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Characteristics and outcome differences in male and female oral cavity cancer patients in Taiwan

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Abstract

Oral cavity squamous cell carcinoma (OSCC) is a leading cause of death in Taiwan. Most of the patients in the literature are male. The risk factors, cancer characteristics, and treatment outcomes were investigated in female patients and compared with male patients in this study.

This retrospective study recruited 2046 OSCC patients between 1995 and 2019. The age, tumor subsites, and survival were reviewed and recorded. Overall survival and disease-free survival were the main outcomes.

Female patients represented 6.7% of the entire study cohort. Females were diagnosed at an older age and an earlier local stage than male patients ($P < .001$). Female patients were less exposed to cigarettes, alcohol, and betel-quid (all $P < .001$). The tongue (55.1%) was the most frequent subsite in females, while the buccal cavity (38.4%) and the tongue (35.3%) were more likely ($P < .001$) to be associated with the male gender. Female patients in the tongue cancer subgroup presented less frequently with extra-nodal extension compared with male patients ($P = .040$). No significant differences in recurrence or overall deaths were observed between the genders during the follow-up period.

The OSCC male to female ratio in Taiwan was 14:1. Female OSCC occurred more frequently on the tongue, and was diagnosed at an older age and at an earlier tumor stage than in male patients. No survival difference was found between female and male OSCC patients.

Abbreviations: BQ = betel-quid, DFS = disease-free survival, ENE = extranodal spread, HPV = human papilloma virus, HR = hazard ratio, OS = overall survival, OSCC = oral cavity squamous cell carcinoma, PET = positron emission tomography.

Keywords: female, gender, male, oral cavity cancer, survival

1. Introduction

1.1. Background

Oral cavity squamous cell carcinoma (OSCC) is the sixth most prevalent cancer worldwide and is a leading cause of death in Taiwan, particularly in the male population.[1] OSCC is in the top five causes of death according to the Ministry of Health and Welfare of Taiwan.[2] The incidence is about 7000 cases annually in Taiwan, which led to 3027 deaths in 2018. Among the deaths, 2779 were males, accounting for 90% of the mortality caused by OSCC.[2] OSCC globally affects males more frequently than females, and the ratio is highest in Taiwan (male to female ratio: 10.5).[3] The consumption of cigarettes, alcohol, and betel quid (BQ) predisposes male Taiwanese patients to develop OSCC. It is estimated that cigarettes and alcohol contribute to about 80% of OSCC cases.[1] In Taiwan, the significant sex-related differences

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in the frequency of tobacco and BQ chewing may explain the higher incidence of OSCC in males (20.81 cases per 1 million persons) than in females (2.40 cases per 1 million persons).[4]

Due to the substantially lower number of female patients with OSCC, most studies have focused on the male population. Therefore, little is known about differences in risk factors contributing to oral cancer and the treatment outcomes in women. Female patients are exposed to fewer environmental carcinogens in BQ endemic regions, such as Taiwan and India. Some studies have indicated that OSCC may exhibit different risk factors between the genders.[5,6] Nevertheless, one study conducted in Italy and Switzerland showed that tobacco smoking and alcohol consumption represent significant risk factors for women and men. Furthermore, Honorato et al reported no significant difference in the survival rate between the genders.[7,8]

1.2. Objectives

This study aimed to investigate differences in characteristics, risk factors, and treatment outcomes between female and male patients affected with OSCC in Taiwan.

2. Methods

2.1. Study design

This was a retrospective cohort study.

2.2. Setting

Tertiary referral medical center.

2.3. Participants (cohort study)

We retrospectively collected data from a single medical center (Chang Gung Memorial Hospital, Linkou branch, Taiwan). The data consisted of 2046 participants diagnosed with OSCC (involving the tongue, buccal cavity, hard palate, gingiva, and floor of the mouth) between July 1995 and March 2019. All data were collected in compliance with the Declaration of Helsinki. This study was approved by the Institutional Review Board of Chang Gung Memorial Hospital [IRB no: 202000599B0]. All patients received preoperative magnetic resonance imaging, chest X-rays, liver sonography, and bone scan/positron emission tomography. All patients underwent radical surgery as their first treatment.

2.4. Inclusion and exclusion criteria

The inclusion criteria were patients with histologically proven OSCC and those who underwent radical surgery as the first treatment. Patients who had been diagnosed with verrucous carcinoma or a salivary gland malignancy were excluded. Those who had distant metastasis at the time of the diagnosis were also excluded from the analysis.

