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Impact of treatment delay on survival of oral/oropharyngeal cancers: Results of a nationwide screening program

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Abstract

Background: To assess the impact of treatment delay on survival of oral/oropharyngeal cancer (OSCC).

Methods: We followed 5743 OSCCs between 2004 and 2009 from a population-based screening program and ascertained death until the end of 2012.

Results: The hazard ratios (HRs) of mortality from OSCC were 1.46 (1.30-1.65) and 1.18 (1.04-1.33) in univariable and multivariable analyses, respectively, for treatment delay longer than 6 weeks compared with that shorter than 3 weeks. The corresponding figures were 1.12 (1.01-1.24) and 1.00 (0.91-1.11) for treatment delay between 3 and 6 weeks. Advancing age (1.01), higher stage (stage II: 1.84, stage III: 2.97, stage IV: 6.33), cancer in tongue (1.37), or hard palate (1.63) had higher HR of mortality ($P < .05$). However,

William Wang-Yu Su and Yi-Huah Lee contributed equally to this study.

treatment at medical center had a lower mortality (0.83, 0.75-0.91) than local/regional hospital.

Conclusions: Treatment delay longer than 6 weeks for OSCCs detected via a population-based screening program had unfavorable survival.

KEYWORDS

betel quid chewing, cigarette smoking, oral/oropharyngeal cancer, survival, treatment delay

1 | INTRODUCTION

The incidence of oral/oropharyngeal squamous cell carcinoma (OSCC) is the highest in areas such as Melanesia, South-Central/Southeast Asia, and Central/Eastern Europe where habits of cigarette smoking, alcohol drinking, and betel quid chewing are prevalent.[1-3] Although the incidence of OSCC decreases worldwide over the past few decades, the overall 5-year survival is only around 60% (ranging from 10% to 82%). With continual progress in imaging, surgery, radiation, and systemic therapies as well as the collaboration of multidisciplinary team, the overall survival (OS) may have improved 15% in the last 50 years but only 5% in the last 20 years.[4] Since more than 50% of such cancers are diagnosed at advanced stages (stage III or IV), which has a poor 5-year survival of around 20% to 30%,[4] strategy toward early diagnosis and treatment is thus upmost for further improvement of survival.

Population-based oral visual screening targeting at high-risk subjects has been proven effective in reducing 21% of advanced stage and 24% mortality of oral cancer in a randomized controlled trial in India after 15 years of follow-up.[5-7] After the screening is performed by the trained medical personnel, all the participants with positive oral potentially malignant disorders are routinely referred to the head and neck specialists or oral surgeons for further confirmation and management.[8] If biopsy yields the pathologic proof of malignancy, then treatment will be arranged after a battery of staging workup examinations, including at least radiologic examinations (computed tomography and/or magnetic resonance imaging), abdominal sonography, bone scan or positron emission tomography, and serum biochemical laboratory tests as well as the consultation of collaboration of multidisciplinary teams. The length of examination period may be affected by long waiting lists, limited healthcare capacity, or manpower shortage[9] and may be as long as 30 to 69 days or more.[10-12] However, significant tumor progression has been reported during such waiting period for patients diagnosed as having head and neck cancers,[11,13] and tumor upstaging may result in decreased survival for those receiving treatment after prolonged delay.

The association between prolonged diagnosis-to-treatment interval and unfavorable survival in head and neck squamous cell carcinoma (HNSCC) has been reported in several studies with the interval threshold ranging from 20 to 120 days.[14-16] Most of these studies used population-based database for analysis and found positive association between the decreased survival and the prolonged time interval from diagnosis to treatment initiation in the Netherlands,[17] north-eastern Italy,[18] Denmark,[19] and the United States[20] with the corresponding hazard ratios of mortality 1.07, 1.13, 1.6, and 1.23, respectively. However, a recent large-scale study found that there was lack of such an association of treatment delay when focused only on cases of OSCC with OS in the United States, while the report from Taiwan[14] had a significant 12% increased risk of mortality. Although inconsistent results regarding the impact of treatment delay on survival of OSCC have been noted, it is imperative to make use of a large-scale population-based study to elucidate the impact of treatment delay in the area with prevalent OSCC where the demand for treatment is high. Therefore, we aim to assess the effect of treatment delay on survival of OSCC diagnosed via screening of high-risk subjects in a nationwide population-based oral screening program.

