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A histopathological evaluation and potential prognostic implications of oral squamous cell carcinoma with adverse features

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ABSTRACT

Objectives: This study aimed to evaluate the adverse clinicopathologic features of oral squamous cell carcinoma (OSCC), including margin status, depth of invasion, lymphovascular invasion, perineural invasion, and extranodal extension that significantly affect survival outcomes.

Materials and methods: This retrospective cross-sectional study included 341 patients with OSCC who underwent therapeutic surgical treatment in Taiwan. The Kaplan–Meier method was used to estimate survival outcomes. A multivariable Cox regression model was used to evaluate the associations of various clinicopathologic features with 5-year overall survival (OS) outcomes in patients with pN0 and pN+ tumors.

Results: Overall, the patients had 5-year OS and progression-free survival rates of 60.0 and 47.9%, respectively. In the pN0 group, the multivariate analysis identified a positive margin (odds ratio [OR] = 16.3, 95% confidence interval [95% CI]: 3.7–72.3; P = 0.001), depth of invasion > 5 mm (OR = 2.1, 95% CI: 1.2–3.7; P = 0.012), presence of lymphovascular space invasion (OR = 5.4, 95% CI: 1.3–22.0; P = 0.018), and presence of perineural invasion (OR = 4.3, 95% CI: 1.7–11.1; P = 0.002) as independent and significant prognosticators of OS. In the pN+ group, only the presence of extranodal extension independently predicted OS (OR = 1.7, 95% CI: 1.1–2.7; P = 0.0026).

Conclusions: When determining survival prognosis for patients with a pN0 status, we recommended including all adverse features. In contrast, extranodal extension was the most important prognostic factor for patients with a pN+ status.

Introduction

Oral squamous cell carcinoma (OSCC) is the sixth most prevalent malignancy worldwide and the most prevalent malignant tumor of the oral cavity [1]. In Taiwan, OSCC is the fourth most prevalent cancer among men and the sixth most prevalent cancer overall [2]. The major treatment guideline in current use recommends the use of therapeutic resection, followed by adjuvant therapy for postoperative management. Decisions regarding the choice of the adjuvant therapy are based on a histopathologic analysis of the resected specimen [3], and particularly by the presence or absence of adverse features such as a positive margin, perineural invasion (PNI), lymphovascular space invasion (LVSI), depth of invasion, and extranodal extension.

Currently, high-risk cancers are managed postoperatively using systemic therapy or radiotherapy (RT). A US intergroup trial, Radiation Therapy Oncology Group (RTOG) 9501, identified a positive margin

Abbreviations: AJCC, American Joint Committee on Cancer; ECS, extracapsular nodal spread; ENE, extranodal extension; EORTC, European Organization for Research and Treatment of Cancer; LVSI, lymphovascular space invasion; OS, overall survival; OSCC, oral squamous cell carcinoma; PFS, progression-free survival; PNI, perineural invasion; RT, radiotherapy; RTOG, radio therapy oncology group

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and extracapsular nodal spread (ECS) as high-risk factors [4]. In addition to these factors, a European trial, European Organization for Research and Treatment of Cancer (EORTC) 22931, also identified PNI and LVSI as associated with high-risk disease [5]. Many other studies have reported the adverse effects associated with postoperative systemic therapy [6]. Taken together, these differences in the criteria for high-risk disease and potential consequences of treatment suggest a lack of consensus regarding postoperative adjuvant therapy, as well as the need for additional study.

Neck metastasis is a well-known adverse factor that can be easily identified during initial TNM staging [7,8]. However, a subclassification of neck metastasis was needed. Accordingly, the American Joint Committee on Cancer (AJCC) included two significant changes based on clinicopathologic features in the 8th edition of the Cancer Staging Manual. The first change updated the T categorization to include the depth of invasion and identified an association between thicker tumor and worse prognosis [9,10]. The second change updated the N categorization to include extranodal extension (ENE) as an adverse prognostic factor that provides equivocal histological evidence as ECS [11,12]. Accordingly, a survival analysis of OSCC should include the depth of invasion and ENE as high-risk factors.

To date, most studies of the survival outcomes of OSCC have included a limited number of histopathologic features, and no previous study has used a multivariate analysis to compare the effects of each specific adverse feature. In this study, we reassessed the effects of all known adverse features on recurrence and overall survival (OS) in a cohort of patients with OSCC.

Materials and methods

Patients

This retrospective study included patients with oral squamous cell carcinoma who were treated at the Tri-Service General Hospital, a single-unit facility in Taipei, Taiwan, between 2002 and 2015. The Ethical Committee of the Tri-Service General Hospital approved this retrospective study (institutional review board protocol no: 2-108-05-044). All patients provided written informed consent.

The study inclusion criteria were as follows: (1) initial diagnosis of oral cancer and histopathological proof of squamous cell carcinoma, (2) and Eastern Cooperative Oncology Group performance score of 0 or 1, (3) a treatment plan compliant with the latest guideline from the National Comprehensive Cancer Network, and (4) therapeutic surgical resection with curative intent, with or without adjuvant postoperative therapy. Additionally, the following exclusion criteria were applied: (1) incorrect treatment planning, (2) the presence of distant metastasis at the initial visit, (3) previous or synchronous other cancers, (4) contraindication for curative surgery, and (5) final event of death and recurrence due to non-cancer etiology.

