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Clinicopathological risk factors for local recurrence in oral squamous cell carcinoma

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Short title: Local recurrence in OSCC

Abstract. Local recurrence of oral squamous cell carcinoma (OSCC) after primary surgery has been considered to be a poor prognostic entity in terms of survival rate. The purpose of this study is to evaluate the incidence of local recurrence and to identify significant risk factors for the local recurrence in OSCC. We retrospectively reviewed records for 187 patients who underwent radical surgery for OSCC. The local recurrence rate was 16.0% (30/187 patients) in this study. The survival rate of patients with local recurrence was 33.3%, which was significantly lower than that (94.3%) of patients without local recurrence. Pattern of invasion (POI), neoadjuvant chemotherapy (NAC), and the status of the surgical margin were identified as factors influencing local recurrence. In particular, NAC and the status of the surgical margin were independent risk factors by multivariate analysis. The deep margin was resected at a close site in many NAC-treated patients, suggesting that NAC may lead to local recurrence and poor outcomes. No efficacy of NAC was observed, suggesting that the standard treatment of oral cancers is surgery alone.

Introduction

Oral squamous cell carcinoma (OSCC) accounts for nearly 3% of all cancer cases in the world; its estimated incidence is around 275,000 cases per year, with two-thirds of these cases occurring in developing countries.¹ OSCC continues to portend a poor prognosis, and remains a lethal disease for more than 50% of cases diagnosed annually.¹ Of the known prognostic factors, TNM stage, histologic grade, and depth of tumor invasion are well recognized; however, the prognostic value of these clinicopathological factors is often uncertain and controversial.²⁻⁴

Traditional treatment for OSCC comprises surgery and radiotherapy.^{3,5} Surgery is the most well established mode of initial definitive treatment for the majority of OSCC.⁵⁻⁷ Locoregional recurrence in patients with OSCC remains a problem and can affect survival.^{2,6,7} In particular, local recurrence of OSCC after primary surgery has been considered to be a bad prognostic entity in terms of survival rate.²⁻⁸ Several parameters may play a crucial role in determining therapeutic strategies; however, very few studies have focused on clinicopathological factors that may predict local recurrence in OSCC.^{7,8}

The purpose of this study is to evaluate the incidence of local recurrence and to identify significant risk factors for local recurrence in OSCC. This investigation may be helpful with the management of OSCC patients undergoing radical surgery.

Patients and Methods

Patients

We retrospectively reviewed records for 187 patients who underwent radical surgery for

OSCC between January 2001 and December 2010. The study cohort included patients with histologically confirmed diagnoses of OSCC and a minimum follow-up of 12 months. All study patients underwent extensive pretreatment evaluations, including blood chemistry, complete blood cell count, chest X-ray, computed tomography (CT) and/or magnetic resonance imaging (MRI) of the head and neck area, thoracoabdominal CT, and provided informed consent to participate in the study. Data collected included demographic information, site, TNM stage at diagnosis, tumor histologic grade, pattern of tumor invasion, treatment, status of the margin, recurrence, and the adjuvant therapy used for disease control.

Tumor stage was classified according to the TNM classification of the International Union against Cancer.⁹ Tumor histologic grade was defined according to the WHO classification.¹⁰ All pathological assessments were performed by two expert pathologists (SF and TI) who were unaware of the clinical outcomes. Pattern of invasion (POI) was examined at the host/tumor interface. POI types 1 through 4 have been previously defined by Bryne et al. .¹¹ POI type 1 represents tumor invasion in a broad pushing manner with a smooth outline. POI type 2 represents tumor invasion with broad pushing “fingers” or separate large tumor islands, with a stellate appearance. POI type 3 represents invasive islands of tumor greater than 15 cells per island. POI type 4 represents invasive tumor islands smaller than 15 cells per island. This includes cord-like and single cell invasion. These evaluations were performed using biopsy specimens.

