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Impact of dysplastic surgical margins for patients with oral squamous cell carcinoma☆

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ABSTRACT

Objectives: Dysplastic changes at the surgical margin of oral squamous cell carcinoma (OSCC) could be encountered frequently. However, the impact of a dysplastic surgical margin on patients with OSCC remains unclear.

Materials and methods: Retrospectively, we reviewed patients with OSCC who were diagnosed and treated at the National Taiwan University Hospital between January 2010 and December 2015. Patients were divided into four groups: clear (≥5 mm), close (< 5 mm), positive, and dysplastic margins.

Results: Of 1642 patients, 596 had clear margin, 169 had positive margin, 707 had close margin, and 170 had dysplastic margin. The mean age at diagnosis was 55 ± 11 years (range, 16-97 years). Dysplastic margins were frequently present in patients with primary T1/T2 OSCC (odds ratio [OR] = 1.7, p = 0.009), tumor without perineural invasion (OR = 1.48, p = 0.04), and tumor thickness ≤10 mm (OR = 1.94, p = 0.001). In patients with clear, close, positive, and dysplastic margins, the 5-year disease-free survival rates were 63.1%, 51%, 37.2%, and 54.7%, respectively; overall survival (OS) rates were 71.1%, 61.9%, 49%, and 72%, respectively. Disease-free and overall survival were not significantly different in patients with dysplastic and clear margins (p = 0.37 and p = 0.38, respectively). Adjuvant radiotherapy had no significant benefit for patients with dysplastic margins. Finally, a multivariate analysis showed that the presence of a dysplastic margin was not an independent risk factor for disease-free (p = 0.43) and overall survival (p = 0.71).

Conclusions: The survival rates of the patients with OSCC who had dysplastic margin were significantly better than those with positive margin.

Introduction

During curative-intent surgery for oral squamous cell carcinoma (OSCC), it is important to reach a clear margin, where no cancer cells can be viewed under a microscope. In addition to a clear margin, a positive, close, or dysplastic margin may be present after OSCC surgery. Compared with clear margin, positive and close margins result in worse survival and local control. The impact of positive and close margins on patients with OSCC patients has been well studied [1–3], and the presence of such margins are an indication for adjuvant radiotherapy (RT) [4,5]. In contrast, the impact of dysplastic margin on patients with OSCC remains unclear.

For a surgeon, the presence of a dysplastic margin is usually unpredictable. The presence of a dysplastic margin could be attributed to the peculiar pattern of oral cancer formation. The concept of field cancerization was first proposed in the 1950s [6]. It describes a situation where although clinical OSCC is found in a seemingly discrete location, the entire epithelial surface of the upper aerodigestive tract harbors multiple genetic abnormalities and potentially dysplastic lesions. The field effect has been attributed to multiple risk factors including tobacco smoking, alcohol and betel quid consumption [7,8]. The dysplastic lesion surrounding the main tumor is typically widespread and not very evident; hence, cannot be excised completely even in an extensive surgical field. During surgery, the experienced surgeon can prevent the presence of positive margin or close margin by more extensive excision of the primary OSCC. However, with naked eye, even

☆ OSCC, oral squamous cell carcinoma.

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Table 1
Clinical and histopathological characteristics of patients with OSCC who had clear, positive, close, or dysplastic margins.

