Evaluation of factors associated with the risk stratification of survivorship for stage IV squamous cell carcinoma of the oral cavity: A 10-year retrospective study

Han-Chieh Cheng[a,b], Cheng-Chieh Yang[a,b], Shou-Yen Kao[a,b], Tzu-Ying Wu[b,c], Cheng-Hsien Wu[a,b,*]

[a]Department of Stomatology, Oral and Maxillofacial Surgery, Taipei Veterans General Hospital, Taipei, Taiwan, ROC; [b]Department of Dentistry, School of Dentistry, National Yang-Ming University, Taipei, Taiwan, ROC; [c]Department of Stomatology, Orthodontic and Pediatric Dentistry, Taipei Veterans General Hospital, Taipei, Taiwan, ROC

Abstract

Background: Oral squamous cell carcinoma (OSCC) leads to thousands of deaths every year in Taiwan. Nearly 40% of OSCC patients are diagnosed with stage IV disease, which has a poor prognosis. Multimodality treatments including surgery and adjuvant therapy have been utilized, but their treatment outcomes are generally poor. In this study, we sought to identify possible clinical impact factors that may contribute to the survival of stage IV OSCC.

Methods: Data for patients with malignant neoplasms of the oral cavity registered in the Cancer Registry Database of Taipei Veterans General Hospital between 2002 and 2011 were retrieved. The study patients consisted of OSCC patients with clinical stage IV disease who had undergone a surgery and adjuvant therapy. The primary endpoints were the 5-year disease-free survival (DFS) and overall survival (OS) rates. The clinicopathological characteristics of the patients were also stratified and compared.

Results: A total of 191 OSCC patients were included for retrospective analysis. The different subgroups of stage IV disease presented different treatment outcomes. The 5-year OS versus DFS rates of each subgroup were as follows: T4N0: 70.9% versus 52.6%; T1-3N23: 66.1% versus 49.8%; T4N1: 49.6% versus 31.6%; and T4N23: 40.9% versus 31.0% ($p < 0.01$). Patients with diabetes, moderate or poor cell differentiation, perineural invasion, and extracapsular spread presented lower 5-year OS rates (hazard ratio [HR] = 1.87, 1.65, 2.42, and 2.14, respectively), and patients with perineural invasion, positive cut margin, and extracapsular spread presented lower 5-year DFS rates (HR = 1.57, 1.62, and 1.71, respectively).

Conclusion: In this study, we elucidated the different survival rates of different subgroups of stage IV OSCC following the same treatment scheme. The results of the study provide clinical physicians with references by which to evaluate prognosis and determine post-operative disease monitoring timetables based upon different characteristics.

Keywords: Locally advanced; Oral squamous cell carcinoma; Stage IV; Survival

1. INTRODUCTION

Oral squamous cell carcinoma (OSCC) is the sixth most commonly occurring cancer in Taiwan, and causes thousands of deaths every year. According to the Taiwan Cancer Registry Database, most OSCC patients first present with the disease in middle age,[1,2] such that it typically places heavy social and economic burdens on their families and society in general.[1,2] Furthermore, among all cases of OSCC, 37.4% of the patients first present with advanced stage IV disease.[1]

In the past few decades, the survival rates of locally advanced oral cancers have not significantly improved despite the different combinations of chemotherapeutic agents and radiation protocols that have been used to treat them. At the same time, the overall survival (OS) rates for stage IV oral cancers reported in the past literature have been varied and inconclusive due to the different kinds of treatment modalities applied. Patil et al. reported a 2-year OS rate of 47% after treatment with induction chemotherapy followed by surgery.[3] Eder-Czembirek et al.[4] reported a 5-year OS rate of 58% after treatment with adjuvant radiotherapy combined with Erbitux followed by surgery. Meanwhile, with regard to cases treated with primary surgery followed by postoperative adjuvant therapy, several studies reported 5-year OS ranging from 30% to 47%.[5–8] However, Stathopoulos et al. reported a lower 5-year OS rate of only 28% after surgery followed by concurrent chemoradiotherapy.[9] These inconsistent results pose a dilemma for clinical physicians insofar as they make it difficult to determine prognoses and evaluate treatment outcomes for locally advanced oral cancers.

Our own clinical observations over the past few decades have suggested that there are differences in OS rates among different subgroups of patients with stage IV OSCC, even when all such patients receive the same standard treatment according to the

*Address correspondence. Dr. Cheng-Hsien Wu, Department of Stomatology, Taipei Veterans General Hospital, 201, Section 2, Shi-Pai Road, Taipei 112, Taiwan, ROC. E-mail: marcellinwu@gmail.com (C.-H. Wu).

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NCCN guidelines. At the same time, the long-term treatment outcomes for stage IV OSCC have remained somewhat obscure and ambiguous, with the differences among stage IV subgroups not having been sufficiently explored and elucidated. Therefore, the purposes of this retrospective cohort study were to analyze the survival rates of different subgroups of pathological stage IV OSCC and, furthermore, to explore the correlations among histopathological covariates that may have an impact on OS and disease recurrence in stage IV OSCC using evidence from a single institution.