2 | MATERIALS AND METHODS

2.1 | Study subjects

Biennial oral visual screening targeted at high-risk groups has been launched by the Health Promotion Administration of the Ministry of Health and Welfare since 2004 under the reimbursement of the government authorities owing to the high incidence of oral cancer,[21] and this service screening program aims at early detection of oral cancer, which is the fifth leading incident malignancy in Taiwan.[22] The subjects aged 18 years or above with habits of cigarette smoking and/or betel quid chewing were invited to participate in the screening at any medical institution contracted with the National

Health Insurance System. Firstly, face-to-face interview was performed by either public health workers or medical personnel in the community to collect information on oral habits and demographic characteristics, and then eligible subjects were invited to participate in the screening but those with a prior history of oral cancer were excluded from enrollment. Visual inspection of the oral cavity (including lips, buccal mucosa, oral tongue, gingivae, retromolar trigone, floor of mouth, soft and hard palate, uvula, tonsils, and lateral and posterior oropharyngeal walls) was then performed by the otolaryngologists, dentists, or trained physicians under adjunct usage of disposable wooden tongue depressor and proper illumination. Participants with no visible oral lesions were suggested to reparticipate in the screening biennially. Participants with visible oral potentially malignant lesions, such as verrucous hyperplasia, lichen planus, leukoplakia, erythroleukoplakia, erythroplakia, oral submucous fibrosis, unhealed oral ulcer above 2 weeks, or any suspicious malignancy were referred to the head and neck specialists practicing in confirmatory examination and pathologic diagnosis at the hospital. After pathologic confirmation of the presence of malignancy, cancer staging workup followed by further treatment was then arranged accordingly. The costs after referral were all under the reimbursement of the National Health Insurance System, which had a coverage rate of 99.6% of the 23.6 million registered residences in Taiwan. Regarding low-income people who could not afford the payment for insurance, the government provided subsidization to guarantee their rights to access necessary health care.

2.2 | Collection of data

A total of 2 334 299 subjects participating in the screening program between 2004 and 2009 constitutes our study cohort, which is still currently operational and maintained by the Health Promotion Administration of the Ministry of Health and Welfare of Taiwan prospectively.[22] Through the linkage of the cohort with National Cancer and Death Registry until December 31, 2012, the cause and date of death were retrieved. Demographic characteristic and other covariates of interest were retrieved, including sex, age, oral habits, cancer stage at treatment, cancer site, year of diagnosis, hospital level for cancer treatment (medical center, local/regional hospital), date of pathologic diagnosis, date of initial treatment, and date of oral cancer death. Treatment delay was defined as the number of weeks from the date of pathologic diagnosis to the date of treatment initiation. The hospital level was assessed and accredited periodically on the basis of "Hospital accreditation Standards" mandated by the Joint Commission of Taiwan organization to ensure nation's healthcare quality.[23]

Site codes for OSCC were based on the International Classification of Diseases for Oncology (ICD-O-3), third edition, and were classified as lip cancer (C00), tongue cancer (C01, C02), gum cancer (including alveolar ridge mucosa and gingiva) (C03), floor-of-mouth cancer (C04), hard palate cancer (C05.0, C05.8, C05.9), buccal cancer (C06.0), retromolar trigone cancer (C06.2), other forms of oral cancer or with overlapping sites (C06.1, C06.8, C06.9), and oropharyngeal cancer (C05.1, C05.2, C09, C10), respectively. The TNM stage of cancer was categorized in accordance with the guidelines of the American Joint Committee on Cancer staging manual (sixth edition). The pathologic cancer staging was adopted with supplement by the clinical cancer staging when the subjects did not receive surgery as treatment modality. Note that subjects who were diagnosed as OSCC before screening and have not received any treatment, or with treatment delay more than 52 weeks, were excluded from the analyses.

2.3 | Statistical analysis

Continuous variables were expressed as median $\pm$ interquartile range (IQR) or 95% confidence interval (CI), and groups were compared using Student's t test for analysis of baseline characteristics. Categorical variables were expressed as counts (%), and groups were compared using the χ^2 test. The OS of OSCC over the time of follow-up was computed with the Kaplan-Meier method graphically and was tested with log-rank test. Univariable and multivariable Cox's proportional hazards models were used to estimate the crude hazard ratios (cHR), adjusted hazard ratio (aHR), and their 95% CI of mortality for treatment delay, sex, age, oral habits, stage and site of cancer, year of diagnosis, and the hospital level for cancer treatment. All data analyses were performed with the SAS software, version 9.3 (SAS Institute Inc., Cary, NC). Two-tailed P value of $<.05$ was considered statistically significant.

2.4 | ETHICS STATEMENT

This study was approved and funded by the Health Promotion Administration of the Ministry of Health and Welfare of Taiwan (A1081113). All records and information were anonymized and de-identified prior to analysis. The Research Ethics Committee D of National Taiwan

University Hospital approved this project and granted a waiver for informed consent (201809041W) pursuant to the regulations of the Institutional Review Board on October 2, 2018.

