common types of skin cancer. During the surgery, after each removal of tissue, while the patient waits, the tissue is pathologically examined for cancer cells. The results of which will be used to determine whether or not any additional tissue is to be removed. The unique features of MMS are the horizontal method of removal, the careful mapping of the tissue involvement and defect, and the ability to completely examine the surgical margins. However, because low-risk pigmented BCCs are relatively common in Japan, MMS is not performed as

often as it is in other countries.<sup>1</sup>

In this study, we retrospectively evaluated the treatment outcomes of 126 patients with BCCs who underwent surgery at our institution over the past 12 years. We examined a possible correlation between pathological features of tumors and the site of onset, focusing on the histological type and lesion site in cases of positive surgical margins and recurrence. Moreover, we investigated diagnostic inconsistencies between examinations of frozen sections and permanent sections.

### Materials and Methods

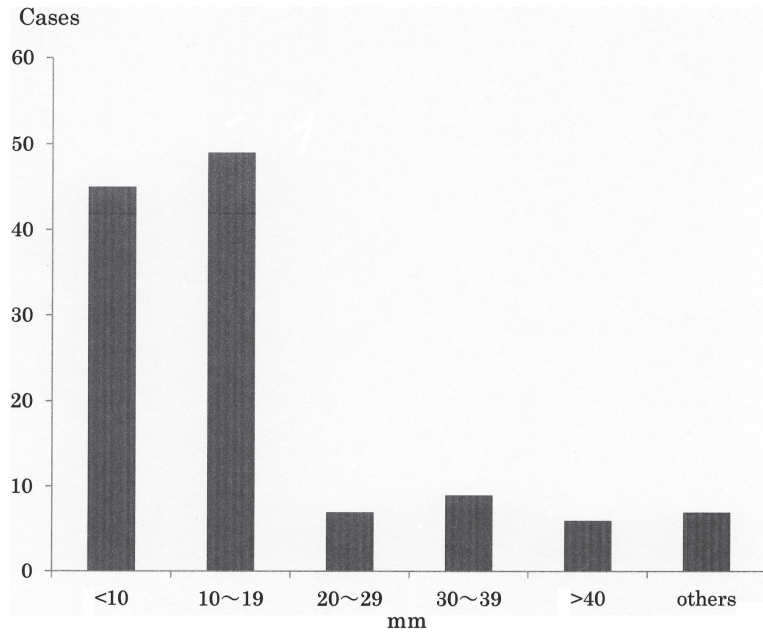
A total of 126 patients with BCCs that we treated at the Kitasato University Hospital, Department of Plastic and Cosmetic Surgery, over a 12-year period from April 1998 to March 2010, comprised the subjects of this study. We investigated the following characteristics: age, gender, site of onset, major axis length of the tumor, assessment of excision and surgical margins in the initial surgery,

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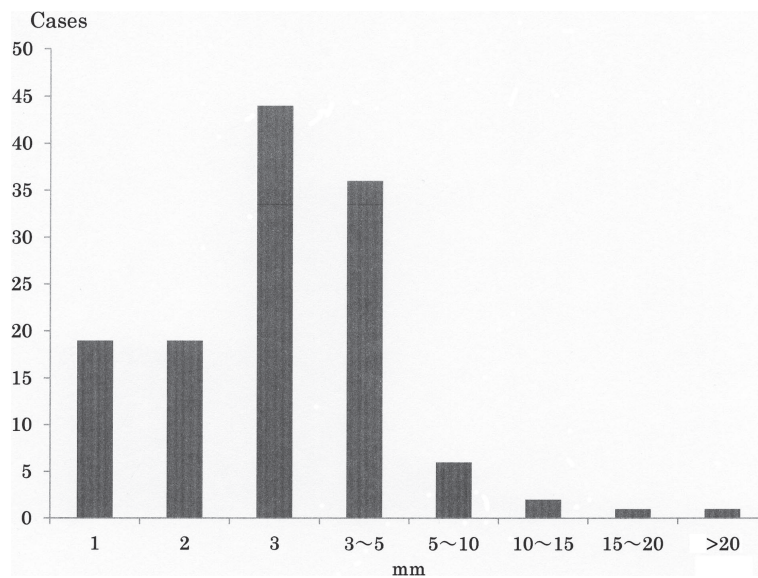
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**Table 1.** Tumor regions