In our study, the pathologic results were initially determined and rechecked by the same oral cancer professional pathologist according to the 8th edition of the AJCC staging manual. The following adverse features were re-checked: PNI, LVSI, depth of invasion, human papillomavirus status, surgical margin involvement, and ENE. The primary tumor sites were the lip, retromolar region, gingiva, tongue, buccal mucosa, floor of mouth, and palate. OS was calculated until the final appointment or the event of death. Progression-free survival (PFS) was calculated until the first date of recurrence. Otherwise, all patients were followed-up for at least 2 years (until December 2016).

Treatments

All patients with primary OSCC underwent a minimum surgical treatment comprising selective neck lymphatic node dissection and primary tumor resection. Adjuvant radiotherapy or concurrent chemoradiotherapy was administered after staging, if adverse features were present. All patients were registered in an institutional database that was corrected and updated to include the most recent treatment conditions observed during follow-up.

Table 1
Patient demographics.

Characteristics		No. of patients	Percentage (%)
Sex	Male	313	91.8
	Female	28	8.2
Mean age, years	52.1 (range, 23–84)	341	100.0
HPV exposure	No	307	90.0
	Yes	34	10.0
Tobacco exposure	No	64	18.8
	Yes	277	81.2
Alcohol exposure	No	84	24.6
	Yes	257	75.4
Betel nut exposure	No	72	21.1
	Yes	269	78.9
Margin status	≥ 5 mm	236	69.2
	< 5 mm	93	27.3
	Positive	12	3.5
DOI	≤ 5 mm	98	28.7
	> 5 mm	243	71.3
PNI	Negative	273	80.1
	Positive	68	19.9
LVSI	Negative	300	88.0
	Positive	41	12.0
ENE	Negative	281	82.4
	Positive	60	17.6
Overall TNM stage	I	62	18.2
	II	75	22.0
	III	75	22.0
	IVA	83	24.3
	IVB	46	13.5
T classification	1	72	21.1
	2	102	29.9
	3	89	26.1
	4a	77	22.6
	4b	1	0.3
N classification	N0	216	63.3
	N1	35	10.3
	N2a	16	4.7
	N2b	25	7.3
	N2c	4	1.2
	N3a	0	0.0
	N3b	45	13.2
Treatment	Surgery only	87	25.5
	Surgery + RT	53	15.5
	Surgery + CT	53	15.5
	Surgery + CCRT	148	43.4
Anatomical site	Lip	2	0.6
	Retromolar trigone	16	4.7
	Gingiva	43	12.6
	Tongue	147	43.1
	Palate	7	2.1
	Buccal mucosa	115	33.7
	Mouth floor	11	3.2
Follow-up duration (months)	Mean: 50.5 ± 35.7 Median: 43 Range: 0–143	341	100.0

HPV, human papillomavirus; DOI, depth of invasion; PNI, perineural invasion; LVSI, lymphovascular space invasion; ENE, extranodal extension; CCRT, concurrent chemoradiotherapy; CT, chemotherapy; RT, radiotherapy; TNM, tumor, node, metastasis.

Table 2
Characteristics of patients without neck metastasis (pN0) and of subgroups stratified by the perineural invasion and lymphovascular space invasion status.

Characteristics (n, %)	Perineural invasion					Lymphovascular space invasion				
	No (n = 204) (n, %)		Yes (n = 12) (n, %)		P	No (n = 212) (n, %)		Yes (n = 4) (n, %)		P
Age, years					0.238					1.000
< 60 (94, 43.5)	91	(44.6)	3	(25.0)		92	(43.4)	2	(50.0)	
≥60 (122, 56.5)	113	(55.4)	9	(75.0)		120	(56.6)	2	(50.0)	
Sex					0.087					0.324
Male (196, 90.7)	187	(91.7)	9	(75.0)		193	(91.0)	3	(75.0)	
Female (20, 9.3)	17	(8.3)	3	(25.0)		19	(9.0)	1	(25.0)	
pT stage					0.033*					0.017*
T1 + T2 (137, 63.4)	133	(65.2)	4	(33.3)		137	(64.6)	0	(0.0)	
T3 + T4 (79, 36.6)	71	(34.8)	8	(66.7)		75	(35.4)	4	(100.0)	
DOI					0.379					0.639
≤5 mm (83, 38.4)	80	(39.2)	3	(25.0)		81	(38.2)	2	(50.0)	
> 5 mm (133, 61.6)	124	(60.8)	9	(75.0)		131	(61.8)	2	(50.0)	
Margin					0.942					0.490
> 5 mm (160, 74.1)	151	(74.0)	9	(75.0)		156	(73.6)	4	(100.0)	
1–5 mm (54, 25.0)	51	(25.0)	3	(25.0)		54	(25.5)	0	(0.0)	
Positive (2, 0.9)	2	(1.0)	0	(0,0)		2	(0.9)	0	(0.0)	
Local recurrence					0.000*					0.026*
No (128, 59.3)	127	(62.3)	1	(8.3)		128	(60.4)	0	(0.0)	
Yes (88, 40.7)	77	(37.7)	11	(91.7)		84	(39.6)	4	(100.0)	
Distant metastasis					0.100					0.013*
No (182, 84.3)	174	(85.3)	8	(66.7)		181	(85.4)	1	(25.0)	
Yes (34, 15.7)	30	(14.7)	4	(33.3)		31	(14.6)	3	(75.0)	
Stage					0.003*					0.000*
I (62, 28.7)	61	(29.9)	1	(8.3)		62	(29.2)	0	(0.0)	
II (75, 34.7)	72	(35.3)	3	(25.0)		75	(35.4)	0	(0.0)	
III (48, 22.2)	46	(22.5)	2	(16.7)		48	(22.6)	0	(0.0)	
IV (31, 14.4)	25	(12.3)	6	(50.0)		27	(12.7)	4	(100.0)	
Tobacco exposure					0.717					1.000
No (45, 20.8)	42	(20.6)	3	(25.0)		44	(20.8)	1	(25.0)	
Yes (171, 79.2)	162	(79.4)	9	(75.0)		168	(79.2)	3	(75.0)	
Betel-nut exposure					0.484					0.575
No (51, 23.6)	47	(23.0)	4	(33.3)		51	(24.1)	0	(0.0)	
Yes (165, 76.4)	157	(77.0)	8	(66.7)		161	(75.9)	4	(100.0)	
Alcohol exposure					1.000					0.584
No (64, 29.6)	61	(29.9)	3	(25.0)		62	(29.2)	2	(50.0)	
Yes (152, 70.4)	143	(70.1)	9	(75.0)		150	(70.8)	2	(50.0)	
HPV exposure					1.000					1.000
No (195, 90.3)	184	(90.2)	11	(91.7)		191	(90.1)	4	(100.0)	
Yes (21, 9.7)	20	(9.8)	1	(8.3)		21	(9.9)	0	(0.0)	

