Comprehensive survival analysis of oral squamous cell carcinoma patients undergoing initial radical surgery

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Abstract

Objective This study was designed to evaluate the five-year overall survival (OS) rate and postoperative survival time of patients diagnosed with oral squamous cell carcinoma (OSCC), as well as examine the clinical and pathological factors influencing survival outcomes in OSCC patients.

Methods Data were collected from OSCC patients who underwent their first radical surgical intervention in the Department of Maxillofacial Surgery at the First Affiliated Hospital of Chongqing Medical University between April 2014 and December 2016. Follow-up was conducted until March 2022.

Results The study included a total of 162 patients. The observed 5-year OS rate was 59.3%. Approximately 45.7% of OSCC patients experienced postoperative recurrence or metastasis, with a 5-year overall disease-free survival rate of 49.4%. There was no significant difference in the impact of sex, age, smoking, alcohol consumption, primary tumour location, depth of invasion or primary tumour size on the 5-year survival rate ($p > 0.05$). Univariate analysis revealed that clinical stage (Hazard Ratio = 2.239, $p = 0.004$), perineural invasion (PNI) (Hazard Ratio = 1.712, $p = 0.03$), lymph node metastasis (pN) (Hazard Ratio = 2.119, $p = 0.002$), pathological differentiation (Hazard Ratio = 2.715, $p < 0.001$), and recurrence or metastasis (Hazard Ratio = 10.02, $p < 0.001$) were significant factors influencing survival. Multivariate analysis further indicated that pathological differentiation (Hazard Ratio = 2.291, $p = 0.001$), PNI (Hazard Ratio = 1.765, $p = 0.031$) and recurrence or metastasis (Hazard Ratio = 9.256, $p < 0.001$) were independent risk factors of survival. Intriguingly, 11 OSCC patients were diagnosed with oesophageal squamous cell carcinoma (ESCC) within 1-4 years following surgery.

Conclusion The survival prognosis of OSCC patients is significantly associated with clinical stage, PNI, lymph node metastasis, pathological differentiation, and recurrence or metastasis. Pathological differentiation, PNI and recurrence or metastasis are independent risk factors affecting survival. Routine clinical screening for ESCC may be recommended for OSCC patients with a history of alcohol consumption and tobacco use.

Keywords Oral squamous cell carcinoma, Survival rate, Prognosis, Factors, Oesophageal squamous cell carcinoma

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Introduction

Head and neck cancer (HNC) is the sixth most common cancer in the world [1]. Oral squamous cell carcinoma (OSCC) is the second most malignant form of HNC after laryngeal squamous cell carcinoma [2], and it is a difficult problem worldwide, which is closely related to the histopathologic morphology, clinical characteristics, molecular biomarkers and gene variation of the tumor.

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According to the Global Cancer Statistics 2020, oral squamous cell carcinoma (OSCC) ranks as the 16th most prevalent cancer, with an annual incidence exceeding 377,000 cases [3]. Compared to 2012 [4], the data from 2018 indicates a significant increase in both the number of cases and deaths. An analysis of cancer patient survival in China from 2003 to 2015 revealed 7,627 cases of oral/oropharyngeal cancer (out of 659,732), including 4,938 males (out of 371,471) and 2,689 females (out of 288,261). The 5-year relative survival rates improved from 42.2% in 2003-05 to 50.4% in 2012-15 [5]. The occurrence of OSCC is the result of multiple factors, including smoking and drinking, eating habits (e.g., chewing betel nuts), human papillomavirus (HPV) infection and carcinogenic DNA virus infection [6–8]. OSCC is associated with certain high-risk areas, which may be related to local dietary habits. OSCC is common in South Asia (e.g., India and Sri Lanka) and the Pacific Islands (e.g.,Papua, New Guinea),and is also the leading cause-related death among men in India and Sri Lanka [6]. The overall survival(OS) rate of patients with OSCC has remained approximately 50-70% [9].

The occurrence and development of cancer involves complex, multistep and multifactorial interactions [10]. Although many studies have investigated the mechanism of tumour occurrence and reviewed the progress of treatment, the mortality and recurrence rates of OSCC are still very high. Because OSCC exhibits high local invasiveness and a high potential for lymph node metastasis [11], patients are often in a mid or late stage of disease at the time of diagnosis. With continued developments in the medical field, the treatment of OSCC has been improving, especially due to the concept of individualized comprehensive sequential therapy, which has been widely accepted. Despite these advancements, the prognosis of OSCC patients has not significantly improved in recent years, and the OS rate remains in the range of 50-70% [9]. In China, there have been few studies of postoperative outcomes among patients with OSCC who undergo radical surgery, especially retrospective studies on factors influencing 5-year survival. Therefore, this retrospective study was performed to analyse the postoperative follow-up data and clinicopathological information of OSCC patients and explore the clinical factors affecting the prognosis and 5-year OS rate of OSCC patients. Furthermore, the relevant clinical and pathological factors influencing the postoperative survival time of patients were investigated. The aim of this research was not only to enrich the existing clinical research data on OSCC in China but also to provide theoretical support for future related studies and the personalized treatment of patients.