2. METHODS

2.1. Study population

We used the International Classification of Diseases, Ninth Revision (ICD 9), codes with prefixes labelled from 140 to 145 to retrieve all the cases of stage IV OSCC (AJCC 7th edition) registered from 2002 to 2011 in the Cancer Registry Database of Taipei Veterans General Hospital in Taipei, Taiwan. The medical chart of these cases was reviewed.

Each of these patients underwent a preoperative survey for clinical staging, including computed tomography or magnetic resonance imaging scans of the face, whole abdominal sonograms, whole-body bone scans, with or without whole-body positron emission tomography scans. They further received radical surgery, including wide excision of the primary tumor and neck dissection, followed by concurrent chemoradiotherapy, which consisted of cisplatin-based chemotherapy and more than 60 Gy of radiation applied to the primary tumor bed. The patients then received regular follow-up assessments after their treatment. The study inclusion and exclusion criteria are listed in the following section.

2.2. Inclusion and exclusion criteria

Inclusion criteria

1. The primary lesion sites were confined to the oral cavity (lip, anterior 2/3 of tongue, buccal mucosa, gingivae, retromolar trigone, mouth floor, hard palate).
2. The pathology type was squamous cell carcinoma.
3. The patients received primary cancer treatment, including surgery with post-operative adjuvant chemoradiotherapy, at Taipei Veterans General Hospital.

Exclusion criteria

1. Those stage IV patients who had previously received cancer treatment and were defined as having newly recurrent disease were excluded.
2. The patients with unfinished treatment courses, such as those with unfinished concurrent chemoradiotherapy or surgery alone, were excluded.
3. The patients found to have a distant metastatic lesion or another malignancy at the time of diagnosis were excluded.
4. The patients with double primary cancer or a history of malignancy aside from oral cavity malignancy were excluded.

2.3. Data collection

The medical records of each of the included patients were comprehensively reviewed to collect each patient's clinicopathological parameters, including his or her pathological TNM stage, gender, age, comorbidities, period of disease-free status, and location of primary tumor. Furthermore, the impacts of these clinicopathological factors on survival were also evaluated. The protocol was approved by the institutional review board of Taipei Veterans General Hospital (IRB 2016-12-009AC). The differences in survival between the different stage IV OSCC subgroups were compared, and the impacts of the different pathological factors on survival were analyzed.

2.4. Statistical analysis

Survival was evaluated using the Kaplan-Meier method, and the differences in survival were calculated using the log-rank test. Descriptive means with SDs were generated for continuous variables. The distributions of the clinicopathological covariates were evaluated using Fisher's exact test or the chi-squared test for categorical variables and the Mann-Whitney test or the one-way analysis of variance for continuous variables. A series of univariate Cox proportional hazard models were applied to examine the correlations between the clinicopathological characteristics and OS or disease-free survival (DFS). To identify potential independent risk factors, variables whose significance was less than 0.15 in the univariate Cox analyses were put into a multivariable Cox model. The differences between values were considered significant when the two-tailed p was <0.05. The results were analyzed with the software MedCalc, version 17.2 (MedCalc Software, Ostend, Belgium).

3. RESULTS

3.1. General characteristics of the study population

Records for a total of 293 consecutive stage IV OSCC patients treated at Taipei Veterans General Hospital from January 1, 2002 to December 31, 2012 were retrieved from the hospital's Cancer Registry Database. After applying the inclusion and exclusion criteria, data for a final total of 191 patients, including 177 male and 14 female patients, were deemed eligible for subsequent analysis (Fig. 1). The majority of the selected subjects were male (92.7%), and the mean age of the subjects was 50.1 ± 10.4 years. The follow-up time for these patients ranged from 1.5 to 132.0 months. The median follow-up time was 29.8 months (mean: 42.2 ± 37.9 months).

The clinicopathologic features of the patients, including age, gender, personal habits, primary site, comorbidities, pathological stage, and pathological risk features, are detailed in Table 1. The predominant tumor locations were, in descending order, the buccal mucosa (30.9%), the tongue (25.1%), and the gingivae (19.4%). In terms of disease progression and mortality, there were no differences in the clinicopathological profiles, meaning the study subjects were homogenous in these regards for the purposes of the subsequent analysis. The cases were divided into four subgroups, namely, the T4N0 (77, 40.3%), T4N1 (19, 9.9%), T4N23 (53, 27.7%), and T1-3N23 (42, 22.1%) subgroups. As a primary site, the tongue is predisposed to develop higher grades of neck nodal metastasis, which accounted for 40% of the cases in the T4N23 and T1-3N23 subgroups. This was especially true of the T1-3N23 subgroup, in which the primary site of 50% of tumors was the tongue (Table 2).

