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Original Article

# A very close margin of ≤1 mm predicts a poor outcome in resected buccal cancer patients with a pathological margin of ≤3 mm

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ABSTRACT

*Objectives:* A close margin of ≤3 mm results in a high risk for locoregional recurrence, but still is not an independent factor that helps to guide the use of aggressive postoperative therapies in patients with resected buccal mucosa carcinoma. This suggests there is a diversity of clinical outcomes in this group of patients. The present study explores the predictors among this clinically debated group of patients.
*Materials and Methods:* From 2000 to 2008, 30 resected buccal mucosa carcinoma patients with a close margin of ≤3 mm were retrospectively included in this study. All patients were treated with radical surgery together with postoperative radiotherapy (RT) or chemoradiotherapy (CCRT). Locoregional/local/regional control, disease-free status, disease-specific survival and overall survival were the study end points.
*Results:* Two factors were observed that were able to predict 5-year locoregional control. These were a pathological N classification (pN0 vs. pN1-2, 71.5% vs. 30.0%, $p = 0.044$) and a very close margin (> 1 mm vs. ≤1 mm, 81.8% vs. 50.7%, $p = 0.040$). Remarkably, the predicting effect of a very close margin was well translated into disease-free status (81.8% vs. 47.1%, $p = 0.024$) and disease-specific survival (100% vs. 70.6%, $p = 0.037$). After multivariate analysis, a very close margin of ≤1 mm was found to independently predict a high risk of locoregional recurrence (HR, 9.528; 95% CI, 1.326–18.481; $p = 0.025$) and disease failure at any site (HR, 12.778; 95% CI, 1.934–25.217; $p = 0.013$).
*Conclusion:* More aggressive postoperative treatments should be considered for resected buccal mucosa carcinoma patients with a very close margin of ≤1 mm.


## 1. Introduction

Buccal mucosa carcinoma has rapidly increased in incidence, especially in recent years [1]. Radical surgery with or without postoperative therapies is the treatment of choice in patients with resectable disease, depending on pathological adverse features at the time of radical surgery [2]. For example, extracapsular nodal spread and a positive surgical margin are independent guides with respect to postoperative chemoradiotherapy (CCRT). Other adverse features guide postoperative radiotherapy (RT) with or without chemotherapy and these include classification as pT3-4, positive nodal disease, nodal disease at neck level IV-V, vascular embolism and peri-neural invasion; however a close margin is not one of these [2].

A close margin has been reported to predict a high risk of cancer recurrence in many studies [3–6], despite the fact that a definition

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is still debated. For example, either ≤5 mm or ≤4 mm has been suggested as a definition for "a close margin", according to on-line oncological guidelines [2,3] and studies in Taiwan [6], respectively. However, we have previously observed that patients with a margin of ≤3 mm demonstrate poor clinical outcomes [5]. However, as mentioned above, a close margin alone is still not an independent indicator for guiding postoperative adjuvant therapies [2,7]. Thus, further stratification of these patients seems to be essential and has been debated clinically.

Based on the above, this study explores the factors that are able to predict clinical outcome and thus guide appropriate postoperative treatments in resected buccal mucosa carcinoma patients with a close margin of ≤3 mm. Specifically, locoregional/local/regional control, disease-free survival, disease-specific survival and overall survival were defined as the study end points.

## 2. Materials and methods

### 2.1. The ethic considerations

The procedures followed here were approved by our Institution Review Board (IRB) and are in accordance with the Helsinki Declaration of 1975 as revised in 1983.

### 2.2. Patient allocation and clinical data collection

From August 1, 2000, to December 30, 2008, we retrospectively collected data from 30 resectable buccal mucosa carcinoma patients who had a pathological margin of ≤3 mm and were treated with postoperative RT or CCRT (Fig. 1 and Table 1). Two researchers doubly reviewed all medical records. Data discrepancies were resolved by consensus. All 30 patients had no distant metastasis at