Materials and methods
Patient selection and study design
A total of 185 OSCC patients who were admitted to the First Affiliated Hospital of Chongqing Medical University between April 2014 and December 2016 participated in this study. All patients underwent radical surgery for the first time and received further treatment in the oncology department. The inclusion criteria were as follows: i) the patient was diagnosed with primary OSCC by pathology and treated by radical surgery for the first time; ii) there patient had no other malignancy within 5 years before surgical treatment and a Karnofsky performance status (KPS) score > 60; iii) the first surgical treatment was the main treatment, and the comprehensive sequential treatment was combined with selective radiotherapy and chemotherapy; and iv) the clinical and pathological data were complete. The exclusion criteria were as follows: i) OSCC recurrence; ii) death from other diseases within 5 years after surgery; and iii) loss to follow-up because of failure to return or a change in contact information. Institutional coding utilized the International Classification of Diseases for Oncology (International Classification of Diseases [ICD]-10), where OSCC was defined by the following topographies: Tongue (C02.0, C02.1, C02.2), Buccal mucosa (C06.0) Gingiva (C03.0, C03.1) Palate (C05.0), and Floor of mouth (C04.0, C04.1). This study was approved by the Ethics Committee of the First Affiliated Hospital of Chongqing Medical University (No. 2022-35).

Histological analysis was conducted by consecutively sectioning paraffin blocks, followed by routine haematoxylin and eosin staining. Two experienced pathologists, employing a double-blind approach, independently evaluated the slides under a microscope. In cases of divergent results, decisions were reached through discussion. The depth of invasion (DOI) was recorded as the perpendicular distance (plumb line) from the horizon of the adjacent basement membrane to the deepest point of tumour invasion. Perineural invasion (PNI) was considered present when tumour cells were observed in any of the three layers of the nerve sheath and/or within the perineurium, encircling at least one-third of its circumference.

Follow-up
Postoperative, followed-up was performed through periodic outpatient visits, telephone calls, and electronic medical record tracking. The follow-up date included survival status, time of death, cause of death, postoperative treatment, recurrence, recurrence site, and retreatment. The staging classification was revised according to the 8th edition of the AJCC Cancer Staging Manual [12]. The overall follow-up time was more than 5 years, starting on the date of surgery and ending at the time of

death or the last follow-up after 5 years. Follow-up was conducted once every three months in the first two years, once every six months in the third to fifth years, and once a year thereafter. The last follow-up was completed in March 2022. The 5-year OS rate and survival time were used as prognostic indicators.

Statistical analysis

Statistical analysis was conducted with SPSS 22.0 software. 1) Descriptive analysis: Measurement data were analysed using the nonparametric Mann-Whitney U test., and count data are expressed as percentages. Independent-samples t tests or χ^2 tests were used to compare the incidence of event results. Because of non-normal distribution of variables, Spearman rank correlation analysis was performed to investigate the relation among clinic-pathological variables. 2) Survival correlation analysis: The Kaplan–Meier method was used to construct survival curves, and when estimating the effect of clinicopathological variables on survival, a univariate Cox regression model was established, and only p value < 0.05 was considered statistically significant. The clinicopathological variables with statistical significance in univariate analysis were included in the stepwise backward multifactor COX regression analysis. Tests were two-sided, with $\alpha = 0.05$ ($P < 0.05$).

Results

Clinicopathological characteristics

Data were collected from 185 OSCC patients, but fifteen patients were lost to follow-up due to reasons such as a lack of follow-up visits or changes in contact information. Eleven patients (5.9%) developed oesophageal squamous cell carcinoma (ESCC) within 1-4 years after surgery. Eight of these eleven patients died of ESCC within 3 years. Ultimately, after excluding the fifteen patients who were lost to follow-up and eight patients who died of ESCC within 3 years, a total of 162 patients were eligible for inclusion in the analysis. The median follow-up time was 62.5 (5-94) months, the shortest follow-up time was 5 months (death), the longest was 94 months last follow-up after five years), and the average age was 61.5 ± 11.1 years. The ratio of males to females was approximately 2:1. A total of 22.2% of patients had hypertension, 10.5% had diabetes, 50.6% had a smoking history, and 43.2% had a drinking history. The most common site was the tongue (31.5%), followed by the buccal mucosa (29.0%). Recurrence or metastasis occurred in 45.7% of OSCC patients, and distant metastasis occurred in 9.3% of patients (mainly in the brain, bone, lungs, liver, and kidneys). The overall disease-free survival rate was 49.4%. Among the patients who died within 5 years, the survival times varied, with the shortest being 5 months,

the longest being 56 months, and the median being 16 (10 ~ 35) months. Fifty-eight patients (88%) developed recurrence or metastasis, and 3 patients experienced wound healing disorder or infection (Table 1).