2.5. Variables

Clinical data were collected from the medical records. The staging system was based on the American Joint Committee on Cancer TNM staging system (AJCC, 2010 edition).[9] After the radical surgery, tumors with adverse pathological factors, such as advanced tumor stage (T3 or T4), poor tumor differentiation, lymph node extra nodal spread (ENE), or tumor depth $\geq$10 mm underwent adjuvant radiotherapy or chemo-radiotherapy.[10,11] Patients were included if they had complete information and patients with distant metastasis or recurring OSCC were excluded.

2.6. Bias

All data were collected in as much detail as possible. We minimized the missing data as much as possible.

2.7. Study size

A total of 2046 participants diagnosed with OSCC were recruited over 14 years.

2.8. Data measurement

Tobacco, alcohol, and BQ consumption history were divided into never used and ever/current user groups. The cancer sites included the tongue, the mouth floor, the lips, the buccal cavity, the alveolus (gums), the hard palate, and the retromolar trigone. The pathological parameters included tumor size, tumor depth, perineural invasion, and lymph node metastasis. Lymph node status was further classified into negative and positive lymph node metastasis without ENE and positive lymph node metastasis with ENE. Tumor size was classified as "small" if the patient had a T1/T2 tumor and "large" for a T3/T4 tumor. Cancer stages I and II were classified as early cancer, and stage III/IV was classified as "advanced". All patients were regularly followed up after the surgery. They returned to the clinic every month during the first year, every 2 months during the second year, every 3 months during the third year, every 4 months during the fourth year, and every 6 months after 5 years.

2.9. Statistical methods

The age, tumor subsite, cigarette smoking, BQ chewing, and alcohol drinking distributions of all OSCC patients were calculated. Statistical analysis was utilized to compare variables, such as age, tumor subsites, and lymph node metastasis between males and females. To assess the differences, the chi-square test was used for categorical variables and the *t*-test was used for continuous variables. All *P*-values $<.05$ were considered significant. Multivariate analysis was conducted using Cox regression. The curves of age at disease onset between the genders were compared using the Kolmogorov-Smirnov test. Overall survival (OS) and disease-free survival (DFS) were assessed using the Kaplan-Meier method, and the differences were estimated with the log-rank test. All analyses were conducted using STATA version 15 software (StataCorp Llc, College Station, TX).

3. Results

3.1. Participants

Age, tumor subsite, and habitual exposure distributions are listed in Table 1. A total of 2046 patients met the inclusion criteria and were included for further analysis. The study population consisted of 1910 males (93.4%) and 136 females (6.6%).

Table 1

Demographic data, environmental exposure, and tumor stage distribution of all OSCC patients (n = 2046).

		N (%)	S.D.
Gender	Male	1910 (93.4)	
	Female	136 (6.7)	
Age		50.7	11.2
Smoking	Never	313 (15.3)	
	Yes	1733 (84.7)	
Alcohol	Never	570 (27.9)	
	Yes	1476 (72.1)	
Betel-quid	Never	411 (20.1)	
	Yes	1635 (79.9)	
Cancer site	Tongue	723 (35.3)	
	Mouth floor	72 (3.5)	
	Lip	70 (3.4)	
	Buccal	786 (38.4)	
	Gum	237 (11.6)	
	Hard palate	49 (2.4)	
	Retromolar	109 (5.3)	
Nodal stage	N– ECS–	1273 (62.2)	
	N+ ECS–	313 (15.3)	
	N+ ECS+	460 (22.5)	
Tumor stage	T1/T2	1228 (60.0)	
	T3/T4	818 (40.0)	
Overall stage	Early	857 (41.9)	
	Advanced	1189 (58.1)	
Recurrence	Yes	649 (31.7)	
	No	1397 (68.3)	

S.D. = standard deviation.

3.2. Descriptive data

The male-to-female ratio was 14:1 in this study. The average age of the participants was 50.7 years (standard deviation [SD]: 11.2, range: 24.0–92.0.) Most of the participants had a history of smoking (84.7%), alcohol use (72.1%), and BQ chewing (79.9%). Cancer sites were more frequently detected on the tongue (35.3%) and buccal mucosa (38.4%). More than half of the participants (58.1%) were diagnosed at an advanced stage. During the follow-up period, 649 (31.7%) participants developed a recurrence.