Treatment and pathologic examination

In our institute, the modality of surgery alone was preferred for the treatment of patients

with oral cancer. However, patients who hesitated in accepting surgical intervention or who did not have surgery available because of a busy schedule were selected for neoadjuvant chemotherapy (NAC). During the period of NAC, patients were encouraged to undergo surgery after completion of chemotherapy. All patients who received NAC underwent radical surgery. The regimen of NAC consisted of a combination of cisplatin-based multidrugs. In most patients, modifications in chemotherapy dosages were made for toxicity as indicated using standard criteria.

Primary tumors were excised with ≥ 1.5 cm safety margins (both superficial and deep margins). The extent of surgery was not modified according to tumor response with NAC. Surgery included removal of primary tumor and radical neck dissection was performed in patients who had clinically positive cervical lymph node metastasis. Elective neck dissection was not performed routinely in our institutions. Postoperative adjuvant radiotherapy with a dose field of 60 Gy was performed on patients with involved margins or extra-capsular lymph node spread. Local recurrence was defined as lesions arising in the oral cavity relative to primary tumor beyond 6 weeks within the first 5 years after the first definitive treatment. Locoregional recurrence arising in both the primary site and neck was also considered to be local recurrence. Recurrence arising only in the neck was defined as regional recurrence. Patients with recurrences that were considered potentially curable and operable underwent salvage surgery and radiotherapy. Patients with recurrences that were considered incurable were treated with palliative chemotherapy.

For pathological examination of the surgical margin, all permanent section histological slides of primary resection specimens were reviewed retrospectively. Regarding surgical margin distance, a large cohort study demonstrated that the

pathological margin distance ≤ 4 mm was significantly associated with locoregional recurrence.¹² In this study, the status of the surgical margin was classified as >4 and ≤ 4 mm in the superficial or deep margin, respectively.

Statistical analysis

Disease specific survival (DSS) rate was calculated using the Actuarial life table method. Significance was evaluated using the log-rank test. Univariate logistic and multivariate logistic regression analyses were used to identify independent risk factors for local recurrence. Predictors that were not associated with local recurrence in univariate analysis were not included in multivariate analysis. Statistical analyses were performed using StatMate IV (Atms Co., Tokyo, Japan). In all analyses, *P* values < 0.05 were considered to be significant.

Results

Patient characteristics and appearance of local recurrence

Patient characteristics are summarized in Table 1. The male-to-female ratio was 1.2 with 102 male subjects. The mean age at diagnosis was 67.3 years (range, 28-95 years). The most common primary site was the tongue (73/187 patients, 39.0%); 23.5% of patients were those of lower gingival cancer and 19.3% of patients were those of upper gingival cancer.

Local recurrence rate was 16.0% (30/187 patients) during the follow-up period. The mean follow-up period was 36.7 months for the whole series (range, 10-125 months). The mean period that had elapsed until recurrence was 10.6 months (range,

1-48 months), with most recurrences (21/30 patients, 70.0%) occurring during the first year after treatment (90% before 2 years). Site distribution of local recurrence cases was as follows: 8 tongue (11.0%), 3 oral floor (11.5%), 8 upper gingiva (22.2%), 9 lower gingiva (20.5%), and 2 buccal mucosa (25.0%).

Univariate and multivariate logistic analyses for local recurrence

Univariate logistic analysis revealed that POI ($P<0.001$), NAC ($P<0.001$), the superficial margin ($P<0.001$), the deep margin ($P<0.001$), and postoperative adjuvant radiotherapy ($P<0.001$) were significantly associated with local recurrence (Table 2). Gender, age, T-stage, N-stage, UICC stage, and histologic grade were not significantly associated with local recurrence. Multivariate analysis revealed that NAC (OR=3.17, $P=0.047$), the superficial margin (OR=7.12, $P<0.001$), and the deep margin (OR=4.90, $P=0.011$) were independent factors for local recurrence (Table 3).

Effect of NAC on surgical margin status

As mentioned above, multivariate logistic analysis revealed that only NAC and margin status were independent factors for local recurrence. To examine the relationship between NAC and margin status, we performed a logistic regression analysis (predictor variable, NAC; response variable, margin status). NAC was significantly associated with the closed deep margin (OR=7.87, $P<0.001$), but not the superficial margin (Table 4).