Region	(N = 126)
Nose	42
Eyelid	41
Cheek	14
Lip	5
Eyebrow	2
Ear	7
Head	5
Limb	1
Body	9



**Figure 1.** Tumor major axes ranged from 3 mm to 105 mm, averaging 15.1 mm.



**Figure 2.** Surgical excision margins

Surgical excision margins ranging from 3 mm to  $\leq 5$  mm in the initial surgery accounted for approximately 60% of the cases. These margin sizes were indicated in sites such as the nasal and buccal regions. Margins of 1 mm and 2 mm were indicated for small lesions in the eyelid and alar regions.

recurrence, histopathological type, and diagnostic inconsistencies between frozen and permanent sections. For histopathological type in particular, all pathological tissues were re-examined, classified, and compared using the International World Health Organization (WHO) classification system<sup>2</sup> and the Japanese general rules for clinical and pathological studies on malignant neoplasms of the skin.<sup>3</sup>

**Results**

The 126 patients ranged in age from 26 to 96 years old, with a mean age of 67.6 years. The mean female age (70.7 years) was 6 years older than the mean male age (64.5 years). The male to female ratio was 1:1, with 63 male and 63 female patients. Tumors occurred most often on the face, with tumor sites around the midline frontonasal prominence, which undergoes fusion during the embryonic period, including the nose and eyelids, the sites affected in 82.5% of the cases (Table 1). The major axis lengths of the tumors ranged from 3 mm to 105 mm, with a mean length of 15.1 mm (Figure 1).

Initial surgical excision margins from 3 mm to ≤5 mm accounted for approximately 60% of the cases. These margins were indicated for tumors located in the nasal and buccal regions. Moreover, 1- and 2-mm margins were indicated for small lesions around the eyelid and alar regions (Figure 2). Sites that were particularly common among positive surgical margin cases, detected during the initial surgical procedure, were the eyelid and nasal regions (5 and 11 cases, respectively).

Most cases of surgical margin positivity detected intraoperatively in the eyelid region were on the nasal side and particularly common inside the inferior punctum. Initial excision margins for the eyelid region were 2.58 ± 1.30 mm and tended to be 1 mm smaller compared

with the mean margin (3.78 mm) of all 126 patients. Positivity rates for the surgical margins were high in the nasal region, and excision margins of 3.96 ± 2.81 mm laterally exhibited almost no difference from the mean margin of all the subjects. Six of 18 cases with positive excision margins exhibited deep positive surgical margins, 5 of which were located in the nasal region. The positivity rate for deep surgical margins was higher for the nasal region than for other sites. Additional excision surgery was performed in 4 of 5 cases with positive surgical margins in the eyelid region and in 8 of 11 cases in the nasal region. No recurrence was observed in any patient who underwent additional excision surgery. Postoperative recurrence was observed in 3 of 126 cases (2.38%) in the auricular, upper eyelid, and alar regions. Recurrence occurred during 1 to 3 years after surgery. Two of 3 recurrence cases were histologically classified as the morphea type, and all were classified as the invasion type.

When categorized according to the WHO classification<sup>2</sup> for histological type, 65 cases were the nodular type and the remaining 36 cases were mixed-cell nodular-type tumors. When classified according to the general rules for clinical and pathological studies on malignant neoplasms of the skin,<sup>3</sup> 53 cases were the nodular type and a majority of the remaining cases were mixed-cell nodular-type tumors (Table 2).

On histological classification, cases with positive surgical margins included infiltrative, morphea, micronodular, and nodular mixed types, with many aggressive subtypes observed. Nodular-type cases with positive surgical margins exhibited a tumor with a major axis length of 15 mm that developed around the eyelid region (Table 3).