Correlations between survival and other clinic-pathological variables

Linear clinic-pathological variables were firstly explored by Spearman rank correlation analysis. The 5-year OS of patients outcome correlated with T classification ($\rho = 0.200$; $p < 0.05$), Clinical stage ($\rho = 0.213$; $p < 0.01$), PNI ($\rho = 0.179$; $p < 0.05$), Lymph node metastasis ($\rho = 0.201$; $p < 0.05$), Pathological differentiation ($\rho = 0.324$; $p < 0.01$) and Recurrence and metastasis ($\rho = 0.727$, $p < 0.01$). Furthermore, PNI positive/negative correlated with T classification ($\rho = 0.195$; $p < 0.05$) and DOI ($\rho = 0.211$; $p < 0.01$). Spearman rank correlation results for all linear clinic-pathological variables are collected (Table 2).

Chi-square test was used to further explore differences among groups. The 5-year OS of patients outcome was considered as a dichotomous variable, Chi-square test showed a statistically significant difference among Recurrence or metastasis and number of Survivors/Nonsurvivors (Chi-square test, p-value < 0.001). When adjusting p-value for multiple comparisons, the 5-year survival rate of patients with in situ recurrence (p-value < 0.001), neck metastasis (p-value < 0.001) and distant metastasis (p-value < 0.001) was observed to be lower. Additionally, chi-square tests were used to analyze correlations among clinical variables. This study found that clinical stage not only correlated significantly with T staging (Chi-square test, p-value < 0.001) but also closely with pathological differentiation (Chi-square test, $p = 0.037$), with a higher proportion of poorly differentiated tumors in advanced clinical stages.

Furthermore, this study explored the relationship between lymph node metastasis and T staging, as well as pathological differentiation. The results showed significant correlations between lymph node metastasis and T staging (Chi-square test, p-value $= 0.006$), as well as pathological differentiation (Chi-square test, p-value $= 0.029$). Of interest, the 5-year survival rate of PNI positive patients was significantly lower (Chi-square test, p-value $= 0.023$). Further analysis found that PNI is related to DOI, and Mann-Whitney analysis showed that the difference between PNI-positive and PNI-negative patients was statistically significant ($p = 0.007$).

Five-year OS

The five-year OS rate was 59.3% (96/162), Sex, age, hypertension, diabetes, smoking, alcohol consumption, primary tumour location, DOI and primary tumour

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Table 1 Associations of basic demographic data with survival

Variable		Five-year survival						
		Cases		Survivors (96)		Nonsurvivors (66)		$P(\chi^2)$
		n	%	n	%	n	%	
Sex	Male	105	64.8	63	65.6	42	63.6	0.795
	Female	57	35.2	33	34.4	24	36.4	
Age (years)	≤60	76	46.9	50	52.1	26	39.4	0.112
	>60	86	53.1	46	47.9	40	60.6	
Hypertension	Yes	36	22.2	19	19.8	17	25.8	0.369
	No	126	77.8	77	80.2	49	74.2	
Diabetes	Yes	17	10.5	13	13.5	4	6.1	0.127
	No	145	89.5	83	86.5	62	93.9	
Smoking	Yes	82	50.6	48	50.0	34	51.5	0.850
	No	80	49.4	48	50.0	32	48.5	
Alcohol consumption	Yes	70	43.2	40	41.7	30	45.5	0.633
	No	92	56.8	56	58.3	36	54.5	
Primary tumour location	Tongue	51	31.5	34	35.4	17	25.8	0.710
	Buccal mucosa	47	29.0	25	26.0	22	33.3	
	Gingiva	24	14.8	13	13.5	11	16.7	
	Palate	10	6.2	6	6.3	4	6.1	
	Floor of mouth	30	18.5	18	18.8	12	18.1	
Clinical stage	I or II	62	38.3	45	46.9	17	38.3	0.007
	III or IV	100	61.7	51	53.1	49	61.7	
T classification	T1	17	10.5	13	13.5	4	6.1	0.079
	T2	61	37.7	40	41.7	21	31.8	
	T3	66	40.7	36	37.5	30	45.4	
	T4	18	11.1	7	7.3	11	16.7	
Lymph node metastasis	pN+	55	34.0	25	26.0	30	45.5	0.010
	pN-	107	66.0	71	74.0	36	54.5	
Pathological differentiation	G1	104	64.2	74	77.1	30	45.5	<0.001
	G2/G3	58	35.8	22	22.9	36	54.5	
Recurrence or metastasis	No	88	54.3	80	83.3	8	12.2	<0.001
	In situ recurrence	27	16.7	11	11.5	16	24.2	
	Neck metastasis	32	19.7	4	4.2	28	42.4	
	Distant metastasis	15	9.3	1	1	14	21.2	
DOI		162	100	96	59.3	66	40.7	0.054
PNI	Positive	71	43.8	35	36.5	36	54.5	0.023
	Negative	91	56.2	61	63.5	30	45.5	

