

Multiple Primary Tumours in Oral Cancer: Patient Characteristics and Survival Patterns

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ABSTRACT

Background: The development of multiple primary tumours (MPTs) is an important consequence of oral cancer and one of the leading causes of mortality among these patients. This study aimed to identify some of the risk factors for MPT development in oral cancer patients and to examine its impact on survival rates.

Methods: In this retrospective, population-based cohort study, we retrieved administrative data from the Alberta Cancer Registry database for 3549 patients diagnosed with primary oral cancer (POC) between 2005 and 2020.

Results: Among these patients, 513 developed MPTs for an overall incidence of 14.5%. The average time interval for development of the first MPT was 4.04 ± 3.67 years. The proportion of patients with any comorbid conditions was significantly higher in MPT patients compared with non-MPT patients. Advanced age, average income, comorbidities including chronic obstructive pulmonary disease, diabetes and cardiovascular disease, and increased time from diagnosis to treatment were found to be potential risk factors for MPT development. Analysis revealed a sharp decrease in survival rate of oral cancer patients after developing MPTs. Furthermore, age >45 years, body mass index <18.5, synchronous tumours, stage III and IV POC, >2 comorbid conditions and MPT developing in the digestive system were associated with poor disease-specific survival.

Conclusion: The development of MPTs significantly affects the survival of oral cancer patients. Advanced age, comorbidities and delayed initiation of treatment were identified as key risk factors for MPTs. The poor survival outcomes, particularly in patients with synchronous tumours, advanced-stage primary cancers and specific comorbid conditions, highlight the need for early detection and proactive management strategies to mitigate these risks and improve long-term survival in this population.

Introduction

Oral cancer is a significant public health concern globally. It is the sixth most common cancer in the world, with an annual incidence of approximately 300 000 reported cases, about two-thirds of which are in developing countries.¹ According to the Canadian Cancer Society, more cases of oral cancer are diagnosed every year than ovarian or cervical cancer, and its average 5-year survival rate is only 64%.² Oral cancer is a broad term that includes 2 subcategories: oral cavity cancer (OCC) and oropharyngeal cancer (OPC). Despite the decline in tobacco consumption and a decreasing incidence of other head and neck cancers, the incidence of oral cancer has increased, mainly because of an increase in HPV-associated OPC.³ Patients with HPV-positive OPC have been found to be younger and present clinically with an advanced nodal stage; however, they respond

favourably to treatment and have better survival rates than patients with HPV-negative $\mbox{OPC.}^4$

According to an earlier study conducted in Alberta,⁵ 47.9% of patients diagnosed with oral cancer died, indicating a high mortality rate associated with oral cancer. The suggested reasons included late presentation of advanced disease and the risk of MPT development.⁶ MPTs are defined as the second, third, fourth or even more primary tumours and are not the same as residual/ recurrent tumours.⁷ To identify multiple primary tumours, SEER (surveillance, epidemiology and end results program) considers histologic findings, site, laterality and time since the diagnosis of the primary tumour.⁸ Population-based studies have documented



the incidence of MPTs in oral cancer patients ranging from 3% to 21%. 9

An overall poor prognosis and a significant decrease in 5-year survival rates from 69% to 32% have been documented in patients with MPTs compared with patients without MPTs.¹⁰ According to a Canadian study, the impact of MPTs on 5-year relative survival is greatest in bladder cancer (-2.4% age-standardized) followed by oral cancer (-1.9%).¹¹ Considering this significant effect of MPTs on the survival rate of oral cancer patients, this study aimed to identify risk factors of MPT development in oral cancer patients and to examine the survival rates of oral cancer patients with MPTs and associated factors. The findings will help inform health care professionals about the group of oral cancer survivors who are at higher risk for developing MPTs and help them carry out preventive strategies including close monitoring and follow-up appointments.

Materials and Methods

Study Population

Using a retrospective, population-based cohort design, we obtained data from the Alberta Cancer Registry (ACR) for Alberta residents diagnosed with primary oral cancer (POC) at age \geq 18 years between 2005 and 2020. The data were retrieved on 31 July 2020. The ACR, a population-based registry certified by the North American Association of Central Cancer Registries, maintains comprehensive data on all new cancer diagnoses and deaths in Alberta.

The location of oral cancers was based on the International Classification of Diseases for Oncology (3rd edition, ICD-O-3).¹² Patients with MPT were identified from the original cohort.