Table 2 shows a comparison of the characteristics between the genders. Male patients were diagnosed with OSCC at a younger age (mean ± SD: 50.2 ± 10.90 years) compared to female patients (mean ± SD: 57.1 ± 13.11 years, $P < .001$, Fig. 1). The consumption of cigarettes, alcohol, and BQ varied between the genders. The majority of male patients had a history of consuming cigarettes, alcohol, and BQ, whereas the female patients did not (Table 2, all $P < .001$).

3.3. Outcome data

The cancer sites also varied significantly between the genders ($P < .001$). The most common cancer site in male patients was the buccal cavity (39.8%) followed by the tongue (33.9%). Unlike male patients, more than half of the female patients were diagnosed with tongue cancer (55.1%), followed by buccal cancer (19.1%). The overall stage of the diagnosed disease was similar between the genders: 41.5% were early-stage in males and 47.1% were early-stage in females ($P = .206$). During the follow-up period, about one-third (32.1%) of male patients developed a

Table 2

Comparison of patient characteristics between male and female OSCC patients (N = 2046).

		All OSCC patients			Tongue cancer patients		
		Male [n (%)] 1910 (93.4)	Female [n (%)] 136 (6.7)	*P*-value	Male [n (%)) 648 (89.6)	Female [n (%)) 75 (10.4)	*P*-value
Age		50.2 (49.7–50.7)	57.1 (54.9–59.4)	**<.001**	48.4 (28.0–49.6)	53.6 (50.6–56.6)	**<.001**
Smoking	Never	214 (11.2)	99 (72.8)	**<.001**	86 (13.3)	57 (76.0)	**<.001**
	Yes	1696 (88.8)	37 (27.2)		562 (86.7)	18 (24.0)	
Alcohol	Never	464 (24.3)	106 (77.9)	**<.001**	158 (24.4)	59 (78.7)	**<.001**
	Yes	1446 (75.7)	30 (22.1)		490 (75.6)	16 (21.3)	
Betel-quid	Never	313 (16.4)	98 (72.1)	**<.001**	118 (18.2)	60 (80.0)	**<.001**
	Yes	1597 (83.6)	38 (27.9)		530 (81.8)	15 (20.0)	
Cancer site	Tongue	648 (33.9)	75 (55.1)	**<.001**			
	Mouth floor	68 (3.6)	4 (2.9)				
	Lip	64 (3.1)	6 (4.4)				
	Buccal	760 (39.8)	26 (19.1)				
	Gum	219 (11.5)	18 (13.2)				
	Hard palate	46 (2.4)	3 (2.2)				
	Retromolar	105 (5.5)	4 (0.2)				
Nodal stage	N- ENE-	1190 (62.3)	83 (61.0)	.557	390 (60.2)	48 (64.0)	**.040**
	N+ ENE -	288 (15.1)	25 (18.4)		97 (15.0)	17 (22.7)	
	N+ ENE +	432 (22.6)	28 (20.6)		161 (24.9)	10 (13.3)	
Tumor stage	T1/T2	1127 (59.0)	101 (74.3)	**<.001**	476 (73.5)	70 (93.3)	**<.001**
	T3/T4	783 (41.0)	35 (25.7)		172 (26.5)	5 (6.7)	
Overall stage	Early	793 (41.5)	64 (47.1)	.206	325 (50.2)	46 (61.3)	.067
	Advanced	1117 (58.5)	72 (52.9)		323 (49.9)	29 (38.7)	
Recurrence	Yes	613 (32.1)	36 (26.5)	.173	454 (70.1)	55 (73.3)	.557
	No	1297 (67.9)	100 (73.5)		194 (29.9)	20 (26.7)	

ENE = extra-nodal extension.

The values in bold stand for *P* value <0.05.