DOI depth of invasion, *PNI* perineural invasion

size had no significant effect on 5-year OS ($P > 0.05$), while clinical stage, lymph node metastasis, pathological differentiation, PNI and recurrence or metastasis had significant effects on 5-year OS ($P < 0.05$). The 5-year OS of patients with early-stage (I or II) disease (71.8%) was better than that of patients with intermediate and late stage-stage (II or IV) disease (51.0%) ($P = 0.008$). The 5-year OS of patients with lymph node metastasis (pN +) was lower than that of patients without metastasis ($P = 0.01$). The 5-year OS of patients with G1 (grade I) was significantly better than that of patients with G2 (grade II)/G3 (grade III) ($P < 0.001$). The 5-year OS of patients with PNI was lower than that of patients without PNI. The 5-year OS of patients without recurrence or metastasis was significantly better than that of patients with recurrence or metastasis. The 5-year OS of patients with recurrence or metastasis exhibited the following trend: in situ recurrence > neck metastasis > distant metastasis ($P < 0.001$, Table 1). The Kaplan–Meier survival analysis (Fig. 1) showed that

Table 2 Spearman rank correlation of evaluation variables in OSCC cohort

Variable	Age (years)	Hypertension	Diabetes	Smoking	Alcohol consumption	Primary tumour location	T classification	Clinical stage	DOI	PNI	Lymph node metastasis	Pathological differentiation	Survivors/ Nonsurvivors	Recurrence and metastasis
Age (years)	1.000													
Hypertension	0.145	1.000												
Diabetes	0.039	0.011	1.000											
Smoking	-0.063	0.082	-0.024	1.000										
Alcohol consumption	-0.054	0.073	-0.055	0.762[a]	1.000									
Primary tumour location	0.168[b]	0.168[b]	0.090	0.098	0.120	1.000								
T classification	0.134	0.066	0.032	-0.065	-0.116	0.170[b]	1.000							
Clinical stage	0.150	0.085	0.021	-0.016	-0.057	0.187[b]	0.772[a]	1.000						
DOI	0.147	0.095	-0.029	-0.061	-0.061	0.106	0.672[a]	0.512[a]	1.000					
PNI	0.033	-0.053	0.022	0.076	0.033	-0.054	0.194[b]	0.132	0.211[a]	1.000				
Lymph node metastasis	0.047	0.024	0.095	0.082	0.111	0.097	0.222[a]	0.538[a]	0.088	-0.003	1.000			
Pathological differentiation	0.083	0.065	-0.046	0.042	0.076	0.010	0.093	0.164[b]	0.113	0.015	0.172[b]	1.000		
Survivors/ Nonsurvivors	0.125	0.071	-0.120	0.015	0.038	0.058	0.200[b]	0.213[a]	0.152	0.179[b]	0.201[b]	0.324[a]	1.000	
Recurrence and metastasis	0.144	0.033	-0.051	-0.013	0.000	0.152	0.132	0.146	0.056	0.087	0.163[b]	0.117	0.727[a]	1.000