Characteristics	Clear margin (n = 596)	Positive margin (n = 169)	Close margin (n = 707)	Dysplastic margin (n = 170)	P value
Age (years)					
≥50	400 (67.11%)	108 (63.91%)	491 (69.45%)	118 (69.41%)	0.50
< 50	196 (32.89%)	61 (36.09%)	216 (30.55%)	52 (30.59%)	
Sex					
Male	490 (82.21%)	153 (90.53%)	619 (87.55%)	147 (86.47%)	0.01
Female	106 (17.79%)	16 (9.47%)	88 (12.45%)	23 (13.53%)	
Location					
Tongue	299 (50.17%)	44 (26.04%)	274 (38.76%)	60 (35.29%)	< 0.001
Buccal	152 (25.50%)	54 (31.95%)	227 (32.11%)	62 (36.47%)	
Others	145 (24.33%)	71 (42.01%)	206 (29.14%)	48 (28.24%)	
Differentiated type					
Well	360 (60.40%)	82 (48.52%)	348 (49.22%)	103 (60.59%)	0.001*
Moderately	223 (37.42%)	81 (47.93%)	335 (47.38%)	65 (38.24%)	
Poorly	13 (2.18%)	6 (3.55%)	24 (3.39%)	2 (1.18%)	
T classification					
T3/T4	159 (26.68%)	73 (43.20%)	195 (27.58%)	33 (19.41%)	< 0.001
T1/T2	437 (73.32%)	96 (56.80%)	512 (72.42%)	137 (80.59%)	
N classification					
N2/N3	104 (17.45%)	43 (25.44%)	141 (19.94%)	15 (8.82%)	< 0.001
N0/N1	492 (82.55%)	126 (74.56%)	566 (80.06%)	155 (91.18%)	
Tumor thickness					
> 10 mm	188 (31.54%)	68 (40.24%)	249 (35.22%)	36 (21.18%)	0.001
≦10 mm	408 (68.46%)	101 (59.77%)	458 (64.78%)	134 (78.82%)	
PNI	142 (23.83%)	64 (37.87%)	254 (35.93%)	40 (23.53%)	< 0.001
ENE	78 (13.09%)	28 (21.88%)	105 (14.85%)	12 (5.69%)	< 0.001
LVI	73 (12.25%)	36 (21.30%)	126 (17.82%)	19 (11.18%)	0.002
Margin distance					
≥5mm	596(100%)	19 (11.24%)	–	75 (44.12%)	–
< 5mm	–	22 (13.02%)	707 (100%)	95 (55.88%)	
< 1mm		27 (15.98%)			
Dysplastic margin					
Severe/CIS	–	41 (24.26%)	–	–	–
Moderate	–	–	–	117 (68.82%)	
Mild	–	–	–	53 (31.18%)	
Adjuvant radiotherapy					
Adjuvant RT	200 (33.56%)	92 (54.44%)	268 (37.91%)	49 (28.82%)	< 0.001
Recurrence pattern					
Local	81 (13.59%)	50 (29.59%)	124 (17.54%)	30 (17.65%)	< 0.001
Regional	71 (11.91%)	25 (14.79%)	102 (14.43%)	20 (11.76%)	0.49
Distant	41 (6.88%)	22 (13.02%)	63 (8.91%)	7 (4.12%)	0.01
Second primary	45 (7.55%)	11 (6.51%)	68 (9.62%)	21 (12.35%)	0.14

Abbreviation: OSCC, oral squamous cell carcinoma; PNI, perineural invasion; ENE, extranodal extension; LVI, lymphovascular invasion; CIS, carcinoma in situ; RT, radiotherapy.

* Using Fisher's exact test.

an experienced head and neck surgeon cannot definitely identify the ambiguous dysplasia adjacent to the OSCC mass during surgery [9,10]. Additionally, excising the dysplasia adjacent to an invasive OSCC also can affect the quality of life; larger resections generally result in the worse functional outcome.

As a dysplastic surgical margin may be encountered during OSCC surgery, the purpose of this study was to assess its impact on survival and local control in patients with OSCC.

Materials and methods

We retrospectively reviewed the medical records and pathological reports of patients who were newly diagnosed with OSCC and who underwent curative-intent wide excision of the primary tumor at the National Taiwan University Hospital between January 2010 and December 2015. The study was reviewed and approved by the institutional review board at the National Taiwan University Hospital. Patients with previously treated OSCC, primary head and neck cancer other than SCC, malignancies outside the head and neck regions, a simultaneous second primary cancer, and previous RT history involving the head and neck region due to other diseases were excluded from the study. In our hospital, the frozen section analysis from surgical bed would be consulted if the section margin seems not enough or positive section margin was concerned during operation. According to the pathological report of the resected margin, the patients were divided into four groups: clear margin (≥5 mm), close margin (< 5 mm), positive margin (microscopic cut-through of OSCC, margin < 1 mm, involved by severe dysplasia or carcinoma in situ), and dysplastic margin (with mild or moderate dysplastic changes) [11,12]. The grading of the dysplastic surgical margin was in accordance with the World Health Organization grading system [13]. The indications for adjuvant RT were the presence of advanced T3/T4 disease, advanced N2/N3 disease, positive margin, or positive extranodal extension (ENE) [4,5]. However, the final decision regarding adjuvant RT was mostly decided by the suggestion of tumor board or the discussion among the patients, major caregivers and attending physician after taking all things besides tumor factor into account. All the OSCC patient included in our series received the followed-up according to the recommendations suggested by National Comprehensive Cancer Network clinical practice guidelines [11].

The TNM status of each tumor was classified according to the 2010 criteria of the American Joint Committee on Cancer (AJCC) [14]. All statistical analyses were performed using the SPSS software package, version 18.0 (SPSS Inc., Chicago, IL). The Fisher's exact test and chi-square test were used to determine the difference in clinical characteristics of the patients (including age, sex, primary tumor location,