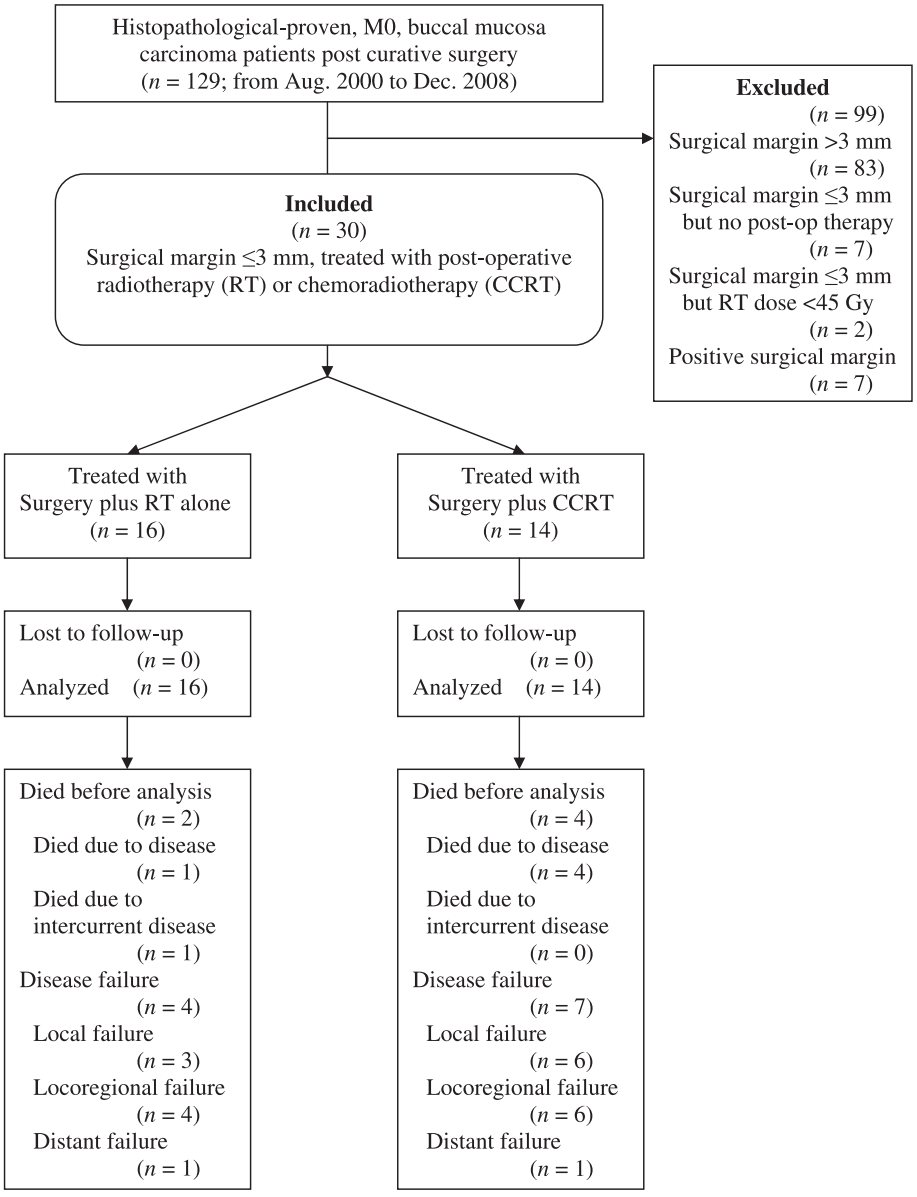


**Fig. 1.** Patient allocation flowchart. CCRT = chemoradiotherapy; RT = radiotherapy.

**Table 1**
Patient characteristics according to postoperative therapy.

| | Postoperative treatment, *n* (%) | | *p* value[a] | Total, *n* (%) |
|---|---|---|---|---|
| | RT alone | CCRT | | |
| Age (years) | | | | |
| ≤50 | 7 (43.8) | 8 (57.1) | 0.715 | 15 (50.0) |
| >50 | 9 (56.3) | 6 (42.9) | | 15 (50.0) |
| Gender | | | | |
| Female | 2 (12.5) | 2 (14.3) | 0.990 | 4 (13.3) |
| Male | 14 (87.5) | 12 (85.7) | | 26 (86.7) |
| ECOG PS [b] | | | | |
| 0–1 | 10 (62.5) | 11 (78.6) | 0.440 | 21 (70.0) |
| ≥2 | 6 (37.5) | 3 (21.4) | | 9 (30.0) |
| Smoking | | | | |
| No | 2 (12.5) | 4 (28.6) | 0.378 | 6 (20.0) |
| Yes | 14 (87.5) | 10 (71.4) | | 24 (80.0) |
| Betel nut chewing | | | | |
| No | 3 (18.8) | 4 (28.6) | 0.675 | 7 (23.3) |
| Yes | 13 (81.3) | 10 (71.4) | | 23 (76.7) |
| Histology | | | | |
| Well to moderate | 15 (93.8) | 13 (92.9) | 0.990 | 28 (93.3) |
| Poor differentiation | 1 (6.3) | 1 (7.1) | | 2 (6.7) |
| Invasion depth (mm) | | | | |
| <10 | 8 (50.0) | 4 (28.6) | 0.284 | 12 (40.0) |
| ≥10 | 8 (50.0) | 10 (71.4) | | 18 (60.0) |
| pT status | | | | |
| pT1-3 | 16 (100) | 4 (28.6) | <0.001 | 20 (66.7) |
| pT4 | 0 | 10 (71.4) | | 10 (33.3) |
| pN status | | | | |
| pN0 | 15 (93.8) | 10 (71.4) | 0.157 | 25 (83.3) |
| pN1-2 | 1 (6.3) | 4 (28.6) | | 5 (16.7) |
| Pathology stage | | | | |
| I-III | 15 (93.8) | 2 (14.3) | <0.001 | 17 (56.7) |
| IVA/B | 1 (6.3) | 12 (85.7) | | 13 (43.4) |
| Pathological margin (mm) | | | | |
| >1 | 9 (56.3) | 4 (28.6) | 0.159 | 13 (43.3) |
| ≤1 | 7 (43.7) | 10 (71.4) | | 17 (56.7) |
| RT dose (Gy) | | | | |
| ≤66 | 14 (87.5) | 2 (14.3) | <0.001 | 16 (53.3) |
| >66 | 2 (12.5) | 12 (85.7) | | 14 (46.7) |
| Total | 16 (100) | 14 (100) | | 30 (100) |

CCRT = chemoradiotherapy; ECOG PS = Eastern Cooperative Oncology Group performance status; Gy = Gray; RT = radiotherapy.
[a] All *p* values were estimated using Fisher's exact test.
[b] ECOG performance status was recorded by a radiation oncologist at the time of initial presentation at the RT department.

the time of diagnosis and had received definitive treatments. Our pathologists prospectively defined pathological features at the time of radical surgery using an oral cancer-specific checklist and the documented items were audited by another independent pathologist. Pathological invasion depth was measured in millimeters with a cut-off point of 10 mm [8,9], not the original measurement of anatomic layers, as previously reported [10,11]. Cancer staging was defined according to the American Joint Committee on Cancer [12].

