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Narrow Histopathological Margins are Acceptable in Surgical Resection of Basal Cell Carcinoma in Japanese: A Single-Center Retrospective Study

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Background: Basal cell carcinoma (BCC) is the most common cutaneous malignancy. BCCs occur mainly in exposed areas, such as the face and scalp. Therefore, surgical resection with narrow margins is highly desirable. However, narrow margins may increase the risk of positive histopathological margins. Outcomes for such treatment might be unfavorable, but evidence for such a conclusion is lacking.
Methods: Between April 2015 and November 2023, a total of 230 Japanese cases with BCC which underwent surgical resection with 2-mm, 3-mm, or 5-mm margins were followed in our hospital. We conducted a retrospective review that focused on the recurrence rate and histopathological margins.
Results: Recurrence was recorded if the follow-up time was longer than 3 months. One of the 198 cases (0.5%) developed a recurrence. The mean lateral and deep histopathological margins were 2,525.4 μm (30.8-14,034.6 μm) and 3,409 μm (199.9-16,523.6 μm), respectively. Recurrence rate was associated with tumor size and clinical tumor border. However, histopathological margin was not associated with recurrence rate, even when it was less than 1,000 μm.
Conclusions: A narrow histopathological margin is acceptable for surgical resection of BCC in Japanese patients. (J Nippon Med Sch 2024; 91: 296–306)

Key words: basal cell carcinoma, Japanese, recurrence, surgical margin, histopathological margin

Introduction

Basal cell carcinoma (BCC) is one of the most common cutaneous malignancies, and its incidence continues to increase in many countries[1–3]. BCC originates from basal cells of the interfollicular epidermis or hair follicles[3] and frequently occurs on the head and neck[4,5]. The face is the most frequent site (70.7% of cases in Japan)[4,5]. BCC is as an indolent tumor that rarely metastasizes but can cause tissue destruction when not treated properly[6–8]. BCC is cured in 90-99% of cases by local treatment[7,9,10]. Therefore, surgical resection has long been considered the most effective treatment for BCC[7,9,10]. Excepting Mohs surgery, which is not common in Japan, local recurrence is better treated by surgical resection than by radiotherapy, cryotherapy, or electric curettage[11]. Conventional surgical resection, if feasible, is strongly recommended as the first-line treatment for BCC, which is not the case for all solid cancers[7,12,13]. Because BCC mostly develops on the face, cosmetic considerations are important when surgical resection is selected, especially because the disease increasingly affects younger people.

Clinical manifestations vary widely, and BCC lesions usually grow slowly, are nonhealing, and can exhibit ulceration or bleeding[14–17]. In Whites, 6.7% of BCCs are pigmented[18,19]. However, pigmented BCCs are the most frequent clinical feature in Asians, especially Japanese: 88.3% of all BCCs in Japanese patients are pigmented[5]. This characteristic is helpful in determining the tumor boundary[7]. In the present study, clinical manifestations were classified into two types. Nodular, superficial, and fibroepithelial Pinkus types were defined as clinically non-aggressive, while the morpheic/morpheaform/scle-

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rosing BCC was defined as clinically aggressive.

Histopathologically, BCC is classified according to the probability of recurrence. BCCs with a low risk of recurrence-nodular, superficial, keratotic, infundibulocystic, and fibroepithelial Pinkus types-are indolent and defined as histopathologically non-aggressive[7,10]. In contrast, BCCs with a high risk of recurrence-morpheic/sclerosing, micronodular, infiltrating, basosquamous, and sarcomatous differentiated BCCs-exhibit aggressive histopathologic features and are defined as histopathologically aggressive[7,10].

In surgical resection, evaluation of tumor boundaries and surgical margins is extremely important[7,20]. The current National Comprehensive Cancer Network (NCCN) guidelines recommend at least a 4-mm surgical margin[10], a recommendation based on expert opinion[21]. Current Japanese guidelines also recommend at least a 4-mm surgical margin[7]. Although wider resection margins are required for aggressive tumors, specific margins are not suggested[7,10].

In Japanese clinical practice, clinical resection margins vary from 2 mm to 10 mm, depending on the individual case[7]. Retrospective clinical studies of resection margins have recently been published in Japan. In patients with well-defined pigmented BCC, histopathological margins were negative in 95.3% of cases with 2-mm surgical margins and 100% of those with 3-mm surgical margins[22]. In the low-risk group, 100% of patients with 2-mm or 3-mm surgical margins had negative histopathological margins. Even in the high-risk group, 96.3% of patients with 3-mm surgical margins and 88.0% with 2-mm surgical margins had negative histopathological margins[10,23]. In another study, 96.2% with 2-mm surgical margins and 98.6% with 3-mm surgical margins had negative histopathological margins[24]. Surgery with reduced surgical margins is permissible if a stump-free operation can be ensured. Determining tumor boundaries as accurately as possible is, again, essential[20].

The deep histopathological margin is also an issue when considering resection margins. Determining a deep boundary is difficult because no standard boundary site exists at depth. Ultrasonography, and less commonly, reflection confocal microscopy and optical coherence tomography may help in assessing deep invasion[25–28]. Several factors are associated with deep invasion of BCC, including histopathological type and tumor size[29,30]. In 694 cases of BCC, nodular (average diameter 9.6 mm), superficial (average diameter 11.3 mm), and mixed non-aggressive tumors (average diameter 10.5 mm) were resected up to the subcutaneous fat tissue: 94.6% were negative for deep histopathological margins[31]. Conversely, only 80% of cases of histopathologically aggressive tumors had negative deep histopathological margins, even if resected to a deeper level. In addition, even in histopathologically non-aggressive tumors, resecting the entire nasal alar without the submucosal layer on the nasal cavity side may be necessary[32].

Histopathological examination of the stump in a permanent specimen may confirm that the histopathological extent of the tumor closely matches the clinical extent. Conversely, tumors may have a histopathological spread greater than the clinical tumor spread, with exposed tumors at the surgical margins, in which case the histopathological margins are classified as positive. In addition, even when histopathological margins are negative, they can be too narrow. If the margins are histopathologically negative, some patients are followed-up without additional resection. It is therefore important to discuss whether additional resection should be performed in cases in which histopathological margins are close to the tumor and whether the recurrence rate is tolerable even after follow-up. Recurrence requires re-excision, which imposes a considerable burden on patients. Moreover, additional procedures are expensive and inevitably consume medical resources. Therefore, the recurrence rate is a critical issue. In this study, the association of recurrence rate and histopathological margin was investigated.