MPTs were defined according to Warren and Gates criteria.¹³ Patients who developed second, third, fourth or even more tumours were identified as patients with MPT. MPTs were categorized as synchronous if diagnosed within 6 months of the index tumour and metachronous if diagnosed later.

Data Extraction

Sociodemographic and Clinical Characteristics: Baseline demographics and clinical variables were gathered from patients' records. Demographic factors included age at diagnosis, gender, year of diagnosis, age at death, vital status and household income. Clinical characteristics included number of SPTs, duration of development of MPT from POC, site distribution of tumour according to ICD-O-3 grading,¹² tumour stage as reported in pathology reports according to the American Joint Committee on Cancer, 7th and 8th editions (AJCC 7 and AJCC 8)^{14,15} and history of medical conditions. Treatment modality factors included surgery, chemotherapy, radiation, immunotherapy and combinations of treatment.

The patients were then divided into 2 groups: patients with POC who developed MPTs and patients who did not develop MPTs. A comparative analysis was carried out to study the demographic and clinicopathological characteristics of both groups. Regression analysis was carried out to determine whether there was an association between risk factors and MPT development.

Outcome Variable (Survival): The vitality status of oral cancer patients was recorded as alive or deceased. The time from diagnosis of POC until date of death was used to calculate survival rate for patients with and without MPTs.

The survival period was up to 15 years if POC was diagnosed in 2005; however, the study endpoints consisted of 5-, 10- and 15-year overall survival rates based on the year of POC diagnosis. Disease-specific survival was calculated for 5 years, comparing the survival rates of patients who developed MPT to those who did not.

Statistical Analyses

Descriptive statistics for demographic and clinical characteristics for all patients and each group were computed. Categorical variables were summarized in frequency and percentages and numerical variables were expressed as mean ± standard deviation (SD) or median interquartile range (IQR) for each group. Comparisons of the demographic and clinical characteristics were made between MPT and non-MPT patients. Chi-squared tests and Fisher exact tests were employed where appropriate for categorical variables. For numerical variables, an independent Student t test was used. To determine the significant prognostic factors associated with the development of MPT, binary logistic regression was used at univariable and multivariable levels. The primary outcome measure was 5-year disease-specific survival. Kaplan-Meier survival curves were plotted to estimate the overall survival of patients with and without MPT. Unadjusted and adjusted hazard ratios were computed using Cox proportional hazard models to present the risk of death. Cox regression analysis is a specific regression model to evaluate the influence of multiple independent variables on survival time (a time to event outcome). Time from a start point (e.g., disease diagnosis) to an event (e.g., death due to the disease) is the main component of Cox regression models.

By using multivariable regression analyses, the relative odds ratios of MPTs for each possible related factor was estimated by adjusting for possible confounding variables. A p value < 0.05 was considered statistically significant. All statistical analyses were performed using statistical software SPSS v. 22.

Ethics Approval

This study was conducted with the approval of the Health Research Ethics Board of Alberta Cancer Committee (HREBA. CC-17-0370) and the University of Alberta. All data were fully anonymized to ensure patient confidentiality.



Results

Sociodemographic Characteristics

Records of 3549 POC patients between 2005 and 2020 were retrieved from the ACR database; 71.8% were males (**Table 1**). The patients were 18–97 years of age (mean 61 ± 12.5 years). Of the original cohort, 513 (14.5%) patients developed MPTs.

Comparative analyses showed no significant difference in gender distribution between MPT and non-MPT patients (p = 0.36); more males were in both MPT (69.8%) and non-MPT (71.8%) groups. For both groups, the average age at first diagnosis was 61 years (61 ± 12.5 and 61 ± 11.7 , respectively). There was no significant difference in body mass index (BMI) of patients in the 2 groups (p = 0.067). However, we found a significant difference in average annual income (p = 0.019): the largest proportion of non-MPT patients (47.2%) had an income >\$75 000, while the largest proportion of MPT patients (48.7%) reported an average income of \$45 000–75 000. No significant differences between MPT and non-MPT patients were found based on geographic location of diagnosis (p = 0.730).

Clinical Characteristics

Occurrence and Distribution of MPTs: Of the 513 patients with MPTs, 82.8% (n = 425) were diagnosed with 1 MPT 15.6% (n = 80) with 2 MPTs and 1.6% (n = 8) with more than 2 MPTs. It was observed that 77.9% of the MPTs were metachronous and 22.03% were synchronous. The mean time to occurrence of MPTs following the diagnosis of POC was 4.2 ± 3.8 years.