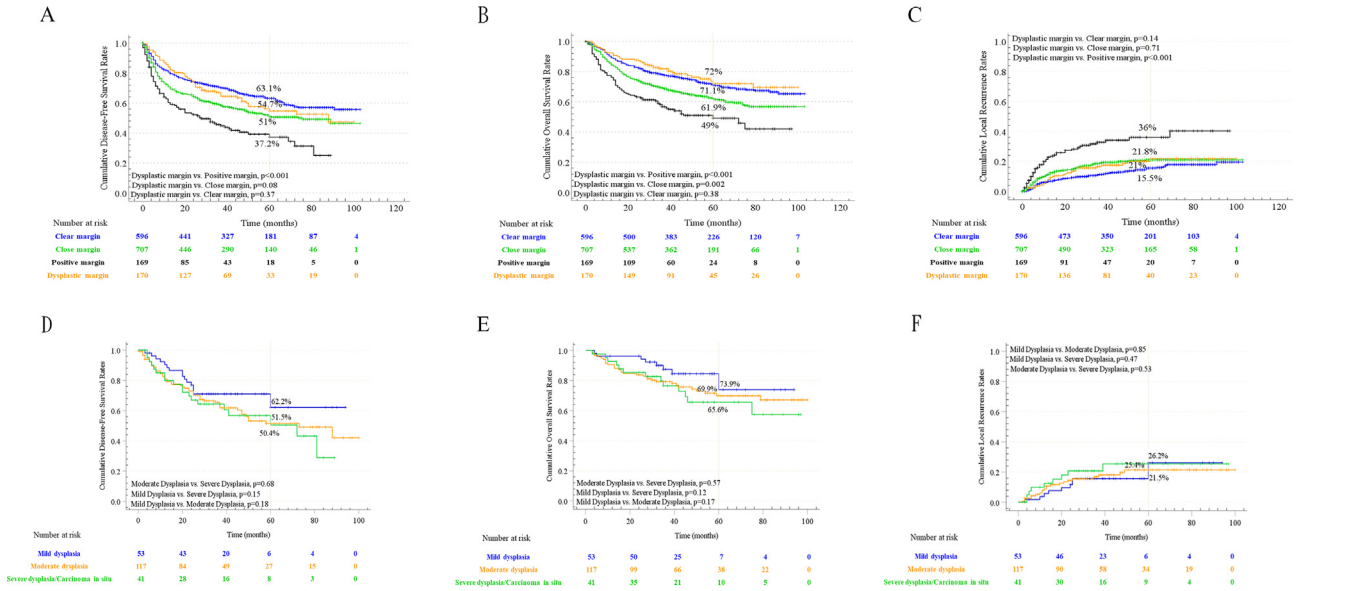

Fig. 1. (a) Disease-free survival rates, (b) overall survival rates, and (c) local recurrence rates of patients with OSCC who had clear, close, positive, and dysplastic margins; (d) disease-free survival curves, (e) overall survival curves, and (f) local recurrence rates of the patients with varying degree of dysplastic margin (mild, moderate, and severe dysplasia).

tumor differentiation, primary tumor (T) classification, neck nodal N classification, perineural invasion (PNI), extra nodal extension (ENE), lymphovascular invasion (LVI), tumor thickness, adjuvant RT, and recurrence pattern). The starting point of the follow-up period was defined as the time since the completion of the initial treatment for each patient. The endpoint of the follow-up was defined as the time when the patient died or December 2018. All patients received follow-up examination for ≥ 24 months or until death after primary definitive treatment. The primary endpoints were disease-free survival and overall survival. The secondary endpoint was the local control rate. The rates of disease-free survival, overall survival, and cumulative local recurrence rates were calculated using the Kaplan-Meier product-limit method. Significance levels among curves were determined using the log-rank test. A multivariable Cox proportional hazards model with a forward selection procedure was used to estimate the effects of different covariates on survival endpoints. A p-value < 0.05 was considered statistically significant.

Results

Patient demographics

Of 1642 patients, 1409 (85.81%) were men and 233 (14.19%) were women; the mean age at diagnosis was 55 ± 11 years (range, 16–97 years). There were 596 patients with clear margin, 169 with positive margin, 707 with close margin, and 170 with dysplastic margin. The basic and clinicopathologic characteristics of the patients are shown in Table 1. There were significant differences among the patients with clear, positive, close, and dysplastic margins in terms of sex ($p = 0.01$), primary tumor location ($p < 0.001$), tumor differentiation ($p = 0.001$), T classification ($p < 0.001$), N classification ($p < 0.001$), tumor thickness ($p = 0.001$), PNI ($p < 0.001$), ENE ($p < 0.001$), LVI ($p = 0.002$), application of adjuvant RT ($p < 0.001$), local recurrence ($p < 0.001$), and distant metastases ($p = 0.01$).