HPV, human papillomavirus; DOI, depth of invasion.
* Indicates a significant difference ($p < 0.05$).

Adverse features

Definitive tumor staging was based on pathological features, in accordance with the 8th edition of the AJCC Staging Manual. Pathological examinations of the macroscopic features were performed by the same group of experienced head and neck pathologists according to a standardized protocol. Adverse features were reported and registered via the cancer registry center at the same unit hospital. The margin status was defined as the inclusive distance from the surgical incision to the tumor bed and was subsequently divided into three groups in accordance with previous studies: clear (> 5 mm), close (≤5 mm with no tumor involvement), or involved (tumor involvement) [13,14]. The depth of invasion of a carcinoma was defined as the perpendicular distance between the extents of deep tumor invasion to the basement membrane of the adjacent mucosa. The patients were then subdivided into groups according to the depth of invasion of > 5 mm or ≤5 mm.

PNI was defined as the pathologic observation of tumor cell infiltration into the neural cell bundle within any of the three nerve sheath layers (epineurium, perineurium, and endoneurium). LVSI was defined as the presence of tumor cells within a vascular space (e.g., lymphatic space or blood vessel). ENE was defined as an extension of the tumor through the lymphatic capsule to invade the surrounding connective tissue. Because nodal metastasis is a well-known adverse feature, we classified our patients into two groups: nodal metastasis-free (pN−) and node-positive (pN+). The general characteristics of the study participants were compared using the Fisher's exact test and stratified by the three invasions (PNI, LVSI, and ENE). Categorical data (e.g., sex, pathologic staging, depth of invasion, and margin status) were analyzed using the chi-square or Fisher's exact test.

The Kaplan–Meier method was used to estimate survival. A Cox regression analysis with the backward removal of variables was used to assess the relationships between adverse features and survival outcomes. All statistical analyses were conducted using SPSS, version 20.0 software (IBM Corp., Armonk, NY, USA).

Table 3
Characteristics of patients with neck metastasis (pN+) and of subgroups stratified by the extranodal extension status.

Characteristics (n, %)	Extranodal extension				P
	No (n = 66) (n, %)		Yes (n = 59) (n, %)		
Age, years					0.050
< 60 (69, 55.2)	42	(63.6)	27	(45.8)	
≥60 (56, 44.8)	24	(36.4)	32	(54.2)	
Sex					0.474
Male (117, 93.6)	63	(95.5)	54	(91.5)	
Female (8, 6.4)	3	(4.5)	5	(8.5)	
pT stage					0.239
T1 + T2 (37, 29.6)	23	(34.8)	14	(23.7)	
T3 + T4 (88, 70.4)	43	(65.2)	45	(76.3)	
DOI					0.593
≤5 mm (15, 12.0)	9	(13.6)	6	(10.2)	
> 5 mm (110, 88.0)	57	(86.4)	53	(89.8)	
Margin					0.319
> 5 mm (76, 60.8)	42	(63.6)	34	(57.6)	
1–5 mm (39, 31.2)	21	(31.8)	18	(30.5)	
Positive (10, 8.0)	3	(4.5)	7	(11.9)	
Local recurrence					0.047*
No (34, 27.2)	23	(34.8)	11	(18.6)	
Yes (91, 72.8)	43	(65.2)	48	(81.4)	
Distant metastasis					0.088
No (84, 67.2)	49	(74.2)	35	(59.3)	
Yes (41, 32.8)	17	(25.8)	24	(40.7)	
Stage					0.000*
III (27, 21.6)	27	(40.9)	0	(0.0)	
IV (98, 78.4)	39	(59.1)	59	(100.0)	
Tobacco exposure					0.804
No (19, 15.2)	11	(16.7)	8	(13.6)	
Yes (106, 84.8)	55	(83.3)	51	(86.4)	
Betel-nut exposure					0.347
No (21, 16.8)	9	(13.6)	12	(20.3)	
Yes (104, 83.2)	57	(86.4)	47	(79.7)	
Alcohol exposure					0.626
No (20, 16.0)	12	(18.2)	8	(13.6)	
Yes (105, 84.0)	54	(81.8)	51	(86.4)	
HPV exposure					0.568
No (112, 89.6)	58	(87.9)	54	(91.5)	
Yes (13, 10.4)	8	(12.1)	5	(8.5)	

