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

By

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Abstract

Background: Multiple Primary Tumor (MPT) development is an important consequence of oral cancer and one of the leading causes of mortality among these patients. Patients with MPTs are usually excluded from cancer registries analyses, which can lead to biased comparisons of survival and clinical characteristics of patients.

Objectives: To identify the risk factors of MPT development in oral cancer patients and to examine the survival rates of oral cancer patients with MPTs and its associated factors.

Methods: This retrospective cohort study included patients diagnosed with primary oral cancer between 2005 and 2020 who were 18 years of age or older at diagnosis and lived in Alberta. Data was obtained from the Alberta Cancer Registry database. The inclusion and exclusion criteria were applied to filter the records. Patients were divided into two groups: 1) patients with primary oral cancer (POC) who developed a second primary tumor, and 2) patients with primary oral cancer who did not develop a second primary tumor. The records of the patients were then thoroughly screened to identify the demographic and clinical variables for each patient. The outcome measure was the survival status of oral cancer patients with MPTs. The collected data was analyzed using SPSS software by using Pearson's Chi-square, Fischer's Exact, Kaplan-Meier curves and univariate and multivariate regressions.,

Results: Of 3549 patients diagnosed with primary oral cancer during the study period, 513 patients developed MPTs with an overall incidence of 14.5%. Among them, 82.8% (n= 425) were diagnosed with one MPT, 15.5% (n=80) with two MPTs, and 1.5% (n=8) with three or more MPTs. The mean (SD) age at first diagnosis was 61.0 (12.5) years. The majority of MPT tumors were metachronous (78.0%) and the average time interval of development of MPT was 4.04±3.67 years.

Advanced age and average income between 45,000 – 75,000 were found to be predominant risk factors to develop MPT in POC patients. However, the proportion of comorbid conditions was significantly higher in MPT patients (52.0%) as compared to non-MPTs (40.02%).

MPTs were most prevalent in those with oral cavity cancer (OCC) as primary tumors, out of which tongue (37.6%) was the most common site followed by floor of the mouth (21.9%). The most common secondary tumor sites were oral region (31.8%) followed by lung/bronchus (19.1%) and digestive system (12.3%). The mean duration from diagnosis to treatment in MPT patients was slightly longer than that in non-MPT patients (2.27 vs 2.19 months, p value < 0.001).

The Kaplan-Meier survival analysis revealed a sharp decrease in survival rate of oral cancer patients after developing MPTs (from 70% to 47%, p = 0.004). In the multivariate Cox-regression analyses, age (>65-year), number of comorbid conditions, synchronous tumors, and MPT site (digestive system) were found to be significantly associated with an increased risk of death. The hazard of death was found more than twice in patients older than 65 with reference to the patients who were 45 years or younger [HR; 2.9, CI; 1.9,3.7, p < 0.001].

Conclusions: This study reported the occurrence of MPTs in patients with primary oral cancer and their survival rate. Oral cancer patients with an advanced age and associated co-morbid conditions were more likely to develop MPTs. Patients with MPTs had higher mortality rate than the non-MPT patients. Age, BMI, number of comorbidities and MPT site including digestive system and lungs were identified as independent prognostic factors. Long-term follow-ups and close monitoring are necessary for oral cancer patients to diagnose the occurrence of MPTs in due time to improve the prognosis of the disease.

Preface

This thesis is an original work of Salima Asifali Sawani. The research project, of which this thesis is a part, received research ethics approval from the University of Alberta Research Ethics Board under the project named: “Multiple Primary Tumors in Oral Cancer: Patient Characteristics and Survival Patterns”, No. Pro0009687, July 2019.

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1 Chapter One: Introduction

In this chapter, I will briefly describe the definition, clinical staging, and prognosis of oral cancer. I will then discuss the incidence of Multiple Primary Tumors (MPTs) in oral cancer patients, its epidemiological characteristics, and ways of reporting MPTs. Next, I will present the problem statement, followed by the research objectives.

1.1 Oral cancer

1.1.1 Definition

Squamous cell carcinoma (OSCC) is defined as a malignant tumor that originates in the stratified squamous epithelium (Chow, 2020). It is the most common malignant tumor of the head and neck region and accounts for approximately 90% of all malignancies in oral cavity (Chow, 2020). There are multiple terms used interchangeably for oral cancer including, Oral Cavity Cancer (OCC), Oropharyngeal Cancer (OPC), Oral Squamous Cell Carcinoma (OSCC), Oral Malignancy and Oral Malignant Tumors.