### 2.3. Treatment modality

Radical surgery with curative intent was carried out in all patients. All radical surgery was conducted to gain a 1–2 cm surgical margin, depending on the surgeon's available adjustments and the individual's condition. Intra-operatively, routine frozen sectioning was also performed to confirm margin status. Among the 30 patients, 15 individuals received bone resectioning as part of their primary tumor management, either partial mandibulectomy ($n = 12$) or maxillectomy ($n = 3$). In terms of neck management, 15 patients received supra-omohyoid neck dissection and 12 patients received modified radical neck dissection. Altogether, 23 patients received ipsilateral neck dissection and four patients received bilateral neck dissection. All patients received postoperative RT with or without chemotherapy. Postoperative therapies were started 4–7 weeks after surgery.

Intensity-modulated radiotherapy (IMRT) with inverse planning system (PLATO, Nucleotron Inc., The Netherlands) was used for delivering the RT, as previously described [5]. Briefly, the prescribed doses were as follows: 60–72 Gy to the primary surgical bed; 60–66 Gy to the high-risk nodal station; and 50–60 Gy to the low-risk nodal basin. Conventional fractionation was given, i.e., 1.8–2.0 Gy/day and 5 days per week for 6–7 weeks. During the RT course, weekly electronic portal imaging was performed for verification. The dose to the spinal cord was limited to 45 Gy. The prescribed RT dose for patients treated with RT alone or with CCRT was similar.

Chemotherapy was used in conjunction with RT, if indicated, as previously described [5]. Briefly, chemotherapy was indicated in patients with extracapsular nodal spread or with a combination of any two minor risk factors, including perineural invasion, vascular permeation, pT3-4 and positive nodal disease. The chemotherapy protocol contained a concurrent phase of two-cycle cisplatin single agent during RT and an adjuvant phase of another two-cycle cisplatin and fluorouracil (5-FU) after RT. The regimen and doses were as follows: concurrent phase, cisplatin alone (60–100 mg/m$^2$/day on Day 1); and adjuvant phase, cisplatin (60–100 mg/m$^2$/day on Day 1) and 5-FU (1000 mg/m$^2$/day on Days 1–5). The cycle was repeated for 3 weeks.

### 2.4. Statistical methods and definitions

Commercial software (SPSS version 12.0; SPSS Inc., Chicago, IL, USA) was used to conduct the statistical analysis and involved the following. A Kaplan-Meier analysis was used to estimate survival and cancer control rates. The log-rank test was used to assess curve differences between groups. Fisher's exact test was used to evaluate differences between categorical variables. Cox proportional hazard regression was used to perform univariate and multivariate

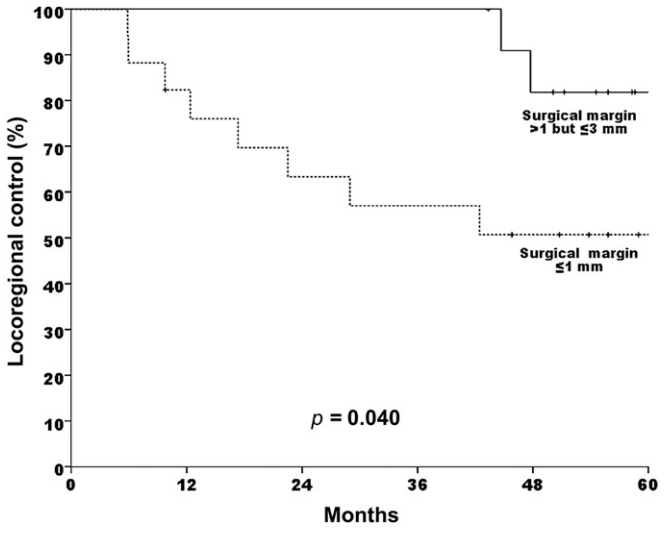


**Fig. 2.** Kaplan-Meier estimate of locoregional control according to pathological margin. * The *p* value was calculated using the log rank test.