A pathological frozen-section examination was conducted in 36 of the 126 cases. In those 36 cases, 24

**Table 2.** Histological typing of skin tumors

Pathological classification	The WHO	The Japanese Skin Cancer Society
Nodular	65	53
Infiltrative	10	19
Superficial	5	5
Cystic	3	2
Morphea	1	3
Pinkus	1	2
Keratotic	1	2
Others (e.g., basosquamous)	8	2
Nodular + infiltrative	30	37
Superficial + nodular	2	1

**Table 3.** The histological types of the lateral and vertical margin incomplete excisions

Histological type	(N = 18)
Nodular	2
Nodular + infiltrative	6
Nodular + micronodular	2
Infiltrative	1
Micronodular	3
Morphea	2

tumors  $\geq 6$  mm were revealed in the facial region: 16 in the nasal region, 8 in the eyelid region, and the others in the parietal, preauricular, and buccal regions. Seven of these cases revealed positive surgical margins in frozen sections, and 5 did so in permanent sections. Two cases exhibited positive margins in frozen sections but negative margins in permanent sections. Five cases exhibited negative frozen section results but positive permanent section results. None of these cases recurred, but diagnostic inconsistency was observed in 19.4% of the cases.

## Discussion

Oka et al. reported a number of methods for classifying BCC histopathologic subtypes.<sup>2-6</sup> Diagnoses may depend on individual tumor morphology, the depth of invasion into surrounding healthy tissue, or tumor growth patterns, or a combination of both. One characteristic of BCC is pigmentation. Although pigmented BCC occurs in only approximately 1% to 7% of Caucasian patients with BCCs,<sup>1</sup> pigmentation is observed in 85% to  $\geq 90\%$  of Japanese patients with BCCs. Therefore, it may not be appropriate to use the pigmented type as a histologic subtype for Japanese patients. The classification system reported by Lever et al.<sup>4</sup> also included pigmented BCC as a subtype, in addition to noduloulcerative, morphea-like or fibrosing, and fibroepithelioma subtypes. All of these classifications, except pigmented BCC, are based on BCC tissue structures.

Our investigation revealed that almost all of the cases exhibited pigmentation; therefore, the classification "pigmented type" is likely not suitable for Japanese patients. Salasche et al.<sup>6</sup> reported that BCC expansions  $>2.1 \pm 0.4$  mm were present in nodular-type cases, even in regions that macroscopically appeared as normal skin. Hendrix et al.<sup>7</sup> reported a subclinical extension of  $3.0 \pm 1.6$  mm for nodular-type cases and  $5.4 \pm 2.7$  mm for micronodular cases, the latter of which were significantly large.

Extra care should be taken in such cases because these histologic types are subcategorized into aggressive and nonaggressive subtypes. In cases of BCC histologic subtypes such as morphea, which exhibit strong aggressive tendencies, tumor extension of  $7.2 \pm 3.8$  mm has been reported. These histopathological diagnoses greatly affect the appropriate excision range determined.<sup>8</sup> The WHO classification and general rules for clinical and pathological studies on malignant neoplasms of the skin were used in the present study. However, because of varied definitions for small tumors, some micronodular

type cases were classified as the nodular type according to the WHO classification. Therefore, in Japan, the general rules for clinical and pathological studies on malignant neoplasms of the skin are more appropriate compared with the WHO classification for determining the range of the surgical excision to be made.

It has been reported that recurrence occurs in approximately 1% of complete excision cases and in 33% of incomplete excision cases.<sup>10</sup> This suggests that risks are higher for incomplete excision cases than they are for complete excision cases, as was expected. Furthermore, postsurgical excision recurrence rates ranging from 2.3% to 8.4% have been reported in Europe and the United States,<sup>10-13</sup> and these rates are higher compared with those reported for Japan. Because 90% to 94% of Caucasian patients with BCC are of the nonpigmented type, it appears that tumor margins can be more accurately assessed in patients of colored races. In addition, it has been indicated that this difference in frequency of occurrences of pigmented and nonpigmented types influences positive surgical margin rates and recurrence rates. The recurrence rate at our institution was 2.38%, which is lower compared with rates reported in Europe and the United States (2.3% – 8.4%).<sup>10-13</sup> A simple comparison cannot be determined because of the racial differences, but it does appear that the presence or absence of pigmentation may influence recurrence rates.