Oral cancer (OC) itself is a broad term that includes two subcategories: Oral Cavity Cancer (OCC) and Oropharyngeal Cancer (OPC). Anatomically, the boundary of oral cavity begins at the border of the wet and dry mucosa of the upper and lower lips and extends to the anterior tonsillar pillars, the circumvallate papilla and the junction of the hard and soft palate. The oral cavity comprises of buccal mucosa, wet mucosal surfaces of the lips, dental alveolar structures, floor of mouth, oral tongue, and hard palate. The oropharynx is defined by its boundary with the oral cavity anteriorly, the extension of the soft palate to the posterior pharyngeal wall posteriorly superiorly, and the

plane of the hyoid inferiorly. The oropharynx includes the palatine tonsils, the base of the tongue and lingual tonsils, and the lateral and posterior pharyngeal walls between the soft palate and hyoid bone (Madani et al., 2014). In this study, oral cancer is defined according to the International Classification of Disease for Oncology, third edition, in adherence to the 10th version (ICD-10) including Topographical Codes-C00-C06, C09-C10 and C14: malignant neoplasm of oral cavity and oropharynx.

1.1.2 Clinical staging

The American Joint Committee on Cancer (AJCC) based on the tumor, node, metastasis (TNM) staging system facilitates the oncologists and clinicians to define the disease status and prognosis of the disease and plan the treatment accordingly. The first edition of TNM classification was published in 1977 and has been widely used since then with newer editions over the years. (Yarbro et al., 1999). The three categories in TNM refers to:

T: Size of tumor and extent of spread into surrounding structures

N: Regional lymph node involvement.

M: Presence or absence of distant metastasis.

Based on the extension of the disease, the status of patient is staged as I, II, III or IV. A recent modification was made in the AJCC staging system by the AJCC Head and Neck Cancer task force group, which took effect on January 1, 2018 and was published as the 8th edition of AJCC staging system (Lydiatt et al., 2018). The major modifications in the 8th edition include:

1. Incorporation of depth of invasion in the T category for oral cavity cancer.
2. Introduction of new staging system for Human papillomavirus positive (HPV+) OPC.

3. Addition of separate clinical and pathologic staging system for (HPV+) OPC.
4. Inclusion of extra nodal extension (ENE) in N staging for all head and neck cancers except nasopharynx and high-risk HPV+OPC.

1.1.3 Incidence and prognosis

Oral cancer (OC) 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, two-thirds of them in the developing countries (Sung et al., 2021). It is expected that by 2035, there will be an increase in number of OC cases from 300,000 to ~ 500,000 (+65%). It is more alarming that ~ 115,000 OC cases currently diagnosed in an elderly population (<65 years) are expected to double (+104%) in the next 20 years (Sung et al., 2021). Despite the decline in tobacco consumption and decreasing incidence of other head and neck cancers, the incidence of oral cancer has increased mainly due to an increase in HPV associated oropharyngeal cancers (Ang & Sturgis, 2012). Patients with HPV positive OPC have been found to be younger and present clinically with an advanced nodal stage; however, they respond favorably to the treatment and have better survival rates than patients with HPV negative OC (Ang et al., 2010). According to the Canadian Cancer Statistics Society, it is anticipated that in 2022 about 7,500 Canadians will be diagnosed with new oral cancer cases, out of which 2,100 will die. Furthermore, it is also reported that more cases of oral cancer are diagnosed every year than ovarian or cervical cancer, with an average 5-year survival rate of 64% (Canadian Cancer Society, 2022a).

Out of all the provinces of Canada, Alberta is positioned as the fourth for oral cancer incidence and related death prevalence (Canadian Cancer Society, 2022b). The previous studies conducted in Alberta, reported 45.2% of OCC and 82.4% of OPC cases with 47.9% mortality rates (Badri et al., 2021). The reasons for this low survival rate have been suggested to be due to late presentation

of advanced disease and the risk of multiple primary tumour (MPT) development (Glicksman & Fulton, 2013).(Cancer Centre, 2018)

1.2 Multiple Primary Tumors (MPT)

1.2.1 Definition

MPTs are defined as the second, third, fourth or even more primary tumors and are not the residual/recurrent tumors (Zhai et al., 2018). At a molecular level, MPTs are independent tumors and are not related to recurrences and metastasis of primary or index tumors. There are several terms used interchangeably in the literature for MPTs including second primary cancer/tumor (SPT) or secondary cancer, tertiary primary tumor, multiple primaries, or multiple primary cancer. Different rules are used by registries to differentiate between primary cancer and those that are an extension of an existing cancer. Over time, the definition of MPT has changed and therefore differs in the literature.