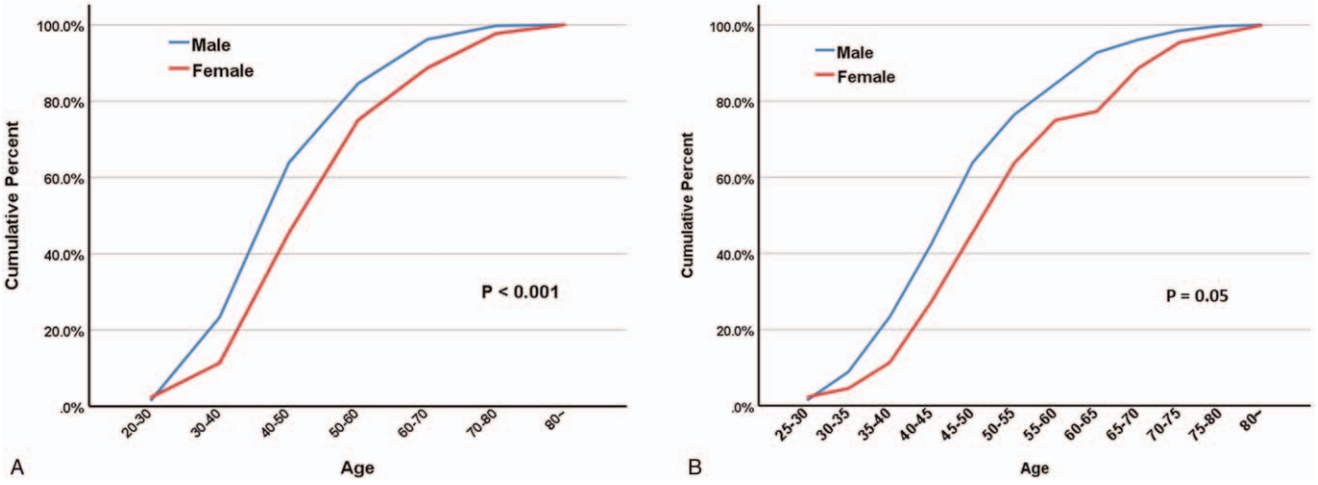

Figure 1. (A) The cumulative case number percentage according to the age of the OSCC patients ($P < .001$, by Kolmogorov-Smirnov test). (B) The cumulative case number percentage according to the age of the tongue cancer patients ($P = .05$ by Kolmogorov-Smirnov test).

recurrence, whereas one-quarter (26.5%) of female patients developed a recurrence ($P = .17$).

3.4. Main results

We further analyzed the patients with tongue cancer, as the tongue was the most commonly affected site in male (33.9%) and female patients (55.1%). The disease characteristics and treatment outcomes were compared between the genders. Table 2 shows a comparison between the genders in the patients with tongue cancer. The females accounted for about 10% of tongue cancer cases, which was similar to the gender distribution of all OSCC patients. Females were about 5 years (53.6, 95% confidence interval [CI]: 50.6–56.6) older when diagnosed with tongue cancer than males (48.4, 95% CI: 28.0–49.6) (Fig. 1, $P = .05$). As in all OSCC patients, most males were heavy tobacco, alcohol, and BQ users, whereas females were not. More females (93.3%) with tongue cancer were diagnosed at an early tumor status, which was significantly different compared to 73.5% of males diagnosed at an early stage ($P < .001$). The proportion of tongue cancer patients without lymph node involvement was similar between the genders. However, the females had less ENE if they had lymph node involvement compared with males (N+ENE+, females: 13.3%; males: 24.9%, $P = .040$). The difference in the overall stage between the genders was not significant ($P = .07$).

Table 3 summarizes the results of the multivariate analysis in all OSCC and tongue cancer patients. In the OSCC patients, advanced tumor stage and lymph node involvement with or without ENE were independent risk factors for survival or recurrence. ENE was a strong risk factor for death and recurrence (DFS: hazard ratio [HR] 2.04 (95% CI: 1.69–2.45, $P < .001$); OS: HR 2.78 (95% CI: 2.31–3.33, $P < .001$)). After adjustment, patients >50 years had a higher HR for death than those <50 years (95% CI: 1.10–1.52, $P < .001$). In tongue cancer patients, lymph node involvement with or without ENE was an independent risk factor for recurrence and survival, particularly in the ENE group (DFS: HR 2.16 (95% CI: 1.56–3.00, $P < .001$); OS: HR 3.61 (95% CI: 2.60–5.03, $P < .001$)). The tumor stage only played a role in the survival of tongue cancer patients; patients with an advanced tumor stage had a higher HR for death (95% CI: 1.09–2.05, $P = .012$). After adjustment, sex and age were not significantly associated with death or recurrence.

Table 3

Multivariate analysis of variables influencing patient survival.

