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Clinical and prognostic features of multiple primary cancers with oral squamous cell carcinoma

Xinjia Cai [a,b], Jianyun Zhang [a,b], Fengyang Jing [a,b], Xuan Zhou [a,b], Heyu Zhang [c,*], Tiejun Li [a,b,**]

[a] Department of Oral Pathology, Peking University School and Hospital of Stomatology & National Center of Stomatology & National Clinical Research Center for Oral Diseases & National Engineering Research Center of Oral Biomaterials and Digital Medical Devices, Beijing 100081, PR China
[b] Research Unit of Precision Pathologic Diagnosis in Tumors of the Oral and Maxillofacial Regions, Chinese Academy of Medical Sciences (2019RU034), Beijing 100081, PR China
[c] Central Laboratory, Peking University School and Hospital of Stomatology, Beijing 100081, PR China

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ABSTRACT

Objective: To characterize the epidemiological, clinical, and prognostic features of multiple primary cancers (MPC) following oral squamous cell carcinoma (OSCC).
Design: Data from the Surveillance, Epidemiology, and End Results Program database were analyzed to determine the standardized incidence ratio (SIR) of multiple subsequent sites, difference in clinical and prognostic features between MPC and single primary OSCC.
Results: The sites with the highest SIRs were the oral cavity (SIR = 69.48), other oral cavity and pharynx (SIR = 55.46), pharynx (SIR = 39.21), tonsils (SIR = 33.52), trachea (SIR = 33.24), esophagus (SIR = 18.00), and larynx (SIR = 13.12). The 5- and 10-year survival rates for single primary OSCC were 57.9% (95% CI: 56.7–59.2%) and 47.1% (95% CI: 45.7–48.6%), respectively, while those for MPC were 66.9% (95% CI: 64.6–69.4%) and 42.2% (95% CI: 39.5–45.2%), respectively. The mean age of MPC patients was significantly higher than that of single primary OSCC patients. MPC are more common in the gums and other sites of the oral cavity, and more likely to be detected in early TNM stage and pathological grade. Age, site, T-stage, and N-stage were significantly associated with prognosis of MPC.
Conclusions: Significant differences in clinical and prognostic features were found between MPC and single primary OSCC. Considering MPC has a poor long-term prognosis, it is necessary to identify MPC and single primary OSCC early.

1. Introduction

Head and neck cancer is the seventh most common cancer worldwide, while oral squamous cell carcinoma (OSCC) is the most common cancer in the oral and maxillofacial region (Chi et al., 2015; Mody et al., 2021; Sung et al., 2021). OSCC is caused by a malignant transformation of the keratinocytes in the lip, tongue, gums, and oral mucosa (Chen et al., 2021). Tobacco, alcohol, areca nut, human papillomavirus, and oral potentially malignant disorders are common risk factors for OSCC (Cai et al., 2021; Mody et al., 2021). Despite the use of surgery, radiotherapy, and systemic therapy for the treatment of OSCC, the 5-year survival rate is only about 64% (Bai et al., 2020; Mody et al., 2021). The global burden of OSCC is rising (Ren et al., 2020). A comprehensive understanding of OSCC biology could improve the clinical diagnosis and treatment of OSCC (Johnson et al., 2020).

Multiple primary cancer (MPC) is diagnosed when both primary and secondary tumors, excluding the metastasis, are malignant on histological examination and anatomically separated by normal mucosa (Braakhuis et al., 2002). The risk of MPC depends on the anatomical location of the primary tumor (Shibuya et al., 1987). OSCC patients are

Abbreviations: MPC, multiple primary cancer; OSCC, oral squamous cell carcinoma; SIR, standardized incidence ratio; SEER, Surveillance, Epidemiology, and End Results Program; CSC, cancer stem cell.

* Corresponding author at: Central Laboratory, Peking University School and Hospital of Stomatology, No.22, Zhongguancun South Avenue, Haidian District, Beijing 100081, PR China.
** Corresponding author at: Department of Oral Pathology, Peking University School and Hospital of Stomatology, No.22, Zhongguancun South Avenue, Haidian District, Beijing 100081, PR China.
E-mail addresses: zhangheyu1983@sina.cn (H. Zhang), litiejun22@vip.sina.com (T. Li).