We found that tumors were located around the inner eyelid or nasal regions in several positive surgical margin cases. The difficulty of performing cosmetic and functional reconstruction of the eyelid region may result in a smaller excision range trend in this region for these neoplasms. The fact that critical organs, such as the lachrymal passages, that are superficially located inside the eyelids, may be particularly significant influential factors. Five of 18 cases exhibited positive surgical margins in the eyelid region. These margins were 1- to 5-mm wide and determined on the basis of tumor size. However, 4 of these 5 cases were aggressive and either infiltrative, micronodular, morphea, or basosquamous, histological growth types. Cases that did not exhibit aggressive histological growth types had a small excision range (mean margin, 1 mm).

In 11 of 18 positive surgical margin cases in the nasal region, base margins, rather than lateral margins, were positive. The fact that deep positive surgical margin cases were also common suggested that aggressive tendencies affected the frequency of positive surgical margins. There is a reportedly strong tendency for the deep invasion of nasal tumors, and this tendency has been named the "iceberg effect."<sup>14</sup> Therefore, the excision

volume is often insufficient. Furthermore, because of the complex structure of the nose and the difficulty regarding determining excision depth before surgery, a 2-stage surgery, in which excision and reconstruction are performed separately, is recommended. Moreover, it is dangerous to judge the success of the excision on the basis of postoperative, pathological, frozen-section testing, and such testing should only be used as a reference. It is best to make a final decision postoperatively based on permanent sections. In regions other than the nose, it is useful to perform immediate reconstruction after combined use with frozen-section testing. In 9 of 14 patients, who underwent 2-stage reconstruction, tumors were revealed in their nasal regions.

Griffith<sup>15</sup> investigated 1,392 sites in 1,165 patients and reported histologically incomplete excisions in 99 patients (7%), and when 74 of those patients (75%) underwent re-excisions; and subsequently, among those, there were incomplete excisions again in 40 patients (54%). In addition, Griffith<sup>15</sup> reported that the periorcular regions were common sites for incomplete excisions. Bisson et al.<sup>16</sup> conducted a prospective study on 100 sites in 86 patients and reported that the incomplete excision rate was 44% for 1-mm, 79% for 2-mm, and 92% for 3-mm excision margins, whereas only 4 cases (4%) had incomplete excisions for all sizes of excision margins. Because the incomplete excision rate for recurrent lesions increases with repeat surgery, it is important to perform a thorough excision of the lesion during the initial surgery. Therefore, even in pigmented cases where margins can be easily determined macroscopically, care must still be taken for lesions in nasal and eyelid regions because of their complex structures and histological subtypes.<sup>15,17</sup>

In Europe and in the United States, it has been reported that MMS leads to significantly lower postoperative recurrence rates compared with those following surgical excision. However, Smeets et al.<sup>18</sup> compared recurrence rates for MMS with those for surgical excision combined with frozen-section testing and reported no significant difference. This report suggested that low recurrence rates comparable with those for MMS could be achieved by the appropriate use of frozen-section testing combined with surgical excision. Frozen-section testing results did not match the final diagnosis in 19.4% of the cases in the present study. This indicates that there are limits in the accuracy of intraoperative, frozen-section diagnosis. However, when lesions exhibit aggressive growth patterns, either infiltrative or morphea types, and exhibit recurrence or are at high risk (e.g., facial tumors  $\geq 2$  mm), it is best to use frozen-section testing along with surgical

excision. Furthermore, depending on the site of the lesion (e.g., the nose), even lower recurrence rates can be achieved by using a 2-stage reconstruction. The present investigation revealed that lesions located in the alar groove or the inner eyelids, and those of aggressive histological types, may be risk factors for positive surgical margins.

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