		DFS (All subsites) (n = 1979)		OS (All subsites) (n = 1979)		DFS (Tongue cancer) (n = 710)		OS (Tongue cancer) (n = 710)	
Variables		**HR (95% CI)**	***P*-value**	**HR (95% CI)**	***P*-value**	**HR (95% CI)**	***P*-value**	**HR (95% CI)**	***P*-value**
Sex	Male	1	.49	1	.38	1	.57	1	.12
	Female	0.86 (0.63–1.25)		0.86 (0.61–1.21)		0.87 (0.54–1.40)		0.64 (0.36–1.13)	
Age	<50 y	1	.095	1	**.001**	1	.25	1	.27
	≥50 y	0.87 (0.74–1.02)		1.30 (1.10–1.52)		0.84 (0.63–1.13)		1.18 (0.88–1.58)	
T stage	Early	1	**<.001**	1	**<.001**	1	.10	1	**.012**
	Advanced	1.50 (1.28–1.77)		1.83 (1.55–2.15)		1.31 (0.95–1.79)		1.50 (1.09–2.05)	
N stage	N- ENE-	1		1		1		1	
	N+ ENE-	1.40 (1.12–1.76)	**.003**	1.92 (1.54–2.39)	**<.001**	1.62 (1.11–2.36)	**.012**	2.23 (1.50–3.32)	**<.001**
	N+ ENE+	2.04 (1.69–2.45)	**<.001**	2.78 (2.31–3.33)	**<.001**	2.16 (1.56–3.00)	**<.001**	3.61 (2.60–5.03)	**<.001**

DFS = disease-free survival, ENE = extra-nodal extension, HR = hazard ratio, OS = overall survival.

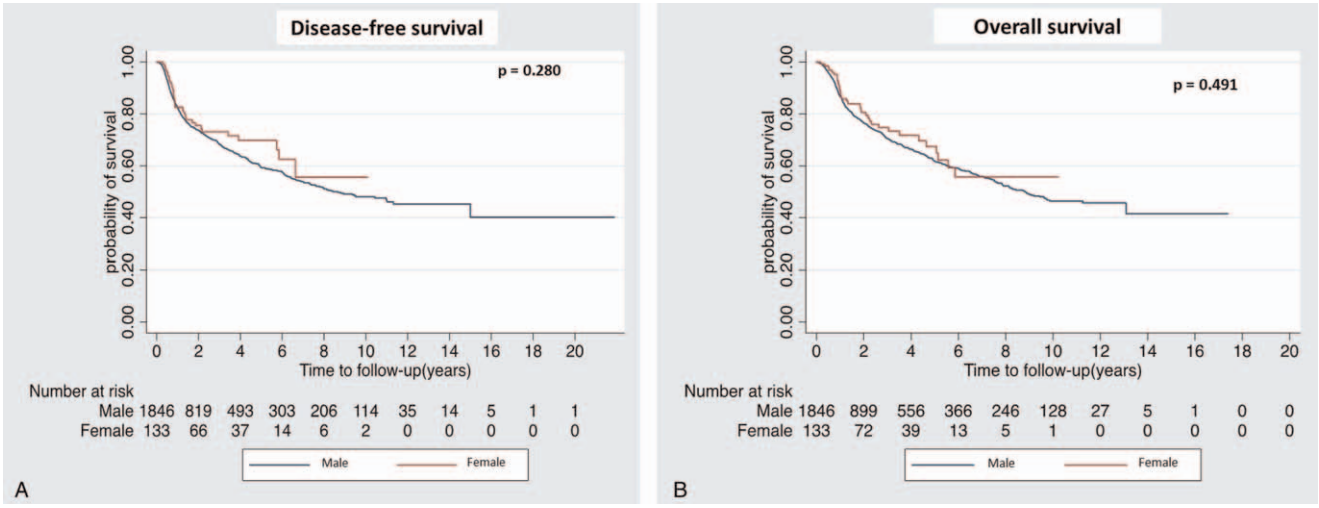

Figure 2. (A) Kaplan-Meier disease-free survival curve between the genders (log rank test: $P = .280$). (B) Kaplan-Meier overall survival curve between the genders (log rank test: $P = .491$).