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at a significantly higher risk for MPC (Cianfriglia et al., 1999; Kramer et al., 2004). Studies have demonstrated that gene mutations, epigenetic alterations, single-nucleotide polymorphisms, and chromosomal instability may contribute to MPC susceptibility in OSCC (Zhang, Zhu, Huang, Tang, Tang & Liang, 2019). MPC has a negative impact on OSCC prognosis, and is the second most common cause of death in OSCC (Baxi et al., 2014; Braakhuis et al., 2002; Gonzalez-Garcia et al., 2009; Tabor et al., 2002). It is important to pay attention to patients with MPC because it is challenging to devise an anti-cancer treatment strategy that can cover multiple cancer types without negatively affecting the overall outcome (Gonzalez-Garcia et al., 2009). It is also difficult to distinguish recurrence, metastasis, and MPC in patients who suffer from a second cancer after a history of cancer and anti-cancer treatment (Vogt et al., 2017). In view of the high ratio of MPC subsequent to OSCC, and the poor prognosis (Vogt et al., 2017; Zhang et al., 2019), this study retrospectively analyzed the clinicopathological parameters of a large number of patients with MPC.

2. Materials and methods

The Surveillance, Epidemiology, and End Results Program (SEER) database provides statistical information from cancer registries that cover one-third of the US population, and is often used to analyze the epidemiological, clinical, and prognostic features of cancers (Cai & Huang, 2019). In the coding rules manual of SEER database, recurrence means cancer starts from cancer cells that were not removed or destroyed by the original therapy, while multiple primary cancer includes multiple malignancies that do not count recurrent or metastatic lesions (Johnson et al., 2007). We were permitted to have access to the 1975–2018 SEER Research Data, and SEER data between 1975 and 2018 were analyzed herein to investigate the clinical and prognostic features of MPC. Data including sex, age recode with single ages and 100+, site recode ICD-O-3/WHO 2008, sequence number, total number of in situ/malignant tumors for each patient, derived AJCC T-stage (6th edition; 2004–2015), derived AJCC N-stage (6th edition; 2004–2015), derived AJCC M-stage (6th edition; 2004–2015), grade (through 2017), RX Summ-Surg Prim. Site (1988+), radiation recode, chemotherapy recode (yes, no/unk), diagnostic confirmation, survival months, vital status recode (study cutoff used), SEER cause-specific death classification, and COD to site recode were downloaded from the SEER database using SEER*Stat 8.3.9.2. The oral cavity included the lip, tongue, floor of the mouth, gums, and other areas of the mouth. The search strategies for MPCs subsequent to OSCC in the SEER database are listed in Supplementary Information and flow chart Fig. 1.

The standardized incidence ratios (SIR) were used to conduct an analysis examining multiple subsequent cancers by creating an observed to expected (O/E) ratio based on the observed secondary events for the cohort using a SEER 9 registry rate file (Cai et al., 2018). The SIR of MPC was determined using SEER*Stat 8.3.9.2. The SIR of MPC in different sites and survival analysis were visualized using GraphPad Prism 8.0.1. SPSS Statistics 24 software was used to perform Chi-square test and Cox regression analyses. *P*-values < 0.05 were considered statistically significant.

3. Results

3.1. OSCC increased the risk of MPC in different sites

The MPC involved a total of 11,167 patients, in 8090 (72.45%) males and 3077 (27.55%) females. There were 2257 (20.21%) cases in the oral cavity and 8910 (79.79%) in other sites (Supplementary Table 1). Within the oral cavity, there were 197 (8.73%) cases in the lips, 923 (40.89%) in the tongue, 298 (13.20%) in the floor of the mouth, and 839 (37.17%) in gums and other areas of the mouth. There were 7126 (63.81%) cases of a second primary cancer, 2777 (24.87%) of a third primary cancer, 835 (7.48%) of a fourth primary cancer, 247 (2.21%) of a fifth primary cancer, and 182 (1.63%) of a sixth (or more than six) primary cancer. MPC occurred at 2–11 months in 987 (8.84%) cases, 12–59 months in 3695 (33.09%) cases, 60–119 months in 3102 (27.78%) cases, and $\geq$ 120 months in 3383 (30.29%) cases. There were 439 (3.93%) and 10,728 (96.07%) cases of synchronous and metachronous MPC, respectively. In general, SIR increased in all sites (SIR = 5.33), in both males (SIR = 4.81) and females (SIR = 7.44). SIR increased in both the oral cavity (SIR = 69.48) and other sites (SIR = 4.32). Within the oral cavity, gums and other areas of mouth had the highest SIR (104.84), followed by the floor of the mouth (SIR = 71.32), tongue (SIR = 70.78), and lips (SIR = 27.13). SIR increased with the sequence number of MPC, and was 4.79 for the second primary cancer, 7.27 for the third primary cancer, 8.96 for the fourth primary cancer, 11.63 for the fifth primary cancer, and 14.81 for the sixth (or more than six) primary cancers. However, SIR decreased with the course of MPC. SIR was 7.56 at 2–11 months, 6.50 at 12–59 months, 5.52 at 60–119 months, and 4.06 at $\geq$ 120 months.