3.2. Survival and recurrence analysis

According to the Kaplan-Meier survival analysis, the 5-year OS rates of the subgroups were 70.9% for the T4N0 subgroup, 66.1% for the T1-3N23 subgroup, 49.6% for the T4N1 subgroup, and 40.9% for the T4N23 subgroup (Fig. 2A). The results further showed that the T4 patients with nodal metastasis had poorer OS rates compared to those without nodal metastasis or those with advanced lymph nodes metastasis but lower T classifications (p < 0.01). The same trend was

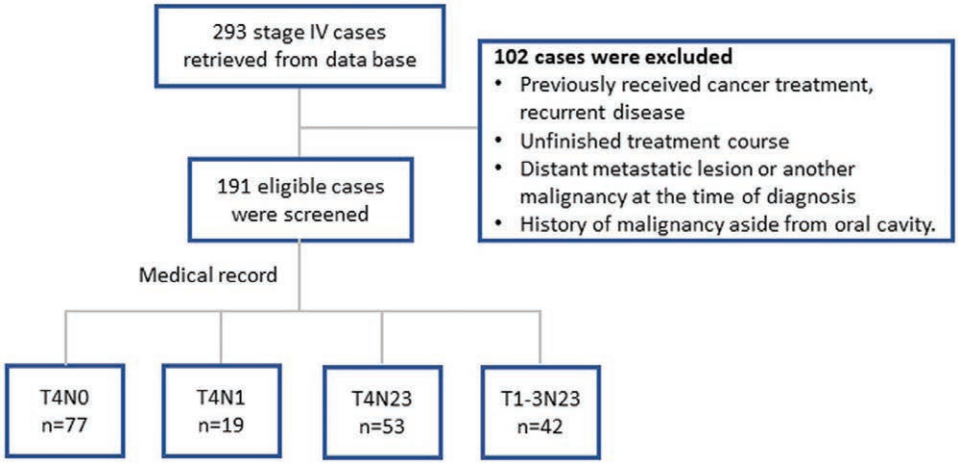

Fig. 1. Flow of the patients enrolled in this study.

Table 1

Clinicopathological characteristics of enrolled cases according to freedom from the disease or mortality

		Disease free			Mortality		
Variable	**Total (%) (N = 191)**	**No (%) (N = 87)**	**Yes (%) (N = 104)**	***p***	**No (%) (N = 115)**	**Yes (%) (N = 76)**	***p***
Age				0.437			0.461
<40 years	28 (14.7)	9 (10.3)	19 (18.3)		14 (12.2)	14 (18.4)	
40–49 years	62 (32.5)	30 (34.5)	32 (30.8)		38 (33.0)	24 (31.6)	
50–59 years	60 (31.4)	30 (34.5)	30 (28.8)		40 (34.8)	20 (26.3)	
≥60 years	41 (21.5)	18 (20.7)	23 (22.1)		23 (20.0)	18 (23.7)	
Age (year)	50.9 ± 10.4	51.1 ± 9.7	50.8 ± 11.0	0.839	50.9 ± 9.9	51.0 ± 11.1	0.955
Primary site				0.759			0.302
Buccal mucosa	59 (30.9)	26 (29.9)	33 (31.7)		31 (27.0)	28 (36.8)	
Gingiva	37 (19.4)	16 (18.4)	21 (20.2)		28 (24.3)	9 (11.8)	
Retromolar trigone	18 (9.4)	8 (9.2)	10 (9.6)		12 (10.4)	6 (7.9)	
Tongue	48 (25.1)	26 (29.9)	22 (21.2)		27 (23.5)	21 (27.6)	
Other	29 (15.2)	11 (12.6)	18 (17.3)		17 (14.8)	12 (15.8)	
Alcohol	133 (69.6)	62 (71.3)	71 (68.3)	0.752	78 (67.8)	55 (72.4)	0.525
Smoking	154 (80.6)	77 (88.5)	77 (74.0)	0.016	98 (85.2)	56 (73.7)	0.061
Betel nuts	145 (75.9)	66 (75.9)	79 (76.0)	1.000	88 (76.5)	57 (75.0)	0.863
Diabetes	32 (16.8)	12 (13.8)	20 (19.2)	0.338	15 (13.0)	17 (22.4)	0.114
Comorbidity score	3.2 ± 1.3	3.2 ± 1.3	3.2 ± 1.3	0.937	3.1 ± 1.2	3.3 ± 1.3	0.303
Stage				0.067			0.005
T4N0	77 (40.3)	42 (48.3)	35 (33.7)		55 (47.8)	22 (28.9)	
T4N1	19 (9.9)	6 (6.9)	13 (12.5)		10 (8.7)	9 (11.8)	
T4N23	53 (27.7)	18 (20.7)	35 (33.7)		22 (19.1)	31 (40.8)	
T13N23	42 (22.0)	21 (24.1)	21 (20.2)		28 (24.3)	14 (18.4)	
Differentiation (n = 183)				0.081			0.022
Well	125 (68.3)	63 (75.0)	62 (62.6)		84 (75.0)	41 (57.7)	
Moderate/poor	58 (31.7)	21 (25.0)	37 (37.4)		28 (25.0)	30 (42.3)	
Perineural invasion (n = 173)	97 (56.1)	41 (51.2)	56 (60.2)	0.283	50 (47.2)	47 (70.1)	0.004
Lymphovascular permeation (n = 173)	74 (42.8)	33 (41.3)	41 (44.1)	0.759	43 (40.6)	31 (46.3)	0.529
Cut margin (n = 181)				0.042			0.125
Free/close	133 (73.5)	66 (81.5)	67 (67.0)		84 (77.8)	49 (67.1)	
Positive	48 (26.5)	15 (18.5)	33 (33.0)		24 (22.2)	24 (32.9)	
Extracapsular spread (n = 177)				0.250			0.062
No	124 (70.1)	62 (74.7)	62 (66.0)		83 (75.5)	41 (61.2)	
Yes	53 (29.9)	21 (25.3)	32 (34.0)		27 (24.5)	26 (38.8)	

