Int. J. Oral Maxillofac. Surg. 2019; 48: 143–151
https://doi.org/10.1016/j.ijom.2018.07.005, available online at https://www.sciencedirect.com

International Journal of Oral & Maxillofacial Surgery

Clinical Paper
Head and Neck Oncology

Pathological factors involved in local failure in squamous cell carcinoma of the oral cavity: retrospective study and proposal of a new clinical classification

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S. Toratani, I. Ogawa, H. Sasahara, Y. Yoshioka, T. Kanda, R. Tani, T. Okamoto: Pathological factors involved in local failure in squamous cell carcinoma of the oral cavity: retrospective study and proposal of a new clinical classification. Int. J. Oral Maxillofac. Surg. 2019; 48: 143–151.

Abstract. The control of local failure (LF) is essential to improve outcomes in patients with squamous cell carcinoma of the oral cavity (OSCC). In this study, LF of OSCC was classified into three clinical types: deep recurrence (type 1R), adjacent superficial recurrence (type 2R), and distant primary tumour (type 3R). LF was analyzed after surgical resection of OSCC to determine the validity and usefulness of this classification system. Of 257 patients with OSCC, 58 experienced LF; 21 had type 1R, 23 had type 2R, and 20 had type 3R. Clinical factors influencing LF were analyzed by log-rank test and Cox test. Type 1R was significantly related to the TN classification, resection margin status, and invasive pattern. Type 2R was strongly associated with the grade of epithelial dysplasia at the surgical margins. Type 1R rarely developed more than 1 year after surgery, whereas type 2R did not develop within 2 years. Type 1R may be caused by residual cancer cells in the deep margins, and type 2R by precancerous cells remaining in the marginal epithelium and gradually becoming invasive cancer. Type 3R may be considered an independent tumour. The newly proposed clinical classification is convenient and roughly reflects the causes and mechanisms of relapse.

Key words: oral squamous cell carcinoma; local recurrence; clinical classification.

Accepted for publication
Available online 3 September 2018

0901-5027/020143 + 09

Local failure (LF), along with cervical lymph node metastasis and distant metastasis, is the most important factor determining the prognosis of patients with squamous cell carcinoma of the oral cavity (OSCC)[1,2]. Classifying LF may aid in effective postoperative surveillance, including the selection of diagnostic imaging methods, leading to the early detection of relapses and the prevention of new tumours. Moreover, determining the mechanism of LF may lead to specific therapeutic strategies to improve the survival of patients with OSCC.

Clinically, two types of local relapse have been identified: relapse originating from the deep part and relapse originating from the surface layer of the resection margins at the primary tumour site. Factors reported to be related to LF include the TNM and stage classification, invasive pattern, and resection margin status[3–6]. These factors are regarded to be associated with the clinical conditions and properties of the tumour tissue remaining after surgery. Despite clear surgical margins with an absence of residual cancer cells, relapses can arise from residual epithelial dysplasia at the same site[6–8]. Recurrence may be due to residual precancerous cells that undergo malignant transformation[9], or to minimal residual cancer (MRC) not detected microscopically[10]. Furthermore, multiple primary squamous cell carcinomas may frequently occur in independent areas of the oral cavity and upper aerodigestive tract. The pathogenesis of secondary tumours has been linked to the concept of 'field cancerization' proposed by Slaughter et al.[11], with the development of these lesions being associated with the effects of cumulative widespread genetic and molecular changes[12,13].

There have been attempts at classifying LF using the molecular genetic criteria of OSCC relapses[14,15]. Although the use of genetic analysis to classify LF cases is technically feasible, it is economically impractical. A clinical classification system for LF of OSCC based on their patterns of relapse, with each pattern possibly reflecting its causes and mechanisms, is therefore proposed (Fig. 1). This classification system is composed of three categories: deep recurrence (type 1R), adjacent surface recurrence (type 2R), and distant primary tumour (type 3R). Type 1R is regarded as relapses arising from residual cancer cells existing in the deep area within the resection margins; type 2R as relapses arising from malignant transformation of residual precancerous cells in the superficial epithelium adjacent to the primary tumour; and type 3R as tumours occurring at sites different from the primary tumour. This study analyzed LF after surgical resection of OSCC to determine the validity and usefulness of this classification system.