Association of dysplastic margins with clinical and pathological characteristics of primary OSCC

We attempted to understand the association of the presence of dysplastic margin with clinical and pathological characteristics of patients with primary OSCC. Regarding age, compared with patients aged < 50 years, the odds ratio (OR) of the presence of dysplastic margin in patients aged ≥ 50 years was 1.07 (95% confidence interval [CI] = 0.76–1.52, $p = 0.73$). Regarding sex, compared with women, the OR of the presence of dysplastic margin in men was 1.06 (95% CI = 0.67–1.69, $p = 0.82$). Compared with patients with OSCC in sites except tongue and buccal mucosa, the ORs of the presence of dysplastic margin in patients with tongue OSCC and buccal OSCC were 0.86 (95% CI = 0.57–1.27, $p = 0.44$) and 1.26 (95% CI = 0.84–1.88, $p = 0.26$), respectively. Regarding OSCC differentiation, compared with patients with well-differentiated OSCC, the ORs of the presence of dysplastic margin in patients with moderately and poorly differentiated OSCC were 0.78 (95% CI = 0.56–1.08, $p = 0.14$) and 0.36 (95% CI = 0.09–1.50, $p = 0.16$), respectively. Regarding the primary tumor (T) classification, compared with patients with T3/T4 OSCC, the OR of the presence of dysplastic margin in patients with T1/T2 OSCC was 1.70 (95% CI = 1.14–2.52, $p = 0.009$). Similarly, compared with patients with PNI, the OR of the presence of dysplastic margin in patients without PNI was 1.48 (95% CI = 1.02–2.14, $p = 0.04$). Additionally, compared with OSCC with LVI, the OR of the presence of dysplastic margin in OSCC without LVI was 1.51 (95% CI 0.92–2.48, $p = 0.10$). Regarding tumor thickness, compared with OSCC with tumor thickness > 10 mm, the OR of the presence of dysplastic margin in OSCC with tumor thickness ≤ 10 mm was 1.94 (95% CI = 1.33–2.85, $p = 0.001$). Furthermore, compared with patients with margin distance ≥ 5 mm, the OR of the presence of dysplastic margin in patients with margin distance < 5 mm was 1.07 (95% CI = 0.78–1.47, $p = 0.69$). To summarize, a dysplastic margin tends to be present more frequently in patients with primary T1/T2 OSCC, OSCC without PNI, and OSCC tumor thickness ≤ 10 mm.

Survival outcome of patients based on type of margin

The overall follow-up period in this study was from 1 to 103 months, with a mean of 45 ± 26 months. The time to disease progression was from 1 to 103 months, with a mean of 37 ± 27 months. Disease-free survival, overall survival, and local control rate of patients with different types of margins are shown in Fig. 1. There was a significant difference in disease-free survival between patients with dysplastic margin and those with positive margin

($p < 0.001$); however, the difference was not significant between patients with between dysplastic margin and those with clear margin ($p = 0.37$) or close margin ($p = 0.08$; Fig. 1A). There was a significant difference in overall survival between patients with dysplastic margin and those with positive margin ($p < 0.001$). Similarly, overall survival was significantly different between patients with dysplastic margin and those with close margin ($p = 0.002$). However, but there was no significant difference in overall survival between patients with dysplastic margin and those with clear margin ($p = 0.38$; Fig. 1B). There was a significant difference in the local control rates between patients with dysplastic margin and those with positive margin ($p < 0.001$); however, the difference was not significant between patients with dysplastic margin and those with clear margin ($p = 0.14$) or close margin ($p = 0.71$; Fig. 1C). There was no significant difference in disease-free survival (Fig. 1D), overall survival (Fig. 1E), and local control rate (Fig. 1F) among mild, moderate, and severe dysplastic margin.

In the univariate analysis, sex ($p < 0.001$ and 0.04, respectively), OSCC differentiation ($p < 0.001$), primary T classification ($p < 0.001$), neck N classification ($p < 0.001$), PNI+ ($p < 0.001$), ENE+ ($p < 0.001$), LVI+ ($p < 0.001$), tumor thickness > 10 mm ($p < 0.001$), and type of margin ($p < 0.001$) were identified as significant risk factors for disease-free and overall survival (Table 2). Additionally, age ($p = 0.03$), sex ($p < 0.001$) and primary tumor location ($p = 0.009$) were significant risk factors for disease-free survival.

The significant risk factors for disease-free and overall survival were further examined by multivariate Cox regression analysis (Fig. 2). Male ($p = 0.01$), moderately differentiated OSCC ($p < 0.001$), PNI+ ($p < 0.001$), LVI+ ($p = 0.008$), ENE+ ($p < 0.001$), tumor thickness > 10 mm ($p = 0.001$), positive margins ($p < 0.001$), and close margins ($p = 0.03$) were independent risk factors for disease-free survival. T3/T4 ($p = 0.004$), N2/N3 ($p = 0.02$), moderately differentiated OSCC ($p = 0.001$), PNI+ ($p < 0.001$), LVI+ ($p < 0.001$), ENE+ ($p < 0.001$), tumor thickness > 10 mm ($p = 0.002$), positive margins ($p < 0.001$), and close margins ($p = 0.02$) were independent risk factors for overall survival. However, the presence of a dysplastic margin is not an independent risk factor for disease-free ($p = 0.43$) and overall survival ($p = 0.71$).

Table 2
Univariate analysis of possible risk factors for survival.