**Table 2**
Multivariate analysis for locoregional disease-control end points.

| | Locoregional control[a] | Local control[a] | Regional control[a] |
|---|---|---|---|
| | HR (95CI) | HR (95CI) | HR (95CI) |
| Age (years) | | | |
| ≤50 | 1 | 1 | 1 |
| >50 | 4.540 (0.219–19.032), $p = 0.328$ | 8.503 (0.274–26.768), $p = 0.222$ | 2.432 (0.014–16.968), $p = 0.832$ |
| Gender | | | |
| Female | 1 | 1 | 1 |
| Male | 3.592 (0.004–19.849), $p = 0.710$ | 9.866 (0.034–29.849), $p = 0.316$ | 1.673 (0.083–17.347), $p = 0.762$ |
| ECOG PS [b] | | | |
| 0–1 | 1 | 1 | 1 |
| ≥2 | 1.159 (0.050–16.692), $p = 0.927$ | 1.319 (0.319–11.689), $p = 0.619$ | 4.622 (0.192–26.193), $p = 0.892$ |
| Smoking | | | |
| No | 1 | 1 | 1 |
| Yes | 11.937 (0.567–25.692), $p = 0.369$ | 9.198 (0.740–24.082), $p = 0.066$ | 2.198 (0.279–18.685), $p = 0.866$ |
| Betel nut chewing | | | |
| No | 1 | 1 | 1 |
| Yes | 1.451 (0.061–23.160), $p = 0.824$ | 1.770 (0.013–13.960), $p = 0.900$ | 0.916 (0.123–15.933), $p = 0.831$ |
| Histology | | | |
| Good to moderate | 1 | 1 | 1 |
| Poor differentiation | 7.078 (0.179–19.769), $p = 0.419$ | 13.276 (0.560–29.639), $p = 0.306$ | 7.472 (0.656–37.662), $p = 0.696$ |
| Invasion depth (mm) | | | |
| <10 | 1 | 1 | 1 |
| ≥10 | 1.790 (0.790–20.980), $p = 0.715$ | 2.843 (0.046–17.240), $p = 0.620$ | 1.043 (0.234–17.140), $p = 0.942$ |
| PNI | | | |
| No | 1 | 1 | 1 |
| Yes | 3.912 (0.409–14.921), $p = 0.492$ | 5.932 (0.466–22.925), $p = 0.629$ | 4.998 (0.462–18.832), $p = 0.590$ |
| LVSI | | | |
| No | 1 | 1 | 1 |
| Yes | 4.983 (0.832–13.984), $p = 0.493$ | 3.073 (0.873–15.962), $p = 0.783$ | 5.893 (0.872–19.972), $p = 0.653$ |
| ECS | | | |
| No | 1 | 1 | 1 |
| Yes | 6.829 (0.473–22.872), $p = 0.682$ | 8.962 (0.739–22.982), $p = 0.783$ | 9.392 (0.893–29.301), $p = 0.198$ |
| pT status | | | |
| pT1-3 | 1 | 1 | 1 |
| pT4 | 1.686 (0.089–18.768), $p = 0.730$ | 3.686 (0.098–19.369), $p = 0.557$ | 3.742 (0.291–21.949), $p = 0.851$ |
| pN status | | | |
| pN0 | 1 | 1 | 1 |
| pN1-2 | 3.981 (0.678–13.189), $p = 0.109$ | 7.470 (0.426–18.439), $p = 0.113$ | 6.81 (0.916–21.431), $p = 0.063$ |
| Pathology stage | | | |
| I-III | 1 | 1 | 1 |
| IVA/B | 1.986 (0.036–13.765), $p = 0.750$ | 4.631 (0.115–15.239), $p = 0.211$ | 2.433 (0.395–19.293), $p = 0.764$ |
| Pathological margin (mm) | | | |
| >1 | 1 | 1 | 1 |
| ≤1 | 9.528 (1.326–18.481), $p = 0.025$* | 14.022 (1.128–29.762), $p = 0.043$* | 3.902 (0.385–11.911), $p = 0.672$ |
| RT dose (Gy) | | | |
| ≤66 | 1 | 1 | 1 |
| >66 | 6.548 (0.504–18.148), $p = 0.151$ | 4.649 (0.531–13.042), $p = 0.165$ | 7.891 (0.031–19.147), $p = 0.763$ |

95CI = 95% confidence interval; CCRT = chemoradiotherapy; ECOG PS = Eastern Cooperative Oncology Group performance status; ECS = extracapsular spreading of nodal disease; Gy = Gray; HR = hazard ratio; LVSI = lymphvascular space invasion; PNI = peri-neural infiltration; RT = radiotherapy.
* $p < 0.05$.
[a] All $p$ values were estimated using Cox proportional hazards regression.
[b] ECOG performance status was recorded by a radiation oncologist at the time of initial presentation at the RT department.

analyses in order to calculate a corresponding hazard ratio (HR). In order to provide a good estimate of effective size, all HRs were provided with a corresponding 95% confidence interval (95% CI) in addition to a conventional $p$ value. All tests were two-tailed and considered to be statistically significant when $p < 0.05$. Only factors that gained a statistical significant trend ($p < 0.1$) in univariate analysis were used for multivariate analysis.

All time-to-event analyses calculated the time interval from the day of pathological diagnosis to the day of the corresponding end event. The corresponding end events were defined as follows: *locoregional control*, the first day of local or regional cancer recurrence; *local control*, the first day of local recurrence; *disease-free survival*, the first day of disease failure at any site; *disease-specific survival*, the day of death from cancer; *overall survival*, the day of death from any cause; and, *the follow-up time*, the day of death from any cause or the day of last follow-up. In addition, all time-to-event analyses were censored at the day of last follow-up or the day of non-end-event death.