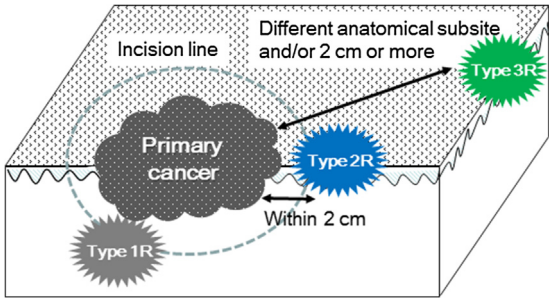

Fig. 1. Schematic diagram demonstrating local failure according to the new classification. Type 1R (deep recurrence) was defined as relapses arising in the deep part of the resection margin. Type 2R (adjacent superficial recurrence) was defined as a new squamous cell carcinoma arising at the surface within 2 cm of the primary tumour. Type 3R (distant primary tumor) was defined as a malignancy appearing >2 cm from the primary or in a different anatomical region.

Materials and methods

Patients

The data of patients who underwent surgery for OSCC in the Oral and Maxillofacial Surgery Department of Hiroshima University Hospital, Japan, from 1997 to 2015 were analyzed retrospectively. Data were retrieved from the medical records, pathology reports, and reports on various diagnostic imaging modalities. Primary tumours were classified according to the Union for International Cancer Control (UICC) staging system[16].

All patients had undergone radical resection of the primary tumour with clinical margins >1 cm. Additional resection, based on intraoperative frozen-section analysis, was performed when involved margins, carcinoma in situ, or severe epithelial dysplasia was observed. Patients with cervical lymph node metastasis and those requiring reconstruction also underwent neck dissection. Patients with early stage OSCC resected by transoral approach did not undergo neck dissection and were followed up by observation. Criteria for adjuvant radiotherapy or chemoradiotherapy included involved surgical margins, extracapsular spread, or multiple lymph node metastases. Patients underwent follow-up examinations performed by oral surgeons, including diagnostic imaging, every 1–3 months for the first 5 years and every 3–6 months thereafter. All patients were followed up for more than 12 months, except those who died.

Clinical classification of LF of OSCC

Postoperative LF of OSCC was classified into three categories according to clinical, diagnostic imaging, and histopathological findings (Fig. 1). Type 1R was defined as recurrence arising from the deep part of the tumour margin, despite the oral mucosa appearing visually normal on follow-up. Type 2R was defined as a new OSCC arising at the surface within 2 cm of the primary tumour, with pathological confirmation of the absence of cancer and carcinoma in situ in the mucosal margin surrounding the surgical specimen. Based on strict follow-up observations, type 2R LF originated from the adjacent epithelium, not from the deep margins. Type 3R was defined as a malignancy appearing >2 cm from the primary within the oral cavity; these tumours could be metachronous or synchronous. Tumours of the pharynx, larynx, and oesophagus were excluded from this study.

Pathological evaluation

Pathological reports were reviewed, with any questions resolved by an experienced pathologist (I.O.) examining permanent pathological sections. The degree of tumour differentiation and degree of epithelial dysplasia at the resected margin were classified according to the criteria of the World Health Organization (WHO)[16,17]. The pattern of tumour invasion was classified according to the YK classification[18]. Margin status was determined by microscopic evaluation of the distance between the tumour and deep normal tissues. Clear margins were defined as an absence of cancer cells within 5 mm of the resection margins; close margins as tumours within 5 mm of the resection margins but no evidence of cancer cells at the margin; and involved margins as the presence of

cancer cells at the resection margins. Carcinoma in situ was categorized as having involved margins[3,10,19,20].

Statistical analysis

Survival rates and the incidence of each type of LF were analysed using the Kaplan–Meier method. Univariate analysis (log-rank test) and multivariate analysis (Cox regression test) were performed to determine the association between each LF type and clinical factors. Statistical significance was defined as $P < 0.05$.

Results

Patients

The medical records of a total of 458 patients with OSCC were reviewed. Of these, 201 were excluded for not meeting the study criteria. During the study period, 257 consecutive patients with OSCC underwent surgical resection with or without adjuvant radiotherapy or chemoradiotherapy.

Patient characteristics are described in Table 1. The population consisted of 144 male and 113 female subjects, ranging in age from 29 to 92 years (mean 64.3 years). The median duration of follow-up was 65.1 months (range 4–212 months). The primary tumour site was the tongue in 107 patients, the floor of the mouth in 20, the alveolar mucosa in 113, and the buccal mucosa in 17. UICC stage classification showed that 64 patients were stage I, 102 were stage II, 22 were stage III, and 69 were stage IV. Thirty patients received adjuvant radiotherapy with or without chemotherapy.