[a] Correlation is significant at the 0.01 level
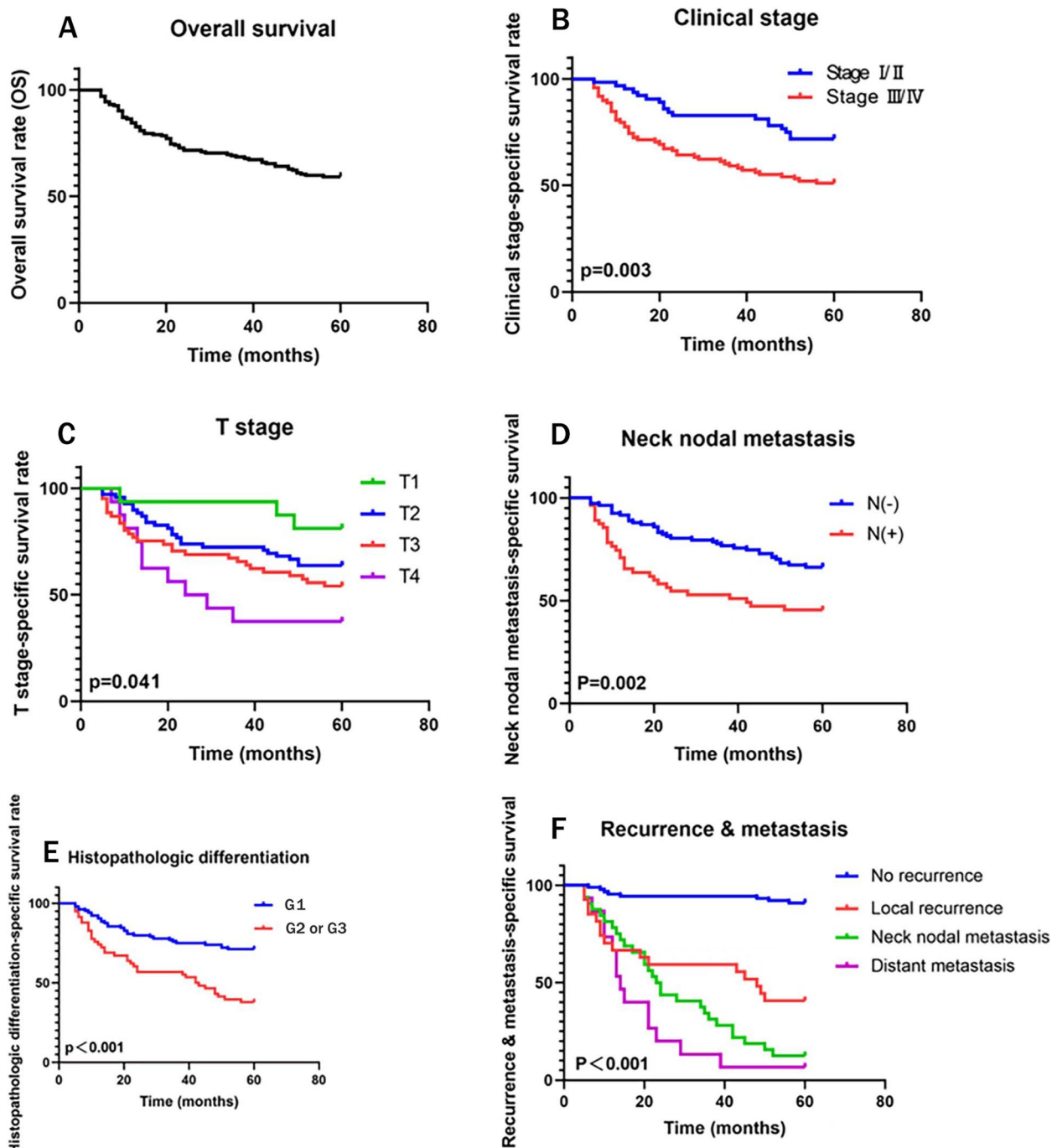
[b] Correlation is significant at the 0.05 level

Fig. 1 Kaplan-Meier curves for overall survival (OS) of patients with oral squamous cell carcinoma (OSCC) (**A-F**). **A** OS curves of 162 patients with OSCC. **B** Survival curves by clinical stage. **C** Survival curves by tumour size. **D** Survival curves by lymph node metastasis. **E** Survival curves by pathological differentiation. **F** Survival curves by recurrence or metastasis

the survival rate was higher among patients with early-stage (I or II) OSCC ($P = 0.004$), patients without lymph node metastasis ($P = 0.002$), patients with well-differentiated OSCC ($P < 0.001$), and patients without postoperative recurrence and/or metastasis ($P < 0.001$).

Cox univariate and multivariate analyses of survival time

Cox univariate analysis was applied to the clinical variables. Clinical stage, PNI, lymph node metastasis (pN+), pathological differentiation, and recurrence or metastasis were identified as factors affecting survival time

($P < 0.05$). The survival prognosis of patients with early-stage (I or II) disease was better than that of patients with advanced-stage (III or IV) disease (Hazard Ratio = 2.239, 95% C.I. 1.289 ~ 3.890, $P = 0.004$), The survival prognosis was worse among patients with PNI than patients without PNI (Hazard Ratio = 1.712, 95% C.I. 1.054 ~ 2.781, $P = 0.03$) and among patients with lymph node metastasis (pN+) than patients without lymph node metastasis (Hazard Ratio = 2.119, 95% C.I. 1.304 ~ 3.445, $P = 0.002$). The survival prognosis of patients with G1 was better than that of patients withG2/G3 (Hazard Ratio = 2.715, 95% C.I. 1.167 ~ 4.414, $P < 0.001$). The survival prognosis of patients without recurrence or metastasis was better than that of patients with recurrence or metastasis (situ recurrence vs no, Hazard Ratio = 10.02, 95% C.I. 4.281 ~ 23.45, $P < 0.001$; neck metastasis vs no, Hazard Ratio = 18.78, 95% C.I. 8.431 ~ 41.84, $P < 0.001$; Distant metastasis vs no Hazard Ratio = 28.34, 95% C.I. 11.53 ~ 69.62, $P < 0.001$). Covariates with $P < 0.05$ in the univariate analysis were analysed via Cox multivariate analysis (Table 3). Pathological differentiation (Hazard Ratio = 2.291, 95% C.I. 1.377 ~ 3.810, $P < 0.001$), PNI (Hazard Ratio = 1.765, 95% C.I. 1.053 ~ 2.960, $P = 0.031$) and recurrence or metastasis (situ recurrence vs no, Hazard Ratio = 9.256, 95% C.I. 3.937 ~ 21.76, $P < 0.001$; neck metastasis vs no, Hazard Ratio = 17.77, 95% C.I. 7.847 ~ 40.25, $P < 0.001$; Distant metastasis vs no, Hazard Ratio = 28.56, 95% C.I. 11.20 ~ 72.82, $P < 0.001$) were found to be independent factors related to postoperative survival time.