3.5. DFS and OS

A total of 1979 patients with complete information at the time of diagnosis and death, and 509 deaths among them, were related to OSCC. In total, 480 (7.7%) males and 29 (7.5%) females died during the follow-up. In contrast, 624 patients developed a recurrence. Half of the recurrences occurred within 8.79 years after treatment. Of the patients who developed a recurrence, 589 were male and 35 were female. The frequencies of recurrence among the female and male populations were 9.4% and 10.5%, respectively. Figure 2A shows the DFS curves and Figure 2B shows the Kaplan-Meier OS curves between the genders. There was weak evidence of a difference in OS between females and males during the follow-up period (log-rank test: $P = .491$). No difference in DFS was observed between the genders (log-rank test: $P = .280$). DFS was not different between females and males with tongue cancer ($P = .336$) (Fig. 3A). However, OS in females with tongue cancer tended to be better than males (5-year OS: 91.6% vs. 87.1%, $P = .074$) (Fig. 3B).

4. Discussion

4.1. Generalizability

This study included 2046 patients from a single medical center. However, it overlapped different staging systems (6th, 7th, and 8th AJCC editions). We adopted the 7th edition throughout this study. In this study, more than 90% of the participants were male. Males were more likely to be diagnosed with OSCC at a younger age and with late tumor status compared to female patients. This age difference can be explained in two ways. First, patients in BQ endemic areas develop OSCC at a younger age, compared to other populations not exposed to this risk factor.[1,12] Second, female patients were rarely exposed to

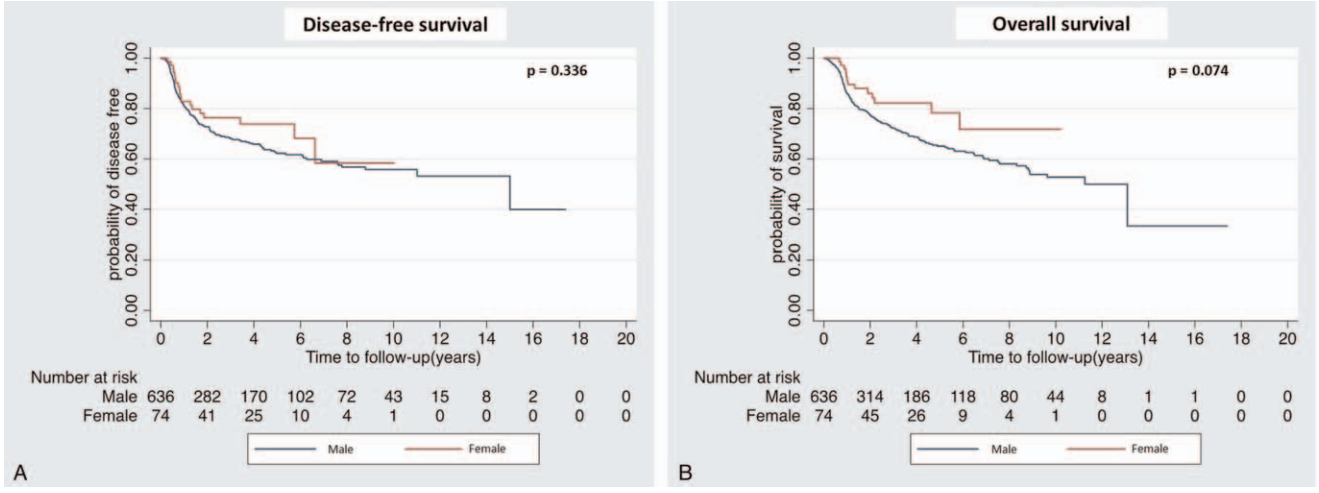

Figure 3. (A) Disease free survival in tongue cancer patients of both genders (log rank test: 0.336). (B) Overall survival in tongue cancer patients of both genders (log rank test: 0.074).

cigarettes, alcohol, or BQ, unlike the male patients; therefore, other factors, such as poor oral hygiene, inadequate dental status, and chronic irritation, which represent independent risk factors for OSCC, regardless of tobacco and alcohol use, may have played a role in carcinogenesis.[13] Patients who do not smoke or drink alcohol tend to present at extreme ages.[14] It is reasonable to say that the female population, with less carcinogen exposure, developed BQ later in their lives.