Materials and Methods

Patients

In this retrospective study, we used the hospital medical records system to collect data from 230 cases treated surgically at the Department of Dermatology of Nippon Medical School Hospital between April 2015 and November 2023 (**Table 1**). Patients with unresectable BCC or metastatic BCC were excluded, as were patients with cutaneous malignancies in addition to BCC in the same tumor. In this study, clinical type was classified into two categories. Nodular, superficial, and fibroepithelial Pinkus types were defined as clinically non-aggressive, and the morpheic/morpheaform/sclerosing type was defined as clinically aggressive[7]. Similarly, the histopathological type of BCC was classified into two categories. Nodular, superficial, keratotic, infundibulocystic, and fibroepithelial Pinkus types were defined as non-aggressive. The morpheic/sclerosing, micronodular, infiltrating, basosquamous, and sarcomatous differentiated BCCs, which have aggressive histopathologic features, were de-

Table 1 Demographic data

	Cases (n = 230)		Cases followed for >3 months (n = 198; mean 35.6 months; maximum 96.6 months)	
Age, mean (range)	74.53 (37-101)		74.1 (37-98)	
Gender				
Male	118 (51.3%)		102 (51.5%)	
Female	112 (48.7%)		96 (48.5%)	
Race				
Japanese	230 (100%)		198 (100%)	
Clinical tumor boundary				
Well-defined	193 (83.9%)		163 (82.3%)	
Poorly defined	37 (16.1%)		35 (17.7%)	
Color				
Pigmented	229 (99.6%)		197 (99.5%)	
Unpigmented	1 (0.4%)		1 (0.5%)	
Clinical type				
Non-aggressive	215 (93.5%)		186 (93.9%)	
Aggressive	15 (6.5%)		12 (6.1%)	
Tumor site				
Head	18 (7.8%)		15 (7.6%)	
Face	150 (65.2%)		133 (67.1%)	
Forehead		6 (2.6%)		6 (3.0%)
Nose		74 (32.2%)		62 (31.3%)
Periocular region		29 (12.6%)		28 (14.1%)
Cheek		18 (7.8%)		17 (8.6%)
Ear		14 (6.1%)		12 (6.1%)
Jaw		1 (0.4%)		0 (0%)
Lip		8 (3.5%)		8 (4.0%)
Trunk	53 (23.0%)		43 (21.7%)	
Extremities	9 (3.9%)		7 (3.5%)	
Tumor size				
≥20 mm	42 (18.3%)		36 (18.2%)	
<20 mm	188 (81.7%)		162 (81.8%)	

Values are number unless noted.

fined as aggressive. When two or more histopathologic types were mixed, priority was given to the histopathologic type with the highest malignancy grade, after which the tumor was classified as one of the two histopathologic types, as reported previously[7,10]. The clinical tumor border was classified as well-defined or poorly defined[7,10]. Three dermato-oncologists evaluated the clinical tumor border, and cases were excluded when the opinions were inconsistent.

BCC lesions were excised with 2-mm, 3-mm, 5-mm, or wider surgical margins. Excised specimens were fixed with 10% formalin and mounted with paraffin. Cross-sections of paraffin-embedded skin samples (4 μm) were deparaffinized and stained with hematoxylin and eosin (HE)[33]. HE sections were observed and analyzed with a Nikon ECLIPSE 80i microscope (Nikon, Tokyo, Japan), a DS-Fi1 DS Camera Head (Nikon), and a DS-L2 DS Camera Control Unit (Nikon). Histopathological margins were measured. Lateral histopathological margins were measured in least four orthogonal directions, and deep margins were measured using sections that had minimal deep histopathological margins. Measurements were performed three times and mean values were used in this study. If tumor-free margins were not obtained, re-excision was performed. Histopathological margins less than 1,000 μm were defined as narrow[34]. Histopathological type was defined as the histopathological type determined from the entire excised tumor. Age (at the time of surgical resection), gender, race, tumor site, color, clinical type, clinical tumor border, tumor size (diameter), histopathological type, surgical margin, lateral histopathological margin, deep histopathological margin, follow-up time, and recurrence status were recorded (**Table 1, 2**). Recurrence status was recorded only if the duration of

Table 2 Treatment, histopathological status, and outcomes

	Cases (n = 230)	Cases followed for >3 months (n = 198; mean 35.6 months; maximum 96.6 months)
Surgical margin		
2 mm	8 (3.5%)	7 (3.5%)
3 mm	169 (73.5%)	144 (72.7%)
5 mm	47 (20.4%)	42 (21.2%)
Others	6 (2.6%)	5 (2.5%)
Histopathological type		
Non-aggressive	175 (76.1%)	154 (77.8%)
Aggressive	55 (23.9%)	44 (22.2%)
Lateral histopathological margin*	2,525.4 (228; 30.8-14,034.6)	2,471.8 (196; 30.8-14,034.6)
Surgical margin*		
2 mm	1,253.7 (8; 160.1-2,369.0)	1,257.8 (7; 160.1-2,369.0)
3 mm	2,251.8 (167; 30.8-6,261.3)	2,191.4 (142; 30.8-5,667.4)
5 mm	3,504.9 (47; 301.7-8,688.1)	3,360.7 (42; 301.7-7,587.1)
Histopathological margin		
Narrow (<1,000 μm)	27 (11.7%)	26 (13.1%)
Others	203 (88.3%)	172 (86.9%)
Deep histopathological margin*	3,409.9 (228; 199.9-16,523.6)	3,327.7 (196; 217.6-16,523.6)
Surgical margin*		
2 mm	2,181.2 (8; 217.6-4,420.8)	2,335.5 (7; 217.6-4,420.8)
3 mm	3,164.1 (167; 199.9-13,282.2)	3,087.5 (142; 359.6-10,014.8)
5 mm	4,175.1 (47; 317.0-13,871.6)	3,890.18 (42; 317.0-13,871.6)
Histopathological margin		
Narrow (<1,000 μm)	24 (10.4%)	21 (10.6%)
Others	206 (89.6%)	177 (89.3%)
Recurrence**		1/198 (0.5%)
Tumor size		
≥20 mm		1/36 (2.7%)
<20 mm		0/162 (0%)
Clinical tumor boundary		
Well-defined		0/154 (0%)
Poorly-defined		1/44 (2.8%)

Values are number unless noted; *values are mean histopathological margins (μm) (numbers; ranges); **values are numbers/subtotal numbers.

follow-up was longer than 3 months. Lesions that occurred in the same place as a previous lesion were considered a recurrence. The study was approved by the ethics committee of the Nippon Medical School (No. 2023-743). Consent was obtained from all patients by the opt-out method.