The sites with the highest SIRs for all MPC were the oral cavity, other oral cavity and pharynx, pharynx, tonsils, and trachea (Fig. 2A). The sites with the highest SIRs in males were the oral cavity, other oral cavity and pharynx, pharynx, trachea, and tonsils, while the oral cavity, other oral cavity and pharynx, pharynx, tonsils, and esophagus were the sites with the highest SIRs in females. The oral cavity had the highest SIR for the second, third, fourth, and sixth or more than six primary cancer groups, while the trachea had the highest SIR for the fifth primary cancer (Fig. 2B–F). The sites with the highest SIRs are shown in Fig. 2G–J according to the disease course. The oral cavity had the highest SIR in the 2–11–, 60–119–, and $\geq$120-month subgroups, while the other oral cavity and pharynx had the highest SIR in the 12–59-month subgroup.

3.2. Differences between single primary OSCC and MPC

There were 6378 (80.65%) cases of single primary OSCC and 1530 (19.35%) of MPC that were screened using the SEER database between 2004 and 2015 (Fig. 1). The 5- and 10-year survival rates for single primary OSCC were 57.9% (95% CI: 56.7–59.2%) and 47.1% (95% CI: 45.7–48.6%), respectively, while those for MPC were 66.9% (95% CI: 64.6–69.4%) and 42.2% (95% CI: 39.5–45.2%), respectively. The overall survival rate for MPC was better than that for single primary OSCC within 8 years, but worse after 8 years ($P < 0.001$, Fig. 3A). The cancer-specific survival of MPC was better than that of single primary OSCC within the first 12 years, but worse after 12 years ($P < 0.001$, Fig. 3B). The differences in clinicopathological parameters between single primary OSCC and MPC were compared using the Chi-square test (Table 1). The most common age for MPC was 60–69 years, while that for single primary OSCC was 50–59 years ($P = 0.000$). More MPC than single primary OSCC originated in the floor of the mouth, gums and other areas of the mouth ($P = 0.000$). More single primary OSCC than MPC were diagnosed at an advanced T-stage ($P = 0.000$), N-stage ($P = 0.000$), M-stage ($P = 0.045$), and grade ($P = 0.003$). More MPC than single primary OSCC were treated surgically ($P = 0.000$), rather than chemotherapeutically ($P = 0.004$).

3.3. Risk factors associated with poor prognosis of MPC

Table 2 shows the prognostic risk factors for MPC. The risk of death in MPC increased with age (hazard ratio [HR] = 1.034, 95% CI: 1.027–1.041) in multivariate Cox regression analyses. The risk of death for MPC was higher when the first cancer was in the floor of the mouth (HR = 1.802, 95% CI: 1.309–2.481) than in lips. The risk of death for MPC was higher with an advanced T-stage (HR = 1.766, 95% CI: 1.496–2.085) and N-stage (HR = 1.250, 95% CI: 1.051–1.487) compared to early stages.