found in the 5-year DFS rates, which were revealed to be 52.6% for the T4N0 subgroup, 49.8% for the T1-3N23 subgroup, 31.6% for the T4N1 subgroup, and 31.0% for the T4N23 subgroup ($p < 0.01$, Fig. 2B). Furthermore, the 5-year rates for freedom from locoregional recurrence were 82.9% for the T4N0 subgroup, 73.3% for the T1-3N23 subgroup, 69.3% for the T4N1 subgroup, and 58.7% for the T4N23 subgroup ($p < 0.01$, Fig. 2C), while the 5-year rates for freedom from distant metastasis were 85.3% for the T4N0 subgroup, 83.2% for the T1-3N23 subgroup, 76.0% for the T4N1 subgroup, and 59.8% for the T4N23 subgroup ($p = 0.11$, Fig. 2D).

Table 2

The distribution of tumor primary sites among different pstage IV OSCC subgroups

	Stage IV subgroups			
Tumor primary site	**T4N0**	**T4N1**	**T4N23**	**T1-3N23**
Buccal mucosa	31 (40.3%)	8 (42.1%)	12 (22.6%)	8 (19.0%)
Gingiva	21 (27.3%)	6 (31.6%)	9 (17.0%)	1 (2.4%)
Retromolar trigone	4 (5.2%)	4 (21.1%)	4 (7.5%)	6 (14.3%)
Tongue	10 (13.0%)	0	17 (32.1%)	21 (50.0%)
Others	11 (14.3%)	1 (5.3%)	11 (20.85)	6 (14.3%)
Total	77	19	53	42

OSCC=oral squamous cell carcinoma.

3.3. Clinicopathological parameters associated with survival

The univariate analysis results regarding the associations between the clinicopathological parameters and OS are illustrated in Fig. 3A. The patients with diabetes mellitus showed increased risks of mortality in stage IV disease (p = 0.024, with hazard ratio [HR] = 1.87, 95% confidence interval [CI] = 1.09–3.21), while age, personal habits, primary tumor location, and comorbidity score showed no statistically significant impacts on OS. Among the stage IV subgroups, the T4N23 subgroup presented with the worst mortality score (p < 0.001, with HR = 3.16, 95% CI = 1.83–5.48). The T4N1 subgroup also exhibited a trend of poor OS, although there was no statistical significance (p = 0.094, HR = 1.95, 95% CI = 0.89–4.24). As for the pathological variables, the presence of perineural invasion and