Analysis

Variables were coded and statistically analyzed using R version 4.3.1 (R Foundation for Statistical Computing, Vienna, Austria), EZR version 1.62 (Jichi Medical University, Saitama, Japan), and StatView version 5.0 (SAS Institute, NC), to avoid potential software bugs[35].

A p value of <0.05 was considered significant in all tests. Comparisons among three groups were performed using the Kruskal-Wallis test, and Bonferroni-adjusted p values were used. Comparisons between lateral and deep histopathological margins were performed using Pearson's product-moment correlation. Tumor size and clinical tumor border were compared between recurrent and non-recurrent lesions by using the log-rank test. Histopathological margins in different surgical margins, tumor sites, clinical tumor borders, and histopathological types were compared by using the Wilcoxon rank sum test with continuity correction.

Results

A total of 230 BCC lesions were excised from 206 patients between 2015 and 2023, and 198 cases were followed for

at least 3 months (mean 35.6 months; maximum 96.6 months); recurrence was noted in one of these 198 cases (0.5%) (**Table 2**). The mean lateral and deep histopathological margins were 2,525.4 μm (30.8 - 14,034.6 μm) and 3,409.9 μm (199.9 - 16,523.6 μm), respectively. Lateral and deep histopathological margins were 14,034.6 μm and 2,389.4 μm, respectively, in the recurrent case.

Age, Gender, and Tumor Site

The mean age of the patients was 74.5 years (range, 37-101 years). Of the 206 patients, 118 (51.3%) were male and 112 (48.7%) were female. BCC was most frequent on the face (150; 65.2%), especially the nose (74; 32.2%) and the periorbital region (29; 12.6%). The extremities (9; 3.9%) were the least frequent site. These findings were consistent with those of previous studies in Japan[22–24,29].

Race, Color, and Clinical and Histopathological Type

All patients were Japanese (100%). The numbers of pigmented and unpigmented BCCs were 229 (99.6%) and 1 (0.4%), respectively. The numbers of BCCs with well-defined and poorly defined borders were 193 (83.9%) and 37 (16.1%), respectively. The numbers of clinically non-aggressive and aggressive BCCs were 215 (93.5%) and 15 (6.5%), respectively. The numbers of histopathologically non-aggressive and aggressive BCCs were 175 (76.1%) and 55 (23.9%), respectively. These findings were also consistent with previous reports in Japan[22–24,29].

Histopathological Margins and Surgical Margins

In the resection of BCC lesions, the lateral histopathological margins are substantially affected by surgical margins. To confirm this, we compared the lateral histopathological margins of the 2-mm, 3-mm, and 5-mm surgical margin groups (**Fig. 1A**). Lateral histopathological margins were significantly wider in the 5-mm surgical margin group than in the 2-mm or 3-mm surgical margin groups ($p < 0.001$). Wider surgical margins are thus associated with wider lateral histopathological margins. In the 2-mm and 3-mm surgical margin groups, we analyzed the correlation between lateral and deep histopathological margins. Interestingly, a deep histopathological margin was strongly correlated with the lateral histopathological margin in the 2-mm surgical margin group ($r = 0.782$, $p = 0.022$; **Fig. 1B**). Moreover, a deep histopathological margin was moderately correlated with the lateral histopathological margin in the 3-mm surgical margin group ($r = 0.417$, $p < 0.001$; **Fig. 1C**). However, there was no such correlation in the 5-mm surgical margin group ($r = 0.231$, $p = 0.118$; **Fig. 1D**).

Recurrence Associated with Several Factors

Next, we identified several factors that affected recurrence. BCCs <20 mm had a significantly higher relapse-free survival rate than those ≥20 mm ($p < 0.03$; **Fig. 2A**). BCCs with well-defined clinical tumor borders had a significantly higher relapse-free survival rate than those with poorly defined clinical tumor borders ($p < 0.0333$; **Fig. 2B**). Thus, tumor size and clinical tumor border were significantly associated with recurrence rate. Surprisingly, in this study, there was no significant association between the histopathological margin and recurrence rate (data not shown).

Resected BCCs from the Nose and Periorbital Regions had Narrower Histopathological Margins

Next, we analyzed the relationships between histopathological margins and tumor sites. For this analysis, the 3-mm surgical margin group was selected because it was the most common (167/228; 73.2%). Lateral and deep histopathological margins were significantly narrower in the periorbital region than in the cheek ($p = 0.046$ and $p < 0.001$, respectively; **Fig. 3A, B**). Lateral and deep histopathological margins were significantly narrower in the nose than in the cheek ($p = 0.043$ and $p < 0.001$, respectively; **Fig. 3C, D**).

Clinical Tumor Border and Histopathological Type Affect Histopathological Margins

Finally, we analyzed the relationships between histopathological margins and factors other than tumor sites. Lateral histopathological margins were significantly narrower in BCCs with poorly defined clinical tumor borders ($p = 0.045$; **Fig. 4A**). Deep histopathological margins were significantly narrower in histopathologically aggressive BCC ($p = 0.001$; **Fig. 4B**).

Discussion

This study focused on the association between recurrence rate and the histopathological margin after appropriate surgical resection of BCCs. A total of 198 lesions were followed for longer than 3 months (mean 35.6 months; maximum 96.6 months), and one of 198 cases (0.5%) developed BCC recurrence. We confirmed that recurrence rates were associated with tumor size and clinical tumor border. Surprisingly, however, histopathological margins were not associated with the recurrence rate. We should note that our study had several limitations. There were limited numbers of patients and lesions, and recurrence was observed in only one of 198 cases. Moreover, all cases were analyzed retrospectively.