## 3. Results

### 3.1. Patient, tumor and treatment outcomes

Table 1 shows patient characteristics according to postoperative treatment modality in terms of factors related to the patient, tumor and treatment domains. There were 26 male and four female patients, with a median age of 51.5 years (range, 35–82 years). Most patients had pN0 disease (83.3%, 25/30). All patients had R0 resectioning with a nearest surgical margin of $>0$ mm but $\leq 3$ mm (Fig. 1).

The 5-year control and survival rates for all 30 buccal cancer patients who had a close margin of $\leq 3$ mm were as follows: local control, 67.2%; regional (neck) control, 93.1%; locoregional control, 64.8%; distant metastasis control, 93.1%; disease-free survival, 62.4%; disease-specific survival, 83.3%; and overall survival, 83.3%. The median duration of follow-up for the patients was 52.8 months (mean, 56.8 months; standard deviation, 11.5 months; and, range, 6.4–65.8 months). At the time of analysis, six patients (20%, 6/30) had died and 10 patients (33.3%, 10/30) had locoregional recurrence (Fig. 1). Salvage therapy was performed on eight individuals (80%, 8/10). Among those who underwent salvage therapy, six (75%, 6/8) were still alive and two (25%, 2/8) were dead at the time of the analysis.

### 3.2. The predictors that are correlated with treatment outcomes

Two major predictors for 5-year locoregional control were detected: a pathological margin ($>1$ mm vs. $\leq 1$ mm; 81.8% vs. 50.7%, $p = 0.040$; Fig. 2) and pathological N classification (pN0 vs. pN1-2; 71.5% vs. 30.0%, $p = 0.044$). After multivariate analysis, only a very close margin ($\leq 1$ mm) was an independent predictor for high-risk locoregional failure (HR, 9.528; 95% CI, 1.326–18.481; $p = 0.025$; Table 2).

The 5-year locoregional control rates according to pathological stage and treatment factors were as follows: pathological T classification (pT1-3 vs. pT4, 69.6% vs. 54.0%, $p = 0.553$), overall pathological stage (I-III vs. IVA/B, 76.0% vs. 49.9%, $p = 0.123$), extracapsular spreading of nodal disease (no vs. yes, 71.5% vs. 30.0%, $p = 0.044$), perineural invasion (no vs. yes, 80% vs. 61.7%, $p = 0.446$), postoperative therapy (RT alone vs. CCRT, 74.5% vs. 53.4%, $p = 0.246$) and RT dose ($\leq 66$ Gy vs. $>66$ Gy, 81.3% vs. 42.7%, $p = 0.059$). Furthermore, the effect of surgical margin was well translated into disease-free and disease-specific survival (Fig. 3). After multivariate analysis, a very close margin was also the only independent predictor for a high risk of disease failure at any site (HR, 12.778; 95% CI, 1.934–25.217; $p = 0.013$; Table 3). All time-to-event end points are reported according to their predictive factors in Table 4 and Table 5.

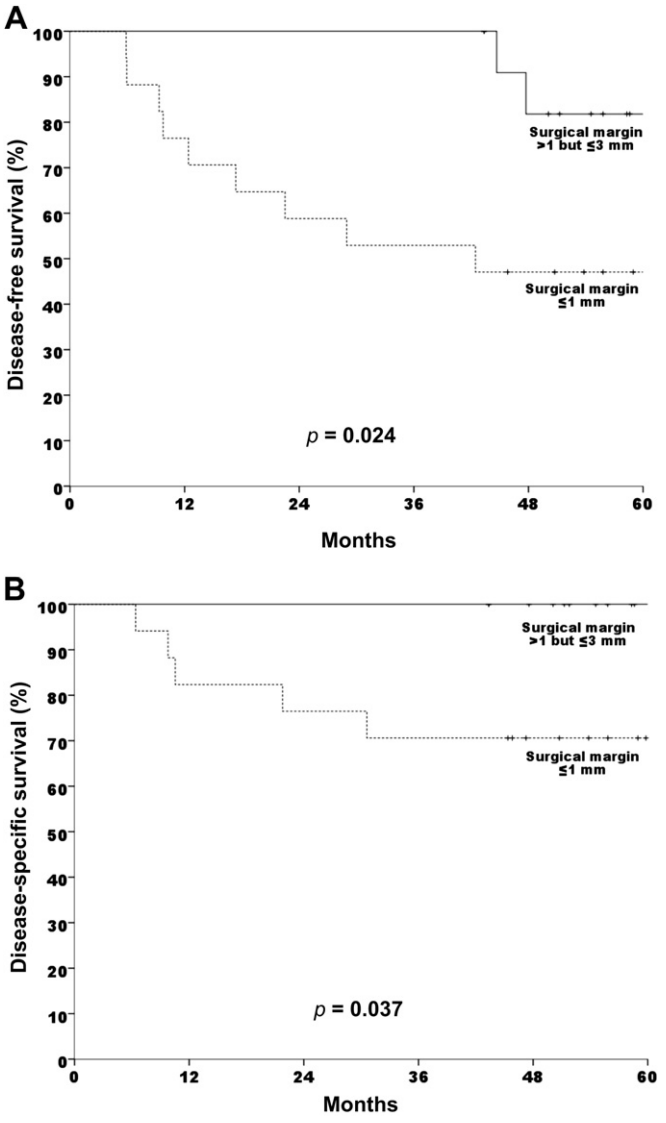


**Fig. 3.** Kaplan-Meier estimates of disease-free survival (A) and disease-specific survival (B) according to the pathological margin. * The $p$ value was calculated using the log rank test.