Of 3549 patients with POC, 1712 (48.2%) had OCC, while 1837 (51.8%) had OPC. The proportion of OCC patients who developed MPTs (53.4%) was slightly higher than that of OPC patients who developed MPTs (46.6%) (**Table 2a**). Of the primary OCC subsites in the study, tongue tumours (37.6%) showed a higher probability of developing MPTs followed by floor of mouth tumours (21.9%). Of the primary OPC subsites in the study, tonsil (48.7%) was the most predominant site to develop MPTs followed by base of tongue (37.6%). The most common site for development of MPT was the oral region (31.8%) followed by lung/bronchus (19.1%), digestive system (12.3%) and head and neck sites other than the oral region (11.3%). A similar pattern was observed for 3rd, 4th and 5th primary tumours (**Table 2b**).

History of Medical Conditions: The proportion of patients with any comorbid condition was found to be higher among those with MPTs (51.0%) compared with those without MPTs (40.0%). The most prevalent and statistically significant comorbid conditions in MPT patients were chronic obstructive pulmonary disease (COPD, 24.6%, p < 0.001), diabetes (18.7%, p 0.004) and cardiovascular disease (11.5%, p = 0.040) (**Table 3**).

Treatment Modalities: There was no significant difference between the type of treatment received for POC and development of

MPTs (p = 0.22). Surgery alone (57.0%) was the most common type of treatment among the entire cohort, followed by chemotherapy plus radiotherapy for both MPT (20.5%) and non-MPT patients (20.1%) (**Table 3**). Most patients received their first treatments within 3 months of POC diagnosis (58.1%). However, the mean time from diagnosis to treatment was slightly longer for MPT patients compared with non-MPT patients (2.27 vs. 2.19 months, p = 0.090).

Staging of Oral Cancer: According to the American Joint Committee on Cancer's staging manual, 7th edition (AJCC 7),¹⁴ most POC patients were at stage IV regardless of whether they developed MPT or not (51.6% and 61%, respectively). Based on AJCC 8,¹⁵ there was no significant difference between the 2 groups (p = 0.535; **Table 3**).

Regression Analysis

The univariable analysis identified the following factors to be significantly associated with an increased risk of MPT development: age > 45 years (p < 0.001); average annual income \$45 000-\$75 000 (p = 0.019); POC with 2 comorbid conditions (p < 0.001) including cardiovascular disease (p = 0.022), diabetes (p < 0.001) and COPD (p < 0.001); and increasing time from diagnosis to treatment (p < 0.001; **Table 4**). However, stage IV POC was found to be inversely associated with the development of MPT (p = 0.048).

After including the potential significant risk factors from univariable analysis in the multivariable model, all these variables retained their independent prognostic significance in the multivariable model.

Survival Analysis

Of 3549 oral cancer patients, only 1963 (55.3%) survived from 2005 to 2020. Those who survived did not develop a secondary tumour, were <45 years, had a BMI >18.5, had no underlying comorbid conditions and their POC was treated during stages I and II.

The 5-year disease-specific survival rate (DSS) for the entire cohort was 71%. The mean number of years of survival of patients after developing MPT was 5.7 (SD 3.8) years compared with 3.0 (4.7) years among non-MPT patients.

Kaplan-Meier Analyses

Kaplan-Meier analysis showed that patients who survived >5 years (9.7%) from the diagnosis of POC had a sharp decrease in 5-year DSS if they developed MPTs (from 70% to 47%, p = 0.004; **Figure 1**). Furthermore, patients with MPTs in the oral region had better DSS than those with MPTs in the digestive system (oral vs. digestive system: 68% vs. 52%, p = 0.001). The prognosis of MPT patients with synchronous and metachronous tumours was further analyzed. MPT patients with metachronous tumours had significantly higher survival rate than those with synchronous tumours (75% vs. 45%, p < 0.001; **Figure 2**).



Cox Regression Model

Univariable Analysis: Patients >45 years (p < 0.001), BMI <18.5 (p < 0.001) and annual income <\$75 000 (p < 0.001) were significantly associated with high risk of death. Patients >65 years had a 2-fold higher risk of death than patients ≤45 years (hazard ratio [HR] 2.9, Cl 1.9–3.7, p < 0.001). In addition, an increasing number of comorbid conditions was significantly associated with increasing risk of death. Furthermore, synchronous tumours (p < 0.001), site of POC (p = 0.002) and site of 1st MPT (p < 0.001) were high-risk prognostic factors for DSS in MPT patients. The HRs of MPT cancer stage III and IV were found to be significantly higher than stage I and II: HR 1.9, Cl 1.1–3.3, p = 0.027 and HR 2.3, Cl 1.5–3.7, p < 0.001, respectively (**Table 5**).