3 | RESULTS

3.1 | Demographic characteristics and distribution of treatment delay

The distribution of treatment delay among 5743 oral/oropharyngeal cancers is illustrated in Figure 1. There were 56.9% of the cases receiving treatment within 3 weeks after diagnosis, 86.5% within 6 weeks, and only 13.5% more than 6 weeks. Table 1 shows the demographic characteristics of sex, age, oral habits (betel quid chewing, cigarette smoking, and alcohol drinking), cancer site and stage, year of diagnosis, and hospital level for cancer treatment. Most of the cases were male (97%), aged between 30 and 59 years (71.4%), and received treatment at medical center (73.5%). The median time of treatment delay was 20 days (IQR: 12-30 days) and did not show significant difference in sex, age, oral habits, and year of diagnosis. However, the delay varied significantly with different cancer sites with the shortest in lip (16 days) and the longest in gum, retromolar trigone, and oropharynx (21 days). With increasing cancer stage, the median time of treatment delay increased from 16 days in stage I to 21 days in stage IV (trend test $P < .01$). Subjects who received treatment at medical center had a median treatment delay of 20 days while at local/regional hospital was 19 days ($P = .03$). Those with unspecified cancer site (28 days), unknown cancer stage (28 days), and unknown hospital level for treatment (22 days) had longer median treatment delay when compared to their counterparts. Since outpatient appointment was usually scheduled on weekly basis and the overall median delay in our cohort centered around 19-22 days (approximately 3 weeks), we then classified the treatment delay into three groups [≤ 3 weeks (≤21 days), 3 to 6 weeks (22-42 days), and >6 weeks (>42 days)] for computing the effect on OS, which included 56.9%, 29.6%, and 13.5% of the cases, respectively. Baseline characteristics showed significant variation in distribution of the sex, age, cancer sites, cancer stage, and hospital level among treatment delay groups.

3.2 | Cox's proportional hazards regression analysis

We estimated the effects of different characteristics on OS using Cox's proportional hazards regression analysis (Table 2). Treatment delay longer than 3 weeks showed significantly higher mortality when compared to ≤3 weeks in univariable analysis but was not significant until >6 weeks in multivariable analysis (aHR: 1.18, 95% CI: 1.04-1.33). Regression analyses showed that age at diagnosis (aHR: 1.01, 95% CI: 1.01-1.01) was significantly associated with OS in multivariable analyses. Using lip as reference for comparison, all cancer sites had higher risks of mortality in univariable analysis but only tongue (aHR: 1.37, 95% CI: 1.03-1.83) and hard palate (aHR: 1.63, 95% CI 1.11-2.41) were significant in multivariable analyses. Cancer stage had significant effect on OS and the HR increased as upstaging in both univariable and multivariable analyses. Using stage I as reference, the

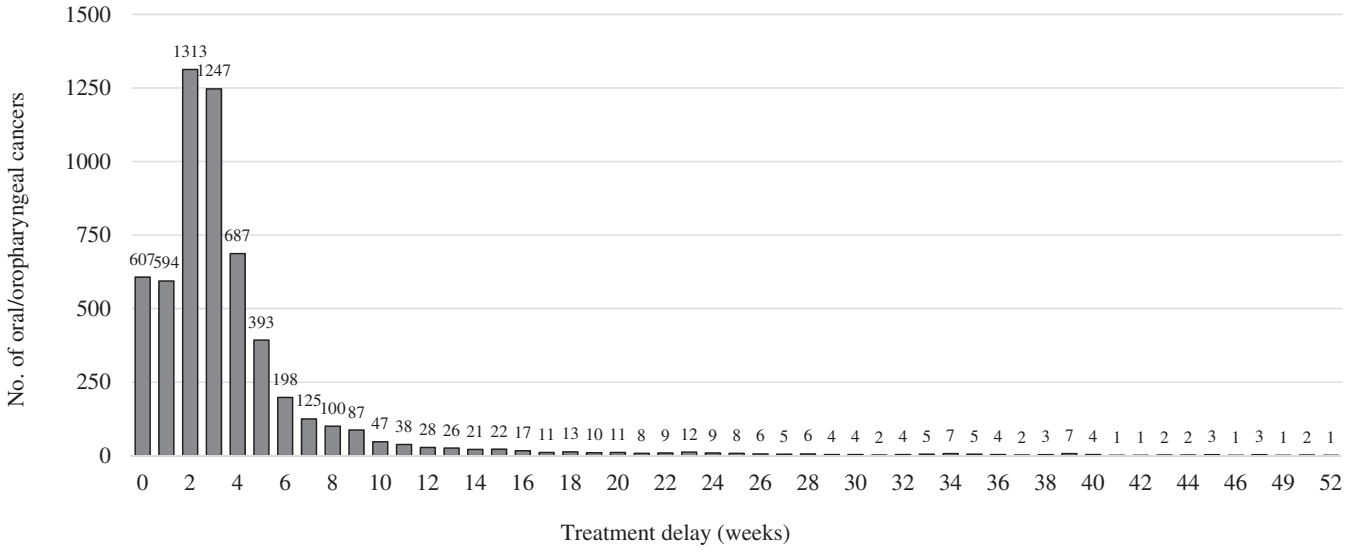

FIGURE 1 Distribution of treatment delay in 5743 oral/oropharyngeal cancers

TABLE 1 Demographic characteristics and treatment delay of 5743 oral/oropharyngeal cancers