Clinical course and survival analysis

At the time of analysis, 30 patients developed local recurrence. Salvage surgery was

performed in 19 of the 30 patients; radiation alone was performed in 6, and palliative chemotherapy in the remaining 5 patients. DSS rate for patients with local recurrence was 33.3% 10 years postoperatively. The most frequent outcome in the local recurrence group was death due to primary lesion (16 patients), followed by death due to cervical lesion (3 patients), and death due to distant metastasis (1 patient). Local control was impossible in all 11 patients in whom recurrent lesion was treated with radiotherapy or chemotherapy, and they died due to primary lesion, showing that salvage surgery was performed in all 10 survivors, and the salvaged rate was 52.6% (10/19 patients). DSS rate for patients with no local recurrence was 94.3% 10 years postoperatively. The outcome was death due to cervical and distant metastases in 6 and 3, respectively. The presence of local recurrence had an influence on survival ($P<0.001$) (Fig. 1).

Discussion

The clinical course of a patient with OSCC is determined by specific primary tumor factors, host characteristics, and, naturally the type of treatment modality.⁴ Locoregional recurrence in patients with OSCC remains a problem and can affect their survival.^{2, 6, 7} Particularly, local recurrence is a high potential risk factor for survival. Some studies demonstrated that demographic variables such as site, TNM stage, and simultaneous disorder, and pathological variables such as depth of invasion, surgical margin, and POI could be reliable parameters for local recurrence.^{2, 7, 8, 12-18} Previous studies reported that local recurrence occurred in 6.9% to 22.0%,^{2, 7, 8, 13-15} similar to the 16.0% rate in our series. Tumor site may be critical for local control. In previous reports, oral floor and buccal mucosa tumors may have worse local control than other sites within the oral

cavity.^{16, 17} However, our study did not significantly demonstrate this difference, which may have been due to the small number of patients with tumors arising in these particular subsites enrolled in our study (oral floor, n=26, 13.9%; buccal mucosa, n=8, 4.3%). Association between TNM classification and local recurrence has been reported,^{8, 13} but recurrence including primary lesion was not associated with gender, age, TNM classification, disease stage, or histologic differentiation stage. Studies on the relationship between the depth of invasion and local recurrence have been reported,^{2, 13} but we did not investigate it because the primary region varied in our patients, and evaluation of the depth of invasion based on specific criteria may have been difficult due to differences in anatomical characteristics.

We observed that a higher incidence of local recurrence was associated with POI, NAC, closed margin, and postoperative adjuvant radiotherapy. A relationship between POI and the incidence of local recurrence has been reported by some researchers.^{2, 18} Brandwein-Gensler et al. stated that the worst POI was associated with local recurrence, and this was because of the presence of tumor satellites with 1 mm or greater distance of intervening normal tissue at the tumor/host interface.² On the other hand, Spiro et al. reported that POI had a significant influence on survival, but not local recurrence.¹⁸ In this study, POI was identified as a significant predictive factor for local recurrence by univariate analysis but, it was not an independent factor by multivariate analysis. There was a trend for increasing incidence of local recurrence with diffuse POI, but the number of patients with local recurrence was too small to find significant differences between local recurrence and POI. Although we did not examine the presence of tumor satellites at the tumor/host interface as stated by Brandwein-Gensler et al.,² this evaluation may be useful for the assessment of local tumor control.