Discussion

OSCC is a potentially lethal malignancy that may originate from a primary lesion in the oral cavity [13]. Among malignant tumours in the oral and maxillofacial regions, it has the highest incidence, accounting for more than 90% of cases [9]. Therefore, the diagnosis and treatment of OSCC are essential in clinical practices. Patients with OSCC often have extensive primary invasion and lymph node metastasis when they are definitively diagnosed. Radical surgical resection remains the most important treatment for OSCC. Advances in medical technology, such as computer-aided surgery and microsurgery, have allowed functional recovery to be achieved in OSCC patients. However, the survival rate in the past 10 years has not significantly improved because OSCC tends to exhibit high local infiltration, early lymph node metastasis and a high recurrence rate [14]. A total of 162 patients were analysed in this study, and the 5-year OS rate was 59.3%, which was not significantly different from the results reported in recent international research [9]. This study aimed to explore the clinicopathological factors influencing the survival time of OSCC patients through retrospective analysis and provide an important theoretical basis for the clinical treatment of OSCC patients.

OSCC development is attributed to the combined action of multiple factors. While the underlying mechanism is unclear, the development of OSCC is primarily linked to the inflammatory response resulting from long-term chronic stimulation [15]. Smoking and drinking are important aetiological factors of OSCC. However, tobacco and alcohol use were not found to be correlated with the prognosis or survival of patients with OSCC ($P > 0.05$) in this study, which is consistent with the findings of many other studies [16–18]. Karine [19] et al. reported that smoking is an independent predictive factor of OS in patients with OSCC. Pretreatment smoking is significantly associated with poorer survival rates in patients undergoing curative treatment. This difference may be attributed to inconsistencies in our study population and research methods. Some studies [20] have reported a higher incidence of oral cancer in men than in women, with a ratio of approximately 2:1. This sex difference may be attributed to men's preferences for tobacco use, alcohol consumption, and betel nut chewing; however, the results of the present study showed no significant difference in survival time between men and women, which is consistent with research results reported by Wang et al. [21].

OSCC is classified into three grades according to the Borders classification, as follows: grade I, grade II, and grade III [22]. Some scholars have argued that, despite being based on structural rather than functional characteristics of tumour cells, the Borders classification still reveals significant differences in survival among the different degrees of differentiation [16]. The Kaplan–Meier survival analysis (Fig. 1) indicated that the OSCC patients in the G1 group have better survival prognosis in both short-term and long-term survival compared to those in the G2/G3 groups. Many studies [23–26] have shown that better pathological differentiation in OSCC is associated with higher expression levels of factors such as miR-138-5p, cytokeratin 16 (CK16), CD163, and b7-h6 protein. Conversely, worse pathological differentiation is linked to lower expression of these factors, correlating with poorer OS. Wang Bo et al. [27] analysed the factors of recurrence and survival among 275 patients with OSCC and found significantly lower overall 5-year recurrence and survival rates among patients with poorly differentiated OSCC than patients with well-differentiated OSCC. In this study, Cox analysis showed that the degree of pathological differentiation was an independent risk factor of patient prognosis ($P < 0.001$), which provides an important basis for evaluating the prognosis and planning the clinical treatment of OSCC patients.

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Table 3 Univariate and multivariate Cox regression of factors associated with survival time