HPV, human papillomavirus; DOI, depth of invasion.
* Indicates a significant difference ($p < 0.05$).

Results

Patient demographics

The demographic features of the patient population, including age; sex distribution; human papillomavirus infection status; histopathologic T and N stage; histopathologic determinations of PNI, LVSI, and ECS; treatment modality; and anatomical site, are presented in Table 1. The patients had a mean age of 52.1 years (range: 23–84 years), and the study population included only 28 women, which yielded a male to female ratio of 11.18.

The final histopathologic reports identified 216 (63.3%) patients with a pN0 status and 125 (36.7%) patients with node-positive disease. Table 2 presents the characteristics of patients in the pN0 group stratified by PNI and LVSI. Here, we found no relationship between the presence of PNI or LVSI and most features, although patients with a high T status and stage were likely to exhibit both PNI and LVSI. Regarding metastasis, local recurrence was a frequent event among patients with PNI or LVSI; however, the distribution of distant metastasis differed significantly within the LVSI group (p = 0.013). Table 3 presents the characteristics of patients in the pN positive group; significant differences were observed in the distributions of local recurrence and stage.

Survival analysis

Overall, the 341 included patients were followed for a mean of 50.5 (standard deviation: 35.7) months. The overall 1-, 3-, and 5-year OS rates were 83.0%, 71.5%, and 60.0%, respectively, and the corresponding DFS rates were 70.4%, 54.8%, and 47.9%, respectively. The pN0 and pN+ groups had 5-year OS rates of 73.7% and 35.4%, respectively ($p = 0.000$), and 5-year DFS rates of 60.2% and 26.2%, respectively ($p = 0.000$).

Regarding the predisposing factors, smoking and non-smoking patients had 5-year OS rates of 57.9% and 69.0%, respectively (p = 0.146); and the corresponding 5-year PFS rates were 44.2% and 64.1% (p = 0.019). Regarding betel nut chewing, betel nut chewing and non-betel nut chewing patients had 5-year OS rates of 57.9% and 70.3%, respectively (p = 0.150); and the corresponding 5-year PFS rates were 44.1% and 63.4% (p = 0.045). Regarding alcohol drinking, drinking and non-drinking patients had 5-year OS rates of 57.0% and 69.8%, respectively (p = 0.049); and the corresponding 5-year PFS rates were 44.8% and 57.9% (p = 0.071).

Regarding the margin status, patients in the pN0 group with margins of > 5 mm, 1–5 mm, or a positive margin had 5-year OS rates of 72.8%, 81.1%, and 0.0%, respectively (p < 0.000; Fig. 1a). The corresponding 5-year PFS rates were 59.3%, 65.5%, and 0.0%, respectively (p < 0.000; Fig. 1b). The 5-year OS rates in the groups with a 5 mm or less and > 5 mm depth of invasion were 84.3% and 67.3%, respectively (p = 0.002; Fig. 1c); the corresponding 5-year PFS rates were 68.5% and 55.5%, respectively (p = 0.057; Fig. 1d). Regarding the LVSI status, the 5-year OS rates were 75.1% and 0.0%, respectively (p = 0.000; Fig. 1e), and the corresponding 5-year PFS rates were 61.3% and 0.0%, respectively (p = 0.000; Fig. 1f). Regarding the PNI status, the 5-year OS rates were 76.2% and 33.3%, respectively (p = 0.000; Fig. 1e), and the 5-year PFS rates were 63.3% and 8.3%, respectively (p = 0.000; Fig. 1f).

In the pN+ group, the 5-year OS rates in the groups without and with ENE were 42.6% and 27.7%, respectively (p = 0.009). The corresponding 5-year PFS rates were 33.3% and 18.3%, respectively (p = 0.010).

Cox proportional hazard model

In the total patient sample, a multivariate Cox proportional hazard regression model analysis identified neck metastasis (odds ratio [OR] = 2.2, 95% confidence interval [CI]: 1.4–3.5, p = 0.001), depth of invasion > 5 mm (OR = 2.0, 95% CI: 1.3–3.2, p = 0.002), and human papillomavirus-negative status (OR = 2.5, 95% CI: 1.2–5.4, p = 0.019) as independent prognostic factors for OS (Table 4). However, LVSI, PNI, ENE, and margin status were not identified as significant prognostic factors in the total patient analysis.