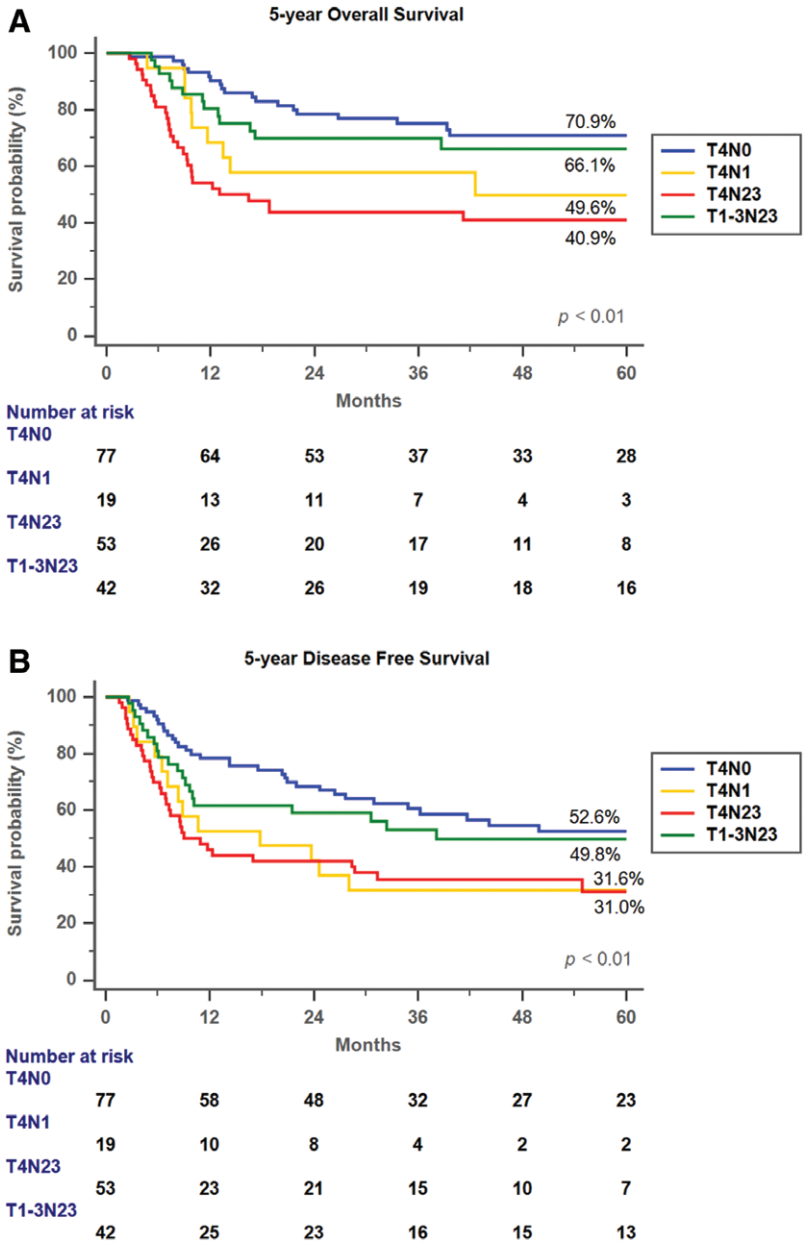

Fig. 2. (*Continued*)

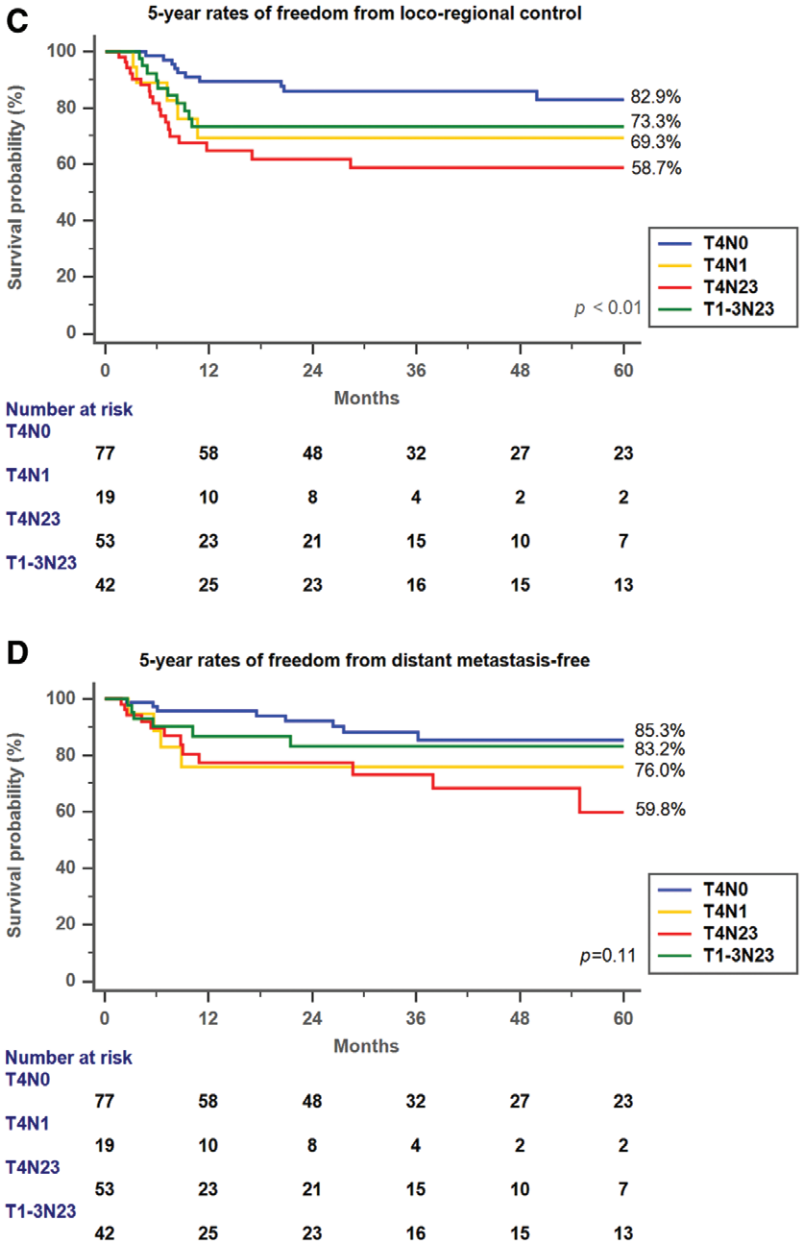

Fig. 2. A, Five-year overall survival (OS) rates of different pstage IV OSCC subgroups. B, Five-year disease-free survival (DFS) rates of different pstage IV OSCC subgroups. C, Five-year rates of freedom from loco-regional control of different pstage IV OSCC subgroups. D, Five-year rates of freedom from distant metastasis-free of different pstage IV OSCC subgroups. OSCC=oral squamous cell carcinoma.