Variable	Univariate analysis			Multivariate analysis		
	B	P	HR (95%CI)	B	P	HR (95%CI)
Sex						
Male						
Female	0.112	0.662	1.118 (0.677~1.847)			
Age(years)						
≤60						
>60	0.370	0.142	1.447 (0.883~2.372)			
Hypertension						
Normal						
Hyperpietic	0.267	0.343	1.306 (0.752~2.269)			
Diabetes						
Normal						
Diabetes	-0.704	0.173	0.495 (0.180~1.360)			
Smoking						
Nonsmoker						
Smoker	0.038	0.897	1.038 (0.641~1.683)			
Alcohol consumption						
Nondrinkers						
Drinkers	0.131	0.595	1.140 (0.702~1.851)			
Primary tumour location						
Tongue		0.761				
Buccal mucosa	0.439	0.175	1.550 (0.832~2.920)			
Gingiva	0.280	0.469	1.323 (0.620~2.826)			
Palate	0.208	0.708	1.231 (0.414~3.659)			
Floor of mouth	0.237	0.530	1.267 (0.605~2.654)			
Clinical stage						
I or II						
III or IV	0.806	0.004	2.239 (1.289~3.890)	0.334	0.311	1.397 (0.731~2.669)
T classification						
T1		0.052				
T2	0.458	0.401	1.581 (0.543~4.607)			
T3	0.855	0.108	2.351 (0.828~6.674)			
T4	1.307	0.025	3.694 (1.174~11.63)			
Lymph node metastasis						
pN-						
pN+	0.751	0.002	2.119 (1.304~3.445)	0.568	0.175	1.492 (0.837~2.662)
Pathological differentiation						
G1						
G2/G3	0.999	<0.001	2.715 (1.167~4.414)	0.829	0.001	2.291 (1.377~3.810)
Recurrence or/ and metastasis						
No		<0.001			<0.001	
In situ recurrence	2.305	<0.001	10.02 (4.281~23.45)	2.225	<0.001	9.256 (3.937~21.76)
Neck metastasis	2.933	<0.001	18.78 (8.431~41.84)	2.878	<0.001	17.77 (7.847~40.25)
Distant metastasis	3.344	<0.001	28.34 (11.53~69.62)	3.352	<0.001	28.56 (11.20~72.82)
PNI						
Negative						
Positive	0.538	0.030	1.712 (1.054~2.781)	0.568	0.031	1.765 (1.053~2.960)

B The exponent of B, *HR* hazard ratio, *CI* confidence interval, *P* P value

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The TNM stage of OSCC is considered a crucial factor of the clinical prognosis and a key determinant in the selection of treatment methods. The tumour size and lymph node metastasis status provide robust foundations for formulating treatment plans [28]. Taghavi et al. [29] noted that although many scholars believe that the TNM stage is a significant factor of survival because it reflects the size of the primary tumour and the status of the lymph nodes, the prognosis cannot be assessed by the TNM stage alone. Both the univariate and multivariate analyses in this study indicated that lymph node metastasis is a risk factor of OSCC patient survival but not an independent risk factor of survival or prognosis, which is consistent with the findings reported by Grimm's et al. [30]. Nevertheless, Janet al. [31] considered cervical lymph node involvement to be one of the most crucial independent prognostic factors of OSCC. This discrepancy might arise from the fact that this study only analysed the presence or absence of lymph node metastasis, while related studies [32, 33] have suggested that the relationship between lymph node metastasis and survival needs to incorporate concepts such as the N stage, the presence of extranodal extension (ENE), lymphovascular invasion (LVI), and the lymph node ratio (LNR), among others. Additionally, other studies [34] have demonstrated that the LNR is an independent prognostic factor of OSCC, with greater significance for the OS of patients than ENE and the N stage.

OSCC is considered a malignancy with a tendency for neural invasion, potentially affecting the nerves in the head and neck region [35]. In our study, 43.8% of OSCC patients were found to have positive PNI, which is consistent with previous research indicating a PNI prevalence ranging from 17.4% to 50% [36]. Tai et al. [37] have identified PNI as an adverse prognostic factor for oral cancer patients, closely linked to treatment failure and a decrease in OS. In a study of 200 cases of oral tongue squamous cell carcinoma, Caponio et al. found that patients with positive PNI typically had lower survival rates compared to those with negative PNI. They suggested that incorporating PNI into the AJCC staging system could potentially improve survival predictions and stratify adverse risks for patients [38]. This is because positive PNI indicates a higher likelihood of tumor spread along nerves, thereby increasing the risks of local recurrence and distant metastasis. Additionally, our study revealed a lower 5-year OS rate among patients with positive PNI. Furthermore, the Cox regression analysis demonstrated that PNI independently contributes to the prognosis of OSCC patients, consistent with the findings reported by Martinez's et al. [39]. The importance of PNI in patients with OSCC is not only closely related to survival but also provides an important basis for evaluating the prognosis and planning the clinical treatment of patients.

Tumour recurrence and metastasis after surgery have been identified as essential factors affecting the survival rate of OSCC patients [29]. Related literature has shown that the mortality rate is approximately 90% and that the 5-year OS rate decreases from 90 to 30% after the diagnosis of recurrence [40]. In this study, tumour recurrence or metastasis was identified as an independent risk factor of prognosis. Of the 162 patients, 74 (45.7%) experienced postoperative recurrence and/or metastasis, resulting in a 5-year overall disease-free survival rate of 49.4%; 88% of the 66 patients who died had experienced recurrence and metastasis; and 15 patients developed distant metastasis 1-3 years after surgery, with a distant metastasis rate of 9.3%. The OS of patients without recurrence or metastasis after 5 years was significantly better than that of patients with recurrence or metastasis ($P < 0.001$). The occurrence of postoperative recurrence or metastasis indicates a poor survival prognosis, and patients who develop postoperative metastasis have a worse survival prognosis than those who develop local recurrence [41]. The cause and mechanism of OSCC recurrence are still unclear. In some studies [42–46], scholars have noted that younger age, a history of recurrence, poor differentiation, and regional lymph node metastasis increase the risk of recurrence in OSCC patients. Moreover, the present study revealed that the survival time of OSCC patients with recurrence and/or metastasis was significantly shorter than that of patients without recurrence or metastasis and that tumour recurrence and metastasis were independent risk factors of prognosis. Recurrence or distant metastasis substantially reduce patient survival, so early detection and effective treatment are particularly important.