Multivariable Analysis: Further analysis showed that age >45 years and BMI <18.5 remained significant prognostic indicators of fatal outcome. Patients who had >2 comorbid conditions along with MPT showed a 3-fold increased risk of death (HR 4.3, Cl 0.9–20.8, p = 0.048). Similarly, patients with synchronous tumours had a higher risk of death than those with metachronous tumours (HR 2.6, Cl; 1.7-4.1, p < 0.001). In the multivariate model, no POC site remained significant in terms of predicting risk associated with MPT; however, the digestive system as an MPT site remained significant (HR 2.1, Cl 1.3–3.5, p = 0.040). In addition, patients with stage III and IV POC and MPTs also remained highly significant as the predictor of death: HR 2.1, Cl 1.09–3.9, p = 0.025 and HR 2.6, Cl 1.5–4.3, p < 0.001, respectively (**Table 5**).

Discussion

This population-based retrospective study revealed that 14.5% of oral cancer patients developed MPTs. The incidence of MPTs in previous studies of other populations has been reported to range from 11% to as high as 27%, which is comparable to this study.^{16–18} In this study, most patients developed MPTs, on average 4.04 years after the diagnosis of POC. This finding is similar to previous studies that reported an average time of 4.5 and 4.7 years until the development of MPTs.^{19,20} It is apparent that patients at risk may develop secondary tumours long after the presentation of primary tumours, thus supporting the need for long-term follow-up and continuous monitoring after treatment to improve the prognosis of the disease.²¹

Our study included more males in both MPT and non-MPT groups, with a mean age of 61 years, which is consistent with other reports in the literature.22 However, studies from the Untied States have reported older females to be more affected with MPTs, possibly because the patients groups were smaller.^{23,24}

Our study demonstrated that lower income may play a role in the risk of developing MPTs. A lower income could be linked to greater

exposure to risk factors, delayed diagnosis and suboptimal treatment outcomes, potentially leading to a higher incidence of MPTs.

In this study, most MPTs were seen in patients with tongue and tonsil tumours. Moreover, MPTs were predominant in the oral region, involving tongue and floor of the mouth, followed by lungs and digestive system. These findings may support the concept of "field cancerization," which refers to the presence of genetically and molecularly altered epithelium in the tissues surrounding the primary tumour. ²⁵ The molecular mechanisms of OCC and OPC differ significantly. OCC typically involves carcinogen-induced genetic changes, whereas OPC, especially when linked with HPV, involves inactivation of tumour suppressor proteins including p53 and Rb (retinoblastoma), through expression of viral oncoproteins E6 and E7 respectively. These differences highlight that field cancerization should be considered separately for each site, as the molecular drivers vary. In addition, field cancerization is influenced by environmental, genetic and viral factors that differ across tumour types and tissues.²⁶ Therefore, it is essential to account for these site-specific and tumourspecific factors when considering field cancerization.

Previous studies have reported that smoking and/or drinking alcohol increases the development of MPTs by 25 times or more.²⁷ However, other studies have found little or no relation between smoking or alcohol use and MPT development. For example, Mochizuki et al.²¹ reported MPTs more frequently in non-smokers, suggesting a genetic or other underlying association. Because of limited information related to smoking and alcohol habits among our patient group, a causal relation could not be established in this study.

In our study, the entire cohort was at an advanced stage of POC, with stage IV the most common at the time of diagnosis. Regression analysis showed that stage was inversely associated with MPT development. This could be because of poor survival of oral cancer patients at an advanced stage of the disease, therefore, not allowing for further tumour development.

This study demonstrated a positive correlation between development of MPTs and existing comorbid conditions, including COPD and diabetes. Various epidemiologic and clinical studies have reported a correlation between increased incidence of oral cancer and diabetes mellitus.²⁸ It has been suggested that long-term exposure to high glucose concentrations causes predisposure to upregulation of oncogenic pathways leading to malignancy.²⁹ Experimental studies on mice also supported the idea that diabetes mellitus facilitated oral tumourigenesis because of various underlying cellular and molecular mechanisms.³⁰ Therefore, oral cancer patients who have an associated comorbid condition must be closely monitored to allow early diagnosis of secondary tumours.