Current NCCN guidelines recommend at least a 4-mm margin[10], and similar recommendations for ensuring clear histopathological margins have been reported in Western

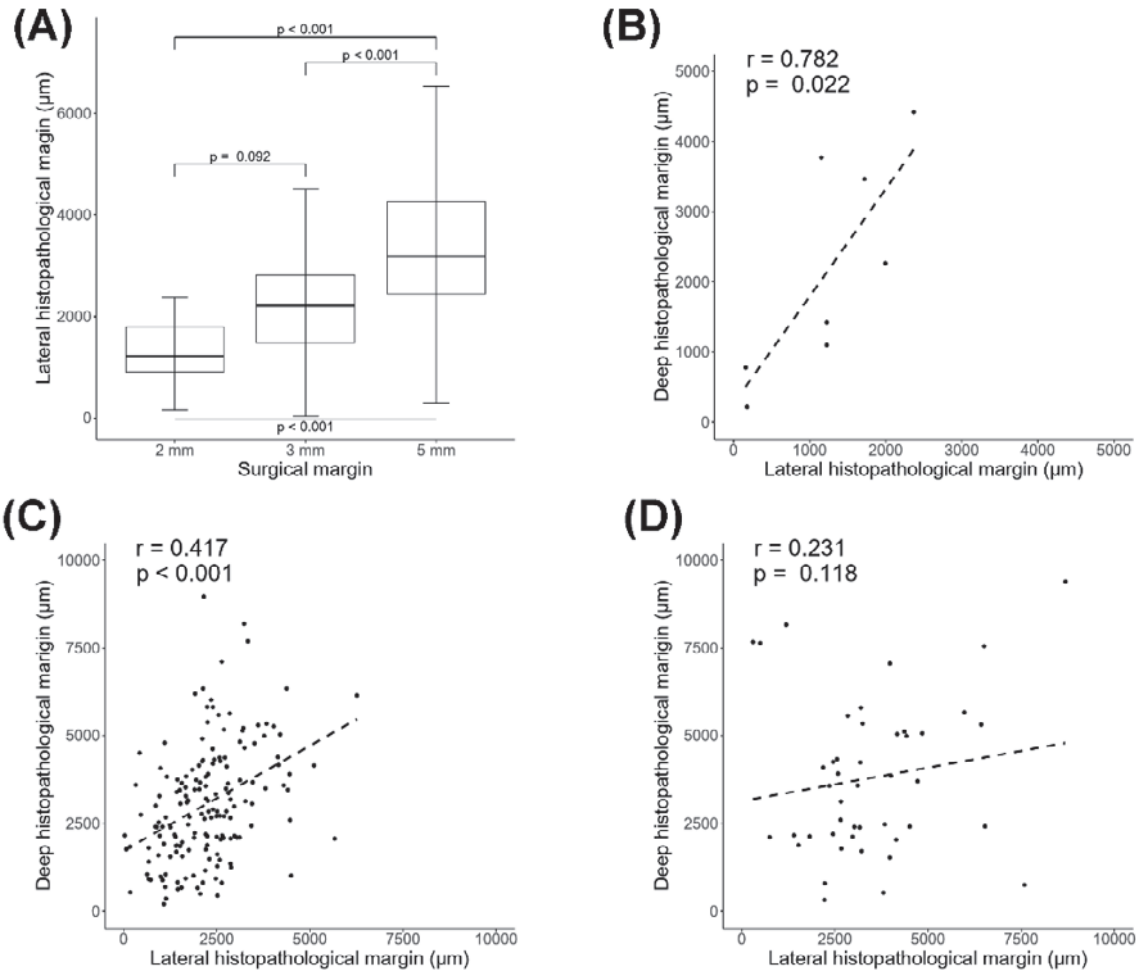

Fig. 1 Correlations of surgical and histopathological margins.

(**A**) The lateral histopathological margin is significantly narrower in the 2-mm and 3-mm surgical margin groups than in the 5-mm surgical margin group (p<0.001 and p<0.001 respectively; Kruskal-Wallis test).

(**B**) The deep histopathological margin significantly correlates with the lateral histopathological margin in the 2-mm surgical margin group (r = 0.782, p= 0.022).

(**C**) The deep histopathological margin significantly correlates with the lateral histopathological margin in the 3-mm surgical margin group (r = 0.417, p<0.001).

(**D**) The deep histopathological margin does not significantly correlate with the lateral histopathological margin in the 5-mm surgical margin group (r = 0.231, p= 0.118).

countries[11,36]. Because most BCCs in Japanese are pigmented (88.3%[5]; 99.5% in this study), surgical excision is performed with clinical resection margins from 2 mm to 10 mm[7,22–24,37]. Histopathological evaluation of the stump in a permanent specimen can confirm that the histopathological tumor extension closely matches the clinical tumor extension. However, tumors may have a histopathological spread greater than the clinical tumor spread. If tumors are exposed at the surgical margins, the surgical margins are diagnosed as positive. In addition, even if pathological margins are negative, they are sometimes too narrow. If margins are histopathologically negative, some patients are followed-up without additional resection.

It is important to discuss whether additional resection should be performed in cases where resection margins are close to the tumor and whether the recurrence rate is tolerable even after follow-up. Recurrence requires re-excision and re-excision imposes a significant burden on patients. In addition, this process is expensive and inevitably consumes medical resources. Therefore, the recurrence rate is an important issue. Pascal *et al*.[38] examined the rate of recurrence 10 years after resection of BCC. Recurrence occurred in 1 of 84 cases with non-proximal margins, 14 of 42 cases with positive margins, and 2 of 17 cases with proximal margins (the tumor was close to the margin at ×400 magnification of histopathological tissue). Longhi *et al*.[39] investigated recurrence of BCC re-