Variable	No. of cases	(%)	Median delay, days (IQR)	*P*	Treatment delay, n (%)						*P*
					≤ 3 weeks		3 to 6 weeks		> 6 weeks		
Sex				.07							.0008
Male	5573	(97.0)	20 (12-29)		3175	(57.0)	1661	(29.8)	737	(13.2)	
Female	170	(3.0)	21 (14–36)		92	(54.1)	39	(22.9)	39	(22.9)	
Age				.26							.02
<30	17	(0.3)	20 (13–28)		10	(58.8)	6	(35.3)	1	(5.9)	
30-59	4101	(71.4)	19 (12–29)		2380	(58.0)	1197	(29.2)	524	(12.8)	
≥60	1625	(28.3)	20 (12-31)		877	(54.0)	497	(30.6)	251	(15.4)	
Betel quid chewing				.48							.18
No	1367	(23.8)	20 (12–31)		771	(56.4)	391	(28.6)	205	(15.0)	
Yes	4321	(75.2)	19 (12–29)		2461	(57.0)	1298	(30.0)	562	(13.0)	
Quit	55	(1.0)	19 (11-27)		35	(63.6)	11	(20.0)	9	(16.4)	
Cigarette smoking				.52							.25
No	494	(8.6)	20 (13-30)		287	(58.1)	132	(26.7)	75	(15.2)	
Yes	5249	(91.4)	20 (12–30)		2980	(56.8)	1568	(29.9)	701	(13.3)	
Alcohol drinking				.83							.84
No	2127	(37.0)	19 (12–30)		1201	(56.5)	632	(29.7)	294	(13.8)	
Yes	3616	(63.0)	20 (12–29)		2066	(57.1)	1068	(29.5)	482	(13.3)	
Cancer site				<.01							<.01
Lip	259	(4.5)	16 (6-26)		166	(64.1)	56	(21.6)	37	(14.3)	
Buccal	1668	(29.0)	19 (12–29)		985	(59.1)	462	(27.7)	221	(13.2)	
Gum	533	(9.3)	21 (15–33)		267	(50.1)	182	(34.1)	84	(15.8)	
Floor-of-mouth	127	(2.2)	19 (13-31)		74	(58.3)	32	(25.2)	21	(16.5)	
Tongue	1518	(26.4)	19 (12-28)		933	(61.5)	409	(26.9)	176	(11.6)	
Hard palate	101	(1.8)	20 (12–28)		55	(54.4)	33	(32.7)	13	(12.9)	
Retromolar trigone	201	(3.5)	21 (13-29)		108	(53.7)	70	(34.8)	23	(11.4)	
Oropharynx	661	(11.5)	21 (13-32)		340	(51.4)	237	(35.9)	84	(12.7)	
Unspecified	675	(11.8)	21 (14–32)		339	(50.2)	219	(32.4)	117	(17.3)	

(Continues)

TABLE 1 (Continued)

Variable	No. of cases	(%)	Median delay, days (IQR)	*P*	Treatment delay, n (%)					*P*
					≤ 3 weeks		3 to 6 weeks		> 6 weeks	
Cancer stage				<.01						<.01
I	1476	(25.7)	16 (7-25)		970	(65.7)	387	(26.2)	119	(8.1)
II	1041	(18.1)	19 (13-27)		629	(60.4)	310	(29.8)	102	(9.8)
III	667	(11.6)	20 (13–30)		358	(53.7)	231	(34.6)	78	(11.7)
IV	2215	(38.6)	21 (14-33)		1159	(52.3)	714	(32.2)	342	(15.4)
Unknown	344	(6.0)	28 (10-64)		151	(43.9)	58	(16.9)	135	(39.2)
Year of diagnosis				.61						.36
2004	202	(3.5)	20 (13–31)		110	(54.5)	61	(30.2)	31	(15.3)
2005	495	(8.6)	19 (12-27)		301	(60.8)	139	(28.1)	55	(11.1)
2006	805	(14.0)	19 (13–29)		465	(57.8)	243	(30.2)	97	(12.0)
2007	1015	(17.7)	19 (12–30)		576	(56.7)	286	(28.2)	153	(15.1)
2008	1395	(24.3)	20 (12–30)		781	(56.0)	411	(29.5)	203	(14.6)
2009	1831	(31.9)	20 (12–29)		1034	(56.5)	560	(30.6)	237	(12.9)
Hospital level				.03						.02
Medical Center	4219	(73.5)	20 (13–29)		2380	(56.4)	1288	(30.5)	551	(13.1)
Local/regional	1504	(26.2)	19 (11-30)		877	(58.3)	405	(26.9)	222	(14.8)
Unknown	20	(0.3)	22 (13-36)		10	(50.0)	7	(35.0)	3	(15.0)
Overall	5743	(100)	20 (12–30)		3267	(56.9)	1700	(29.6)	776	(13.5)

Abbreviation: IQR, interquartile range.