In the present study, we have demonstrated that both NAC and surgical margin status were significant independent predictive factors for local recurrence. NAC, which is the use of systemic chemotherapy before definitive surgery and/or radiotherapy, has been an attractive approach in the management of head and neck squamous cell carcinoma (HNSCC). The benefits of NAC for patients with locally advanced HNSCC, as demonstrated by several clinical studies, include a reduction in distant metastasis, improved survival, and the preservation of organ function.¹⁹⁻²² However, NAC has failed to demonstrate any significant improvement of survival in several randomized control trials.^{19,21} On the other hand, some studies have also shown that patients whose disease responded to NAC had a better survival rate over those who received non-effective NAC.^{20,23} The efficacy of NAC is controversial, as described above, and there has been no report with a high evidence level supporting this. Accordingly, at present, the standard treatment of oral cancers is surgery alone, and radiotherapy or concomitant chemoradiotherapy after surgery is recommended for high-risk cases in which recurrence or metastasis is expected.²⁴⁻²⁶ In our study, NAC increased the local recurrence rate over that in patients without NAC, for which a bias in selecting patients for NAC cannot be ruled out: advanced cases and cases with difficult local control may have been selected. However, NAC was performed in patients who waited for surgery for a relatively long time and those who took a long time to consent to surgery, and 28 (44.4%) of the 63 NAC-treated cases were stage I-II, showing that non-advanced cases were also included. In addition, NAC was extracted as an independent risk factor on multivariate analysis, suggesting that this bias was not involved in this finding. An increase in the risk of local recurrence by NAC has not previously been reported, but, in some studies on local recurrence, the local recurrence rate was higher in patients with

NAC than in those without NAC, although the difference was not significant.^{24, 27} To identify the cause of this, we investigated the influence of NAC on the surgical margin, another independent risk factor of local recurrence extracted. NAC and the deep margin were apparently associated, suggesting that the deep margin is likely to be resected at a close site when NAC is applied. The superficial margin may have been more appropriately set than the deep margin because it was marked before NAC or set outside the unstained area of intraoperative Lugol's iodine staining, and this may have been the reason for the absence of association with the superficial margin.²⁸ In contrast, the deep margin was set based on palpation during surgery or imaging diagnosis before NAC. The most advanced region of tumor invasion became unclear after modification by NAC, which may have resulted in resection with an insufficient safety margin.

Tumor local recurrence implies poor prognosis for patients with OSCC.^{13, 15} The present study showed DSS rate of 33.3% in patients with local recurrence. Other researchers have reported a 5 year survival rate of 24.5% to 50.0% or a 3 year survival rate of 52.6% for those with local recurrence.^{6, 8, 15, 29} Some studies reported that salvage surgery had significantly improved survival time over that with radiation therapy and/or chemotherapy for local recurrent tumors.^{29, 30} Ord et al. reported that salvage surgery for local recurrent tumors was performed in 54.2% (13/ 24 patients), with a 52.6% 3 year survival.¹⁵ No patients receiving radiation therapy and/or chemotherapy for local recurrent tumors were salvaged.^{15, 29} In our study, salvage surgery was performed in 63.3% (19/30 patients), with 33.3% 5 year survival and 52.6% salvaged rate. However, there were obvious biases inherent in these studies, including our data. Patients who required radiation therapy and/or chemotherapy contained the most advanced unresectable disease or patients too medically compromised to undergo curative surgery.

In fact, we were also able to confirm the findings that patients with initial diagnosis stage I/II had a better prognosis for salvage than those with stage III/IV. Therefore, our results support the use of salvage surgery as the best means of salvaging local recurrence, if the patient is resectable.

In conclusion, the local recurrence rate was 16.0% in this study involving 187 patients with OSCC. The survival rate of patients with local recurrence was 33.3%, which was significantly lower than that (94.3%) of patients without local recurrence. The outcome became unfavorable once local recurrence occurred, re-confirming the importance of the first treatment. POI, NAC and the status of the surgical margin were identified as factors influencing local recurrence. In particular, NAC and the status of the surgical margin were independent risk factors. The deep margin was resected at a close site in many NAC-treated cases, suggesting that NAC may lead to local recurrence and poor outcomes. No efficacy of NAC was observed, suggesting that the standard treatment of oral cancers is surgery alone, and when local recurrence occurs, salvage surgery should be performed, if resectable.

Competing interests

None declared.

Funding

None.

Ethical approval

Not required.

Figure legend

Fig. 1. Disease specific survival curve by the Actuarial life table method.