4.2. Key results

The tongue (55.1%) was the most frequent anatomical site of OSCC in female patients. This finding correlates well with the literature. Several studies have reported higher involvement at this subsite, particularly in nonsmoking and nondrinking women with human papillomavirus (HPV)-negative OSCC.[15] In contrast, we noticed a slightly higher median age of our cohort, compared to another study.[16] We interpreted this discrepancy as a result of differences in epidemiology. Most studies have been conducted in western countries and low OSCC prevalent areas. Lin et al[17] investigated the clinicopathological features in the Taiwanese population affected by OSCC and obtained similar results regarding the age of female patients. Furthermore, Foy et al reported a possible relationship between the development of OSCC in nonsmoking, nondrinking French patients, and viral infection. They hypothesized that changes in sexual behaviors in western countries may lead to an increased incidence of the herpes virus in the oral cavity, particularly HSV-2, which is similar to what has already been described for HPV-positive OSCC. Because viral genome integration has not been detected in nonsmoking and nondrinking patients with OSCC, a "hit and run" viral mechanism involving epigenome deregulation could play a key role during the early stages of oral carcinogenesis in this population of patients.[18] In our cohort, males were more likely to develop buccal (38.4%) and tongue (35.3%) OSCC. The buccal mucosa is the most affected site in people with a BQ chewing history due to frequent irritation of the mucosa. As most of the male patients (79.9%) in our study had a BQ chewing history, buccal cancer was more likely to be found in male participants. The tumor stage at diagnosis differed between the genders. Most (74.3%) of the females had early tumor stages at the time of the OSCC diagnosis, whereas only about 60% of male patients had an early tumor stage. However, lymph node status and the overall stage did not vary between the genders. When we performed further analysis on patients with tongue cancer, female patients were diagnosed at an older age and with smaller tumor sizes. Females had less ENE if they had lymph node involvement compared to males (N+ENE+, males: 24.9%; females: 13.3%). In nonsmoking and nondrinking patients with OSCC, the frequency of lymph node metastasis and ENE was less than the smoking and drinking group. The patients who smoked cigarettes and drank alcohol tended to have a higher risk of lymph node ENE,[19] which could be related to the tumorigenesis mechanism. Oral cancers related to smoking and BQ could harbor more genetic changes from environmental carcinogen exposure and could metastasize more easily, or develop ENE. The other possibility is that tongue cancers in males are at a more advanced stage. The accumulated mutations with the tumor stage make tumor cells aggressive and easier to metastasize.

4.3. Interpretation

There was no evidence of a difference in recurrence or death between the genders during the follow-up period. As OSCC was most prevalent in the male population, most of the literature has investigated the characteristics, risk factors, treatments, and outcomes of OSCC in the male population. Few studies have investigated this disease in females. We reviewed the studies about OSCC between the genders. Honorato et al[8] compared the prognostic differences in OSCC between genders in Brazil. The data showed similar alcohol and cigarette habits between the genders, as in our population, whereas the anatomical sites of cancer differed from our results, which was due to the lack of BQ use. The tongue was the most affected site in males and females.[8] Due to the BQ consumption culture in Taiwan, the buccal cavity is the most affected site in OSCC patients in Taiwan, unlike the results for Brazil. A European study presented the risk factors of oral and pharyngeal cancer in women in Italy and Switzerland.[7] That study showed that women share the same major risk factors, such as the use of cigarettes and alcohol, as men.

The rate of HPV infection in OSCC is 13.4%, while the infection rate is 36.7% in patients with oropharyngeal cancer in the United States.[20] The HPV infection rate in OSCC is lower than that in oropharyngeal cancer. The frequency of HPV infection (9.6%) was much lower in female OSCC patients than in males (15.8%). In this large cohort study, female OSCC patients had better OS regardless of HPV status, which is why we speculated that the survival rates in our study would not be significantly affected, as HPV status was not determined in our analysis.

4.4. Limitations

Some limitations of our retrospective study should be discussed. Only 136 patients were female among the 2046 participants in our study. However, this is one of the largest studies recruiting female OSCC patients who underwent surgery as the primary treatment. HPV-related head and neck cancers have been increasing in recent years, particularly in the younger population, and in those not exposed to tobacco or alcohol. This study provides epidemiological data on female OSCC in a BQ endemic area. Furthermore, cohort studies at different periods are required to compare the trends in female OSCC.

5. Conclusions

In this study, we demonstrated that the male to female ratio of OSCC in Taiwan was 14:1. Cigarettes, alcohol, and BQ were significantly less frequently used by female patients. Female OSCC occurred more frequently on the tongue, was diagnosed at an older age (7 years older than male OSCC), and was at an earlier tumor stage than those in male patients. No differences in DFS or OS were found between female and male OSCC patients.