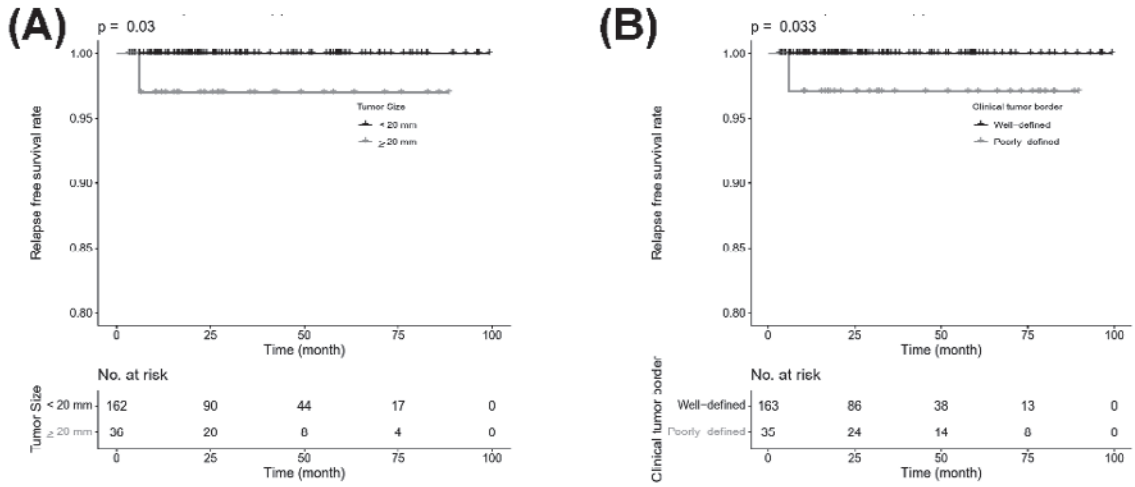

Fig. 2 Recurrence rate and associated factors.
(**A**) BCCs <20 mm had a significantly higher relapse-free survival rate than those ≥20 mm (p<0.03).
(**B**) BCCs with well-defined clinical tumor borders were associated with a significantly higher relapse-free survival rate than were those with poorly defined clinical tumor borders (p<0.0333).

sected during the 8-year period between 1996 and 2004. Recurrence was observed in 0 of 866 of patients with non-proximal stumps and 1 of 40 of patients with proximal stumps (<1 mm). Lin *et al*.[40] reviewed 146 cases of BCC resected between 2002 and 2013. Recurrence after BCC resection was also investigated. For pathological margins >1 mm, the recurrence rate was 0 for 77 cases during a mean follow-up period of 5.53 years. For pathological margins <1 mm, recurrence developed in 1 of 43 cases during a mean follow-up period of 4.48 years. Auw-Haedrich *et al*.[41] investigated outcomes for 101 periocular BCCs resected between 1997 and 1999. The mean follow-up period after resection of BCC was 7.3 years (104 days to 9.7 years). Recurrence was observed in 3 of 18 patients with pathological margins <0.2 mm and in 1 of 72 patients with pathological margins >0.2 mm. Recurrence was observed in 0 of 15 patients with pathological margins <0.2 mm and in 0 of 59 patients with pathological margins >0.2 mm. When limited to the morphea type, recurrence was observed in 3 of 3 cases with pathological margins <0.2 mm and in 1 of 13 cases with pathological margins >0.2 mm. Wavreille *et al*.[42] investigated outcomes for resected cases of BCC between 2003 and 2005. By 2011, 3 of 11 patients with pathological margins >1 mm developed recurrence, and 8 of 67 patients with pathological margins <1 mm developed recurrence. Recurrence was observed in 0 of 47 patients (pathological margins > 0.8 mm) and 4 of 33 patients (pathological margins <0.8 mm) with nodular tumors. Dallari *et al*.[43] investigated recurrence after resection in 51 patients aged 75 years or older who underwent resection from 2005 to 2016 for head and neck BCC. Recurrence was observed in 2 of 20 patients with positive margins, 0 of 8 patients with pathological margins ≤1 mm, and 1 of 23 patients with pathological margins >1 mm. Yildizdal *et al*.[34] investigated BCC recurrence after appropriate resection of 539 lesions in patients with a median age of 67 years (range, 12-98 years) between 2012 and 2018. Recurrence was observed in 19% of cases with histopathological margins ≤1 mm, and in 8% of those with histopathological margins >1 mm and ≤3 mm. The overall recurrence rate was 0.8%, and the recurrence rates for non-aggressive and aggressive cancers were 10.8% and 22.8%, respectively. However, no association between histopathological type and histopathological margin was observed.

In this study, the recurrence rate was very low (0.5%), and the histopathological margins were not associated with recurrence rate. It should be noted that most BCCs in this study were pigmented and that determination of tumor extent was relatively easy[7,22–24,37]. In Japanese patients with BCCs, even narrow surgical margins ensure a high rate of tumor-free histopathological margins[7,22–24,37]. In light of these previous findings, our data are acceptable. Specifically, our findings suggest that surgical excision with a narrow surgical margin (<4 mm) is acceptable. However, a long-term randomized controlled trial with a large number of Japanese patients is eagerly awaited.

We would like to discuss the relationships between surgical margins and histopathological margins. A wider surgical margin is strongly associated with a wider lateral histopathological margin, as reported previously[22–24,37]. Interestingly, the deep histopathological margin was sig-