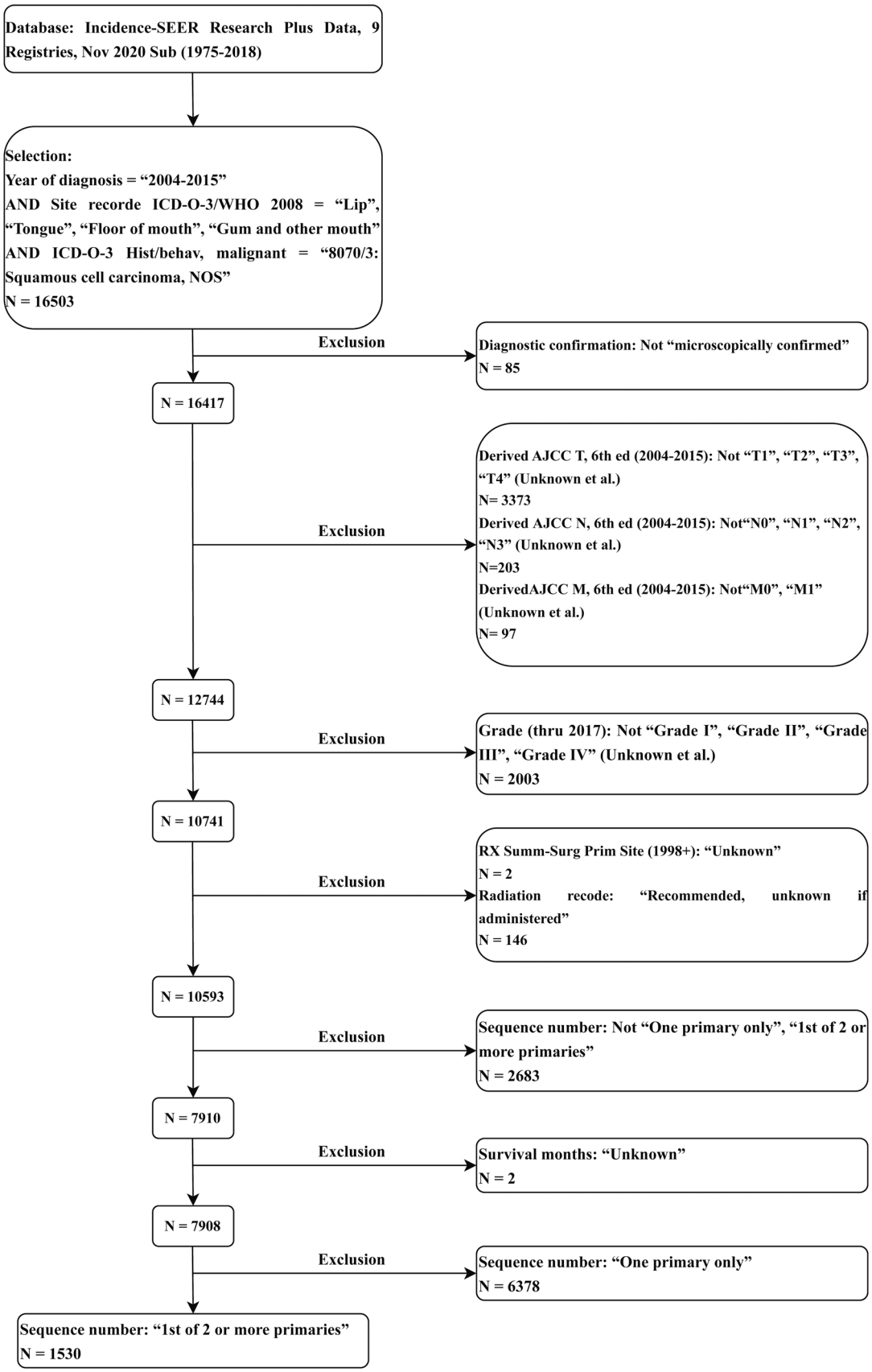

Fig. 1. Flow chart of the search strategies of clinical and prognostic parameters for single primary OSCC and MPC subsequent to OSCC in the SEER database.