1.2.2 Reporting

The two commonly used methods for reporting MPTs are 1) Surveillance Epidemiology and End Results (SEER) program, which is mainly used by North American cancer registries, and 2) International Association of Cancer Registries and International Agency for Research on Cancer (IACR/IARC), which is mainly used internationally. To identify multiple primary tumors, SEER considers histology, site, laterality and time since the diagnosis of the primary tumor (Surveillance System Branch, 2012). To abstract a tumor as a multiple primary, there are following rules laid out by SEER Head and Neck tumor board which were updated in September 2021 (National Cancer Institute, 2021). According to the rules, multiple primaries are abstracted when:

a) There are separate tumors in any two of the following sites:

- Hard palate and/or soft palate and/or uvula
- Maxilla and mandible
- Maxillary sinus and/or ethmoid sinus and/or frontal sinus and/or sphenoid sinus
- Nasal cavity and middle ear
- Upper gum and lower gum
- Upper lip and lower lip

b) Separate tumors present in the sites with ICD-0 site codes that differ at the second CXxx and/or third CxXx characters.

c) Separate tumors are on both right and left side of a paired site.

d) The patient has a subsequent tumor after being clinically disease free for 5 years from the initial diagnosis.

e) The patient has separate tumors in oral cavity, oropharynx, nasal cavity, nasopharynx, salivary glands, maxilla and mandible, ear, larynx and middle ear, pyriform sinus, larynx, hypopharynx, trachea and parapharyngeal space.

For all the above rules, timing and histology of the tumor is irrelevant. However, IACR/IARC registers only one tumor for an organ, irrespective of time; unless there are histological differences ("International rules for multiple primary cancers," 2005). Furthermore, the definition of MPTs has also been documented by different authors and the most used in the literature is the one proposed by Warren and Gates (Warren S, 1932). The criteria for diagnosis of multiple primary tumors defined by Warren and Gates are as follows:

I. Each tumor must be diagnosed as malignant histologically.

II. Each tumor must be anatomically and histologically distinct and separated by normal tissue (at least 2cm).

III. The possibility of a second tumor representing metastasis from index tumor must be excluded.

There are some controversies regarding the correct reporting of MPT. The Warren and Gates criteria was later revised by Hong et al (Hong et al., 1990) which has been adopted by most of the researchers. According to the clinical criteria proposed by Hong et al, when the two neoplastic lesions show same histologic type, the lesion is defined as MPT if they are located at a distance more than 2 cm from each other or if the second lesion occurred more than three years after the index tumor. Controversies exist on the minimum distance between the two tumors. While Hong et al proposed a 2 cm distance, Scholes et al (Scholes et al., 1998) proposed a 1.5 cm distance, and Tabor et al (Tabor et al., 2002) a 3 cm distance between the two tumors. Leong et al on the other hand, considered only temporal criteria (Leong et al., 1998). Although histopathological criteria are the most reliable method for discriminating the lesions, most squamous cell carcinomas show similar morphology.

1.2.3 Epidemiology/Incidence

The incidence of MPTs after the treatment of patients' primary cancers have increased over the past decades (Liu et al., 2013). There are multiple factors responsible for the increased frequency of MPTs including improved diagnostic testing and screening of oral cancer patients along with advanced treatment modalities (Hamadah et al., 2010). Population-based studies have documented different incidence rates of MPTs in oral cancer patients, which has been reported from 3-21% (Lubek & Clayman, 2012). The occurrence of a second primary tumor at a particular site is

associated with some risk factors. For example, patients who develop oral cancer due to betel nut chewing, are more likely to develop a second primary tumor in their oral cavity (Warnakulasuriya et al., 2003). However, there are patients who continue to develop second primary tumors without any associated risk factors. The frequency of developing MPT increases as patients live longer and survival improves. It has been estimated that 1 in 4 patients have a chance of developing a second primary tumor (SPT) after treatment (Mariotto et al., 2014).