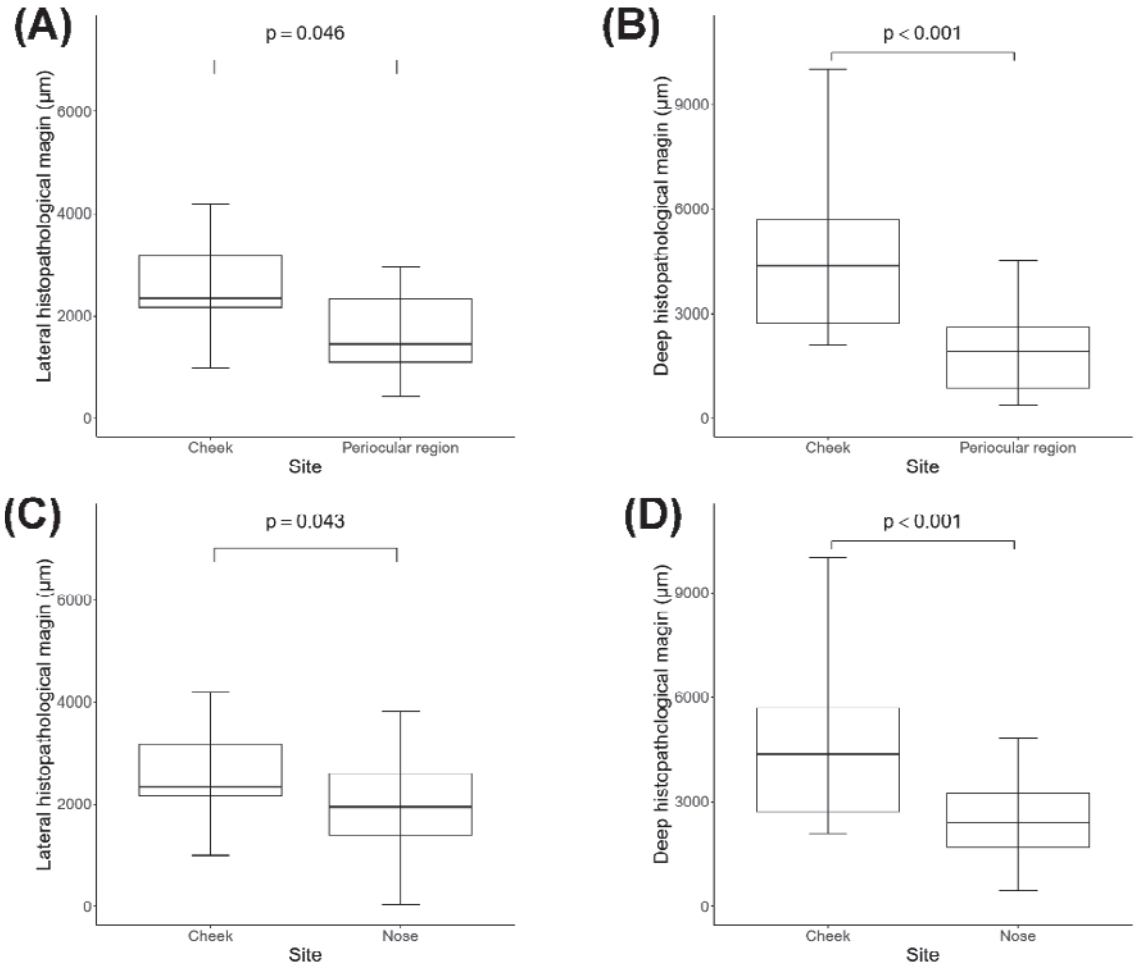

Fig. 3 Lateral histopathological margins in facial BCCs in the 3-mm surgical margin group.
(**A**) Lateral histopathological margins were significantly narrower in the periorbital region than in the cheek (p= 0.046).
(**B**) Deep histopathological margins were significantly narrower in the periorbital region than in the cheek (p<0.001).
(**C**) Lateral histopathological margins were significantly narrower in the nose than in the cheek (p= 0.043).
(**D**) Deep histopathological margins were significantly narrower in the nose than in the cheek (p<0.001).

nificantly correlated with the lateral histopathological margin in the 2-mm surgical and the 3-mm surgical margin groups. However, in our study, if there was a clear histopathological margin, a narrow histopathological margin was not associated with the recurrence rate. However, surgical resection with a narrow surgical margin, although challenging, is acceptable if a negative histopathological margin is achieved[20,24,37]. To avoid a positive histopathological margin, surgical resection with a wider surgical margin might also be acceptable[7,10].

Histopathological margins were significantly narrower in the nose and periorbital region than in the cheek. There are two possible reasons for this. We used formalin-fixed paraffin-embedded sections, and shrinkage is inevitable during fixation. One possibility is that cheek skin might shrink less than nasal or periorbital skin during fixation. However, the shrinkage ratio did not differ for the nose (89%; 118 mm^2/123 mm^2), periorbital region/lip (96%; 118 mm^2/123 mm^2) and other tissue, including cheek, (89%; 93 mm^2/104 mm^2)[44]. Therefore, shrinkage due to fixation is not the explanation. Another possibility is that BCC on the nose or periorbital region might exhibit wider and deeper invasion than in the cheek. Matsushita *et al*.[37] reported that BCCs in the nose, periorbital region, and other facial regions, including the cheek, showed muscular invasion in 5.4%, 12.7%, and 2.7% of cases, respectively. Ceder *et al*.[45] reported that excised BCCs from the nose, periorbital region, and other facial regions, including the cheek, had incomplete excision rates of 32.8%, 33.3%, and 15.9%, respectively. Dalal *et al*.[46] found that excised BCCs in the nose, periorbital region, and cheek had close margins in 23.4% (19/81), 40%

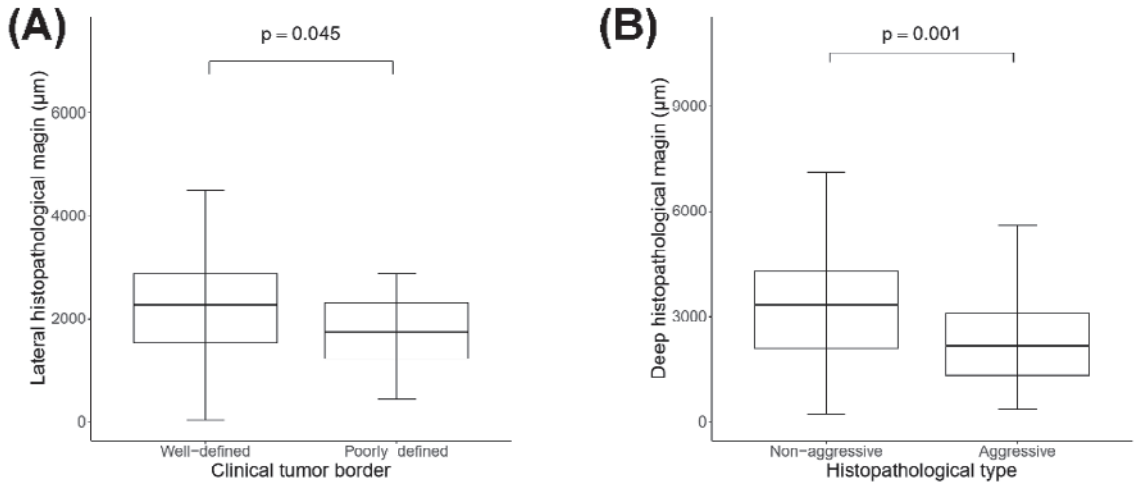

Fig. 4 Factors affecting histopathological margins in the 3-mm surgical margin group.
(**A**) Lateral histopathological margins were significantly narrower in BCCs with poorly defined clinical tumor borders (p= 0.045).
(**B**) Deep histopathological margins were significantly narrower in histopathologically aggressive BCCs (p= 0.001).