In our study, no significant association was found between the type of treatment received for POC and the development of MPTs. Surgery



alone was the most common type of treatment received in the entire cohort, followed by combined chemotherapy and radiotherapy for both non-MPT and MPT patients. These results are consistent with another study showing that surgery alone was carried out in 65% of cases, followed by a chemotherapy plus radiotherapy regime.21 Kramer et al. ³¹ also reported >50% of patients treated by surgery alone. Although surgery is the most common type of treatment for oral cancer patients, ensuring negative surgical margins does not fully eliminate the risk of development of MPT.^{32,33} This further supports the concept of field cancerization of oral mucosa, in that even after complete excision of the primary tumour, new MPTs may develop in the condemned mucosa because of genetically altered epithelial cells distant from the surgical site.³⁴

Our study demonstrated that oral cancer patients who had a survival rate >5 years from the diagnosis of POC, showed a sharp decrease in DSS after developing MPTs. Similarly, other studies have also found a significant decrease in survival rate in oral cancer patients who developed MPTs.^{10,21,35} This could be a result of challenges in diagnosing and treating an additional malignancy because of scar formation from previous surgical treatment of POC.³¹ Moreover, the histopathologic subtypes of MPTs can significantly influence survival outcomes, as different tumour types exhibit varying biological behaviours, treatment responses and prognoses. MPTs often present as squamous cell carcinomas (the most common subtype) or as malignancies arising from other epithelial origins, such as adenocarcinomas. The identification and classification of these subtypes enable clinicians to stratify patients more accurately, tailoring treatment plans to specific molecular and histologic profiles, ultimately improving survival outcomes.³⁶ Thus, a detailed understanding of histopathologic subtypes is essential for predicting survival and guiding therapeutic decisions regarding MPTs.

Our findings that patients >45 years and BMI <18.⁵ had an increased risk of death are similar to previous studies.⁵ However, it is noteworthy that BMI was recorded at the time of initial treatment of POC and not at the time of diagnosis. Furthermore, risk of death associated with synchronous tumours was higher than for metachronous tumours, which is supported by previous studies.^{37,38} This could be because of presentation of synchronous tumours at a more advanced stage (III or IV) compared with metachronous tumours or because of limited treatment options for additional malignancy.38 Panosetti et al.³⁹ also reported that the prognosis for synchronous tumours worsens if the treatment plan has to be modified because of the occurrence of second primary tumour.

Our study revealed a 3-fold increase in risk of death in MPT patients who had associated comorbid conditions. Previous studies focusing on breast, lung and colorectal cancer reported similar trends.^{40–42} Suboptimal treatment of cancer patients with comorbidities, along with chances of development of postoperative complications, may be some of the causes of lower survival rates in such patients.⁴³

We also found that the site of an SPT played a significant role in survival. Although the incidence of SPTs was higher in the oral region than in distant sites, survival rate was worse in patients who developed SPTs in lungs and esophagus. Similar results of negative impact on survival rates of oral cancer patients were reported by Chen et al.⁴⁴ and Dequanter et al.⁴⁵ These findings suggest that regular screening for lung and esophageal MPTs during the follow up of oral cancer patients might provide a health benefit.

Our findings that higher stage of oral cancer was closely associated with lower DSS are consistent with previous literature.⁴⁶ Therefore, early detection of a developing tumour is very important to improve the patient's prognosis.

This study has several limitations. Because it relied on historical patient records, some baseline information was missing that would have been valuable, such as tobacco and alcohol use, which are known to increase the risk of a second primary cancer. Incomplete information about Tumour, Node, Metastasis (TNM) staging also limited our ability to fully understand the differences in clinical profiles and disease outcomes between groups. In addition, the registry database lacks detailed categorization or stratification of comorbid conditions between OCC and OPC patients, which could have provided further insights. Moreover, as the data were extracted from an administrative database, there is a risk of omission or inaccuracies due to human error during data entry.

Despite these limitations, our study, based on a comprehensive provincial database, remains valuable and serves as a foundation for future research on specific morbidities. The breadth of the data provides significant insights into oral cancer trends and offers a starting point for more focused investigations. To build on these findings, future research could benefit from merging multiple databases to gain a deeper understanding of MPT in the context of field cancerization. This approach would enable the inclusion of associated risk factors, such as lifestyle habits and environmental exposures, leading to a more nuanced understanding of MPT development. In addition, incorporating detailed clinical staging in future studies would help clarify the differences between POC and MPT in terms of disease progression and survival outcomes. This would offer a clearer picture of how these conditions vary and impact patient prognosis. Furthermore, expanding the research to a nationwide scale by integrating provincial databases across Canada could provide a more comprehensive view of MPT and oral cancer. Such a study would enhance the generalizability of findings and contribute to the development of national strategies for prevention and management, thereby improving our understanding and approach to these conditions on a broader scale.