Clinical outcomes

Local relapses occurred in 58 patients; 52 of these patients developed postoperative cervical lymph node metastases and 13 developed distant metastases. Thirty-two out of 139 patients with therapeutic or elective neck dissection relapsed in the neck. In the wait-and-see group, 20 of 118 patients had postoperative metastases, and in one of these patients it was not possible to control the neck lesion. Forty-five patients died of disease and 16 died of other causes (**Supplementary Material**, Fig. S1). The 5- and 10-year overall survival (OS) rates were 81.4% and 68.8%, respectively (**Supplementary Material**, Fig. S2). The 5- and 10-year LF rates were 22.4% and 36.7%, respectively; the cervical lymph node metastasis rates were both

Table 1. Clinical and pathological characteristics of the 257 OSCC patients who underwent surgical resection.

Characteristics	Number	%
Sex		
Male	144	56.0
Female	113	44.0
Age, years		
≤49	30	11.7
50–59	59	23.0
60–69	68	26.5
70–79	67	26.1
≥80	33	12.8
Smoking		
No	182	70.8
Yes (past)	73 (8)	28.4
Unknown	2	0.8
Tumour subsite		
Tongue	107	41.6
Floor of mouth	20	7.8
Upper alveolar mucosa	34	13.2
Lower alveolar mucosa	79	30.7
Buccal mucosa	17	6.6
T stage		
T1	68	26.5
T2	114	44.4
T3	20	7.8
T4	55	21.4
N stage		
N0	195	75.9
N1	19	7.4
N2	43	16.7
UICC stage		
I	64	24.9
II	102	39.7
III	22	8.6
IV	69	26.8
Pathological differentiation		
High	172	66.9
Intermediate	78	30.4
Low	7	2.7
Margin status		
Clear	205	79.8
Close	32	12.5
Involved	20	7.8
Grade of dysplasia		
No dysplasia	160	62.3
Mild	28	10.9
Moderate	59	23.0
Severe	10	3.9
Pattern of invasion		
YK-2	27	10.5
YK-3	146	56.9
YK-4c	75	29.2
YK-4d	3	1.2
Neurovascular invasion		
Perineural invasion	34	13.2
Vascular invasion	25	9.7
Neo-adjuvant therapy		
No	232	90.3
Yes	25	9.7
Adjuvant therapy		
No	227	88.3
Yes	30	11.7

OSCC, oral squamous cell carcinoma; UICC, Union for International Cancer Control.