(10/25), and 16% (10/61) of cases, respectively. In sum, BCCs in the nose or periorbital region might exhibit wider and deeper invasion than clinical estimates.

Lateral and deep histopathological margins are significantly narrower in BCCs with poorly defined clinical tumor borders and in histopathologically aggressive BCCs, respectively. Terashi *et al*.[32] recommended a two-step operation for BCCs in the supra-alar crease area, because clearance of a deep histopathological margin might be difficult. BCCs on the nose and periorbital region, with poorly defined clinical tumor borders or of the histopathologically aggressive type, might require surgical resection with a wider surgical margin or two-step operations to avoid a positive histopathological margin.

In conclusion, we evaluated risk factors for BCC recurrence after surgical excision. Tumor size and clinical tumor border were significantly associated with BCC recurrence, but histopathological margins were not. We thus conclude that a narrow histopathological margin is acceptable for surgical resection of BCC in Japanese patients.

Author Contributions: S.M. and T.H. are the main authors in manuscript drafting; T.H. conducted the study; S.M., Y.T, A.P., and S.O. collected the data; S.M. and T.H performed the statistical analysis and prepared the figures; N.K. and H.S. critically revised the manuscript.

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References

1. Lomas A, Leonardi-Bee J, Bath-Hextall F. A systematic review of worldwide incidence of nonmelanoma skin cancer. Br J Dermatol. 2012 May;166(5):1069−80.
2. Hoashi T, Kanda N, Saeki H. Molecular mechanisms and targeted therapies of advanced basal cell carcinoma. Int J Mol Sci. 2022 Oct 8;23(19):11968.
3. Messina J, Epstein EH Jr, Kossard S, et al. Basal cell carcinoma. In: Elder DE, Massi D, Scolyer RA, Willemze R, editors. WHO Classification of Skin tumors. 4th Ed. IARC Publications; 2018. p. 26−34.
4. Muzic JG, Schmitt AR, Wright AC, et al. Incidence and trends of basal cell carcinoma and cutaneous squamous cell carcinoma: a population-based study in Olmsted County, Minnesota, 2000 to 2010. Mayo Clin Proc. 2017 Jun;92(6):890−8.
5. Takenouchi T, Takatsuka S. Long-term prognosis after surgical excision of basal cell carcinoma: a single institutional study in Japan. J Dermatol. 2013 Sep;40(9):696−9.
6. Sobanko JF, Lynm C, Rosenbach M. Basal cell carcinoma. JAMA Dermatol. 2013 Jun;149(6):766.
7. Hoashi T, Ishikawa M, Uehara J, et al. Japanese Dermatological Association Guidelines: outlines of Japanese clinical guidelines for basal cell carcinoma 2021. J Dermatol. 2024 Apr;51(4):e90−105.
8. Kanzaki A, Ansai SI, Ueno T, et al. A case of metastatic basal cell carcinoma treated with cisplatin and adriamycin. J Nippon Med Sch. 2017;84(6):286−90.
9. Fukumoto T, Fukumoto R, Oka M, Horita N. Comparing treatments for basal cell carcinoma in terms of long-term treatment-failure: a network meta-analysis. J Eur Acad Dermatol Venereol. 2019 Nov;33(11):2050−7.