Table 1: Comparison of the demographic characteristics of oral cancer patients with and without multiple primary tumours (MPTs).

	No. patients (%)				
Characteristics	Without MPTs n = 3036	With MPTs $n = 513$	Total n = 3549	p *	
Gender				0.360	
Male	2179 (71.8)	358 (69.8)	2537 (71.5)		
Female	857 (28.2)	155 (30.2)	1012 (28.5)		
Age at diagnosis, years				<0.001	
≤45	288 (9.5)	19 (3.7)	307 (8.7)		
46–65	1776 (58.5)	305 (59.5)	2081 (58.6)		
>65	972 (32.0)	189 (36.8)	1161 (32.7)		
Mean ± SD	61 ± 12.6	61 ± 11.7	61 ± 12.5	0.130	
Body mass index				0.067	
Underweight <18.5	124 (4.1)	21 (4.1)	145 (4.1)		
Normal range <18.5–24.9	859 (28.3)	172 (33.5)	1031 (29.1)		
Overweight 25–29.9	925 (30.5)	161 (31.4)	1086 (30.6)		
Obese ≥30	685 (22.6)	131 (25.5)	816 (23.0)		
No data available†	443 (14.6)	28 (5.5)	471 (13.3)		
Average annual income, \$				0.019	
<45 000	292 (9.6)	40 (7.8)	332 (9.4)		
45 000–75 000	1310 (43.1)	250 (48.7)	1560 (44.0)		
>75 000	1433 (47.2)	216 (42.1)	1649 (46.5)		
No data available†	1 (0.0)	7 (1.4)	8 (0.2)		
Diagnosis location				0.730	
Southern Alberta	229 (7.5)	44 (8.6)	273 (7.7)		
Calgary	1147 (37.8)	184 (35.9)	1331 (37.5)		
Central Alberta	384 (12.6)	69 (13.5)	453 (12.8)		
Edmonton	959 (31.6)	157 (30.6)	1116 (31.4)		
Northern Alberta	317 (10.4)	54 (10.5)	371 (10.5)		
No data available†	0 (0.0)	5 (1.0)	5 (0.1)		

Note: SD = standard deviation.

* X² test or Fisher exact test, as appropriate.

† Not considered when applying X² or Fisher exact test.



Table 2a: Sites of multiple primary tumour (MPT) development for various oral cancer locations.(MPTs).

	No. patients (%)				
Location of oral cancer	Without MPTs n = 3036	With MPTs <i>n</i> = 513	Total n = 3549	p *	
000	1438 (47.4)	274 (53.4)	1712 (48.2)	0.002	
Floor of mouth	185 (12.9)	60 (21.9)	245 (14.3)		
Gum	132 (9.2)	31 (11.3)	163 (9.5)		
Lip	49 (3.4)	9 (3.3)	58 (3.4)		
Mouth, other and unspecified	236 (16.4)	49 (17.8)	285 (16.7)		
Palate	136 (9.5)	22 (8.0)	158 (9.2)		
Tongue, other and unspecified	700 (48.7)	103(37.6)	803 (47.0)		
OPC	1598 (52.6)	239 (46.6)	1837 (51.8)	0.011	
Base of tongue	591 (37.0)	90 (37.6)	681 (37.0)		
Lip, oral cavity and pharynx, other and unspecified	28 (1.8)	4 (1.8)	32 (1.7)		
Oropharynx	201 (12.6)	28 (11.7)	229 (12.5)		
Tonsil	778 (48.7)	117 (48.7)	895 (48.7)		

Note: OCC = oral cavity cancer, OPC = oropharyngeal cancer.

* X² test.

Table 2b: Distribution of 2nd, 3rd, 4th and 5th multiple primary tumours (MPTs) by site.