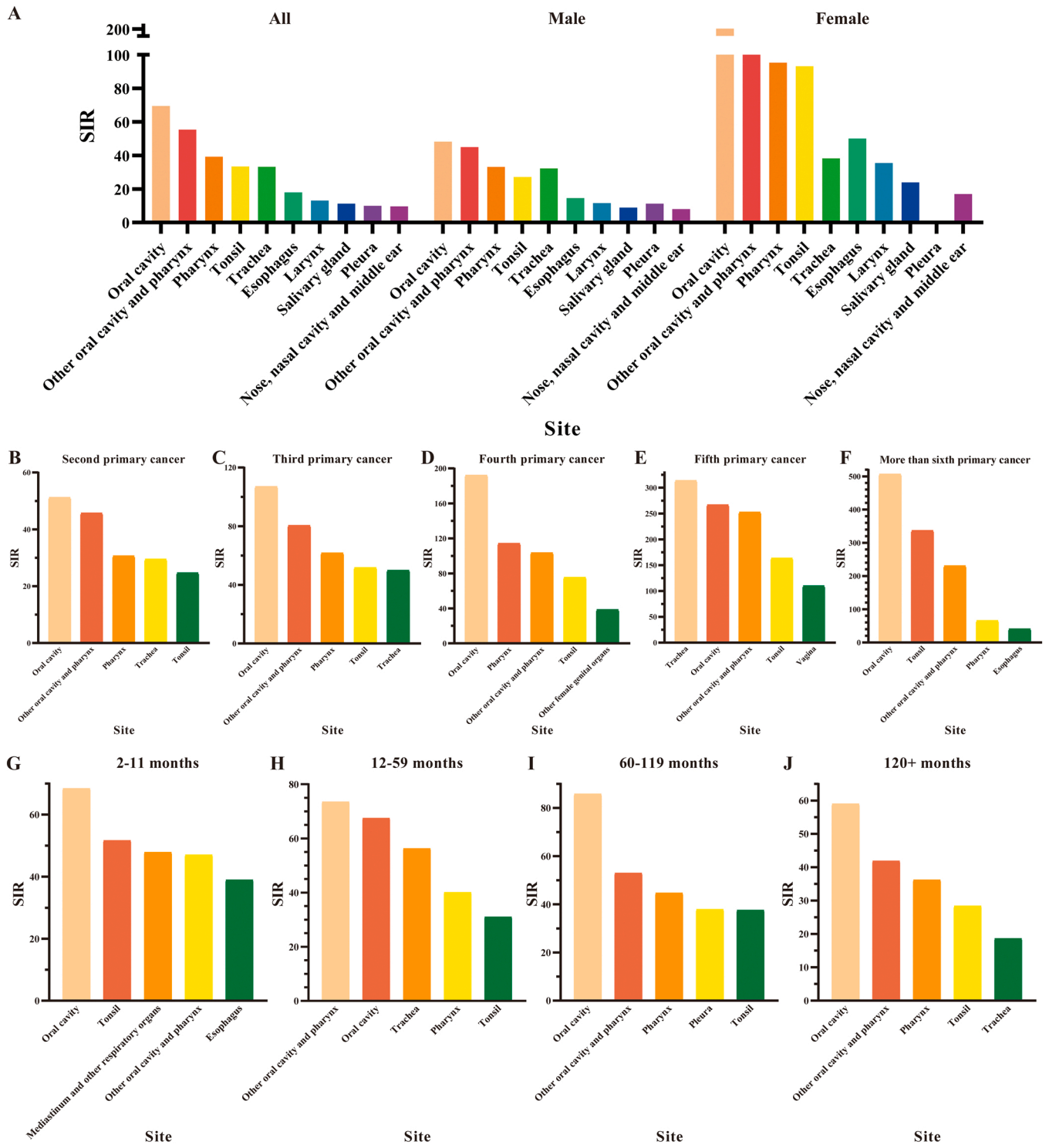

Fig. 2. **A**. Sites with higher standardized incidence ratios (SIRs) for MPC in all patients, males and females. **B**. Sites with higher SIRs in the second primary cancer. **C**. Sites with higher SIRs in the third primary cancer. **D**. Sites with higher SIRs in the fourth primary cancer. **E**. Sites with higher SIRs in the fifth primary cancer. **F**. Sites with higher SIRs in the sixth (or more than six) primary cancer. **G**. Sites with higher SIRs at 2–11 months. **H**. Sites with higher SIRs at 12–59 months. **I**. Sites with higher SIRs at 60–119 months. **J**. Sites with higher SIRs at ≥ 120 months.

4. Discussion

The cases of MPC accounted for 19.35% of all OSCCs in this study. The proportion of MPC reported in the literature ranges widely from 1.4% to 23.7%, possibly due to differences in follow-up durations and samples sizes (Adel et al., 2016; Bugter et al., 2019; Choi & Thomson, 2020; Cianfriglia et al., 1999; Gonzalez-Garcia et al., 2009; Hosokawa et al., 2018; Kao et al., 2017; Kramer et al., 2004; Liao et al., 2007; Lin et al., 2020; Mochizuki et al., 2015; Qaisi et al., 2014; Rodriguez-Bruno et al., 2011).

Similar to a previous study (Jovanovic et al., 1994), the SIR for MPC in our males was lower than the females, both in the oral cavity (48.15 vs. 201.15) and other sites (4.08 vs. 5.30). The occurrence of MPC has been reported in parts of the respiratory and upper digestive tracts, such