The relative risk for developing MPTs is greater in younger individuals with positive family history and Caucasian ancestry, those who continue smoking and alcohol consumption after therapy, and those who were treated with radiotherapy alone or treated after 1990 as compared to those treated in earlier decades (Ferlay et al., 2013). According to a study conducted in Southern England, it was estimated that by 20 years from the time of first head and neck cancer, approximately 20% of female patients and 30% of male patients would develop MPT (Brands et al., 2018). Long-term survival of patients with MPTs is not consistent and depends on the type of cancer and the stage at diagnosis. The outcome is significantly influenced by co-morbidities, genetic, environmental, and lifestyle factors. It has been reported that black patients have a lower incidence of MPTs as well as a lower relative survival independent of cancer site and stage at diagnosis (Coyte et al., 2014).

According to IARC 2020, an estimation of 476,125 new cases of oral cancer and 225,900 associated deaths were reported globally (World Health Organization, 2020). With this increasing number of cases, the incidence of MPTs will also increase significantly. Therefore, follow-up for oral cancer patients should be life long as the risk of developing a second primary increases as survivorship from primary cancer increases (Brands et al., 2018).

1.2.4 Etiological factors

The factors associated with an increased risk of development of MPTs may include longer survivorship from primary cancer, genetic predisposition to cancer, exposure to specific environmental factors, and type of treatment for initial primary cancer (Coyte et al., 2014). Different epidemiological studies have concluded that alcohol consumption and heavy smoking are the most significant risk factors for development of multiple primary tumors with strong association between cancers of the lung and upper aerodigestive tract (oral cavity, pharynx, larynx and esophagus) (Blot et al., 1988; Hashibe et al., 2007). Due to this, the World Health Organization (WHO) has also categorized alcohol and smoking as group 1 carcinogens for oral cavity, pharynx, larynx and esophagus (Secretan et al., 2009). This is reflective of a phenomenon called 'field cancerization'(FC), in which some of the multiple patches of transformed cells in the respiratory and urinary tract may evolve into second or more cancers (Slaughter et al., 1953).

The concept of field cancerization was first introduced in 1953 by Slaughter et al., reporting that there are separate microinvasive islands of cancer in the surrounding mucosa of the oral tumors of 1 cm in diameter or less and that the linear extent of the disease is 10 times greater on the surface epithelium than the depth of the lesion (Slaughter et al., 1953). There are different theories that explain the concept of FC. One of them is polyclonal theory, which explains that various invasive fields develop under the influence of carcinogenic agents (Slaughter et al., 1953). Other theories explain the monoclonal concepts, which states that with the spread of dysplastic cells, new invasive fields develop giving rise to MPTs (Bedi et al., 1996). FC entails that the tumors develop in a field of pre-neoplastic cells that have an anaplastic tendency and do not develop as isolated tumors. This predisposition leads to multifocal development of tumors at various rates within the field (Mohan & Jagannathan, 2014). The mucosa with genetically altered but histologically normal cells show a

high-risk of malignant transformation and is referred as ‘condemned mucosa’. Due to field cancerization, although the tumor is completely excised, MPTs still develop due to the presence of genetically altered condemned mucosa. Clinically, the condemned mucosa shows premalignant changes including leukoplakia and erythroplakia and may transform into cancer earlier as compared to lesions in normal mucosa. Because of genetically altered cells present adjacent to the surgical margins of condemned mucosa, the adjacent mucosa of multiple carcinomas should be monitored closely to identify the occurrence of subsequent tumors (Mochizuki et al., 2015).

For patients with OSCC, this field cancerization tendency is supposed to extend as far as involving lungs and esophagus (Heroiu Cataloiu et al., 2013). Because oral cavity, lungs and esophagus are closely connected to each other, there is a similar pathway of exposure to the mucosa from the environmental carcinogens. An experimental study investigated the relationship between head and neck squamous cell carcinomas and secondary esophageal tumors by using 10 polymorphic microsatellite markers, which showed that the tumors from the two lesions were not clonally related. This further supports that the tumors from head and neck and esophageal mucosa are two separate tumors rather than metastases (Califano et al., 1999).