In the subgroups, an analysis of pN0 patients found margin status, depth of invasion, PNI, and LVSI to be independent prognostic factors for OS (Table 5). In a multivariate analysis, a positive margin was associated with a poorer prognosis, compared to a clear margin (odds ratio (OR) = 16.3, CI = 3.7–72.3, p = 0.001). Both the presence of LVSI (OR = 5.4, CI: 1.3–22.0, p = 0.018) and PNI indicated a poor prognosis (OR = 4.3, 95% CI = 1.7–11.1, p = 0.002), compared to the absence of either type of invasion. Finally, in pN0 cases, a depth of invasion > 5 mm was associated with a poor prognosis (OR = 2.1, 95% CI: 1.2–3.7, p = 0.012). Among patients with a pN+ status, only the ENE status was identified as an independent prognostic factor for OS (OR = 1.7, 95% CI: 1.2–2.7, p = 0.026) (Table 6).

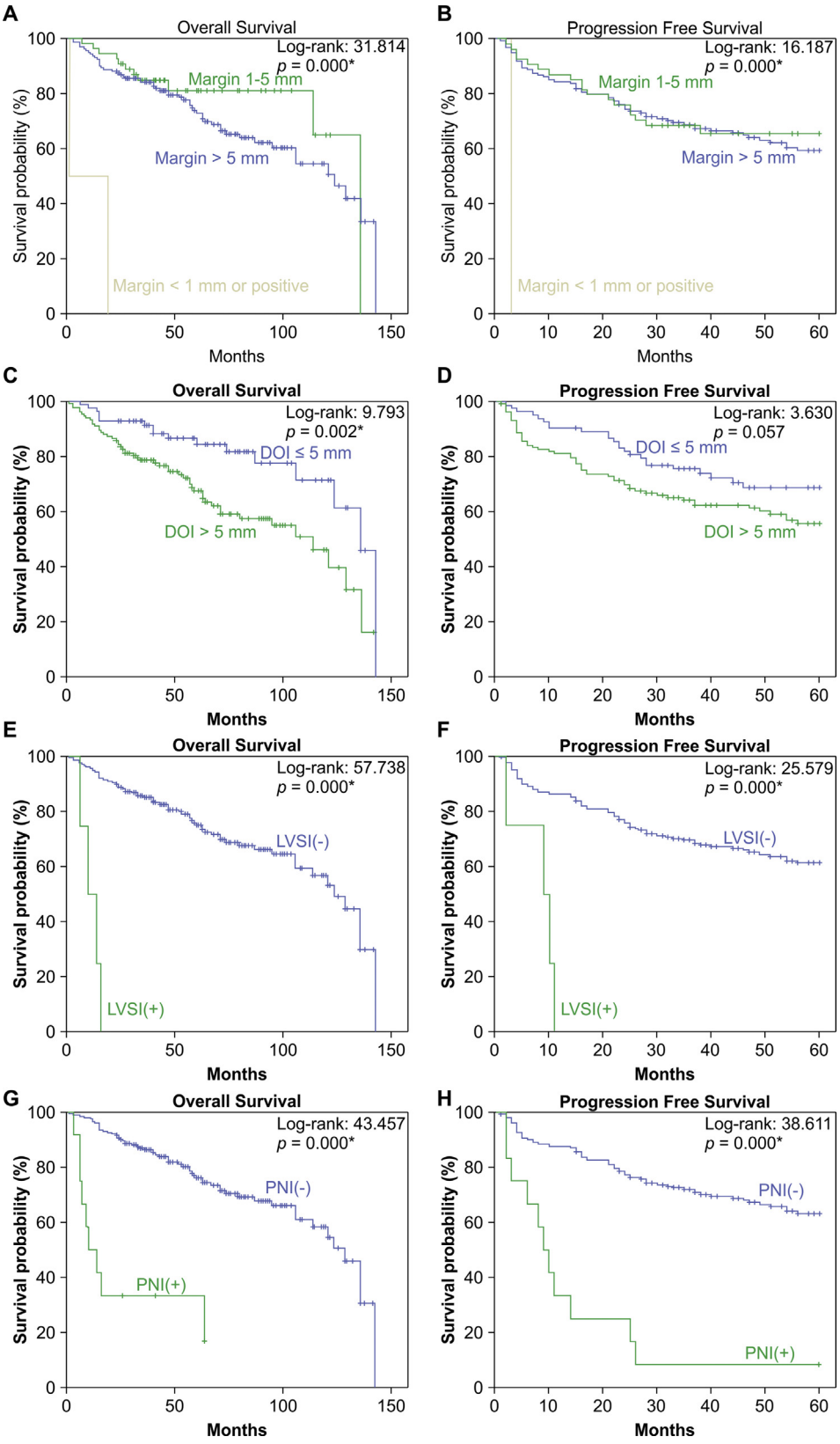

Fig. 1. The 5-year overall survival and progression-free survival rates in the pN0 population were analyzed using the Kaplan–Meier method and compared between groups of patients with adverse features. (a, b) Margin status; (c, d) Depth of invasion, using a cut-off of 5 mm; (e, f) Lymphovascular invasion status; (e, f) Perineural invasion status.