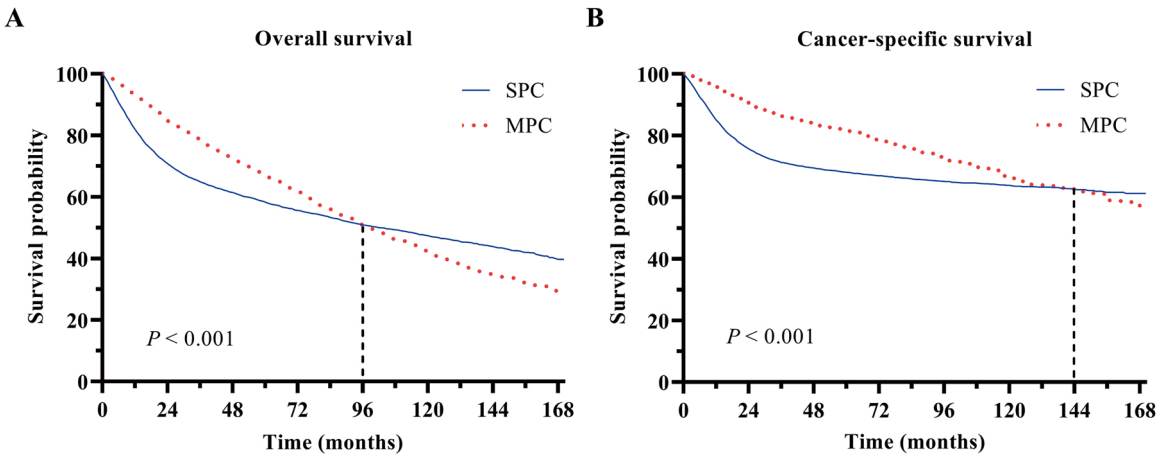

Fig. 3. **A**. Overall survival rates for MPC and single primary OSCC (SPC). **B**. Cancer-specific survival rates for MPC and single primary OSCC (SPC).

Table 1
Differences between single primary OSCCs and OSCC-MPCs.

Variables	Total	SPC (%)	MPC (%)	Chi-square	*P* value
Total	7908	6378	1530		
Age					
<30	70 (0.89)	61 (0.96)	9 (0.59)	67.627	0.000*
30–39	234 (2.96)	208 (3.26)	26 (1.70)		
40–49	873 (11.04)	739 (11.59)	134 (8.76)		
50–59	2236 (28.28)	1812 (28.41)	424 (27.71)		
60–69	2225 (28.14)	1712 (26.84)	513 (33.53)		
70–79	1339 (16.93)	1049 (16.45)	290 (18.95)		
80–89	758 (9.59)	636 (9.97)	122 (7.97)		
90+	173 (2.19)	161 (2.52)	12 (0.78)		
Sex					
Male	5370 (67.91)	4315 (67.65)	1055 (68.95)	0.957	0.328
Female	2538 (32.09)	2063 (32.35)	475 (31.05)		
Site					
Lip	715 (9.04)	599 (9.39)	116 (7.58)	57.381	0.000*
Tongue	4660 (58.93)	3856 (60.46)	804 (52.55)		
Floor of Mouth	866 (10.95)	640 (10.03)	226 (14.77)		
Gum and Other Mouth	1667 (21.09)	1283 (20.12)	384 (25.10)		
T stage					
T1/ T2	5805 (73.41)	4607 (72.23)	1198 (78.30)	23.275	0.000*
T3/ T4	2103 (26.59)	1771 (27.77)	332 (21.70)		
N stage					
N0	4350 (55.01)	3393 (53.20)	957 (62.55)	43.593	0.000*
N1/ N2/ N3	3558 (44.99)	2985 (46.80)	573 (37.45)		
M stage					
M0	7773 (98.29)	6260 (98.15)	1513 (98.89)	4.016	0.045*
M1	135 (1.71)	118 (1.85)	17 (1.11)		
Grade					
I/ II	5760 (72.84)	4599 (72.11)	1161 (75.88)	8.889	0.003*
III/ IV	2148 (27.16)	1779 (27.89)	369 (24.12)		
Surgery					
No	2259 (28.57)	1901 (29.81)	358 (23.40)	24.823	0.000*
Yes	5649 (71.43)	4477 (70.19)	1172 (76.60)		
Radiotherapy					
No/ unknown	3649 (46.14)	2909 (45.61)	740 (48.37)	3.772	0.052
Yes	4259 (53.86)	3469 (54.39)	790 (51.63)		
Chemotherapy					
No/ unknown	5104 (64.54)	4068 (63.78)	1036 (67.71)	8.331	0.004*
Yes	2804 (35.46)	2310 (36.22)	494 (32.29)		

Note: SPC: single primary OSCCs, MPC: OSCC-MPCs

as the oral cavity, pharynx, larynx, esophagus, and trachea (Cianfriglia et al., 1999; Jovanovic et al., 1994; Kramer et al., 2004; Levi et al., 1993; Liao et al., 2007; Shibuya et al., 1987). In this study, the highest SIRs for OSCC-MPCs were found in the oral cavity (SIR = 69.48), other oral cavity and pharynx (SIR = 55.46), pharynx (SIR = 39.21), tonsils (SIR = 33.52), trachea (SIR = 33.24), esophagus (SIR = 18.00), and larynx (SIR = 13.12). The mechanism of MPC is not clear, but field cancerization could explain the high risk of MPC subsequent to OSCC (Shibuya et al., 1987). MPC arise when multiple fields with similar epithelial cell populations are activated in the oral cavity, respiratory, and upper digestive tracts (Braakhuis et al., 2002; Jovanovic et al., 1994; Shibuya et al., 1987; Tabor et al., 2002). Cancer stem cells (CSCs) may also be involved in MPC progression. CSCs with stem-cell-like behavior in the adjacent mucosa may lead to MPC (Simple et al., 2015). Studies have demonstrated that long-term exposure to tobacco, alcohol, and areca nut could increase the risk for MPC in the oral cavity, respiratory, and upper

Table 2
Univariate and multivariate Cox regression analysis of risk factors of prognosis of OSCC-MPCs.