It is evident that there are wide fields of genetic alterations in the mucosal epithelium of cancer patients. It is not feasible to remove the entire mucosa with genetic alterations, but measures could be taken to make the mucosa less sensitive to DNA alterations. Chemoprevention has been proposed to prevent the occurrence of cancer after surgery. Chemical compounds including retinoids have been widely studied and suggested to be used systemically or topically to retard the tumor progression (Ha & Califano, 2003). However, the side effects and clinical efficacy of these compounds are still being studied.

1.2.5 Types of MPTs

MPTs can be categorized as synchronous or metachronous, depending on the timing of diagnosis. Synchronous lesions are those that are diagnosed simultaneously or within 6 months of the initial lesion. However, metachronous lesions are those that are diagnosed after 6 months of the primary lesion (Thomson, 2002). The genetic and molecular characteristics and behaviour of synchronous tumors are known to be more aggressive as compared to metachronous tumors. It is also known that synchronous tumors have a lower disease specific survival rate than metachronous tumors (Mochizuki et al., 2015). Regular screening of oral cancer patients after receiving treatment is very important because they are often overlooked, and therefore, they usually present with metachronous lesions, which would require additional surgical treatments. It is important to differentiate between synchronous and metachronous lesion since the prognosis differs between each type of lesions.

1.2.6 Diagnosis

A patient treated for primary oral cancer has to go through several follow-up appointments over a period of time to rule out recurrence. With the availability of new imaging techniques, namely positron-emission tomography, computed tomography (PET-CT), and whole-body MRI, it is possible to detect suspicious lesions that might have not been diagnosed with standard CT and/or bone scintigraphy imaging techniques. According to a report, a series of 1912 patients who were scanned with PET-CT imaging, 4.1% of patients were reported with suspicious lesions, out of which, 1.2% were histologically confirmed as malignant (Ishimori et al., 2005).

Histological confirmation should be carried out in case of a suspected second primary. With the advancement in imaging techniques, it is possible to detect the lesions and reach to an adequate

diagnosis. It is very important that the tissue from primary cancer to be available in order to carry out a comparison (Vogt et al., 2017).

1.2.7 Prognosis and survival

An overall poor prognosis and a significant decrease in 5-year survival rates from 69% to 32% has been documented in patients with MPTs compared to patients without MPTs (Ellison, 2010). A negative impact on survival in patients who developed MPTs, more specifically with synchronous tumors, has been illustrated. A surprisingly good 5-year survival rate has been reported for patients with metachronous tumors compared to synchronous tumors (85% vs. 25%). It is therefore essential to perform regular screening within the first 6 months after treatment of index tumor to improve the survival of an individual patient (Bugter et al., 2019). Moreover, the site of the SPT also plays a significant role in the survival. Previous studies demonstrated that patients who developed SPT in lungs and esophagus had significantly worse survival rates than patients who had SPT in the head and neck region (Chen et al., 2010; Dequanter et al., 2011a).

According to a national study conducted in Canada, the impact of MPTs on 5-year relative survival was found to be greatest for bladder cancer (age-standardized: -2.4%) followed by oral cancer (-1.9%) (Statistics Canada, 2022).

1.3 Problem Statement

Considering the significant impact of MPTs on the survival rate of oral cancer patients, it is important to identify the risk factors for the development of MPTs to carry out required preventive and diagnostic measures in due time. Therefore, the aim of this research is to address this knowledge gap by examining a database of oral cancer patients who developed MPTs over a period. The analysis will help inform the health care professionals about the group of patients who are more at risk for developing MPTs and to carry out preventive strategies including close monitoring and follow-up for patients treated for primary oral cancers. The data may help inform both clinicians and patients about a more individualised approach to follow up based on the perceived risk over time.

1.4 Objectives

The objectives of this study are:

1. To identify the risk factors of MPT development in oral cancer patients.
2. To examine the survival rates of oral cancer patients with MPTs and its associated factors.

2 Chapter Two: Materials and Methods

In this chapter, I will be describing the research method in detail. I will first explain the database that was used to identify the study cohort. Next, I will outline my inclusion and exclusion criteria and my approach of data extraction. I will also explain the criteria used for site localisation of oral cancer and MPTs. At the end, I will describe the methods used to carry out the statistical analysis.