moderate/poor differentiation exhibited elevated risks of mortality (p = 0.001, with HR = 2.42, 95% CI = 1.43-4.10; and p = 0.036, with HR = 1.65, 95% CI = 1.03–2.65, respectively). Extracapsular spread was also associated with a significantly increased risk of mortality (p = 0.002, with HR = 2.14, 95% CI = 1.31–3.51). Meanwhile, although positive surgical margin showed no statistically significant association with increased risk of mortality, it still exhibited a trend in that direction (p = 0.094, with HR = 1.52, 95% CI = 0.93–2.48).

The result of multivariable Cox model identified the following variables as potential independent risk factors of OS: diabetes (HR = 1.86, 95% CI = 0.93–3.71), T4N23 (HR = 2.79, 95% CI = 1.25–6.23), perineural invasion (HR = 3.21, 95% CI = 1.71–6.02), and positive surgical margin (HR = 1.88, 95% CI = 1.02–3.47) (Table 3).

3.4. Clinicopathological parameters associated with recurrence

The impacts of the clinicopathological parameters on disease recurrence are illustrated in Figure 3B. In patients with T4 disease, the presence of nodal metastasis increased the risk of developing tumor recurrence. The estimated HR for T4N1 was 1.98 (p = 0.037, 95% CI = 1.04-3.75) and that for T4N23 was 2.10 (p = 0.002, 95% CI = 1.31-3.37). However, advanced nodal metastasis in cases involving tumors of smaller size (T1-3) did not show a trend toward recurrence. Among the pathological parameters, perineural invasion, positive surgical margin, and extracapsular spread were associated with tumor recurrence. The estimated HRs were 1.57 (p = 0.035, 95% CI = 1.03–2.38), 1.62 (p = 0.023, 95% CI = 1.07–2.47) and 1.71 (p = 0.015, 95% CI = 1.11–2.63), respectively. Differentiation also exhibited an