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Fig. 1

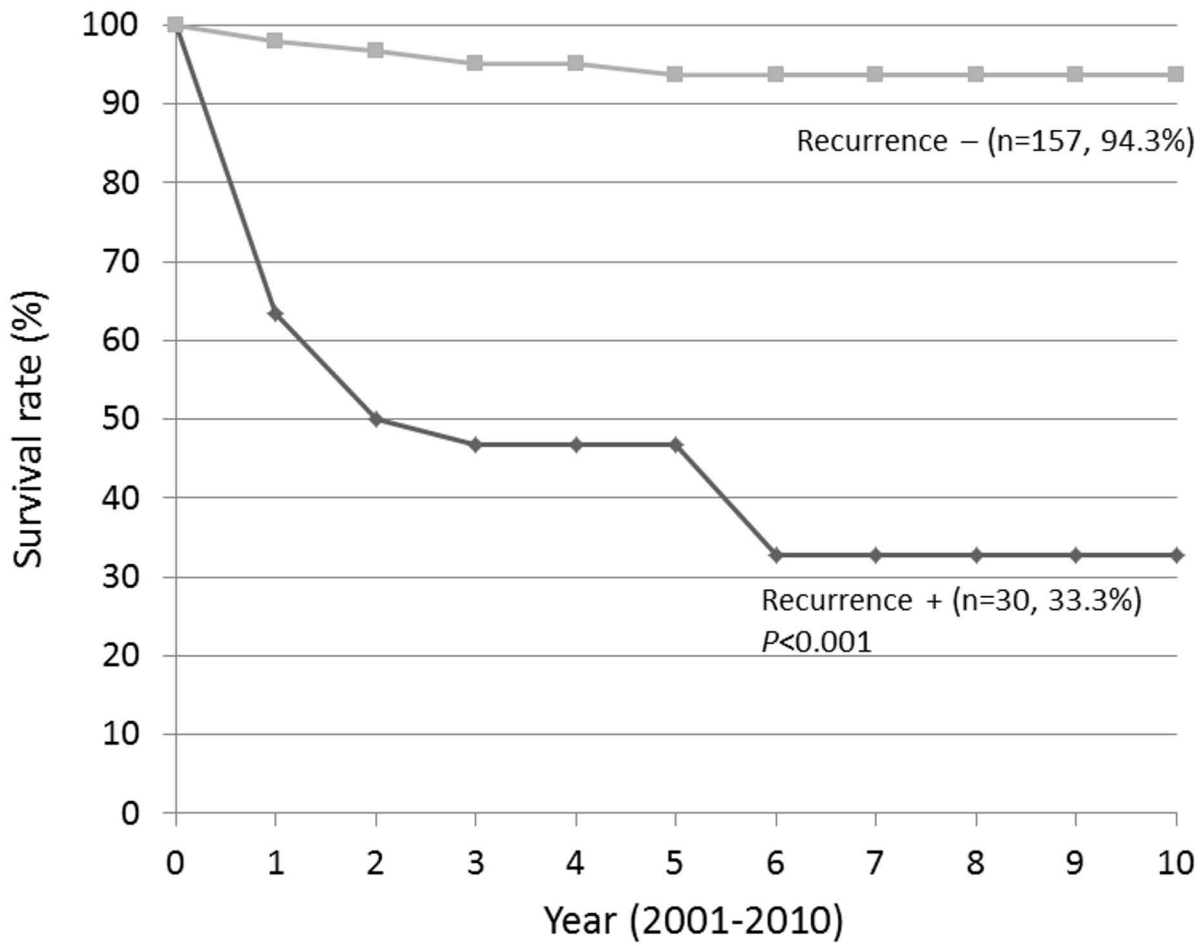


Table 1. Patient characteristics and appearance of a local recurrence

Characteristics	No. of cases (%)	No. of cases with a LR (%)
All cases	187 (100)	30 (16.0)
Gender		
Male	102 (54.5)	15 (14.7)
Female	85 (45.5)	15 (17.6)
Age		
≥68	111 (59.4)	20 (18.0)
≤67	76 (40.6)	10 (13.2)
Site		
Tongue	73 (39.0)	8 (11.0)
Oral floor	26 (13.9)	3 (11.5)
Upper gingiva	36 (19.3)	8 (22.2)
Lower gingiva	44 (23.5)	9 (20.5)
Buccal mucosa	8 (4.3)	2 (25.0)
T stage		
T1	52 (27.8)	6 (11.5)
T2	92 (49.2)	16 (17.4)
T3	14 (7.5)	2 (14.3)
T4	29 (15.5)	6 (20.7)
N stage		
N0	141 (75.4)	20 (14.2)
N1	26 (13.9)	3 (11.5)
N2a	2 (1.1)	0 (0)
N2b	12 (6.4)	6 (50.0)
N2c	6 (3.2)	1 (16.7)
UICC stage		
I	47 (25.1)	5 (10.6)
II	73 (39.1)	11 (15.1)
III	26 (13.9)	5 (19.2)
IV	41 (21.9)	9 (22.0)
Histologic grade		
Well	166 (88.8)	25 (15.1)
Moderately	20 (10.7)	4 (20.0)
Poorly	1 (0.5)	1 (100)

(Continued)

Table 1. (Continued)

Characteristics	No. of cases (%)	No. of cases with a LR (%)
POI		
1	5 (2.7)	1 (20.0)
2	30 (16.0)	4 (13.3)
3	107 (57.2)	10 (9.3)
4	45 (24.1)	15 (33.3)
Preoperative treatment		
Surgery alone	124 (66.3)	9 (7.3)
NAC	63 (33.7)	21 (33.3)
Surgical margin (Superficial)		
>4mm	156 (83.4)	16 (10.3)
≤4mm	31 (16.6)	14 (45.2)
Surgical margin (Deep)		
>4mm	162 (86.6)	14 (8.6)
≤4mm	25 (13.4)	16 (64.0)
Postoperative adjuvant radiotherapy		
Yes	15 (8.0)	8 (53.3)
No	172 (92.0)	22 (12.8)

LR, local recurrence; POI, pattern of invasion; NAC, neoadjuvant chemotherapy.