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Correction

When originally published, Dr. Andrea Iandelli's lastname was spelled incorrectly as Landelli. this has been corrected.

References

[1] Warnakulasuriya S. Global epidemiology of oral and oropharyngeal cancer. Oral Oncol 2009;45:309–16.
[2] Cause of Death Statistics. Available at: https://www.mohw.gov.tw/cp-16-48057-1.html. Published 2017. Accessed September 17, 2021.
[3] Krishna Rao SV, Mejia G, Roberts-Thomson K, Logan R. Epidemiology of oral cancer in Asia in the past decade—an update (2000–2012). Asian Pac J Cancer Prev 2013;14:5567–77.
[4] Liao CT, Wen YW, Yang LY, et al. Comparative clinical outcomes of Taiwanese patients with resected buccal and tongue squamous cell carcinomas. Oral Oncol 2017;67:95–102.
[5] Chen F, He BC, Yan LJ, Qiu Y, Lin LS, Cai L. Influence of oral hygiene and its interaction with standard of education on the risk of oral cancer in women who neither smoked nor drank alcohol: a hospital-based, case-control study. Br J Oral Maxillofac Surg 2017; 55:260–5.
[6] Llewellyn CD, Linklater K, Bell J, Johnson NW, Warnakulasuriya S. An analysis of risk factors for oral cancer in young people: a case-control study. Oral Oncol 2004;40:304–13.
[7] Bosetti C, Negri E, Franceschi S, et al. Risk factors for oral and pharyngeal cancer in women: a study from Italy and Switzerland. Br J Cancer 2000;82:204–7.
[8] Honorato J, Rebelo MS, Dias FL, et al. Gender differences in prognostic factors for oral cancer. Int J Oral Maxillofac Surg 2015;44:1205–11.
[9] Greene FL, Page DL, Fleming ID, et al. AJCC Cancer Staging Manual. 6th ed.New York: Springer-Verlag; 2002.
[10] Huang S-F, Kang C-J, Lin C-Y, et al. Neck treatment of patients with early stage oral tongue cancer. Cancer 2008;112:1066–75.
[11] Liao C-T, Chang JT-C, Wang H-M, et al. Analysis of risk factors of predictive local tumor control in oral cavity cancer. Ann Surg Oncol 2007;15:915–22.
[12] Su CC, Yang HF, Huang SJ, Lian Ie B. Distinctive features of oral cancer in Changhua County: high incidence, buccal mucosa preponderance, and a close relation to betel quid chewing habit. J Formos Med Assoc 2007;106:225–33.
[13] Rosenquist K, Wennerberg J, Schildt EB, Bladstrom A, Goran Hansson B, Andersson G. Oral status, oral infections and some lifestyle factors as risk factors for oral and oropharyngeal squamous cell carcinoma. A population-based case-control study in southern Sweden. Acta Otolaryngol 2005;125:1327–36.
[14] Dahlstrom KR, Little JA, Zafereo ME, Lung M, Wei Q, Sturgis EM. Squamous cell carcinoma of the head and neck in never smoker-never drinkers: a descriptive epidemiologic study. Head Neck 2008;30:75–84.
[15] Brown LM, Check DP, Devesa SS. Oral cavity and pharynx cancer incidence trends by subsite in the United States: changing gender patterns. J Oncol 2012;2012:649498.
[16] Satgunaseelan L, Allanson BM, Asher R, et al. The incidence of squamous cell carcinoma of the oral tongue is rising in young non-smoking women: an international multi-institutional analysis. Oral Oncol 2020;110:104875.
[17] Lin NC, Hsu JT, Tsai KY. Difference between female and male patients with oral squamous cell carcinoma: a single-center retrospective study in Taiwan. Int J Environ Res Public Health 2020;17:3978.
[18] Foy JP, Bertolus C, Boutolleau D, et al. Arguments to support a viral origin of oral squamous cell carcinoma in non-smoker and non-drinker patients. Front Oncol 2020;10:822.
[19] DeAngelis A, Breik O, Koo K, et al. Non-smoking, non-drinking elderly females, a 5 year follow-up of a clinically distinct cohort of oral squamous cell carcinoma patients. Oral Oncol 2018;86:113–20.
[20] Li H, Park HS, Osborn HA, Judson BL. Sex differences in patients with high risk HPV-associated and HPV negative oropharyngeal and oral cavity squamous cell carcinomas. Cancers Head Neck 2018;3:4.