## 4. Discussion

In the present study, we observed that a very close margin ($\leq 1$ mm) was the most important outcome predictor in resectable buccal mucosa carcinoma patients with a close margin $\leq 3$ mm in terms of 5-year locoregional control (Fig. 2, Table 2 and Table 4), disease-free survival and disease-specific survival (Fig. 3, Table 3 and Table 5). Thus, in clinical practice, it is reasonable to treat these patients with aggressive modalities, such as re-resectioning to gain a wider margin or intensive CCRT after surgery, which is similar to the treatment of patients who have a positive margin (0 mm).

Buccal mucosa carcinoma has been observed to have poorer clinical outcomes than carcinoma arising from other sites in the oral cavity [13]. A high recurrence rate has been reported even in early-stage patients and rates as high as 40–80% when treated with wide excision alone have been published [14,15]. However, in Taiwan, a much better treatment outcome has been observed, with a recurrence rate of less than 20% [6]. This discrepancy in treatment outcomes may be because of different proportions of close-margin patients; i.e., surgery in Taiwan is more radical with fewer close-margin patients, which will have an obvious benefit (around 10% in $\leq 4$ mm in a Taiwan series) [6]. Our results indicate that patients with very close margin have poorer outcomes and this supports the role of radical surgery with adequate margin.

Other than a very close margin, pathological T status has previously been observed to be a potential predictor for patient survival among patients with a free margin [16]. However, our results did not support this finding. On the other hand, we observed that pathology N status seems to be correlated with locoregional control and disease-free survival (pN0 vs. pN1-2, 71.5% vs. 30.0%, $p = 0.044$; Table 4 and Table 5). However, after multivariate analysis, this observation was found not to be statistically significant (Table 2 and Table 3).

**Table 3**
Multivariate analysis for the patient survival end points.

| | Disease-free survival[a] | Disease-specific survival[a] | Overall survival[a] |
|---|---|---|---|
| | HR (95CI) | HR (95CI) | HR (95CI) |
| Age (years) | | | |
| ≤50 | 1 | 1 | 1 |
| >50 | 4.088 (0.189–18.388), $p = 0.369$ | 3.280 (0.498–16.488), $p = 0.193$ | 4.8037 (0.298–12.988), $p = 0.239$ |
| Gender | | | |
| Female | 1 | 1 | 1 |
| Male | 4.326 (0.140–16.018), $p = 0.369$ | 1.54 (0.297–11.918), $p = 0.698$ | 4.995 (0.293–9.832), $p = 0.492$ |
| ECOG PS[b] | | | |
| 0–1 | 1 | 1 | 1 |
| ≥2 | 1.266 (0.155–12.189), $p = 0.886$ | 4.826 (0.355–14.935), $p = 0.386$ | 4.998 (0.192–9.921), $p = 0.492$ |
| Smoking | | | |
| No | 1 | 1 | 1 |
| Yes | 9.960 (0.175–17.517), $p = 0.341$ | 12.446 (0.475–29.419), $p = 0.134$ | 11.246 (0.282–25.835), $p = 0.739$ |
| Betel nut chewing | | | |
| No | 1 | 1 | 1 |
| Yes | 1.699 (0.169–12.065), $p = 0.746$ | 0.632 (0.087–5.845), $p = 0.396$ | 0.51 (0.089–7.925), $p = 0.742$ |
| Histology | | | |
| Well to moderate | 1 | 1 | 1 |
| Good differentiation | 8.168 (0.178–21.695), $p = 0.328$ | 5.103 (0.098–18.592), $p = 0.218$ | 8.024 (0.098–19.815), $p = 0.892$ |
| Invasion depth (mm) | | | |
| <10 | 1 | 1 | 1 |
| ≥10 | 3.818 (0.116–15.135), $p = 0.452$ | 5.899 (0.234–18.593), $p = 0.782$ | 8.921 (0.493–18.982), $p = 0.873$ |
| PNI | | | |
| No | 1 | 1 | 1 |
| Yes | 5.302 (0.509–18.943), $p = 0.654$ | 8.981 (0.492–19.734), $p = 0.619$ | 6.932 (0.539–19.819), $p = 0.621$ |
| LVSI | | | |
| No | 1 | 1 | 1 |
| Yes | 5.342 (0.593–14.783), $p = 0.592$ | 6.392 (0.204–14.763), $p = 0.592$ | 4.732 (0.529–13.890), $p = 0.593$ |
| ECS | | | |
| No | 1 | 1 | 1 |
| Yes | 9.872 (0.498–24.981), $p = 0.194$ | 14.902 (0.245–33.981), $p = 0.298$ | 11.734 (0.892–29.124), $p = 0.392$ |
| pT status | | | |
| pT1-3 | 1 | 1 | 1 |
| pT4 | 1.166 (0.178 − 8.645), $p = 0.914$ | 1.239 (0.281 − 8.388), $p = 0.872$ | 2.926 (0.878 − 5.743), $p = 0.192$ |
| pN status | | | |
| pN0 | 1 | 1 | 1 |
| pN1-2 | 7.984 (0.778–18.587), $p = 0.094$ | 11.83 (0.379–28.849), $p = 0.170$ | 9.382 (0.822–25.793), $p = 0.112$ |
| Pathology stage | | | |
| I-III | 1 | 1 | 1 |
| IVA/B | 2.655 (0.158–12.762), $p = 0.616$ | 1.950 (0.745–9.837), $p = 0.136$ | 1.325 (0.086–7.965), $p = 0.671$ |
| Pathological margin (mm) | | | |
| >1 | 1 | 1 | 1 |
| ≤1 | 12.778 (1.934–25.217), $p = 0.013$* | 16.521 (0.882–36.462), $p = 0.198$ | 15.879 (0.538–35.979), $p = 0.879$ |
| RT dose (Gy) | | | |
| ≤66 | 1 | 1 | 1 |
| >66 | 5.648 (0.412–12.158), $p = 0.198$ | 5.541 (0.148–14.982), $p = 0.779$ | 4.958 (0.212–16.192), $p = 0.698$ |