TABLE 2 Cox's proportional hazards analyses on risk of oral/oropharyngeal cancer mortality

Variable	Univariable			Multivariable		
	cHR (95% CI)		*P*	aHR (95% CI)		*P*
Treatment delay						
≤3 weeks	1.00	Reference		1.00	Reference	
3 to 6 weeks	1.12*	(1.01-1.24)	.03	1.00	(0.91–1.11)	.94
> 6 weeks	1.46*	(1.30-1.65)	<.0001	1.18*	(1.04-1.33)	0.01
Sex			0.77			0.84
Male	1.00	Reference		1.00	Reference	
Female	0.96	(0.74-1.25)		0.97	(0.74-1.28)	
Age at diagnosis (years)	1.01*	(1.01-1.01)	<.0001	1.01*	(1.01-1.01)	<.0001
Betel quid chewing						
No	1.00	Reference		1.00	Reference	
Yes	1.01	(0.91-1.12)	0.82	1.00	(0.89-1.11)	0.94
Quit	0.87	(0.53-1.43)	0.58	0.99	(0.60-1.64)	0.96
Cigarette smoking						
No	1.00	Reference		1.00	Reference	
Yes	1.03	(0.88-1.20)	0.76	1.04	(0.88-1.22)	0.69
Alcohol drinking						
No	1.00	Reference		1.00	Reference	
Yes	1.07	(0.97-1.17)	0.18	1.05	(0.95-1.16)	0.32
Cancer site						
Lip	1.00	Reference		1.00	Reference	
Buccal	1.59*	(1.19-2.12)	0.0015	1.08	(0.81-1.44)	0.61
Gum	2.18*	(1.61-2.96)	<.0001	1.01	(0.74-1.37)	0.97
Floor-of- mouth	1.93*	(1.29-2.88)	0.0013	1.12	(0.75-1.68)	0.58
Tongue	1.83*	(1.38-2.43)	<.0001	1.37*	(1.03-1.83)	0.03
Hard palate	3.08*	(2.09-4.52)	<.0001	1.63*	(1.11-2.41)	0.01
Retromolar trigone	2.11*	(1.48-3.00)	<.0001	1.35	(0.94-1.92)	0.10
Oropharynx	2.28*	(1.69-3.08)	<.0001	1.17	(0.86-1.58)	0.32
Cancer stage						
I	1.00	Reference		1.00	Reference	
II	1.84*	(1.52-2.24)	<.0001	1.84*	(1.52-2.24)	<.0001
III	3.03*	(2.49-3.68)	<.0001	2.97*	(2.43-3.62)	<.0001
IV	6.39*	(5.47-7.46)	<.0001	6.33*	(5.39-7.43)	<.0001
Year of diagnosis						
2004	1.00	Reference		1.00	Reference	
2005	0.97	(0.76-1.23)	0.77	1.08	(0.84-1.38)	0.55
2006	0.77*	(0.61-0.97)	0.03	0.80	(0.63-1.01)	0.06
2007	0.85	(0.68-1.07)	0.16	0.91	(0.72-1.15)	0.43
2008	0.84	(0.67-1.05)	0.12	0.86	(0.69-1.08)	0.20
2009	0.80	(0.64-1.00)	0.05	0.86	(0.69-1.07)	0.18
Hospital level						
Medical center	0.82*	(0.75-0.91)	0.0001	0.83*	(0.75-0.91)	0.0001
Local/regional	1.00	Reference		1.00	Reference	

Abbreviations: aHR, adjusted hazard ratio; cHR, crude hazard ratio, CI, confidence interval.
Note: *$P < .05$.