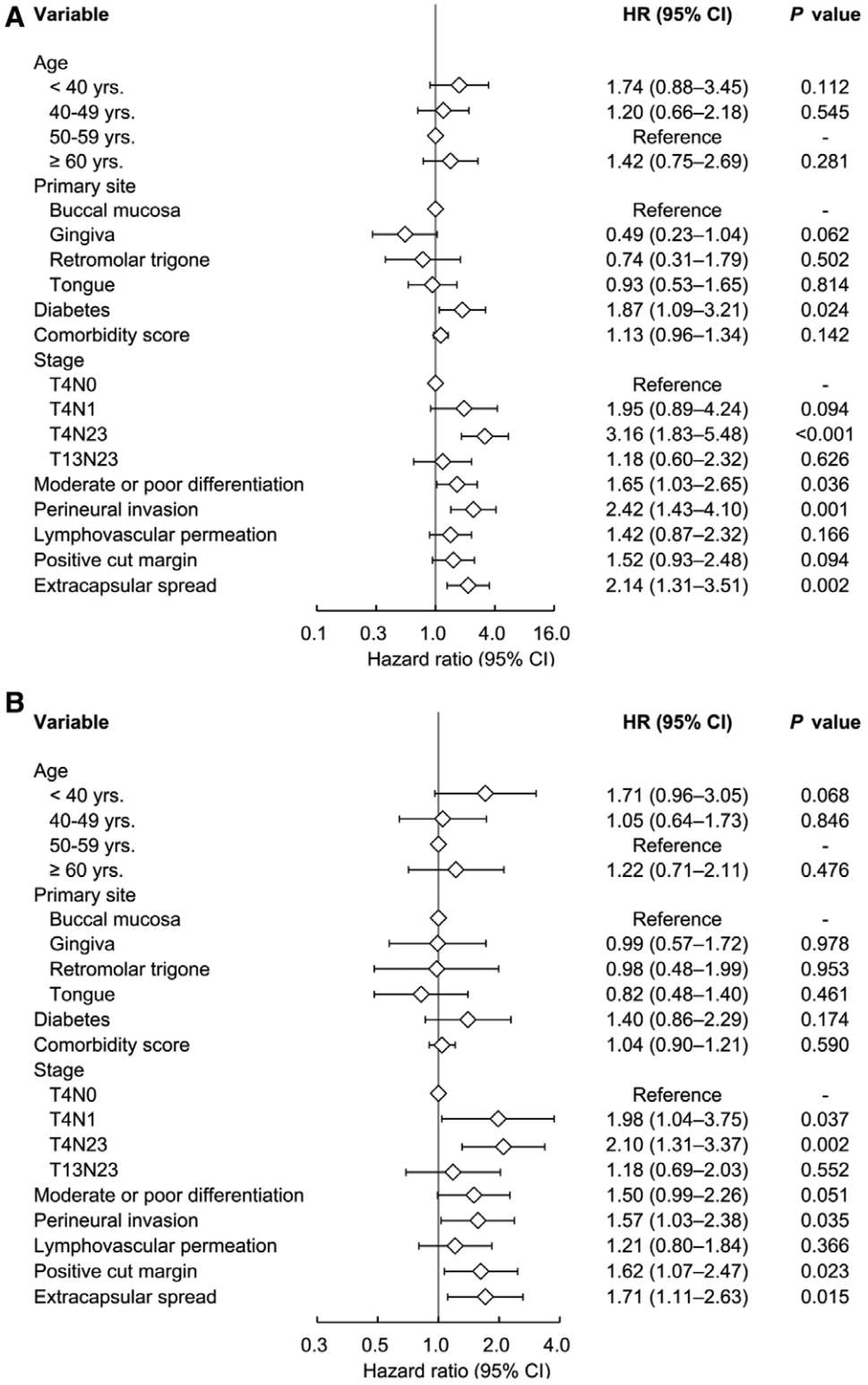

Fig. 3. A, Univariate analysis results regarding the associations between clinicopathological characteristics and overall survival. B, Univariate analysis results regarding the associations between clinicopathological characteristics and disease-free survival.

impact on tumor recurrence, although it did not reach statistical significance (p = 0.05, HR = 1.50, 95% CI = 0.99–2.26).

The result of multivariable Cox model identified the following variables as potential independent risk factors of DFS: T4N23 (HR = 1.78, 95% CI = 0.90–3.51, borderline significant), perineural invasion (HR = 1.89, 95% CI = 1.17–3.05) and positive surgical margin (HR = 1.66, 95% CI = 1.00–2.78, borderline significant) (Table 3).

Table 3

Univariate and multivariable analysis of disease-free survival (DFS) and overall survival (OS)

	Disease-free survival		Overall survival	
Variable	**HR (95% CI)**	***p***	**HR (95% CI)**	***p***
Age				
<40 years	0.73 (0.38–1.41)	0.349		
40–49 years	0.69 (0.36–1.35)	0.282		
50–59 years	Reference	-	Reference	-
≥60 years	0.80 (0.38–1.68)	0.559		
Male				
Primary site				
Buccal mucosa	Reference	-	Reference	-
Gingiva				
Retromolar trigone				
Tongue				
Other				
Unknown				
Alcohol or smoking				
Betel				
Diabetes			1.86 (0.93–3.71)	0.080
Other comorbidity				
Comorbidity score				
Stage				
T4N0	Reference	-	Reference	-
T4N1	1.68 (0.75–3.75)	0.206	1.47 (0.54–4.04)	0.452
T4N23	1.78 (0.90–3.51)	0.097	2.79 (1.25–6.23)	0.012
T13N23	0.86 (0.42–1.77)	0.686	0.88 (0.37–2.11)	0.778
Differentiation				
Well	Reference	-	Reference	-
Moderate/poor	1.31 (0.81–2.13)	0.267	1.41 (0.82–2.42)	0.216
Perineural invasion	1.89 (1.17–3.05)	0.010	3.21 (1.71–6.02)	<0.001
Lymphovascular permeation				
Cut margin				
Free/close (0,1,2)	Reference	-	Reference	-
Positive (3,4,5)	1.66 (1.00–2.78)	0.052	1.88 (1.02–3.47)	0.042
Extracapsular spread				
No	Reference	-	Reference	-
Yes	1.16 (0.65–2.09)	0.609	1.24 (0.63–2.44)	0.530

CI=confidence interval; HR=hazard ratio.