	No. patients who developed MPTs (%)			
Site of MPT	Second (<i>n</i> = 513)	Third (<i>n</i> = 80)	Fourth (<i>n</i> = 6)	Fifth (<i>n</i> = 2)
Oral cancer	163 (31.8)	27 (33.8)	3 (50.0)	
Head and neck	58 (11.3)	8 (10.0)		
Digestive system	63 (12.3)	8 (10.0)		
Lung/bronchus	98 (19.1)	22 (27.5)	1 (16.7)	1 (50.0)
Breast	10 (1.9)	1 (1.25)		
Female genital	4 (0.8)			
Male genital	42 (8.2)	3 (3.8)	1 (16.7)	
Urinary system	20 (3.9)	1 (1.3)	1 (16.7)	
Lymphatic/hematopoietic	31 (6.0)	6 (7.5)		
Skin	7 (1.4)	1 (1.3)		
Other	10 (2.0)			1 (50.0)
Unknown primary	7 (1.4)	3 (3.8)		

* X² test.



Table 3: Clinical characteristics of primary oral cancer patients with and without multiple primary tumours (MPTs).

	No. patients (%)			
Observatoriation	Without MPTs	With MPTs	Total	s sk
	11 = 3030	11 = 513	11 = 3349	p.
		50 (3 1 E)		0.040
Cardiovascular disease	254 (8.4)	59(11.5)	313 (8.8)	0.040
Diabetes	406 (13.4)	96 (18.7)	502 (14.1)	0.004
Renal failure	119 (3.9)	22 (4.3)	141 (4.0)	0.560
Chronic obstructive pulmonary disease	458 (15.1)	126 (24.6)	603 (16.6)	<0.001
Cerebrovascular disease	281 (9.3)	41 (8.0)	322 (9.1)	0.370
Other	167 (5.5)	26 (5.1)	193 (5.4)	0.540
Type of treatment†				0.22
Surgery	741 (24.4)	167 (32.6)	908 (25.5)	
Radiotherapy	244 (8.0)	32 (6.2)	276 (7.6)	
Chemotherapy	4 (0.1)	1 (0.2)	5 (0.1)	
Surgery + chemotherapy + radiotherapy + immunotherapy	1 (0.0)	1 (0.2)	2 (0.1)	
Surgery + chemotherapy + radiotherapy	379 (12.5)	77 (15)	456 (12.8)	
Surgery + chemotherapy	3 (0.1)	0 (0.0)	3 (0.1)	
Chemotherapy + radiotherapy	623 (20.5)	103 (20.1)	726 (20.4))	
Surgery + radiotherapy	409 (13.5)	83 (16.2)	492 (13.8)	
Chemotherapy + radiotherapy + immunotherapy	4 (0.1)	1 (0.2)	5 (0.1)	
Radiotherapy + immunotherapy	40 (1.3)	7 (1.3)	47 (1.3)	
Surgery + immunotherapy	1 (0.0)	0 (0.0)	1 (0.0)	
Surgery + radiotherapy + immunotherapy	9 (0.3)	1 (0.2)	10 (0.3)	
No treatment	578 (19.0)	133 (26)	711 (20)	
Duration from diagnosis to treatment, months				0.260
0-3	1738 (57.3)	325 (63.3)	2063 (58.1)	
3-6	652 (21.5)	131 (25.5)	783 (22.1)	
6–12	65 (2.1)	16 (3.1)	81 (2.2)	
Staging of oral cancer	Without MPTs (<i>n</i> = 3036)	With MPTs (<i>n</i> = 513)		p
AJCC 7±				0.005
	315 (12.9)	80 (17.2)		
II	178 (7.3)	41 (8.8)		
III	212 (8.7)	48 (10.3)		
IV	1482 (61.0)	240 (51.6)		
Unknown	241 (9.9)	56 (12.0)		
AJCC 8‡				0.535
1	177 (29.1)	14 (29.2)		
II	86 (14.1)	10 (20.8)		
111	90 (14.8)	9 (18.7)		
IV	130 (21.3)	7 (14.6)		
Unknown	125 (20.5)	8 (16.7)		

Note: * X² test or Fisher exact test, as appropriate.

† Combination of treatments for primary oral cancer received by MPT and non-MPT patients.

 \ddagger AJCC 7 and 8 are the 7th and 8th editions of the American Joint Committee on Cancer staging manuals.^{ref}



Table 4: Risk factors associated with MPT development based on results of logistic regression analyses.