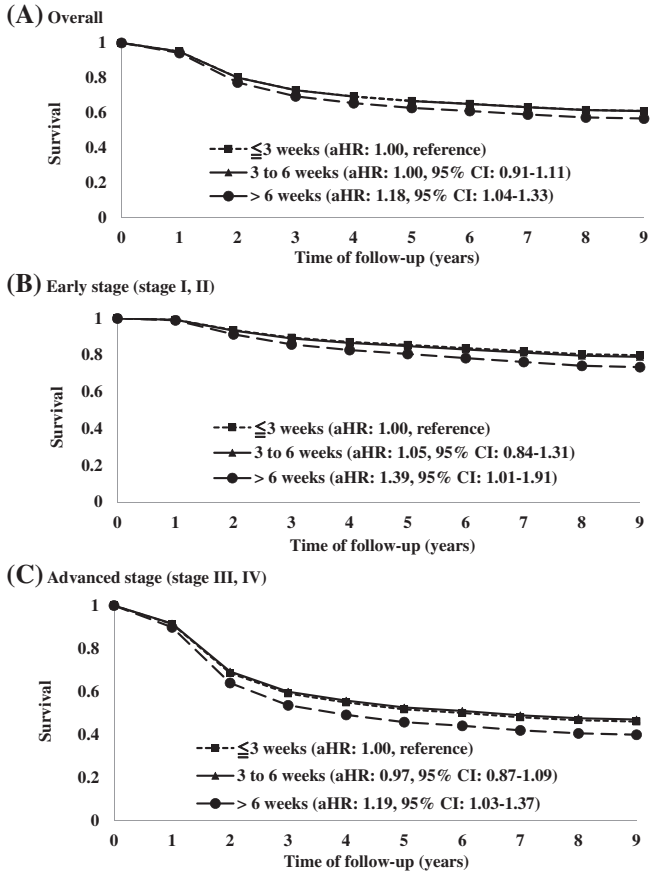

FIGURE 2 Kaplan-Meier survival curves of oral/oropharyngeal cancer by treatment delay

aHR for mortality from OSCC was 1.84 (1.52-2.24) for stage II, 2.97 (2.43-3.62) for stage III, and 6.33 (5.39-7.43) for stage IV in multivariable analyses. Subjects who received treatment at medical center had significant lower risks of mortality than at local/regional hospital with a corresponding cHR of 0.82 (0.75-0.91) in univariable and aHR of 0.83 (0.75-0.91) in multivariable analyses. There were only 20 cases (0.3%) who received treatment at unknown hospital level and the OS was similar to those treated at local/regional hospital (aHR: 0.68, 95% CI: 0.30-1.52). However, sex, different oral habits, and year of diagnosis had no significant effect on OS and these also lack interaction among covariates ($P > .05$). Several potential confounding variables (such as cases with higher cancer stage had longer treatment delay) were adjusted in the multivariable analyses for eliminating the confounding effect on our results.

3.3 | Kaplan-Meier survival curves

The survival curves at different times of treatment delay were analyzed by Kaplan-Meier analysis with adjustment of covariates including sex, age, betel quid chewing, cigarette smoking, alcohol drinking, and hospital level for cancer treatment and are graphically illustrated with the order of aHR (Figure 2). The OS for treatment delay between 3 and 6 weeks was similar to those ≤3 weeks but was not significant until >6 weeks (aHR: 1.18, 95% CI: 1.04-1.33) (log-rank test $P < .05$). Further stratification by cancer stage revealed that both early (stage I, II) and advanced (stage III, IV) stages had less favorable OS when treatment delay >6 weeks with the corresponding aHRs of 1.39 (1.01-1.91) and 1.19 (1.03-1.37), respectively.

4 | DISCUSSION

The definition of "delay in cancer diagnosis and treatment" varies and has been reported as long as 5 to 6 months in the literature. In a review article by Guneri and Epstein,[24] it is categorized into three components: patient delay, professional delay, and system delay. Diagnostic delay is commonly categorized as "patient delay," which refers to the period between the first detection of a sign/symptom and looking for health care for that, while "professional delay" is the duration from the first examination by a healthcare provider to the final histological diagnosis of the condition. "System delay" refers to the duration from diagnosis to the initiation of the treatment and means the same as the term "treatment delay" we adopt in current study. The cancers in our cohort were diagnosed via referral from oral visual screening program targeting at high-risk subjects and mostly were either asymptomatic or unaware of the malignancy. Consequently, patient delay and professional delay were not applicable to our cohort and we thus focused only on treatment delay.

Several terms have been used to describe the time between pathologic diagnosis of malignancy and initiation of treatment in the literature for HNSCC, such as waiting time,[17,25] treatment delay,[12,25-31] time interval from diagnosis to treatment,[15] time to treatment initiation,[18-20,32,33] durations of diagnosis-to-treatment initiation,[27-29,34,35] and diagnosis-to-treatment interval.[14,30,34] It may be confusing for researchers interested in this issue since there is no unified terminology to describe this period in spite of suggestions proposed by the Aarhus statement.[36] However, we believe these terms can be used interchangeably since the same definitions of this period were described in individual study. We thus adopt the term "treatment delay" since it is concise and most frequently used in the literature although it may not be as straightforward literally as "diagnosis-to-treatment initiation/interval."[31] After pathologic diagnosis of the malignancy, certain time will inevitably elapse

owing to the arrangement of cancer staging examination, multidisciplinary team consultation, and then finally scheduling for the treatment. Under Taiwan's National Health Insurance system, the health care is provided according to "first come, first serve" basis without any special priority given to screening-referred cases, and this could be verified by the median treatment delay in our study was 20 (IQR: 12-30) days while the reported figure in Taiwan was 19 (IQR: 13-28) days.[14]