Because the 5-year survival rate of OSCC patients is so low, this study was conducted to improve the survival time of patients. The results showed that the degree of pathological differentiation not only affects patient survival time but is also an independent risk factor of patient prognosis. Therefore, in the clinical treatment of OSCC patients with G3, local radiotherapy and systemic drugs are needed in addition to surgery to prolong patient survival [47]. Tumour size and lymph node metastasis are major factors of preoperative treatment. Overall, OSCC patients with larger tumours and lymph node metastasis may benefit from a comprehensive treatment plan, including primary tumour resection, selective regional lymph node dissection, and adjuvant radiotherapy and chemotherapy, which can improve the 5-year survival rate [48, 49]. Despite intensified adjuvant therapy and preoperative chemotherapy, the prognosis for patients with

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advanced resectable OSCC remains poor due to high recurrence and metastasis rates. Regular examinations for early detection and treatment are recommended for advanced OSCC patients. Lin [50] reported that increased PD-L1 expression in OSCC is associated with distant metastasis and that blocking the PD-L1/PD-1 signalling pathway can enhance the antitumour response. Immunotherapy with immune checkpoint inhibitors (ICIs) is used as a treatment for recurrent or metastatic OSCC, and two ICIs, the anti–PD-1 monoclonal antibodies pembrolizumab and nivolumab, have improved overall outcomes in patients with recurrent or metastatic OSCC [51, 52]. Therefore, early systemic treatment, including neoadjuvant immunotherapy, is suggested for patients with advanced OSCC patients, which is prone to recurrence and metastasis, to reduce the risk of local and distant recurrence [53].

This study revealed an interesting phenomenon. Among the 162 patients who underwent followed-up, 11 patients were diagnosed with ESCC within 1-4 years after surgery. These patients had a history of smoking and drinking, and 8 of the 11 patients died of ESCC. Tobacco use and alcohol consumption are risk factors for ESCC [54]. ESCC and OSCC share many biological characteristics, but there is no substantial evidence supporting a relationship between ESCC and OSCC. In recent years, studies on the factors related to OSCC complicated with ESCC have shown that *Porphyromonas gingivalis* may be involved in the pathogenesis of ESCC [55–57]. Among 166 patients with OSCC, Matsui et al. detected oesophageal cancer in 37 patients and hypopharyngeal cancer in 16 patients by modified oesophagogastric duodenoscopy [58]. Therefore, patients with OSCC and a history of smoking and drinking history should undergo gastrointestinal examinations (e.g., detection of *Porphyromonas gingivalis* serum biomarkers and oesophagogastric duodenoscopy) which could lead to early diagnosis and treatment and thus improved survival among OSCC patients with ESCC. However, the relationship between OSCC and ESCC requires further study. As this was a retrospective study with a relatively small sample size, it has several limitations. Future research endeavours will focus on increasing the sample size and expanding the scope of the study by integrating clinical pathology, genetic, and cytokine research. We plan to conduct further stratified analyses, including analyses of postoperative survival outcomes and related factors such as disease-specific survival, local control, and regional control [59]. We also plan to analyse the risk of cancer-related death risk and local recurrence to provide a more comprehensive assessment of treatment outcomes and the effectiveness of different treatments.

Conclusion

The survival and prognosis of patients with OSCC have not improved significantly. This study analysed the data of 162 patients with OSCC, revealing 5-year OS rate of 59.3%, and a recurrence/metastasis rate of 45.7%. Clinical stage and lymph node metastasis were identified as risk factors of survival in patients with OSCC but were not found to be independent factors of survival or patient prognosis. Pathological differentiation, PNI, and recurrence or metastasis were identified as independent factors of the survival time of patients with OSCC, and low differentiation, PNI and recurrence or metastasis were found to be predictive of poorer survival. For OSCC patients with a smoking or drinking history, routine clinical screening for ESCC is recommended.

Declarations

Ethics approval and consent to participate
Written informed consent was obtained from all patients participating in this study, and all methods were performed in accordance with the Declaration of Helsinki and relevant guidelines and regulations. This study was approved by the Ethics Committee of The First Affiliated Hospital of Chongqing Medical University (No. 2022-35).

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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