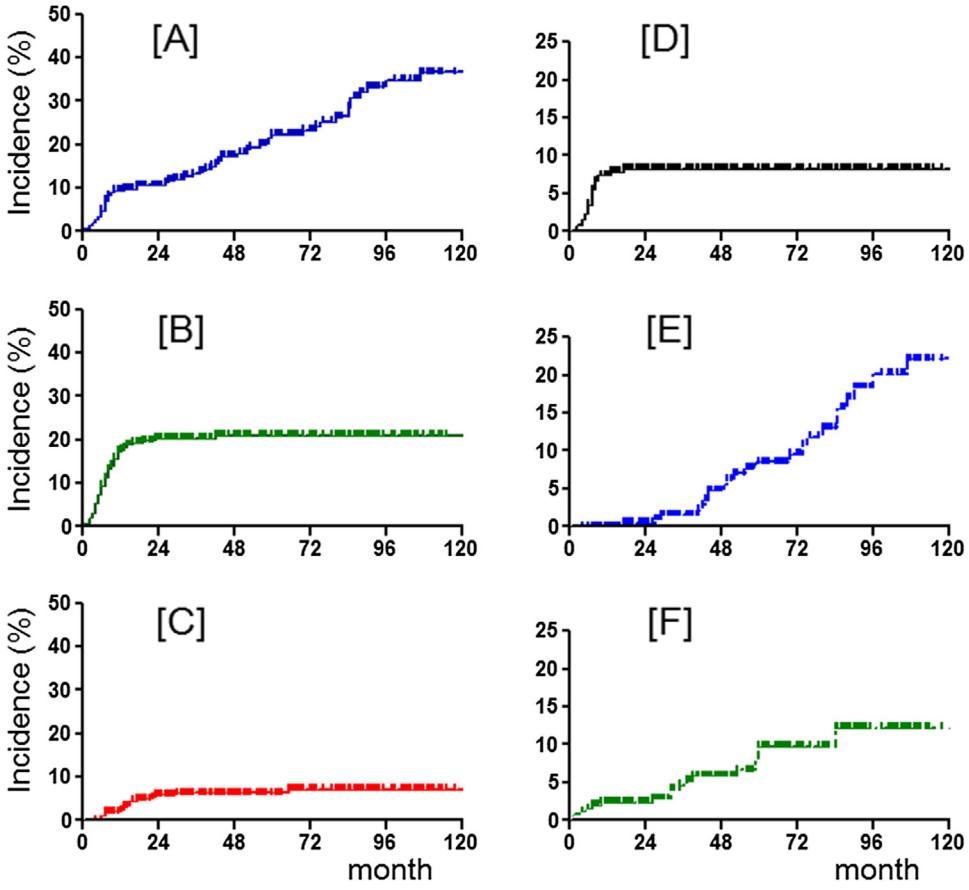

Fig. 2. Kaplan–Meier analysis of the incidence of local failure according to the site of initial failure and according to the new classification, for the 257 OSCC patients who underwent surgical resection. The incidence of local failure according to the site of initial failure: (A) local failure; (B) neck metastasis; and (C) distant metastasis. The incidence of local failure according to the new classification: (D) type 1R, deep recurrence; (E) type 2R, adjacent superficial recurrence; and (F) type 3R, distant recurrence.

21.0%, and the distant metastasis rates were both 5.8% (Fig. 2A–C).

Of the 58 patients with LF, 21 had type 1R, 23 had type 2R, and 20 had type 3R. Two patients had overlapping between type 1R and type 3R, four patients between type 2R and type 3R (**Supplementary Material**, Fig. S3). The average size of the greatest diameter of the relapse tumours was 34.2 mm (range 10–56 mm) in type 1R, 18.8 mm (range 8–35 mm) in type 2R, and 18.5 mm (range 5–45 mm) in type 3R. The mean smallest diameter, i.e. the thickness of the tumour, was 35.1 mm (range 3–47 mm) in type 1R, 2.8 mm (range 1.5–8 mm) in type 2R, and 3.6 mm (range 1.5–12 mm) in type 3R. All mean dimensions of the tumour in type 1R were significantly larger than those in types 2R and 3R (*t*-test, $P < 0.0004$). Specifically the tumours of type 1R exhibited a bulky mass morphology, whereas types 2R and 3R showed shallow lesions.

Twenty-six patients died of LF, with type 1R patients having the highest mortality rate (**Supplementary Material**, Fig. S3). Kaplan–Meier analysis showed 2-, 5-, and 10-year relapse rates of 8.3% each in patients with type 1R; 0.5%, 8.5%, and 20.1%, respectively, in patients with type 2R; and 3.2%, 9.8%, and 12.2%, respectively, in patients with type 3R (Fig. 2D–F). The time of occurrence of the three types differed, with most type 1R occurring within 1 year after treatment, type 2R occurring at >2 years after treatment, and type 3R occurring regardless of time.

Statistical analyses were performed to identify the clinical variables associated with each type of LF. The log-rank test showed that type 1R was significantly associated with the degree of tumour progression, including TN classification and UICC stage, as well as with surgical margin status and pattern of invasion (Table 2). Cox analysis showed that type 1R was associated with N stage, surgical margin status, and pattern of invasion (Table 3). In assessing the relationship between type 1R and margin status, it was found that the 5-year LF rates for clear, close, and involved margins were 4.4%, 19.4%, and 36.6%, respectively, with a significant association (Fig. 3A). Specifically, with the exception of one out of the 12 patients with pathological involved or close margins in type 1R, the relapse site almost coincided with the site adjacent to the primary tumour. The rate of type 1R was 5.2% in patients with invasion patterns YK-2 and -3 and 16% in patients with YK-4c and -4d (Fig. 3B).

The incidence of type 2R differed significantly between patients with no/mild epithelial dysplasia and moderate/severe dysplasia at the surgical margin, both by log-rank test ($P < 0.0001$) and Cox analysis ($P < 0.0001$). In 11 of 15 patients with type 2R and residual epithelial dysplasia at the surgical margin, the recurrence site nearly accorded with the dysplasia site. The 10-year type 2R rate was 13.6% in patients with normal epithelium and 16.4% in patients with mild dysplasia, while it was 45% in patients with moderate and severe dysplasia (Fig. 3C).