After the implementation of screening, the referral-confirmed malignancy will impose burden on healthcare system and may lengthen the time to treatment. Van Harten et al reported that the year of diagnosis was significantly related to treatment delay in their institution with median of 31 days during the period of 1990 and 1994, which significantly lengthened to 38 to 41.5 days in the subsequent time periods (1995-1999, 2000-2004, 2005-2010).[26] Our nationwide cohort had much shorter median delay and it did not change significantly over years as referred cases increased. Since significant cancer progression occurred as increasing delay for treatment, a fast track study was introduced in Denmark since 2007 through employment of a full-time case manager, strengthening the multidisciplinary tumor board and giving higher priority for HNSCC patients.[13] The delay from diagnosis to treatment successfully decreased from a median of 31 days in 1992 and 47 days in 2002 to 25 days in 2010 ($P < .001$). With the implementation of nationwide oral screening program since 2004 in Taiwan, the workload of healthcare system was sure to increase due to the referral of screen-positive subjects and provision of subsequent treatment. Although the confirmed and treated OSCC increased from 202 cases in 2004 to 1831 cases in 2009, our results showed no increase of treatment delay over years with a stable median around 19 to 20 days. Also, there was a nonsignificant trend toward decreasing HR of mortality over year of diagnosis with 14% reduction of HR of mortality in the last year of enrollment. This may be attributed to the high efficiency and healthcare quality in our National Health Insurance System since no targeted strategy had ever been adopted toward the increase in healthcare demand accompanied by screening.

As far as the magnitude of prolonged treatment delay on survival was concerned, there were several large-scale studies reported worldwide, yet with conflicting results (Supplementary Table). A Dutch study using HNSCC from the Netherlands Cancer Registry between 2005 and 2011 concluded that the hazard of dying was increasing with longer waiting time (HR: 1.07, 95% CI: 1.06-1.08).[17] Another study using Danish Head and Neck Cancer group database for 2000 to 2014 identified a HR of 1.6 (95% CI: 1.04-2.45) for mortality in human papillomavirus-negative oropharyngeal squamous cell carcinoma (SCC) patient with time to treatment initiation >60 days.[19] Murphy et al used the National Cancer Database (NCDB) to evaluate the association of OS with treatment delays in HNSCC between 1998 and 2001, showing that the time to treatment initiation more than 60 days vs less than 30 days had a HR of 1.13 for the elevated mortality.[20] However, other studies by Morse et al[27-29,34,35] to characterize treatment delays with OS on HNSCC using also NCDB from year 2004 to 2013 yielded variable results. According to these cohorts, the diagnosis to treatment initiation was not associated with poorer OS in oral cavity SCC,[37] primarily resected oropharyngeal SCC,[29] salivary gland cancer,[35] and hypopharyngeal cancer treated with induction chemotherapy.[27] Instead, treatment delays were associated with poorer survival only in hypopharyngeal cancer treated with primary radiation or chemoradiation.[27] However, a recent systemic review addressed that nine out of 13 studies found association between longer diagnosis-to-treatment interval and poorer OS with delay thresholds ranging from more than 20 days to 120 days or more.[31] Our study showed that the impact of unfavorable OS was significant when treatment delay 3 to 6 weeks (aHR: 1.12) and >6 weeks (aHR: 1.18) in multivariable analysis for OSCC. The result was in concordance with Liao's study that diagnosis-to-treatment interval ≥20 days was associated with poorer 5-year OS in oral cavity SCC, which was based on patients identified in Taiwan Cancer Registry Database from 2004 to 2010.[14] It appeared that strategy toward shortening the treatment delay cannot be overemphasized on the basis of these real-world data to achieve better survival.

The specialists who received referral would perform biopsy or excision of any suspicious oral lesions and then arranged appropriate treatment if malignancy was proven. The subjects may also seek treatment at other specialists or hospitals at discretion as their preference in our healthcare system. When the subjects had care transitioning, longer waiting time for appointment, scheduling, and finally treatment would occur, and it was reported to be associated with poorer survival.[20,32] Transition care to academic facilities was reported to have inherent increase in time to treatment initiation from a median of 26 days to 33 days[32] in the United States, yet the corresponding OS was better given a mortality HR of 0.91 (95% CI: 0.88-0.95).[20] Similar finding was also reported in Italy with an HR of 0.73 (95% CI: 0.66-0.80).[18] It appeared that treatment at high volume facilities mitigated some portion of mortality risk from prolonged waiting, but transitions should be cautious and structured to avoid detrimental delays. However, care transitioning and the consequent increasing time waiting for treatment were highly correlated, which was

statistically inappropriate to be included at the same time in our analysis. That was the reason why we focused only on examining the treatment delay without separate consideration if the subjects had care transitioning.