95CI = 95% confidence interval; CCRT = chemoradiotherapy; ECOG PS = Eastern Cooperative Oncology Group performance status; ECS = extracapsular spreading of nodal disease; Gy = Gray; HR = hazard ratio; LVSI = lymphvascular space invasion; PNI = peri-neural infiltration; RT = radiotherapy.
* $p < 0.05$.
[a] All $p$ values were estimated using Cox proportional hazards regression.
[b] ECOG performance status was recorded by a radiation oncologist at the time of initial presentation at the RT department.

Several potential etiologies have been recognized that may result in a close margin, such as post-formalin-fixed tissue shrinkage, the anatomic limitations and the intrinsically biological aggressiveness of cancer itself [17]. In the third situation, more biological aggressiveness results in a higher cancer cell infiltration rate and thus an unexpectedly close surgical margin after curative-intent radical surgery. Therefore, in addition to physical reasons, intrinsically biological aggressiveness may partly be involved in increasing postoperative disease failure [17]. The fact that our results indicated that a very close margin (≤1 mm) had a higher disease failure supports this biological hypothesis in part at least.

As mentioned above, a close margin may, at least in part, represent the degree of intrinsic cancer aggressiveness, rather than a purely physical problem [17,18]. Thus, despite carefully surgical planning and manipulation, close margins cannot be totally avoided; there is a reported rate of around 10% in Taiwan [6]. In the literature, a close margin has been reported to be linked to a poor treatment outcome [3,5]. However, up to the present study, a close

**Table 4**
Kaplan-Meier analysis for 5-year locoregional disease-control end points.

| | Locoregional control[a] | Local control[a] | Regional control[a] |
|---|---|---|---|
| Age (years) | | | |
| ≤50 vs. >50 | 67.5% vs. 60.0%, $p = 0.362$ | 67.5% vs. 65.0%, $p = 0.547$ | 85.7% vs. 100%, $p = 0.136$ |
| Gender | | | |
| Female vs. male | 67.5% vs. 50.0%, $p = 0.335$ | 70.3% vs. 50.0%, $p = 0.233$ | 96.0% vs. 75.0%, $p = 0.143$ |
| ECOG PS[b] | | | |
| 0–1 vs. ≥2 | 63.1% vs. 66.7%, $p = 0.903$ | 63.1% vs. 76.2%, $p = 0.670$ | 95.2% vs. 87.5%, $p = 0.446$ |
| Smoking | | | |
| No vs. yes | 68.9% vs. 50.0%, $p = 0.192$ | 71.9% vs. 50.0%, $p = 0.120$ | 95.8% vs. 80.0%, $p = 0.228$ |
| Betel nut chewing | | | |
| No vs. yes | 57.1% vs. 66.9%, $p = 0.544$ | 57.1% vs. 70.0%, $p = 0.398$ | 85.7% vs. 95.5%, $p = 0.403$ |
| Invasion depth (mm) | | | |
| <10 vs. ≥10 | 83.3% vs. 60.3%, $p = 0.335$ | 83.3% vs. 63.2%, $p = 0.399$ | 100% vs. 91.3%, $p = 0.465$ |
| pT status | | | |
| pT1-3 vs. pT4 | 69.6% vs. 54.0%, $p = 0.553$ | 73.5% vs. 54.0%, $p = 0.375$ | 94.7% vs. 90.0%, $p = 0.659$ |
| pN status | | | |
| pN0 vs. pN1-2 | 71.5% vs. 30.0%, $p = 0.044$* | 71.5% vs. 40.0%, $p = 0.250$ | 96.0% vs. 75.0%, $p = 0.103$ |
| Pathology stage | | | |
| I-III vs. IVA/B | 76.0 vs. 49.9%, $p = 0.123$ | 76.0 vs. 54.8%, $p = 0.227$ | 100% vs. 83.3%, $p = 0.085$ |
| Pathological margin (mm) | | | |
| >1 vs. ≤1 | 81.8% vs. 50.7%, $p = 0.040$* | 81.8% vs. 54.3%, $p = 0.063$ | 100% vs. 87.5%, $p = 0.195$ |
| RT dose (Gy) | | | |
| ≤66 vs. >66 | 81.3% vs. 42.7%, $p = 0.059$ | 86.7% vs. 42.7%, $p = 0.051$ | 93.8% vs. 92.3%, $p = 0.901$ |

* $p < 0.05$.
ECOG PS = Eastern Cooperative Oncology Group performance status; Gy = Gray; RT = radiotherapy.
[a] All $p$ values were estimated using the log rank test.
[b] ECOG performance status was recorded by a radiation oncologist at the time of initial presentation at the RT department.