Variables	Univariate Cox regression analyses		Multivariate Cox regression analysis	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Age (years)	1.032 (1.025, 1.038)	0.000*	1.034 (1.027, 1.041)	0.000*
Sex				
Male	Reference			
Female	0.935 (0.807, 1.085)	0.377		
Site				
Lip	Reference		Reference	
Tongue	1.102 (0.827, 1.468)	0.508	1.064 (0.789, 1.436)	0.683
Floor of mouth	1.825 (1.336, 2.494)	0.000*	1.802 (1.309, 2.481)	0.000*
Gum and other mouth	1.614 (1.199, 2.174)	0.002*	1.281 (0.945, 1.737)	0.110
Number of MPC	1.015 (0.921, 1.119)	0.763		
T stage				
T1/ T2	Reference		Reference	
T3/ T4	1.938 (1.664, 2.256)	0.000*	1.766 (1.496, 2.085)	0.000*
N stage				
N0	Reference		Reference	
N1/ N2/ N3	1.262 (1.098, 1.450)	0.001*	1.250 (1.051, 1.487)	0.012*
M stage				
M0	Reference		Reference	
M1	1.905 (1.077, 3.369)	0.027*	1.458 (0.816, 2.602)	0.203
Grade				
I/ II	Reference			
III/ IV	1.033 (0.882, 1.211)	0.686		
Surgery				
No	Reference			
Yes	0.884 (0.753, 1.037)	0.129		
Radiotherapy				
No/ unknown	Reference		Reference	
Yes	1.211 (1.057, 1.388)	0.006*	1.014 (0.852, 1.207)	0.873
Chemotherapy				
No/ unknown	Reference			
Yes	1.037 (0.896, 1.200)	0.626		

Note: HR: hazard ratio, CI: confidence interval

digestive tracts, because they are common risk factors for these sites (Adel et al., 2016; Cianfriglia et al., 1999; Farshadpour et al., 2008; Gonzalez-Garcia et al., 2009; Hosokawa et al., 2018; Levi et al., 1993; Lin et al., 2020; Rodriguez-Bruno et al., 2011; Shibuya et al., 1987; Wynder et al., 1977). Both field cancerization and CSC theories imply susceptibility of the mucosal epithelium to cancer, and suggest that MPC are generated due to stimulation by these environmental carcinogens (Simple et al., 2015; Tabor et al., 2002).

In previous studies, the mean age of MPC patients was significantly higher than that of single primary OSCC patients (Hosokawa et al., 2018; Mochizuki et al., 2015). We also found that the age of MPC patients was higher ($P = 0.000$). Most studies suggested that males are more likely to develop MPC (Bugter et al., 2019; Choi & Thomson, 2020; Hosokawa et al., 2018; Kramer et al., 2004), but this has been contested (Mochizuki et al., 2015; Qaisi et al., 2014). We did not find any gender difference in MPC incidence. In agreement with our study, MPCs were more commonly reported in the gums and other areas of the mouth compared to single primary OSCC (Choi & Thomson, 2020; Liao et al., 2007; Mochizuki et al., 2015; Qaisi et al., 2014). MPCs were also positively related to early TNM stages and pathological grade ($P < 0.05$). This may be because patients with advanced OSCCs are more likely to die before the occurrence of MPC (Kramer et al., 2004; Rogers et al., 2019). Close follow-up of MPC patients aid early detection of multiple primary cancer in different sites.