Table 2. Univariate logistic analysis for the factors influencing local recurrence

Factor	Odds ratio	95% CI	P value
Gender (Male vs. Female)	0.80	0.36-1.76	0.730
Age (≥68 vs. ≤67)	1.45	0.64-3.30	0.492
T stage (T1-2 vs. T3-4)	1.26	0.52-3.09	0.776
N stage (N- vs. N+)	1.68	0.72-3.91	0.327
UICC stage (I - II vs. III-IV)	1.72	0.78-3.78	0.253
Histologic grade (Well vs. Moderately + Poorly)	1.76	0.59-5.25	0.475
POI (1+2+3 vs. 4)	4.23	1.87-9.60	<0.001
Preoperative treatment (Surgery alone vs. NAC)	6.60	2.80-15.57	<0.001
Superficial margin (>4mm vs. ≤4mm)	7.20	3.00-17.31	<0.001
Deep margin (>4mm vs. ≤4mm)	16.44	6.16-43.92	<0.001
Postoperative adjuvant radiotherapy (No vs. Yes)	7.79	2.57-23.61	<0.001

POI, pattern of invasion; NAC, neoadjuvant chemotherapy.

Table 3. Multivariate logistic regression analysis for the factors influencing local recurrence

Factor	Odds ratio	95% CI	<i>P</i> value
POI (1+2+3 vs. 4)	1.81	0.58-5.72	0.308
Preoperative treatment (Surgery alone vs. NAC)	3.17	1.02-9.86	0.047
Superficial margin (>4mm vs. ≤4mm)	7.12	2.28-22.35	<0.001
Deep margin (>4mm vs. ≤4mm)	4.90	1.44-16.70	0.011
Postoperative adjuvant radiotherapy (No vs. Yes)	2.55	0.77-8.47	0.125

POI, pattern of invasion; NAC, neoadjuvant chemotherapy.

Table 4. Relationship of the margin status with preoperative treatment

Variable	Odds ratio	95% CI	<i>P</i> value
Superficial close margin (≤ 4 mm)			
Surgery alone	1		
NAC ^a	1.30	0.58-2.88	0.660
Deep close margin (≤ 4 mm)			
Surgery alone	1		
NAC	7.87	2.94-21.08	<0.001

NAC, neoadjuvant chemotherapy.