Characteristics	5-year disease-free survival		5-year overall survival	
	Rates	P value	Rates	P value
Age (years)				
≥50	56.4%	0.03	65.6%	0.64
< 50	50.9%		64.1%	
Sex				
Male	52.2%	< 0.001	63.9%	0.04
Female	69%		71.7%	
Location				
Tongue	60.4%	0.009	67.6%	0.11
Buccal	51.5%		65.4%	
Other sites	49.6%		61.1%	
Differentiated type				
Poorly	42.9%	< 0.001	46.6%	< 0.001
Moderately	46.5%		57.3%	
Well	61.7%		72.1%	
T classification				
T3/T4	43.5%	< 0.001	72.0%	< 0.001
T1/T2	58.9%		47.2%	
N classification				
N2/N3	32.8%	< 0.001	33.1%	< 0.001
N0/N1	59.4%		72.3%	
PNI				
Present	38.1%	< 0.001	43.3%	< 0.001
Absent	61.7%		74.6%	
ENE				
Present	26.7%	< 0.001	23.6%	< 0.001
Absent	58.8%		71.7%	
LVI				
Present	34.0%	< 0.001	37.8%	< 0.001
Absent	58.3%		70.1%	
Tumor thickness				
> 10 mm	42.4%	< 0.001	48.8%	< 0.001
≦10 mm	60.6%		73.1%	
Type of margin				
Positive margin	37.2%	< 0.001	49%	< 0.001
Dysplastic margin	54.7%		72%	
Close margin	51.0%		61.9%	
Clear margin	63.1%		71.1%	

Abbreviation: PNI, perineural invasion; ENE, extranodal extension; LVI, lymphovascular invasion.

Survival results of patients with dysplastic margins who did and did not receive adjuvant CCRT/RT

Among 170 patients with dysplastic margins, 95 (55.88%) had a margin distance < 5 mm and 75 (44.12%) had a margin distance ≥ 5 mm. Disease-free survival, overall survival, and local control rates of patients with dysplastic margins having a margin distance ≥ 5 mm and < 5 mm were shown in Fig. 3A–C. There is no significant difference between the margin dysplasia patients with margin distance ≥ 5 mm and < 5 mm in disease-free survival ($p = 0.85$), overall survival ($p = 0.65$) and local control rates ($p = 0.78$). Finally, there were 49 (28.82%) patients with dysplastic margins who received adjuvant RT. Disease-free survival, overall survival, and local control rates of the patients with and without adjuvant RT are shown in Fig. 3D–E. Surprisingly, patients with dysplastic margins who received adjuvant RT had worse survivals and local control outcomes. Furthermore, there was a significant difference in overall survival between patients with dysplastic margins who did and those who did not receive adjuvant RT ($p = 0.003$). To summarize, a margin distance < 5 mm did not have significant impact on survival and local control rates of patients with dysplastic margins. Besides, the adjuvant RT had no significant benefit for patients with dysplastic margins.

Discussion

In this study, we focused on analyzing the prognostic impact of dysplastic margin (moderate or mild dysplasia) on patients with OSCC. There were several important findings. First, disease-free, overall survival, and local control rates were significantly better of patients with dysplastic margin than those with positive margin. Besides, the difference between dysplastic and clear margin patients in disease-free, overall survivals and local control were not significant. Second, the severity of dysplasia had no significant impact on disease-free survival, overall survival, and local control rates of patients with dysplastic margin. Third, adjuvant RT could not provide significant benefit to patients with dysplastic margin. Therefore, our study suggests that the presence of a dysplastic margin is not a significant risk factor for patients with OSCC. Additionally, our findings show that the distance of the margin (close or positive margin), and not the morphology (mild or moderate dysplastic changes), should be considered as an indicator for adjuvant RT.

For safety, the main goal of curative OSCC surgery should always be excision of the main tumor with macroscopically adequate margins. However, in clinical practice, this appears particularly difficult to achieve considering the peculiar frequent growth pattern of OSCC, defined as the “field cancerization” phenomenon [6]. This concept assumes that multiple, unrelated, precancerous lesion, from patches to fields, may exist adjacent to the original tumor mass. It had been reported that the size of these fields can range from 4 mm to 7 cm. However, the fields never show invasive growth until subsequent accumulation of genetical mutation, which are enough to become invasive carcinoma with metastatic potential [15,16]. In our study, the presence of a dysplastic margin was observed in some patients (n = 170, 10.35%) after OSCC surgery. Moreover, primary T1/T2