Table 2. Association of the incidence of local failure and clinical and pathological factors—univariate analysis (log-rank analysis).

Characteristics	Type 1R			Type 2R			Type 3R		
	5 years	10 years	*P*-value	5 years	10 years	*P*-value	5 years	10 years	*P*-value
Sex			0.1411			0.2096			0.0644
Male	10.6	10.6		4.2	20.9		13.3	18.5	
Female	5.4	5.4		14.2	24.8		7.0	7.0	
Age, years			0.2452			0.4520			0.0208*
≤65	6.4	6.4		4.2	21.9		6.5	6.5	
>65	10.2	10.2		14.5	21.1		13.8	20.2	
Smoking			0.3208			0.2747			0.1967
No	9.5	9.5		10.5	25.4		10.2	13.6	
Yes	5.5	5.5		4.0	14.2		16.5	25.3	
Tumour subsite			0.0044*			0.5287			0.0031*
Tongue	2.9	2.9		6.5	19.6		4.0	6.4	
Floor of mouth	10.3	10.3		0	0		0	0	
Alveolar	11.7	11.7		14.0	38.4		14.2	17.6	
Buccal mucosa	17.6	17.6		0	16.7		33.8	33.8	
T stage			0.0277*			0.8815			0.2142
T1	4.4	4.4		5.7	21.9		2.9	2.9	
T2	5.3	5.3		7.9	26.5		13.4	15.7	
T3	16.0	16.0		8.3	8.3		5.0	5.0	
T4	16.9	16.9		14.5	14.5		11.5	17.7	
N stage			<0.0001*			0.4745			0.0837
N0	2.6	2.6		7.9	24.8		8.5	11.5	
N+	26.4	26.4		12.1	12.1		14.9	29.1	
UICC stage			<0.0001*			0.5903			0.2808
I	1.5	1.5		5.7	21.9		3.1	3.1	
II	12.0	12.0		8.7	30.4		12.0	14.7	
III	22.7	22.7		6.7	6.7		18.2	18.2	
IV	19.5	19.5		12.3	12.3		10.8	15.1	
Pathological differentiation			0.8174			0.6911			0.5559
High	7.1	7.1		7.5	23.1		11.0	12.7	
Moderate	10.6	10.6		10.9	19.0		8.1	12.7	
Low	11.1	11.1		0	0		0	0	
Margin status			<0.0001*			0.4952			0.7642
Clear	4.4	4.4		9.8	22.4		10.4	13.0	
Close	19.4	19.4		0	20.0		3.1	3.8	
Involved	36.6	–		0	–		5.5	–	
Grade of dysplasia			0.3621			<0.0001*			0.9764
No dysplasia	10.2	10.2		4.1	13.6		8.4	12.3	
Mild	3.7	3.7		0	16.4		15.5	15.5	
Moderate/severe	5.8	5.8		25.3	45.8		9.8	9.8	
Pattern of invasion			<0.0003*			0.1539			0.7627
YK-2, -3	5.2	5.2		10.1	25.1		9.3	10.8	
YK-4c, -4d	16.0	16.0		3.7	11.1		8.1	15.2	
Neurovascular invasion			0.1892			0.7839			0.7568
No	7.2	7.2		6.5	23.0		10.2	11.6	
Yes	1 3.0	13.0		3.6	14.3		4.5	18.1	
Adjuvant therapy			0.6651			0.1464			0.4515
No	11.1	11.1		9.2	22.4		10.3	12.9	
Yes	8.0	8.0		0	0		3.3	3.3	

UICC, Union for International Cancer Control.
*Statistically significant ($P < 0.05$).

All 20 patients with type 3R relapse in the oral cavity differed in primary and secondary relapse sites. Four secondary tumours arose within 6 months after the first visit, whereas the 16 metachronous tumours occurred subsequently. Log-rank tests suggested that the incidence of type 3R was significantly higher in patients aged ≥65 years than in younger patients. Cox analysis showed that the incidence of type 3R was lower in patients with cancers of the tongue and floor of the mouth (Fig. 3D, Tables 2 and 3).