Discussion

In this multifactorial study, OSCC was treated according to a guideline based on therapeutic resection and postoperative adjuvant therapy. As the latter was determined based on the histopathologic findings, the odds ratios of adverse features were deemed more

Table 4
Univariate and multivariate analyses of prognostic factors related to 5-year OS in the entire patient sample, adjusted by sex and age.

	Univariate analysis				Multivariate analysis	
Characteristics (n, %)	5-year % (n, Event)	Log-rank *P*	HR (95% CI)	*P*	HR (95% CI)	*P*
Neck metastasis		0.000*		0.000*		0.001
No (216, 63.3)	73.7(68)		Reference		Reference	
Yes (125, 36.7)	35.4(81)		3.368(2.422–4.683)		2.260(1.403–3.640)	
Margin		0.000*		0.001*		0.500
> 5 mm (236, 69.2)	62.9(101)		Reference			
1–5 mm (93, 27.3)	59.9(38)		1.186(0.815–1.726)	0.373		
Positive (12, 3.5)	12.5(10)		3.575(1.856–6.886)	0.000*		
DOI		0.000*		0.000*		0.003*
≤5 mm (98, 28.7)	79.0(26)		Reference		Reference	
> 5 mm (243, 71.3)	52.3(123)		2.661(1.727–4.102)		2.012(1.276–3.173)	
HPV exposure		0.022*		0.027*		0.016*
Yes (34, 10.0)	77.6(7)		Reference		Reference	
No (307, 90.0)	58.2(142)		2.360(1.104–5.046)		2.580(1.197–5.564)	
LVSI		0.000*		0.000*		0.258
No (300, 88.0)	64.7(117)		Reference			
Yes (41, 12.0)	24.1(32)		3.170(2.135–4.709)			
PNI		0.000*		0.000*		0.652
No (273, 80.1)	66.9(101)		Reference			
Yes (68, 19.9)	30.8(48)		3.114(2.196–4.414)			
ENE		0.000*		0.000*		0.152
No (281, 82.4)	66.4(105)		Reference			
Yes (60, 17.6)	28.4(44)		3.532(2.467–5.059)			
Tumor site		0.308		0.333		0.174
Tongue (147, 43.1)	64.1(58)		Reference			
Lip (2, 0.6)	50.0(1)		2.891(0.399–20.953)	0.293		
Retromolar (16, 4.7)	49.2(9)		1.816(0.897–3.675)	0.097		
Gingiva (43, 12.6)	46.4(25)		1.598(0.997–2.561)	0.051		
Palate (7, 2.1)	47.6(3)		1.242(0.388–3.974)	0.715		
Buccal (115, 33.7)	62.2(50)		1.139(0.778–1.667)	0.503		
Mouth floor (11, 3.2)	45.5(3)		0.782(0.244–2.500)	0.678		
Treatment modality		0.000*		0.000*		0.254
Surgery (87, 25.5)	78.4(24)		Reference			
Surgery + RT/CT/CCRT (254, 74.5)	53.9(125)		2.299(1.469–3.597)			

CI, confidence interval; OR, odds ratio; OS, overall survival; HPV, human papillomavirus; DOI, depth of invasion; PNI, perineural invasion; LVSI, lymphovascular space invasion; ENE, extranodal extension; RT, radiotherapy; CT, chemotherapy; CCRT, concurrent chemoradiotherapy.
* Indicates a significant difference, $p < 0.05$.

important than the choice of postoperative adjuvant therapy for the purpose of this study. Furthermore, patients in this study were stratified by the nodal metastasis status for further analysis. In the metastasis-free group, the depth of invasion, margin condition, LVSI status, and PNI status were identified as independent and significant prognostic factors. By contrast, ENE was the only significant prognostic factor in metastasis-positive patients.

PNI of OSCC was first defined in 1963 [15] and has been reported to occur at frequencies of 14–63% [16]. Although some studies have identified PNI as a predictor of neck metastasis and worse overall survival [17], other studies have failed to determine a relationship between PNI and 5-year survival outcomes [18]. A recent study identified PNI as an independent prognostic factor for regional local recurrence [19], consistent with our finding that patients with PNI were more likely to experience a local recurrence (Table 2). Our findings were also consistent with previously reported correlations of PNI with the conventional TNM stage and pT stage [20]. Moreover, we identified PNI as a prognostic factor for overall survival among patients without neck metastasis, consistent with the findings of big data cancer research studies [18,21].

LVSI was initially defined in 1973 as tumor cell aggregation within vessels with an endothelial lining or an invasion of head and neck cancer into lymphatic or capillary ducts [22]. However, the status of involvement of the lymphatic ducts had been ignored for several years due to difficulties in pathologic evaluation. The frequency of LVSI ranges from 10% to 81% [23,24], and various studies have identified LVSI as a predicator of OS [25,26], consistent with our findings. Our observation of significant associations between LVSI and the tumor primary size and pT stage (Table 2) were also consistent with those of other studies [14,25].