2.1 Study population and ethics approval

This study was carried out after obtaining ethical approval from the Health Research Ethics Board of Alberta Cancer Committee (HREBA.CC-17-0370) and the University of Alberta. We retrospectively reviewed patients who were diagnosed with oral cancer (OCC and OPC) between 2005 and 2020 and the data was retrieved from the Alberta Cancer Registry (ACR) database. The ACR is a population-based registry that maintains data on all new cancer diagnosis and deaths in the province of Alberta and is certified by the North American Association of Central Cancer Registries (NAACCR).

The following inclusion criteria were used to identify the patients charts from the database:

a) Patients with a diagnosis of primary oral cancer
b) Patients over the age of 18 years
c) Patients who were documented as Alberta residents at the time of cancer diagnosis.

Patient records were excluded if:

a) Patients were diagnosed with any other tumors prior to oral cancer,

b) The tumors were not diagnosed as malignant histologically,

c) There was metastasis.

2.1.1 Data Extraction

Patient records were retrieved from the registry database and after being certified with the School of Dentistry patient privacy training, access to patient records was granted. After the intensive search, the patient charts that fulfilled the inclusion criteria were comprehensively studied. The International Classification of Diseases for Oncology – third edition – ICD-O-3 coding was utilized for the localization of oral cancer. The selection of these anatomic sites specific to OCC and OPC was based on updated criteria presented at the 2018 American Society of Clinical Oncology Annual Meeting (*Table 2-1*) (Cancer Centre, 2018).

Table 2-1 International classification of diseases for oncology-third edition-ICD-0-3

Site	ICD-0-3 codes
Oral Cavity Cancer (OCC) Subsites	
Lip mucosa	C00.3-C00.9
Oral tongue	C02.0-C02.3, C02.8 and C02.9
Gum	C03.0-C03.9
Floor of the mouth	C04.0-C04.9
Palate	C05.0-C05.9
Other and unspecified parts of the mouth	C06.0-C06.9
Oropharyngeal Cancer (OPC) Subsites	
Base of tongue	C01.9
Lingual tonsil	C02.4
Tonsil	C09.0-C09.9
Oropharynx	C10.0-C10.9
Pharynx not otherwise specified	C14.0
Waldeyer ring	C14.2

After retrieving the data of patients with primary oral cancer, patients with multiple primary tumors (MPT) were identified from the cohort. MPT was defined according to Warren and Gates criteria (Warren S, 1932). Patients who developed second, third, fourth or even more primary tumors were identified as patients with MPT. The SPT was therefore the first MPT. MPTs were categorized as synchronous if diagnosed within 6 months from the index tumor and metachronous if diagnosed after 6 months. The time interval between diagnosis of an index tumor and diagnosis of second

primary tumor was analyzed in months. A summarized list of key terms used during data extraction is enlisted in Table 2-2.

Table 2-2 Key terms used during data extraction

Key terms	Definition
Oral Cancer (OC)	Patients with oral malignancy following ICD-0-3 topographical codes. OC was subcategorized as oral cavity cancer (OCC) and oropharyngeal cancer (OPC).
Primary Oral Cancer (POC)	Patients with oral cancer as a primary tumor. Also referred as index tumor.
Multiple Primary Tumor (MPT)	Patients with 2^{nd}, 3^{rd}, 4^{th} or more malignant tumors after primary oral cancer.
Second Primary Tumor (SPT)	The tumor after occurrence of primary tumor. It is also refereed as first (1^{st}) MPT.
Metachronous tumors	MPT diagnosed after 6 months of primary tumor.
Synchronous tumors	MPT diagnosed in the first 6 months after primary tumor.

2.1.2 Measures

2.1.2.1 Sociodemographic Variables

Baseline demographics data were gathered from patients' records. Sociodemographic measures included sex (male vs female), age (<45, 45-65, >65), family annual income (<$45,000, 45,000-75,000, > 75,000) and body mass index (BMI). The income data was based on the neighbourhood where the patient resided and was obtained from Statistics Canada 2006 Census. Height and

weight were used to calculate the BMI of the patients and was categorized using the WHO standard which is reported as:

Underweight=< 18.5; normal weight= 18.5-24.9; overweight= 25-29.9; and obese= ≥ 30

2.1.2.2 Clinical Characteristics

The clinical characteristics included site of POC (following ICD-0-3 topographical coding), site of MPT (oral and elsewhere in the body), number of MPT (one, two, three, four), duration of diagnosis from POC to MPT (synchronous or metachronous) co-morbidities (none, 1, 2, >2), staging and type of treatment received. The assessed co-morbidities were categorized as cardiovascular disease, cerebrovascular disease, COPD, diabetes, renal failure, and others, which included paraplegia, dementia, liver failure, connective tissue disease, peptic ulcer and HIV. The staging was categorized according to ajcc7 and ajcc8 system. The type of treatment received for primary oral cancer was categorized into surgery, chemotherapy, radiation, immunotherapy, combinations of these treatment and no treatment.