Variable	Odds ratio (95% CI)	p	Odds risk ratio (95% CI)	p
Age at diagnosis, years				
46–65	2.4 (1.5-3.7)	<0.001	2.3 (1.4-3.9)	<0.001
>65	2.6 (1.7-4.1)	<0.001	2.4 (1.4-4)	<0.001
Average annual income, \$				
45 000–75 000	1.2 (1-1.4)	0.019	1.2 (1-1.4)	0.051
Comorbid conditions				
1	1.4 (1.2-1.7)	<0.001		
2	1.8 (1.4-2.3)	<0.001	1.4 (0.3-1.8)	0.005
Cardiovascular disease	1.3 (1-1.7)	0.022	1.4 (1-1.9)	0.056
Diabetes	1.4 (1.1-1.7)	<0.001	1.4 (1.1-1.9)	0.009
COPD	1.6 (1.4-2)	<0.001	1.7 (1.3-2.1)	<0.001
Time from diagnosis to treatment, months				
3–6	2.4 (1.8-3.3)	<0.001	3.7 (2.1-6.7)	<0.001
6–12	2.6 (1.8-3.6)	<0.001	3.8 (2.1-7)	<0.001
Cancer stage				
IV	0.68 (0.6-1)	0.048	0.8 (0.6-1)	0.048

Note: CI = confidence interval, COPD = chronic obstructive pulmonary disorder.

 Table 5: High risk factors affecting disease-specific survival of oropharyngeal cancer patients who developed multiple primary tumours (MPTs).

Variable	Hazard ratio (95% CI)	p	Adjusted hazard ratio (95% CI)	D
Age at diagnosis, years				
46-65	1.8 (1.3–2.5)	<0.001	1.6 (1.2-2.2)	<0.001
>65	3.2 (2.4–4.4)	< 0.001	2.9 (1.9-3.7)	<0.001
BMI				
Underweight <18.5	2.5 (1.8–3.6)	<0.001	2.2 (1.2-2.9)	<0.001
Normal range 18.5–24.9	1.6 (1.2–2.0)	0.001	· ·	
Average annual income, \$				
<45 000	1.8 (1.5–2.3)	<0.001		
45 000–75 000	1.4 (1.2–1.6)	<0.001		
No. comorbid conditions				
1	1.7 (1.4–1.9)	<0.001		
2	2.1 (1.7–2.5)	<0.001	2.3 (1.6–3.3)	0.021
>2	2.2 (2.7-4.1)	<0.001	3.2 (1.8–5.3)	0.048
COPD	2.0 (1.7–2.3)	<0.001		
Time to MPT				
Synchronous vs. metachronous	3.1 (2.3–4.2)	<0.001	2.6 (1.7-4.1)	<0.001
Site of primary oral cancer				
Base of Tongue	2.1 (1.4–4.7)	0.002		
Oropharynx	2.7 (1.3–2.3)	0.004		
Tonsil	1.3 (0.6–2.3)	0.028		
Site of 1st MPT				
Digestive system	2.1 (1.2–3.5)	0.003	2.1 (1.3–3.6)	0.048
Lung/bronchus	2.0 (1.3–3.1)	0.001		
Cancer stage				
III	1.9 (1.1–3.3)	0.027	2.1 (1.1–3.9)	0.025
IV	2.3 (1.5–3.7)	< 0.001	2.6 (1.5-4.3)	<0.001
Unknown	1.9 (1.1–3.2)	0.016	2.5 (1.3-4.6)	0.003

Note: AHR = adjusted hazard ratio, CI = confidence interval, COPD = chronic obstructive pulmonary disorder.



J Can Dent Assoc 2025:91:p7 May 26, 2025





Figure 2: Survival analysis by time to first multiple primary tumour.





Multiple Primary Tumours in Oral Cancer: Patient Characteristics and Survival Patterns

were significant predictors of higher mortality, underscoring

the need for targeted management strategies for these high-risk

individuals. To optimize disease-specific survival and reduce

treatment burden and mortality rates, early detection of SPTs

is crucial. Patients should be informed about the possibility of secondary tumours at discharge and reassured that early detection

and treatment can improve outcomes. Regular monitoring and

follow-up appointments are essential, as is close collaboration

between primary and secondary health care providers to ensure

J Can Dent Assoc 2025:91:p7 May 26, 2025

Conclusion

The study identified several key risk factors for the development of MPT in oral cancer patients, including being >45 years, having an average income, multiple comorbid conditions and a longer interval between diagnosis and treatment. Conversely, stage IV POC was linked to a lower risk of MPT. Survival analysis revealed that patients with MPT had a shorter mean survival compared with those without MPT, with an overall 5-year DSS rate of 71% for the cohort. MPT patients, particularly those with tumours in the digestive system or with synchronous tumours, had poorer survival rates. Older age, low BMI, multiple comorbid conditions and synchronous MPT

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