10. Schmults CD, Blitzblau R, Aasi SZ, et al. Basal cell skin cancer, version 2.2024, NCCN Clinical Practice Guidelines in Oncology. J Natl Compr Canc Netw. 2023 Nov;21(11): 1181–203.
11. Thissen MR, Neumann MH, Schouten LJ. A systematic review of treatment modalities for primary basal cell carcinomas. Arch Dermatol. 1999 Oct;135(10):1177–83.
12. Shinji S, Yamada T, Matsuda A, et al. Recent advances in the treatment of colorectal cancer: a review. J Nippon Med Sch. 2022 Jun 28;89(3):246–54.
13. Minamimura K, Hara K, Matsumoto S, et al. Current status of robotic gastrointestinal surgery. J Nippon Med Sch. 2023;90(4):308–15.
14. Wade TR, Ackerman AB. The many faces of basal-cell carcinoma. J Dermatol Surg Oncol. 1978 Jan;4(1):23–8.
15. Cameron MC, Lee E, Hibler BP, et al. Basal cell carcinoma: epidemiology; pathophysiology; clinical and histological subtypes; and disease associations. J Am Acad Dermatol. 2019 Feb;80(2):303–17.
16. Niculet E, Craescu M, Rebegea L, et al. Basal cell carcinoma: comprehensive clinical and histopathological aspects, novel imaging tools and therapeutic approaches (Review). Exp Ther Med. 2022 Jan;23(1):60.
17. Marzuka AG, Book SE. Basal cell carcinoma: pathogenesis, epidemiology, clinical features, diagnosis, histopathology, and management. Yale J Biol Med. 2015 Jun;88(2): 167–79.
18. Demirtasoglu M, Ilknur T, Lebe B, Kusku E, Akarsu S, Ozkan S. Evaluation of dermoscopic and histopathologic features and their correlations in pigmented basal cell carcinomas. J Eur Acad Dermatol Venereol. 2006 Sep;20 (8):916–20.
19. Maloney ME, Jones DB, Sexton FM. Pigmented basal cell carcinoma: investigation of 70 cases. J Am Acad Dermatol. 1992 Jul;27(1):74–8.
20. Ramdas K, van Lee C, Beck S, et al. Differences in rate of complete excision of basal cell carcinoma by dermatologists, plastic surgeons and general practitioners: a large cross-sectional study. Dermatology. 2018;234(3-4):86–91.
21. Work Group; Invited Reviewers; Kim JYS, et al. Guidelines of care for the management of basal cell carcinoma. J Am Acad Dermatol. 2018 Mar;78(3):540–59.
22. Ito T, Inatomi Y, Nagae K, et al. Narrow-margin excision is a safe, reliable treatment for well-defined, primary pigmented basal cell carcinoma: an analysis of 288 lesions in Japan. J Eur Acad Dermatol Venereol. 2015 Sep;29(9): 1828–31.
23. Nakamura Y, Tanese K, Hirai I, et al. Evaluation of the appropriate surgical margin for pigmented basal cell carcinoma according to the risk factors for recurrence: a single-institute retrospective study in Japan. J Eur Acad Dermatol Venereol. 2018 Dec;32(12):e453–5.
24. Nakamura Y, Matsushita S, Tanaka R, et al. 2-mm surgical margins are adequate for most basal cell carcinomas in Japanese: a retrospective multicentre study on 1000 basal cell carcinomas. J Eur Acad Dermatol Venereol. 2020 Sep;34(9):1991–8.
25. Goyal S, Rathore R, Sharma S, Arora VK, Das GK, Singal A. Cutaneous basal cell carcinoma with mixed histology: cytomorphological features of two unusual cases. J Cytol. 2017 Apr-Jun;34(2):115–8.
26. Pyne JH, Myint E, Barr EM, Clark SP, Hou R. Basal cell carcinoma: variation in invasion depth by subtype, sex, and anatomic site in 4,565 cases. Dermatol Pract Concept. 2018 Oct;8(4):314–9.
27. Navarrete-Dechent C, Aleissa S, Cordova M, et al. Management of complex head-and-neck basal cell carcinomas using a combined reflectance confocal microscopy/optical coherence tomography: a descriptive study. Arch Dermatol Res. 2021 Apr;313(3):193–200.
28. Aleissa S, Navarrete-Dechent C, Cordova M, et al. Presurgical evaluation of basal cell carcinoma using combined reflectance confocal microscopy-optical coherence tomography: a prospective study. J Am Acad Dermatol. 2020 Apr;82(4):962–8.
29. Takenouchi T, Nomoto S, Ito M. Factors influencing the linear depth of invasion of primary basal cell carcinoma. Dermatol Surg. 2001 Apr;27(4):393–6.
30. Morgan FC, Ruiz ES, Karia PS, Besaw RJ, Neel VA, Schmults CD. Factors predictive of recurrence, metastasis, and death from primary basal cell carcinoma 2 cm or larger in diameter. J Am Acad Dermatol. 2020 Sep;83(3): 832–8.
31. Kiely JR, Patel AJK. A retrospective study of 694 Basal Cell Carcinoma excisions to quantify deep margin documentation and clearance compared to histological type and surgical margin. J Plast Reconstr Aesthet Surg. 2019 Nov;72(11):1805–12.
32. Terashi H, Kurata S, Hashimoto H, et al. Adequate depth of excision for basal cell carcinoma of the nose. Ann Plast Surg. 2002 Feb;48(2):214–6.
33. Hoashi T, Sato S, Yamaguchi Y, Passeron T, Tamaki K, Hearing VJ. Glycoprotein nonmetastatic melanoma protein b, a melanocytic cell marker, is a melanosome-specific and proteolytically released protein. FASEB J. 2010 May;24(5):1616–29.
34. Yildizdal S, Kucukguven A, Calis M, Vargel I. Evaluation of histopathological margin and other recurrence parameters in basal cell carcinoma: a retrospective analysis of 8821 lesions. J Plast Reconstr Aesthet Surg. 2022 Sep;75(9): 3390–7.
35. Hoashi T, Watabe H, Muller J, Yamaguchi Y, Vieira WD, Hearing VJ. MART-1 is required for the function of the melanosomal matrix protein PMEL17/GP100 and the maturation of melanosomes. J Biol Chem. 2005 Apr 8;280 (14):14006–16.
36. Gulleth Y, Goldberg N, Silverman RP, Gastman BR. What is the best surgical margin for a Basal cell carcinoma: a meta-analysis of the literature. Plast Reconstr Surg. 2010 Oct;126(4):1222–31.
37. Matsushita S, Nakamura Y, Tanaka R, et al. Prediction of the invasive level of basal cell carcinomas in the facial area: analysis of 718 Japanese cases. J Dermatol Sci. 2020 Sep;99(3):152–7.
38. Pascal RR, Hobby LW, Lattes R, Crikelair GF. Prognosis of "incompletely excised" versus "completely excised" basal cell carcinoma. Plast Reconstr Surg. 1968 Apr;41(4): 328–32.
39. Longhi P, Serra MP, Robotti E. Incompletely excised basal cell carcinomas: our guidelines. Onco Targets Ther. 2008 Jul 1;1:1–4.
40. Lin SH, Cheng YW, Yang YC, Ho JC, Lee CH. Treatment of pigmented basal cell carcinoma with 3 mm durgical margin in Asians. Biomed Res Int. 2016;2016:7682917.
41. Auw-Haedrich C, Frick S, Boehringer D, Mittelviefhaus H. Histologic safety margin in basal cell carcinoma of the eyelid: correlation with recurrence rate. Ophthalmology. 2009 Apr;116(4):802–6.
42. Wavreille O, Martin De Lassalle E, Wavreille G, Mortier L, Martinot Duquennoy V. [Histologic risk factors of basal cell carcinoma of the face, about 184 cases]. Ann Chir Plast Esthet. 2012 Dec;57(6):542–8. French.

43. Dallari S, Zaraca G, Giorgini S, Borgonzoni M. Close and positive margins in non-melanoma skin malignancies of the head and neck. What to do in patients over 75 years of age? A preliminary study. G Ital Dermatol Venereol. 2020 Aug;155(4):464–9.
44. Hudson-Peacock MJ, Matthews JN, Lawrence CM. Relation between size of skin excision, wound, and specimen. J Am Acad Dermatol. 1995 Jun;32(6):1010–5.
45. Ceder H, Ekstrom A, Hadzic L, Paoli J. Clinicopathological factors associated with incomplete excision of high-risk basal cell carcinoma. Acta Derm Venereol. 2021 Jul 13;101(7):adv00496.
46. Dalal AJ, Ingham J, Collard B, Merrick G. Review of outcomes of 500 consecutive cases of non-melanoma skin cancer of the head and neck managed in an oral and maxillofacial surgical unit in a District General Hospital. Br J Oral Maxillofac Surg. 2018 Nov;56(9):805–9.

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