4. DISCUSSION

Nearly 40% of patients newly diagnosed with OSCC on an annual basis present with stage IV disease, and the prognosis for such patients is usually poor even when multimodal treatment is applied. In past studies, the OS rates of stage IV disease have been reported to range widely, varying from 28% to 58%, after different modalities of treatment.[3–9] In the AJCC cancer staging system, stage IV is defined as the stage in which an advanced tumor has invaded adjacent structures (T4a or T4b) or in which there is aggressive neck lymph node metastasis (N2-3). In brief, stage IV cases of OSCC consist of those with a T4 presentation with or without nodal metastasis and any T presentation with N2 or N3 metastasis. Relatedly, different rates of survival may exist among the different stage IV subgroups based on the weightings from the tumor size and nodal metastasis. The results of this study indicated that the T4N0 and T1-3N23 patients had similar OS (70.9% vs. 66.1%) and DFS (52.6% vs. 49.8%) rates. These results were comparable to those of studies that have revealed 5-year survival rates for stage I OSCC ranging from 76% to 84% and 5-year survival rates for stage II ranging from 68% to 71%.[5,8–10] The findings of this study thus might support the idea that adjuvant chemoradiation therapy provides a survival benefit to T4N0 and T1-3N23 patients. However, no survival benefit was observed in T4 patients with nodal metastasis. This was especially true for the T4N23 subgroup, for which the HRs for mortality and recurrence, respectively, were 3.2 and 2.1 times those for the T4N0 subgroup. According to the treatment guidelines, adjuvant chemoradiation therapy is generally applied to stage IV diseases. The present study demonstrated different degrees of tumor control in the different stage IV subgroups, in spite of the fact that all were treated with the same treatment scheme. To our knowledge, this is the first study to disclose such differences. Based on the study results, further intensification of adjuvant therapy should be considered as an integral means of potentially improving the survival of T4 with nodal metastasis patients. Moreover, T4N23 patients in particular appear to warrant more intensive monitoring schedules in order to ensure the early diagnosis of any possible recurrent or metastatic lesions.

The tumor-nodal-metastasis staging system is fundamentally an anatomic staging system. Although the eighth version of the AJCC integrates key pathological factors, namely, the depth of invasion, extranodal extension, and expression of p16, into its staging system, some other important pathological factors, for example, differentiation, perineural invasion, and lymphovascular permeation, that might relate to the biological behavior of tumors and possibly affect the therapeutic responses to chemoradiation therapy are not included. Several

past studies revealed that Bryne's invasive cell grading system, which was proposed in 1992, shows a positive relation to LN metastasis in OSCC and is superior in predicting survival compared to other histology grading systems.[11,12] In this study, meanwhile, cell differentiation, perineural invasion, and extranodal extension were found to have negative impacts on OS in OSCC, consistent with the results of other studies.[5,8,13] The main limitations of TNM staging have been described by Patel and his colleagues as consisting of its relatively low predictive power, its lack of differentiation between groups, and its failure to account for tumor factors.[11,14] They proposed a modular prognostic system in which the TNM stage, validated host variables, tumor variables, and treatment variables could be collected comprehensively in order to generate a prognostic score to predict the treatment outcome. Furthermore, several authors recently proposed that nomograms could serve as a tool to predict the prognosis of oral cavity cancer in a more accurate manner than traditional TNM stages.[15–17] Bobdey et al.[16] proposed one nomogram to predict treatment outcomes in T4 buccal mucosa cancer, and suggested that the intensification of adjuvant therapy might improve the survival of patients with poorer scores. Our data in the present study revealed that moderate/poor differentiation, the presence of perineural invasion, extranodal extension, and positive cut margin are significant risk factors for tumor recurrence and mortality. These findings could be further applied in risk stratification for stage IV diseases.

The coexisting comorbidities have been proven to adversely affect OS in head and neck cancer patients, especially elderly victims.[18–21] In our study, however, the comorbidity score showed no statistical significance in terms of having negative impacts on OS or DFS. Diabetes is the most important comorbidity that we should bear in mind. Strong associations between diabetes and increased cancer incidence and disease progression have already been identified in many cancers, including colorectal, breast, liver, pancreatic, and endometrial cancer.[22] Several studies have also reported increased risks of oral cancer development and elevated risks of disease progression and local recurrence in OSCC patients with diabetes compared with non-diabetic patients.[23–26] Our study results demonstrated that diabetes decreases the OS by 1.87 times, and a trend of increasing disease recurrence was also found, although it was not statistically significant.

There were some limitations to this retrospective study. First, the different survival rates, if any, between the T4a and T4b subgroups with or without nodal metastasis could not be elucidated because of the extremely limited numbers of T4b cases, which were scattered among the different subgroups. Second, the main purpose of this study was to evaluate the treatment outcomes of stage IV OSCC patients treated with curative intent. Relatedly, those patients who received definitive concurrent chemoradiotherapy were excluded. Meanwhile, those patients who underwent induction chemotherapy followed by surgery were also not included. The different treatment outcomes for these various treatment modalities thus could not be illustrated in this study.

In conclusion, in the present study, we revealed the different survival outcomes of different stage IV OSCC subgroups treated with the same treatment scheme. For the T4N0 and T1-3N23 patients, the OS rates shared similarities with the survival rates of stage I–III OSCC patients, whereas, in contrast, the OS rates of the T4 with nodal metastasis patients was poor. Diabetes has negative impacts on OS. Furthermore, clinicopathological parameters including perineural invasion, cell differentiation, extracapsular spread, and tumor cut margin could be considered as risk stratification factors in stage IV OSCC. Overall, the results of our study could serve as a reference for clinical physicians that might assist them in re-evaluating patients and predicting their prognoses more accurately, as well as in determining postoperative disease monitoring timetables based upon the different characteristics of each individual.

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