Initially, an ideal surgical margin of ≥10 mm in all planes was defined for OSCC [27]. However, this was revised to 5 mm for histological purposes, given the effect of formalin fixation and preservation on tissue shrinkage (~30% shrinkage) and a more functional consideration of organs [14,28]. Numerous studies have indicated that a positive margin predicts a poor local recurrence or OS outcome [29,30]. Furthermore, a close margin also affects OS and local recurrence outcomes [31] and must be addressed via postoperative adjuvant therapy [32]. In our study, we identified the surgical margin as an independent prognostic factor among patients who were initially free of neck metastasis, consistent with other studies [33,34].

The depth of invasion of OSCC was first defined in 1986 [35], is related to both nodal spread and DFS, and the first definition of the depth of invasion included the proliferative. However, the definition of the concept of depth of invasion became changed to include the vertical height of the deep invasion relative to the level of the normal epithelium, and thus excluded the proliferative component [36]. The depth of invasion ranges from 4 to 10 mm. A depth > 4 mm was identified as an

Table 5
Univariate and multivariate analyses of prognostic factors related to 5-year OS in the pN0 group.

	Univariate analysis				Stepwise multivariate analysis	
Characteristics (n, %)	5-year % (n, Event)	Log-rank *P*	HR (95% CI)	*P*	HR (95% CI)	*P*
Sex		0.749		0.750		
Female (20, 9.3)	71.2(5)		Reference			
Male (196, 90.7)	73.8(63)		1.160(0.465–2.891)			
Age, years		0.046*		0.049*		0.133
< 60 (94 43.5)	80.8(27)		Reference		Reference	
≥60 (122, 56.5)	68.0(41)		1.672(1.002–2.792)		1.496(0.884–2.530)	
Margin		0.000*		0.000*		0.001*
> 5 mm (160, 74.1)	72.8(55)		Reference		Reference	
1–5 mm (54, 25.0)	81.1(11)		0.712(0.371–1.365)	0.306	0.757(0.390–1.469)	0.410
Positive (2, 0.9)	0.0(2)		17.349(4.038–74.536)	0.000*	16.255(3.653–72.321)	0.000*
DOI		0.002*		0.003*		0.012*
≤5 mm (83, 38.4)	84.3(17)		Reference		Reference	
> 5 mm (133, 61.6)	67.3(51)		2.389(1.357–4.203)		2.095(1.176–3.731)	
HPV exposure		0.081		0.100		
Yes (21, 9.7)	84.7(2)		Reference			
No (195, 90.3)	72.6(66)		3.258(0.796–13.331)			
LVSI		0.000*		0.000*		0.018*
No (212, 98.1)	75.1(64)		Reference		Reference	
Yes (4, 1.9)	0.0(4)		20.446(6.746–61.968)		5.437(1.344–21.997)	
PNI		0.000*		0.000*		0.002*
No (204, 94.4)	76.2(59)		Reference		Reference	
Yes (12, 5.6)	33.3(9)		7.855(3.796–16.253)		4.317(1.680–11.094)	

CI, confidence interval; OR, odds ratio; OS, overall survival; HPV, human papillomavirus; DOI, depth of invasion; PNI, perineural invasion; LVSI, lymphovascular space invasion.

* Indicates a significant difference, $p < 0.05$.

Table 6
Univariate and multivariate analyses of prognostic factors related to 5-year OS in the pN+ group.

	Univariate analysis				Multivariate analysis	
Characteristics (n, %)	5-year % (n, Event)	Log-rank *P*	HR (95% CI)	*P*	HR (95% CI)	*P*
Sex		0.780		0.783		
Female (8, 6.4)	25.0(5)		Reference			
Male (117, 93.6)	36.0(76)		0.880(0.355–2.182)			
Age, years		0.073		0.078		
< 60 (69, 55.2)	42.4(43)		Reference			
≥60 (56, 44.8)	23.9(38)		1.492(0.956–2.328)			
Margin		0.158		0.171		0.197
> 5 mm (76, 60.8)	41.3(46)		Reference		Reference	
1–5 mm (39, 31.2)	30.4(27)		1.465 (0.907–2.367)	0.118	1.458(0.898–2.368)	0.127
Positive (10, 8.0)	15.0(8)		1.705(0.800–3.635)	0.167	1.698(0.774–3.725)	0.187
DOI		0.234		0.243		0.351
≤5 mm (15, 12.0)	48.8(9)		Reference		Reference	
> 5 mm (110, 88.0)	33.6(72)		1.513(0.755–3.033)		1.402(0.689–2.851)	
HPV exposure		0.053		0.063		
Yes (13, 10.4)	65.9(5)		Reference			
No (112, 89.6)	32.3(76)		2.376(0.955–5.914)			
LVSI		0.199		0.206		0.360
No (88, 70.4)	38.7(53)		Reference		Reference	
Yes (37, 29.6)	26.7(28)		1.347(0.849–2.138)		1.342(0.715–2.519)	
PNI		0.350		0.356		0.569
No (69, 55.2)	38.8(42)		Reference		Reference	
Yes (56, 44.8)	30.5(39)		1.229(0.793–1.907)		0.843(0.468–1.518)	
ENE		0.009*		0.011*		0.026*
No (66, 52.8)	42.6(37)		Reference		Reference	
Yes (59, 47.2)	27.7(44)		1.771(1.140–2.752)		1.697(1.066–2.702)	

CI, confidence interval; OR, odds ratio; OS, overall survival; HPV, human papillomavirus; DOI, depth of invasion; PNI, perineural invasion; LVSI, lymphovascular space invasion; ENE, extranodal extension.