Discussion

Clinically, LFs consist of local recurrences and second primary tumours (SPTs)[2]. Local recurrence is defined as the regrowth of cancer cells residing at the resection site. Factors associated with recurrence include advanced stages and pathological status of the surgical margins[3–6,19–21]. On the other hand, OSCCs frequently include a premalignant field surrounding the primary tumours, extending into the surgical margins. Local relapses have been reported to arise from precancerous lesions in the non-resected field following additional genetic alterations[10]. However, there are a few reports in which epithelial dysplasia has been classified as a positive margin[8,19,22]. The type that this form of relapse corresponds to has not been clarified.

The occurrence of multiple primary squamous cell carcinomas in independent areas of the oral cavity and upper aerodigestive tract is not uncommon. The criteria used to diagnose SPT in clinical

Table 3. Multivariate analysis of the relationship between clinical and pathological factors and local failure—Cox test.

Characteristics	Type 1R		Type 2R		Type 3R	
	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
Sex	0.341 (0.114–1.016)	0.0534	1.010 (0.406–2.511)	0.9824	1.774 (0.637–4.944)	0.2728
Age	1.022 (0.979–1.067)	0.3210	1.027 (0.986–1.069)	0.2018	1.024 (0.980–1.070)	0.2856
Tumour subsite	1.892 (1.095–3.268)	0.0223*	1.402 (0.851–2.311)	0.1845	2.177 (1.119–4.237)	0.0220*
T stage	0.962 (0.605–1.531)	0.8708	1.538(0.911–2.597)	0.1074	1.343 (0.827–2.183)	0.2337
N stage	3.401 (1.900–6.086)	<0.0000*	0.566 (0.231–1.386)	0.2131	1.083 (0.585–2.007)	0.7996
Pathological differentiation	0.925 (0.391–2.186)	0.8585	0.983 (0.394–2.452)	0.9702	1.562 (0.527–4.629)	0.4208
Margin status	2.002 (1.192–3.361)	0.0086*	0.262 (0.038–1.790)	0.1719	0.649 (0.208–2.028)	0.4573
Grade of dysplasia	0.851 (0.465–1.558)	0.6002	3.109 (1.787–5.410)	0.0001*	0.848 (0.485–1.482)	0.5619
Pattern of invasion	2.903 (1.209–6.970)	0.0171*	0.774 (0.359–1.672)	0.5149	1.577 (0.639–3.891)	0.3227
Neurovascular invasion	0.854 (0.308–2.369)	0.7614	0.907 (0.174–4.734)	0.9079	2.021 (0.473–8.646)	0.3425
Adjuvant therapy	0.285 (0.075–1.078)	0.0645	0 (0)	0.9764	0.208 (0.024–1.783)	0.1521

HR, hazard ratio; CI, confidence interval.
*Statistically significant ($P < 0.05$).

practice include the following[23]: (1) each tumour must present a definite picture of malignancy, (2) each tumour must be distinct, and (3) the possibility that the second tumour is a metastasis from the index tumour must be excluded. SPTs appearing at the same anatomical subsite must be separated from the index tumour by at least 2 cm of normal epithelium or occur at least 3 years after the diagnosis of the index tumour[24]. However, the basis on which relapse at the same site after ≥3 years is classified as SPT remains unclear. This concept may depend on whether regrowth of MRC or malignant transformation of precancerous cells occurred around the primary tumours. The former should be classified as true recurrence (TR), whereas the latter may be classified as another type of relapse rather than SPT, depending on the genetic origin.

New criteria for classifying OSCC relapses have been proposed based on molecular genetics by Braakhuis et al.[14,15]: (1) relapses sharing the same genetic alterations as primary tumours are considered TRs, with both tumours derived from clonally related tumour cells; (2) relapses sharing only some genetic alterations with the primary tumour, especially mutations associated with the early stages of the carcinogenetic process, but deriving at later stages, are classified as second field tumours (SFT); and (3) relapses differing greatly in genetic profiles from primary tumours, including in early genetic changes, are regarded as true SPTs. However, clinical findings and molecular genetic analysis do not necessarily coincide, and these discrepancies have not yet been resolved. The important feature of this classification is the separation of SFT, a distinct tumour arising from the malignant transformation of the same genetic precancerous cells that give rise to local recurrences. Additionally, SPT arising from mucosal precursor cells in the same field as the primary tumour must be reclassified as SFT, regardless of the time following surgical resection[24]. This classification of relapse of head and neck tumours may be inapplicable based on several genetic criteria[10,14,22,25–27]. The molecular genetic classification of OSCCs is complicated by numerous and diverse genetic and epigenetic abnormalities, as well as by obscure 'driver' and 'passenger' mutations[15,28–30].