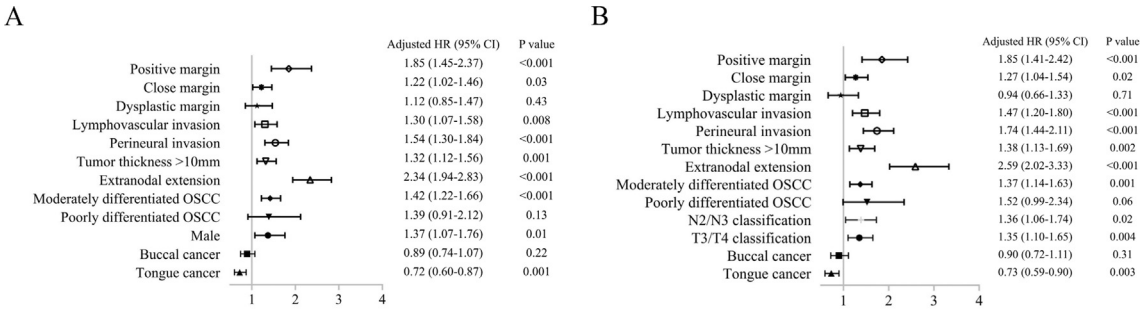

Fig. 2. Forest plot of multivariate analysis of possible risk factors using the Cox logistic regression method in (a) disease-free survival and (b) overall survival.

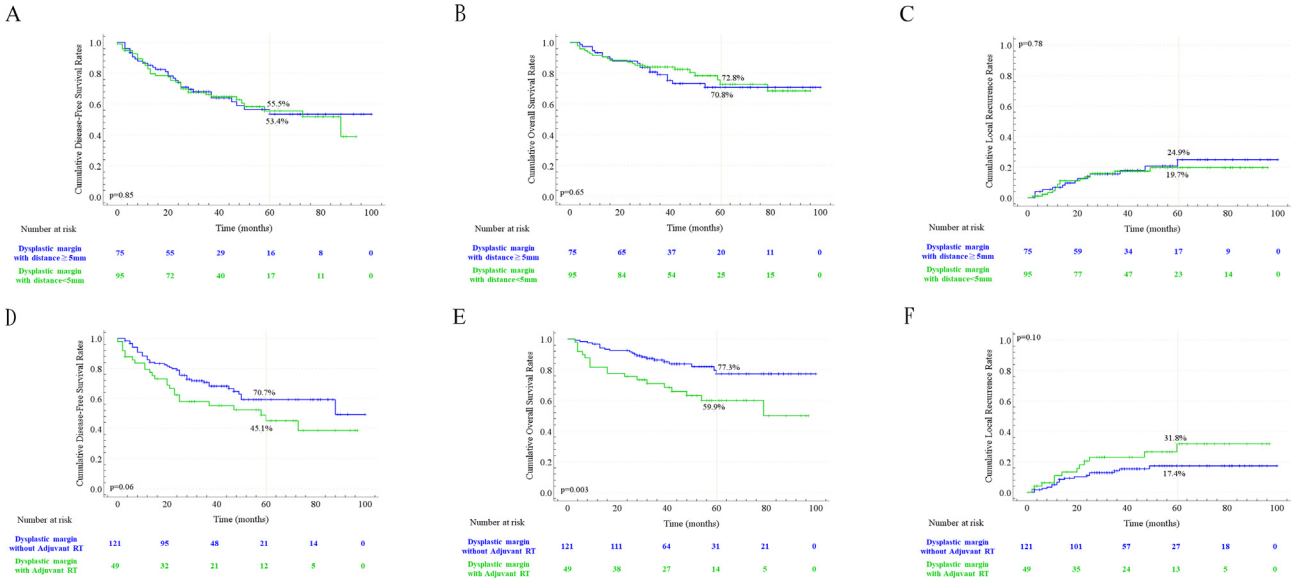

Fig. 3. (a) Disease-free survival rates, (b) overall survival rates, and (c) local recurrence rates of the clear and close margin patients with dysplasia changes; (d) disease-free survival rates, (e) overall survival rates, and (f) local recurrence rates of dysplastic margins in patients who did and did not receive adjuvant radiotherapy (RT).

disease and OSCC with tumor thickness ≤ 10 mm were significantly associated with the presence of dysplastic margins. On the contrary, other clinical or histopathological factors such as primary tumor location and OSCC differentiation were not associated with the presence of dysplastic margins. Compared with patients with margin distance < 5 mm, patients with margin distance ≥ 5 mm had similar OR and had dysplasia changes in the surgical specimen. From the clinical perspective, a wider excision during OSCC operation could not prevent the presence of a dysplastic margin. Previously, it has been reported that innovative optical technologies, such as narrow band imaging [9,17,18] or autofluorescence [19,20] could be used to assist the surgeons to delineate a more accurate mapping for OSCC surgery. In our study, a dysplastic margin is frequently encountered in patients with primary T1/T2 OSCC. Therefore, we suggest that these intraoperative imaging techniques could be considered during surgery of patients with early T1/T2 OSCC or OSCC with tumor thickness ≤ 10 mm, where the surgeon has to find a balance between obtaining an adequate tumor margin and retaining a good quality of life by limiting the cosmetic defect.