* Indicates a significant difference, $p < 0.05$.

independent poor prognostic factor for DFS and OS in OSCC [37,38]. The depth of invasion is also included in the 8th edition of the AJCC TNM staging system. According to previous research, the T stage classification should be upgraded and reclassified to account for a depth of invasion of > 5 and > 10 mm for survival analyses [36]. In our study, we used this edition of the cancer staging system and classified the depth of invasion according to a cut-off of 5 mm. Accordingly, we identified a depth > 5 mm as a poor prognosis factor in patients without neck metastasis, consistent with a big data study of survival outcomes [36].

ENE was initially defined in 1930 as an extracapsular spread [39], which has been associated with poor outcomes in head and neck cancer since 1971 [40]. Several more recent studies have identified ENE as an important prognostic factor for regional recurrence and OS [12,41,42]. The poor prognosis associated with ENE provoked the need for randomized control trials using adjuvant radiotherapy or concurrent chemoradiation therapy [4,5]. Given the impact of ENE in node-positive patients, the 8th edition of the AJCC TNM staging system included this factor as an indicator to upgrade the N stage [43]. In our study, we identified ENE as the only unique OS prognosticator in a multivariate Cox regression analysis of metastasis-positive patients, consistent with the findings of a big data analysis [5,39].

OS is based on the conventional OSCC TNM staging category and adverse features; however, we should consider other survival factors, such as the simultaneous secondary primary tumors [44], lymph node density [45], and even the severity of the ENE [46]. The research indicated that betel nut chewing was associated with a fourth simultaneous primary tumor [44], and the more the simultaneous primary sites, the more the reduced progression free time [47]. Compared to our study, the betel nut exposure was not associated with an adverse feature, and the occurrence of a secondary primary tumor requires further research.

In those areas where betel nut chewing is not popular, smoking and excessive alcohol drinking represents the most important risk factors for the OSCC, and the human papillomavirus exposure may also be associated with an increased risk [48]. The human papillomavirus positive population also has better prognosis than the human papillomavirus negative population due to the improvement in treatment response [49]. However, in betel-nut chewing regions, alkaloids and nitrosamines are confirmed carcinogens that produces malignant or precancerous conditions in betel nut embedded substance [50]. Thus, there is proof of poor disease-free and disease-specific survival rates due to field cancerization with betel nut [51], but the overall survival did not play an important role. As shown by the results of our study, the human papillomavirus positive population was only a small percentage (10%), and the human papillomavirus negative status was a poor prognostic factor compared to the human papillomavirus positive group in the total patient sample, in the Cox regression analysis. When comparing the predisposing factors, only betel nut was associated with the local recurrence.

In the OSCC treatment strategy, surgery remains the mainstay of treatment, and the postoperative adjuvant management is based on the surgical pathologic adverse features. The postoperative adjuvant therapy is grouped into the radiotherapy (RT), chemotherapy (CT), and concurrent chemoradiotherapy (CCRT). ENE was the worst most important prognostic factor, and in most previous studies, the use of CCRT was suggested [4,52], based on the following regimen: cisplatin 30 mg/m^2 weekly or cisplatin 100 mg/m^2 every 3 weeks [53]. The other risk factor was not clearly clarified to be of prognostic importance, and for these factor, postoperative radiotherapy was suggested. In our study of the pN+ group, we suggested that ENE was needed before a patient can receive postoperative CCRT. However, in the pN0 group, the highest odds ratio was for the positive margin (OR = 16.3); followed by the LVSI (OR = 5.4); PNI (OR = 4.3), and depth of invasion of more than 5 mm (OR = 2.1), in that order. In summary, the study suggested that the positive margin group or more than one adverse feature was needed to receive CCRT, and the result is the same as for other research [54].

This study had some limitations of note. For example, the sample size was limited. Future studies should aim to enroll a larger number of patients and include other biomarkers related to oral cancer. Moreover, future studies, including clinical trials, should also consider and compare different postoperative adjuvant therapy modalities. However, despite these limitations, the age, sex distribution, carcinogen exposure history, HPV status, and cancer sub-site distributions of the patients in our study were very similar to those observed in a majority of oral cancer cases diagnosed in Taiwan [55].

Conclusions

In conclusion, this study of the effects of adverse features on the survival prognoses of patients with OSCC found that all investigated features, including the margin status, PNI, LVSI, and depth of invasion, were significant predictors in patients with a pN0 status, and the post operation adjuvant therapy was indicated and need to be used more aggressively, in the positive adverse feature situation. In that group, a positive margin was associated with a large odds ratio for a poor prognosis. By contrast, ENE was the only prognostic factor identified as important in the pN+ group, and the post operation adjuvant therapy was indicated and also need to be used more aggressively in ENE positive population.

Ethical consideration

The Ethical Committee of the Tri-Service General Hospital approved this retrospective study (institutional review board protocol no: 2-108-05-044).

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The funding agencies had no role in the study design, the collection, analysis, or interpretation of data, the writing of the report, or the decision to submit the article for publication.

Declaration of Competing Interest

None declared.

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