The absence of a standard clinical classification of LF, including TR, SFT, and SPT, led to the new system for classifying OSCC relapses presented herein. This classification system is related to mecha-

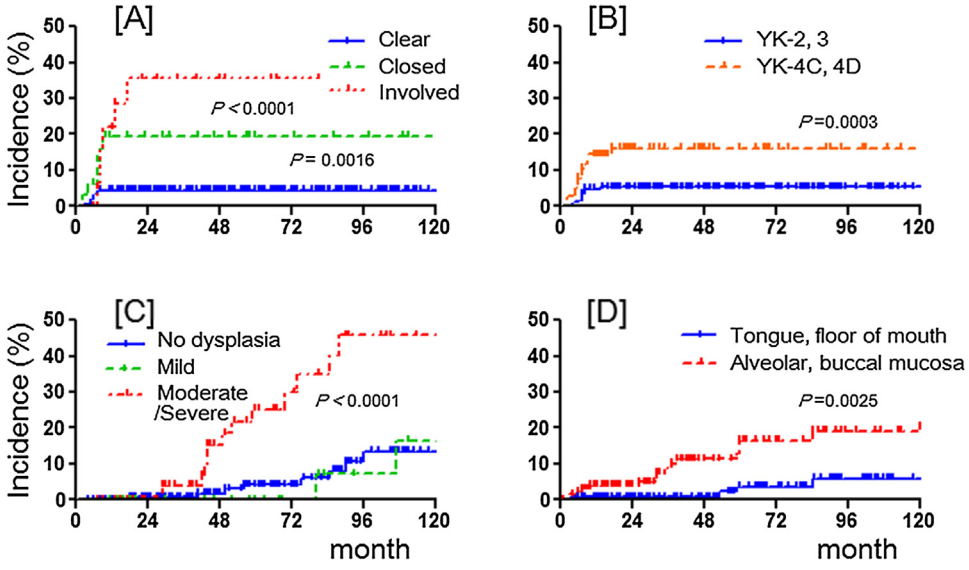

Fig. 3. Kaplan–Meier analysis of local failure according to clinical and pathological characteristics in OSCC patients. (A) Incidence of type 1R by status of the surgical margin; (B) incidence of type 1R by invasive pattern; (C) incidence of type 2R according to the level of epithelial dysplasia of the resected margin; (D) incidence of type 3R by primary site.

nisms of recurrence and growth patterns of residual cancers or malignant transformation of precancerous fields, along with temporal and spatial factors.

Type 1R was defined as relapses arising from cancer cells remaining deep within resected sites, similar to TR. Few oral cancers are present on the mucosal surface, resulting in complete removal of both the tumour and $\geq$1 cm marginal epithelium, as well as other macroscopic oral mucosal lesions, with removal based largely on intraoperative examination of frozen sections. The tumour cell remnants are considered to be within the deep margins and not at the surface. Therefore, the mucosa at the resection site of type 1R lesions is apparently normal, but follow-up has revealed growing indurations or swelling in deep portions, including within sutured areas, accompanied by tenderness and discomfort. This relapse pattern has often been confirmed by diagnostic imaging methods, such as computed tomography (CT), magnetic resonance imaging (MRI), and fluorodeoxyglucose positron emission tomography (FDG-PET).

Type 2R was defined as relapses from malignant alteration of residual precancerous cells of the same origin as the index tumour in the mucosa adjacent to the primary site, similar to SFT[14,15]. Consequently, superficial tumours may arise from the epithelium around the resection site, even if the entire primary tumour has been removed macroscopically during surgery and surgical specimens have shown no evidence of cancer cells at the margins. Careful follow-up has shown the presence of tumour and/or ulcer in the abnormal mucosa (leukoplakia, erythroplakia, and erosion) around the primary tumour, with relapses confirmed by biopsy. This type of relapse, however, is regarded as difficult to distinguish from relapse caused by MRC in the epithelium.

Type 3R was defined as a tumour occurring at least 2 cm distant from the primary lesion with intervening normal epithelium, arising either metachronously or synchronously. These tumours are therefore equivalent to those classified as SPTs[23], excluding the temporal factor of 3 years[24].