The impact of dysplastic margin on patients with OSCC remains unclear and controversial. The results from previous studies showed margin dysplasia would [21–23] or would not [24,25] significantly impact the survivals and local control of the OSCC patients. By definition, the margin dysplasia should be totally different from the positive margin, which means microscopic cut-through OSCC in surgical margin. In theory, the malignant transformation rates of margin dysplasia, to mild or moderate dysplasia, encountered in OSCC patients should be similar to that in the same-degree dysplasia in non-OSCC patients. If a dysplastic margin is present with other major risk factors such as ENE or positive neck nodal metastases, adjuvant RT should be suggested without hesitation. However, if a dysplastic margin is present alone, the advantages and disadvantages of adjuvant RT should be seriously considered. Previously, for the non-OSCC patients, it had been reported that the malignant transformation rates for mild to moderate dysplasia were 10.3% [26]. Also, the mean time to malignant transformation was 4.3 years [26]. Most importantly, the malignant transformation of oral dysplasia could not be eliminated by excision [26,27]. Patients who continued to expose themselves to carcinogens (alcohol, betel quid, and cigarette) were more likely to have recurrence or malignant transformation (OR = 2.43) [28]. In this study, the presence of a dysplastic margin did not have a significant impact on the survival outcomes and local control rates of patients with OSCC. Additionally, adjuvant RT did not provide significant benefit to the patients with OSCC and dysplastic margins. In our opinion, the revision surgery seems to be able to completely remove the dysplasia changes in the surgical margin. However, active surveillance with education regarding carcinogen cessation may be another reasonable choice for OSCC patients with dysplastic margin. On the contrary, adjuvant RT should be not necessary for the OSCC patients with dysplastic margin alone.

There were a few limitations in our study. First, this retrospective study might contain various types of bias. In the survival analyses, there were unavoidable or unnoticed selection biases even though the Cox regression model was used. For instance, the initiation of adjuvant RT was not based on rigorous criteria for OSCC patients with surgical

margin dysplasia alone. Second, the pathological evaluation of the surgical margin was entirely from surgical specimens. Therefore, the actual incidence of dysplastic margins could be underestimated. Third, although we included only the binary “low risk” dysplasia (mild or moderate dysplasia) in the dysplastic margin group, a modest inter-observer reliability of varying degree should be considered [29]. Well-designed prospective randomized trials for the OSCC patients with or without adjuvant RT should be warranted in the future.

Declaration of Competing Interest

None declared.