In our study, the subjects with positive oral lesions after visual screening were informed of the results and the necessity to receive further confirmatory diagnosis by the specialists. A referral sheet was issued and the subjects could make appointment at any hospitals contracted to the National Health Insurance System as their preference. Consequently, we further examined whether survival varied at different levels of hospitals and the result showed that treatment at medical center had a significant 17% decreased risk of mortality compared to local/regional hospital. The hospital level was rated periodically by the healthcare authorities in Taiwan according to structured professional healthcare indexes, and thus the patients prone to seek medical care at higher-rated medical centers owing to better equipment, surgical skills and experience, ample manpower, and most important of all, presumably better prognosis. Our result in part supported this presumption since subjects who received treatment at medical center appeared to have decreased HR in mortality. However, since cancer progression developed during prolonged waiting and consequently negatively affected the prognosis,[25,31] referral all the cases to the medical centers may potentially prolong the waiting and compromise the survival advantage. Although only 13.5% of our cohort received treatment 6 weeks after diagnosis, we believed that certain fewer cases may upstage from early to advanced stage during the delay although we had only cancer stage at treatment. It was noteworthy that cases in early stage may have better prognosis, yet the impact of delay was larger than in late stage (aHR: 1.39 vs 1.19), which was less common but in agreement with a population-based report in northern Italy[18] and thus care should be taken clinically not to exceed such threshold. Therapy for OSCC was complex with surgery as the keystone of curative treatment followed by adjuvant radiotherapy or systemic therapy and it was reasonable to have variable delay in different cancer sites (Table 1, $P < .01$). Although treatment for cancer in tongue and hard palate was mostly within 3 weeks in the current study (median delay: 19 and 20 days), both sites still had the poorest prognosis with corresponding figures of aHR 1.37 and 1.63. One plausible reason may arise from inherent different tumor behavior, which was supported by our previous study regarding varying anatomic sites and mortality that tongue (HR: 1.39) and hard palate (HR: 1.41) had poorest OS among all sites.[38]

There were several limitations in our study. Firstly, although the date and medical facility of initial treatment were available in our cohort, the type of therapy the subjects received, which had impact on survival, was not available from our screening program. Secondly, information regarding dosage and amount of oral habits consumed[39] or cessation[40] was not gathered in the cancer registry, both of which were also documented prognostic factors. Thirdly, no information on transitional care was available since data from Cancer Registry were reported by the hospitals where treatment was provided, not by the original hospitals performing the histopathologic examination. Finally, the HPV infection status was unavailable in the Cancer Registry Database. Although HPV-positive oropharyngeal cancer was reported to have favorable survival,[4,19] the population-based cohort study in Taiwan showed that only females with HPV infection had significantly higher incidence and better survival for HPV-related head and neck cancers.[41] However, since the HPV infection prevalence was low in Taiwan[42] and only 11.5% of our cases was oropharyngeal cancer (0.37% for females), lack of such information was unlikely to alter our results and we thus included all detected OSCC in our study.

5 | CONCLUSION

Our study indicates that oral/oropharyngeal cancers diagnosed via visual screening of subjects with habits of cigarette smoking and/or betel quid chewing had a significant 18% increased hazard of mortality if treatment delay >6 weeks. Although treatment at medical center was associated with better survival, referral may lengthen the treatment delay and potentially worsened the prognosis. Unlike other prognostic factors, such as age at diagnosis, cancer stage, and cancer site that are determinants after pathologic confirmation of malignancy, the treatment delay can be shortened via arrangement of urgent treatment. The referral to other colleagues or hospitals with available healthcare capacity can also be considered. However, further research should be conducted to verify if such strategy really helps to improve survival.

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CONFLICT OF INTEREST

The authors report no conflicts of interest.

AUTHOR CONTRIBUTIONS

William Wang-Yu Su and Hsiu-Hsi Chen: Study concept and design. **William Wang-Yu Su, Yi-Huah Lee, Amy Ming-Fang Yen, Sam Li-Sheng Chen, Chen-Yang Hsu, Sherry Yueh-Hsia Chiu, Jean Ching-Yuan Fann, Yi-Chia Lee, Han-Mo Chiu, Shu-Chun Hsiao, Tsui-Hsia Hsu, Hsiu-Hsi Chen:** Acquisition, analysis, or interpretation of data and critical revision of the manuscript for important intellectual content. **William Wang-Yu Su, Yi-Huah Lee, and Hsiu-Hsi Chen:** Drafting of the manuscript. **Yi-Huah Lee:** Statistical analysis. **Han-Mo Chiu, Shu-Chun Hsiao, and Tsui-Hsia Hsu:** Administrative, technical, or material support. **Hsiu-Hsi Chen:** Supervision.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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