In this study, LFs of OSCC after resection were classified according to these criteria and the relationships with clinical and histopathological factors were examined. Of the 257 patients, 58 (22.6%) experienced relapse, including 21 patients with type 1R, 23 with type 2R, and 20 with type 3R.

Type 1R accounted for about 36% of total LFs. Similar to cervical lymph node metastases, these relapses frequently occurred within 1 year, but no more than 2 years, after resection. Factors associated with type 1R were similar to those previously associated with local relapses[3,4,6], including TN classification and UICC stage, pathological status of the surgical margins, and pattern of invasion. Type 1R, however, was not associated with residual epithelial dysplasia at the tumour margins.

Type 2R constituted about 40% of all LFs. The factors found to be associated with type 1R were not associated with the development of type 2R. However, epithelial dysplasia was strongly correlated with the development of type 2R. The frequency of cancerization from marginal dysplasia has been reported to range from 5.7% to 71%[19,21,31]. The risk of malignant progression of epithelial dysplasia was estimated by histological grading according to the WHO classification[17]. The possibility of malignant change was found to be higher in patients with moderate and severe dysplasia than in those with no or mild dysplasia[7]. The presence of severe dysplasia must be considered an indication for additional resection. In contrast, the optimal management of patients with mild and moderate dysplasia remains unclear[31,32]. However, the recurrence rate from histological normal mucosa was found to be 13.6%, suggesting that patients with OSCC have a tumour-associated genetically altered field surrounding the tumour and extending into the surgical margins[22,25]. These findings suggest that non-microscopic abnormal progenitor cells with accumulated genetic abnormalities remain in the margins and gradually become invasive cancer.

The major difference between types 1R and 2R was the time of occurrence. Most type 1R lesions occurred within 1 year after resection, whereas most type 2R lesions occurred more than 2 years after resection, with some occurring after 10 years or more. These findings suggest that small numbers of residual cancer cells rapidly emerge into clinically detectable cancers. In contrast, precancerous cells in the field need additional time to accumulate genetic aberrations before malignant transformation and progression to invasive cancers[9]. Tabor et al.[10] reported that the mean time to relapse by MRC, determined by loss of heterozygosity (LOH) analysis, was 8.8 months, whereas the mean time to relapse following the transformation of precursor cells into invasive tumours was 20.6 months. Follow-up diagnostic imaging, especially CT and MRI, within 2 years after surgery is therefore needed to detect type 1R and neck metastasis, particularly in patients with poor prognostic factors and those with advanced tumours. In contrast, patients with moderate and worse epithelial dysplasia remaining around the primary tumour should be followed up more frequently, as inspection, palpation, and optical diagnosis may detect type 2R lesions.

Type 3R was unrelated to factors associated with local relapse, suggesting that these tumours had arisen independently. Factors associated with the development of type 3R included patient age and primary site, similar to reports of SPT[33,34]. A high occurrence of type 3R in older patients with gingival cancer and lower occurrence in younger patients with tongue cancer was demonstrated. Cancer is a multi-step process, requiring the accumulation of multiple genetic and epigenetic alterations of oncogenes and tumour-suppressor genes[9]. Increased age may be associated with the accumulation of genetic aberrations in the mucosa of the upper aerodigestive tract, including the oral cavity. Proliferative verrucous leukoplakia (PVL)-related OSCC that predominantly occurs in the gingiva of elderly female subjects and that frequently recurs at the primary site and/or a distant site is known[35,36]. In this study, no case was diagnosed as PVL-related OSCC; however a strict differential diagnosis is required for type 2R and type 3R in this disease.

In conclusion, the spatial and temporal patterns of LF vary widely. The new clinical classification of LFs of OSCC presented herein roughly reflects the causes and mechanisms of relapse. Genetic analysis confirming the relationship between original tumours and local relapses was not performed. However, the classification system may reflect TR, SFT, and SPT[14]. Further development of efficient and economical laboratory procedures may allow the accurate determination of LF classification from molecular genetic analysis.

Funding

This study was not supported by grant funding.

Competing interests

The authors declare no conflict of interest.

Ethical approval

This study was approved by the Ethics Committee for Epidemiology of Hir-

oshima University (Permission No. E-870).

Patient consent

Patient consent was not required.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.ijom.2018.07.005.

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