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References

[1] Binahmed A, Nason RW, Abdoh AA. The clinical significance of the positive surgical margin in oral cancer. Oral Oncol 2007;43:780–4.
[2] Chen TC, Wang CP, Ko JY, Yang TL, Lou PJ. The impact of pathologic close margin on the survival of patients with early stage oral squamous cell carcinoma. Oral Oncol 2012;48:623–8.
[3] Liao CT, Chang JT, Wang HM, Ng SH, Hsueh C, Lee LY, et al. Analysis of risk factors of predictive local tumor control in oral cavity cancer. Ann Surg Oncol 2008;15:915–22.
[4] Cooper JS, Pajak TF, Forastiere AA, Jacobs J, Campbell BH, Saxman SB, et al. Postoperative concurrent radiotherapy and chemotherapy for high-risk squamous-cell carcinoma of the head and neck. New Engl J Med 2004;350:1937–44.
[5] Bernier J, Domenge C, Ozsahin M, Matuszewska K, Lefebvre JL, Greiner RH, et al. Postoperative irradiation with or without concomitant chemotherapy for locally advanced head and neck cancer. New Engl J Med 2004;350:1945–52.
[6] Slaughter DP, Southwick HW, Smejkal W. Field cancerization in oral stratified squamous epithelium; clinical implications of multicentric origin. Cancer 1953;6:963–8.
[7] Simple M, Suresh A, Das D, Kuriakose MA. Cancer stem cells and field cancerization of oral squamous cell carcinoma. Oral Oncol 2015;51:643–51.
[8] Liao CT, Wallace CG, Lee LY, Hsueh C, Lin CY, Fan KH, et al. Clinical evidence of field cancerization in patients with oral cavity cancer in a betel quid chewing area. Oral Oncol 2014;50:721–31.
[9] Tirelli G, Piovesana M, Gatto A, Tofanelli M, Biasotto M, Boscolo Nata F. Narrow band imaging in the intra-operative definition of resection margins in oral cavity and oropharyngeal cancer. Oral Oncol 2015;51:908–13.
[10] Vu AN, Farah CS. Efficacy of narrow band imaging for detection and surveillance of potentially malignant and malignant lesions in the oral cavity and oropharynx: a systematic review. Oral Oncol 2014;50:413–20.
[11] Pfister DG, Ang KK, Brizel DM, Burtness BA, Cmelak AJ, Colevas AD, et al. Head and neck cancers. J Natl Comprehensive Cancer Network: JNCCN 2011;9:596–650.
[12] Alicandri-Ciufelli M, Bonali M, Piccinini A, Marra L, Ghidini A, Cunsolo EM, et al. Surgical margins in head and neck squamous cell carcinoma: what is 'close'? Eur Arch Oto-rhino-laryngology: Official J Eur Fed Oto-Rhino-Laryngological Societies (EUFOS): Affiliated the German Soc Oto-Rhino-Laryngology - Head Neck Surg 2013;270:2603–9.
[13] Barnes L, Eveson J, Reichart P, Sidransky D. Tumours of the oral cavity and oropharynx. World health organization classification of tumours. Pathology and genetics – head and neck tumours. Lyon: IARC Press; 2005.
[14] Edge SB, Compton CC. The American Joint Committee on Cancer: the 7th edition of the AJCC cancer staging manual and the future of TNM. Ann Surg Oncol 2010;17:1471–4.
[15] Braakhuis BJ, Leemans CR, Brakenhoff RH. A genetic progression model of oral cancer: current evidence and clinical implications. J Oral Pathol Med: Official Publ Int Assoc Oral Pathologists Am Acad Oral Pathol 2004;33:317–22.
[16] Mohan M, Jagannathan N. Oral field cancerization: an update on current concepts. Oncol Rev 2014;8:244.
[17] Tirelli G, Piovesana M, Marcuzzo AV, Gatto A, Biasotto M, Bussani R, et al. Tailored resections in oral and oropharyngeal cancer using narrow band imaging. Am J Otolaryngol 2018;39:197–203.
[18] Farah CS, Dalley AJ, Nguyen P, Batstone M, Kordbacheh F, Perry-Keene J, et al. Improved surgical margin definition by narrow band imaging for resection of oral squamous cell carcinoma: A prospective gene expression profiling study. Head Neck 2016;38:832–9.
[19] McMahon J, Devine JC, McCaul JA, McLellan DR, Farrow A. Use of Lugol's iodine in the resection of oral and oropharyngeal squamous cell carcinoma. Br J Oral Maxillofacial Surg 2010;48:84–7.
[20] Tirelli G, Zacchigna S, Boscolo Nata F, Quatela E, Di Lenarda R, Piovesana M. Will the mininvasive approach challenge the old paradigms in oral cancer surgery? Eur Arch Oto-rhino-laryngology: Official J Eur Fed Oto-Rhino-Laryngological Societies (EUFOS): Affiliated the German Soc Oto-Rhino-Laryngology - Head Neck Surg 2017;274:1279–89.
[21] Gokavarapu S, Parvataneni N, Pavagada S, Chandrasekhara Rao LM, Raju KV, Rao TS. Mild to moderate dysplasia at surgical margin is a significant indicator of survival in patients with oral cancer. Oral Surg, Oral Med, Oral Pathol Oral Radiology 2017;123:330–7.
[22] Weijers M, Snow GB, Bezemer PD, van der Wal JE, van der Waal I. The clinical relevance of epithelial dysplasia in the surgical margins of tongue and floor of mouth squamous cell carcinoma: an analysis of 37 patients. J Oral Pathol Medi: Official Publ Int Assoc Oral Pathologists Am Acad Oral Pathol 2002;31:11–5.
[23] Sopka DM, Li T, Lango MN, Mehra R, Liu JC, Burtness B, et al. Dysplasia at the margin? Investigating the case for subsequent therapy in 'low-risk' squamous cell carcinoma of the oral tongue. Oral Oncol 2013;49:1083–7.
[24] Woolgar JA, Scott J, Vaughan ED, Brown JS, West CR, Rogers S. Survival, metastasis and recurrence of oral cancer in relation to pathological features. Ann R Coll Surg Engl 1995;77:325–31.
[25] Kurita H, Nakanishi Y, Nishizawa R, Xiao T, Kamata T, Koike T, et al. Impact of different surgical margin conditions on local recurrence of oral squamous cell carcinoma. Oral Oncol 2010;46:814–7.
[26] Mehanna HM, Rattay T, Smith J, McConkey CC. Treatment and follow-up of oral dysplasia - a systematic review and meta-analysis. Head Neck 2009;31:1600–9.
[27] Balasundaram I, Payne KF, Al-Hadad I, Alibhai M, Thomas S, Bhandari R. Is there any benefit in surgery for potentially malignant disorders of the oral cavity? J Oral Pathol Med: Official Publ Int Assoc Oral Pathologists Am Acad Oral Pathol 2014;43:239–44.
[28] Arduino PG, Surace A, Carbone M, Elia A, Massolini G, Gandolfo S, et al. Outcome of oral dysplasia: a retrospective hospital-based study of 207 patients with a long follow-up. J Oral Pathol Med: Official Publ Int Assoc Oral Pathologists Am Acad Oral Pathol 2009;38:540–4.
[29] Fischer DJ, Epstein JB, Morton TH, Schwartz SM. Interobserver reliability in the histopathologic diagnosis of oral pre-malignant and malignant lesions. J Oral Pathol Med: Official Publ Int Assoc Oral Pathologists Am Acad Oral Pathol 2004;33:65–70.