Patients were then divided into two groups:

1. Patients with primary oral cancer (POC) who developed a second primary tumor, and
2. Patients with primary oral cancer (POC) who did not develop a second primary tumor.

A comparative analysis was carried out to study the demographic and clinicopathological characteristics of both groups. A regression analysis was carried out to find the association of the risk factors with the MPT development.

2.1.3 Outcome Variable

2.1.3.1 Survival

The vitality status of the oral cancer patients was recorded as alive and deceased. The date of diagnosis of POC until the date of death was used to calculate the survival rate. The survival rate was calculated using first primary cancer cases only and then after including second primary cancers. The mortality rate was also calculated for the two groups. Variables recorded from each patient chart are listed in *Table 2-3*.

Table 2-3 Patient chart parameters

Sociodemographic Variables	Clinical Characteristics	Survival
Age	Site of POC (OCC, OPC)	Vitality status
Sex	Number & site of MPT	Survival rate
Income	Duration from POC-MPT	Mortality rate
Postal code (neighborhood)	Co-morbidities	
Height &Weight (BMI)	Ajcc7 and Ajcc8 Staging	
	Type of Treatment	

2.2 Data Analysis

After retrieving the data, grouping was done to conduct statistical analysis. For objective one, socio-demographic variables and clinical characteristics of MPT and non-MPT groups were compared. Patients were divided into two main study groups: POC with MPT and POC without MPT. Descriptive statistics for demographic and clinical characteristics for each group, as well as overall, were computed. Categorical variables were summarized in frequency and percentages and numerical variables were expressed as mean (SD) or median (IQR) for each group based on the normality of data. The normality of data was examined using Kolmogorov-Smirnov test and P-value < 0.005 was considered significant to reject the hypothesis of normality of data. Comparisons of demographic, clinical, and epidemiological characteristics were made between the MPT and non-MPT patients. Chi-square test or Fisher Exact test were employed where appropriate for categorical variables. For numerical variables, independent sample t-test or mann-whitney u test were used based on the normality of the data. To determine the significant prognostic factors associated with the development of MPT, binary logistic regression was used at univariate and multivariate level. Factors found significant with a $p< 0.25$ were included in the final adjusted model. In the final adjusted model, factors with $p < 0.005$ was considered significant.

For objective two, the study endpoints consisted of 5, 10 and 15-year overall survival (OS) rates. The OS was defined as the time from the diagnosis of POC until the date of death. Kaplan-Meier Survival curves were plotted to estimate the overall survival of both MPT and non- MPT groups.

Unadjusted and adjusted hazard ratios were computed using cox proportional hazard models. Univariate regression analyses were used to evaluate the potential risk factors. Factors found with hazard ratio significant at $p < 0.25$ level were then included in the final adjusted model. By using

the multivariate cox proportional hazard models, the hazard ratios of MPTs along with each possible related factor was estimated by adjusting for possible confounding variables. Hazard Ratio (HR) and 95% confidence intervals (CI) were used to present the risk of hazard of death. Confidence Interval indicates that if this experiment was to be done multiple times, in 95% of occasions the hazard risk values from this experiment would contain the actual value. P-value < 0.05 was considered as statistically significant. All the statistical analyses were performed using statistical software SPSS version 22.

3 Chapter Three: Results

In this chapter, I will be presenting my findings and illustrate them in tables and figures. I will also be including my statistical analysis and reporting whether the results were significant or insignificant accordingly based on p-values.

3.1 Descriptive Analyses

A total of 4,035 oral cancer patients were retrieved from Alberta Cancer Registry database between 2005 and 2020. Of all the patients, 3,549 patients were diagnosed with primary oral cancer. A total of 513 (14.5%) patients developed MPTs (*Figure 3-1*). Of the 3,549 primary oral cancer patients, 71.8% were male and 28.2 % were female. The patients age ranged from 18-97 years, with a mean (SD) age of 61 (12.5). The majority of the POC patients reported an average income of above 75,000 or 45,000-75,000 (46.5% and 44% respectively). The sociodemographic characteristics of patients are presented in *Table 3-1*.