Cianfriglia et al.,(Cianfriglia et al., 1999) Adel et al.,(Adel et al., 2016) and Liao et al.(Liao et al., 2007) reported poorer, while Kramer et al.(Kramer et al., 2004) reported better survival rates for MPC compared to single primary OSCC. Other studies have reported no significant differences in survival between MPC and single primary OSCC (Hosokawa et al., 2018; Kao et al., 2017). Gonzalez-Garcia et al.(Gonzalez-Garcia et al., 2009) and Mochizuki et al.(Mochizuki et al., 2015) showed different results over different follow-up periods. In this study, the short-term prognosis of MPC was better than that for single primary OSCC, while the long-term prognosis was worse. In our opinion, the difference in clinicopathological characteristics between MPC and single primary OSCC require the survival rates to be considered in layers. Most of the MPC occurred in conjunction with early stage primary OSCC, and was more likely to be treated surgically ($P = 0.000$). Because MPCs were involved in a wide range of sites, surgery was one of the best treatment options under the surgeon's management. Metachronous MPCs had a longer course of disease, patients may undergo multiple surgeries. Therefore, the prognosis might be better. However, with later occurrences of MPCs, the systemic burden of cancer increases and the patient's physical condition deteriorates rapidly, which lowers the survival rate significantly. While single primary cancer group had a higher short-term mortality rate because they included the patients who were detected at an older age and those with more advanced cancers, and the resulting shorter follow-up period probably lowered the chance of detecting multiple primary cancers.

We identified age, site, T-stage, and N-stage as risk prognostic factors for MPC. In fact, these clinical parameters were not only associated with the poor prognosis of MPC, but also associated with single primary OSCC. Male, radiotherapy, and non-surgical therapy have been reported as risk factors (Baxi et al., 2014; Choi & Thomson, 2020; Kramer et al., 2004; Liao et al., 2007; Qaisi et al., 2014), but no associations were found in this study.

This study summarized the clinical and prognostic features of MPC by analyzing data from the SEER database, including nine registries from 1975 to 2018. This is the largest report of MPC subsequent to OSCC to date. However, there were several limitations. First, the SEER database does not include data on oral potentially malignant disorders present before the OSCC. Oral leukoplakia, oral submucous fibrosis, oral lichen planus, and proliferative verrucous leukoplakia have shown associations with MPCs (Kramer et al., 2004; Liao et al., 2007; Lin et al., 2020; Qaisi et al., 2014). Second, the SEER database does not contain information about tobacco, alcohol, or areca nut use, which are correlated with the progression and prognosis of MPCs (Liao et al., 2007; Wynder et al., 1977). Furthermore, this study focused on the clinicopathological features of MPCs; the genetic susceptibility and molecular mechanisms of MPCs require further investigation. Braakhuis et al. (Braakhuis et al., 2002) suggested that only cancers with different molecular profiles could be classified as MPCs. Both clinical and molecular classifications are important for MPCs. Molecular profiles are expected to improve MPC diagnosis and prognostic predictions, and affect the prognosis itself (e.g., through screening high-risk populations and applying targeted therapy) (Braakhuis et al., 2002; Zhang et al., 2019). With the advancements and availability of genetic testing, more investigations will be conducted on the potential of MPC subsequent to OSCC patients, which may lead to specific management strategies (Gonzalez-Moles et al., 2013; Montebugnoli et al., 2014; Vogt et al., 2017). Future research on MPCs should focus on three areas: identifying MPCs at the first primary OSCC; distinguishing MPCs from recurrent/-metastatic OSCCs; and investigating potential therapeutic targets. This task cannot be accomplished through clinical research alone, basic research on MPCs is also required.

In this study, we summarized the clinical and prognostic features of

MPC and the comparison with single primary OSCC. These findings might contribute to the clinical management of OSCC and MPCs. There was a high ratio (19.35%) of patients with MPC in OSCC, and long-term survival rates declined consistently in MPC patients. Compared with MPCs, single primary OSCC was often found with an advanced TNM stage and grade, indicating that more attention was needed to the screening and treatment of early OSCC. While MPC was more common in the gum and floor of the mouth, and MPC in the floor of the mouth had a higher risk of mortality. Therefore, OSCC which occurred in the gum and floor of the mouth at initial clinic visit might need to be wary of the risk of multiple primary cancer in the future clinical examination.

5. Conclusion

MPCs subsequent to OSCC increase the risk of cancers in multiple sites and have a poor long-term prognosis. The prognosis of MPC is related to age, site, T-stage, and N-stage. Significant differences in clinical parameters were found between MPC and single primary OSCC, emphasizing the demand for early identification.

CRediT authorship contribution statement

Xinjia Cai: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Software, Visualization, Writing – original draft. **Jianyun Zhang:** Conceptualization, Data curation, Formal analysis, Investigation, Software, Visualization, Writing - original draft. **Fengyang Jing:** Conceptualization, Data curation, Formal analysis, Investigation, Writing - original draft. **Xuan Zhou:** Conceptualization, Data curation, Formal analysis, Investigation, Writing - original draft. **Heyu Zhang:** Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Supervision, Validation, Writing – review & editing. **Tiejun Li:** Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Supervision, Validation, Writing – review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.archoralbio.2023.105661.

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