**Table 5**
Kaplan-Meier analysis for 5-year patient survival end points.

| | Disease-free survival[a] | Disease-specific survival[a] | Overall survival[a] |
|---|---|---|---|
| Age (years) | | | |
| ≤50 vs. >50 | 63.0% vs. 60.0%, $p = 0.564$ | 93.3% vs. 73.3%, $p = 0.159$ | 93.3% vs. 73.3%, $p = 0.116$ |
| Gender | | | |
| Female vs. male | 64.7% vs. 50.0%, $p = 0.446$ | 84.6% vs. 75.0%, $p = 0.673$ | 84.6% vs. 75.0%, $p = 0.673$ |
| ECOG PS[b] | | | |
| 0–1 vs. ≥2 | 66.7% vs. 59.9%, $p = 0.954$ | 90.5% vs. 66.7%, $p = 0.108$ | 90.5% vs. 66.7%, $p = 0.079$ |
| Smoking | | | |
| No vs. yes | 65.9% vs. 50.0%, $p = 0.280$ | 87.5% vs. 66.7%, $p = 0.194$ | 87.5% vs. 66.7%, $p = 0.194$ |
| Betel nut chewing | | | |
| No vs. yes | 57.1% vs. 63.7%, $p = 0.698$ | 71.4% vs. 84.0%, $p = 0.413$ | 71.4% vs. 87.0%, $p = 0.672$ |
| Invasion depth (mm) | | | |
| <10 vs. ≥10 | 83.3% vs. 57.4%, $p = 0.281$ | 100% vs. 79.2%, $p = 0.242$ | 100% vs. 79.2%, $p = 0.092$ |
| pT status | | | |
| pT1-3 vs. pT4 | 69.6% vs. 48.0%, $p = 0.318$ | 85.0% vs. 80.0%, $p = 0.732$ | 85.0% vs. 80.0%, $p = 0.982$ |
| pN status | | | |
| pN0 vs. pN1-2 | 71.5% vs. 30.0%, $p = 0.044$* | 92.0% vs. 68.0%, $p = 0.101$ | 92.0% vs. 68.0%, $p = 0.101$ |
| Pathology stage | | | |
| I-III vs. IVA/B | 76.0 vs. 44.9%, $p = 0.062$ | 94.0 vs. 69.2%, $p = 0.061$ | 94.1 vs. 69.2%, $p = 0.150$ |
| Pathological margin (mm) | | | |
| >1 vs. ≤1 | 81.8% vs. 47.1%, $p = 0.024$* | 100% vs. 70.6%, $p = 0.037$* | 94.1% vs. 70.6%, $p = 0.099$ |
| RT dose (Gy) | | | |
| ≤66 vs. >66 | 81.3% vs. 39.2%, $p = 0.052$ | 93.8% vs. 71.4%, $p = 0.107$ | 93.8% vs. 71.4%, $p = 0.227$ |

* $p < 0.05$.
ECOG PS = Eastern Cooperative Oncology Group performance status; Gy = Gray; RT = radiotherapy.
[a] All $p$ values were estimated using the log rank test.
[b] ECOG performance status was recorded by a radiation oncologist at the time of initial presentation at the RT department.

margin alone has not been a recommended indicator in terms of independently guided postoperative therapies [2]. Nonetheless, these patients comprise a unique study population that demonstrates a clinically debating and biologically interesting profile. Further studies focusing on this study population should be considered, especially attempts to explore the underlying biological mechanism. In such circumstances, developing a biopredictor that involves a very close margin is a reasonable next step in order to further stratify these patients. In consideration of this, an epigenetic-based biopredictor has been reported to be a potential candidate for further investigation [19].

The important features of this study are as follows. Firstly, all pathology features were prospectively defined at the time of radical surgery using an oral cancer-specific pathological checklist. Secondly, the documented pathological report was denoted by a pathologist and then audited in-house by another independent pathologist. Finally and most importantly, the study population was relatively pure in terms of resectable buccal mucosa carcinoma patients who had a close margin of $\leq$3 mm. This study population was constructed specifically as a clinical population that should allow investigation in this area using current evidence-based treatment guidelines [2].

Two main limitations of this study are obvious. Firstly, the study design is retrospective. Thus, selection bias inevitably exits and cannot be fully adjusted for, even after time-to-event-specific multivariate analysis such as Cox proportional hazard regression [20,21]. Secondly, a relatively small number of cases was included, although the positive factor of these being a relatively unique study population remains valid. Therefore, a further prospective study with a larger sample size is needed to confirm our results. Nonetheless, the findings of the present study shed light on how to aggressively treat patients with a very close margin and are worthy of serious consideration. In summary, we observed that a very close margin of $\leq$1 mm seems to be the most important factor when predicting treatment outcomes in resectable buccal mucosa carcinoma patients with a free but close margin of $\leq$3 mm.

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