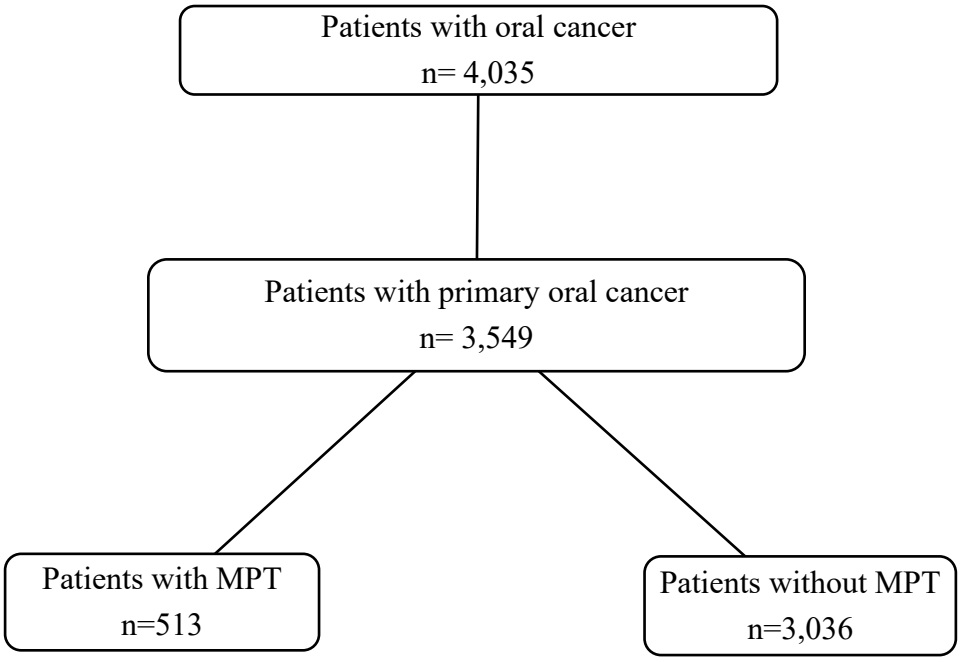

Figure 3-1 Flowchart of study participants

3.2 Comparative Analyses

3.2.1 Sociodemographic Characteristics

The comparative analyses showed no significant difference in the gender distribution between the two groups (p = 0.360), with a stronger male predilection; 358(69.8%) and 2179(71.8%) for both MPT and non MPT groups, respectively. The average age at first diagnosis for both MPT and non-MPT patients was 61 years (61 ±12.5, 61±11.7), with no significant differences between the two groups (p = 0.130). There was no significant difference reported in the BMI of the patients between the groups (p=0.067). A significant difference in average income was found (p= 0.019) between

MPT and non-MPT patients, with 47.2% of patients without MPT having a higher income of more than $75,000, while 48.7% of patients with MPT reported to have an average income of $45,000-75,000. No statistically significant differences in the number of MPT and non-MPT patients were found by the geographical location of diagnosis (p = 0.730).

Table 3-1 Comparison of MPT and non-MPT patients by their demographic characteristics

Characteristics	Without MPT	MPT	Total	p-value
	N=3,036	N=513	N=3,549	
Gender				0.360
Male	2,179 (71.8%)	358 (69.8%)	2,537 (71.5%)	
Female	857 (28.2%)	155 (30.2%)	1,012 (28.5%)	
Age at Diagnosis				<0.001
<= 45 Years	288 (9.5%)	19 (3.7%)	307 (8.7%)	
46-65 Years	1,776 (58.5%)	305 (59.5%)	2,081 (58.6%)	
> 65 Years	972 (32.0%)	189 (36.8%)	1,161 (32.7%)	
Age at Diagnosis (Mean± SD)	61±12.6	61±11.7	61±12.510	0.130
BMI (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%)	1,031 (29.1%)	
overweight 25-29.9	925 (30.5%)	161 (31.4%)	1,086 (30.6%)	
Obsess >=30	685 (22.6%)	131 (25.5%)	816 (23.0%)	
No Anthropometric data available[a]	443 (14.6%)	28 (5.5%)	471 (13.3%)	
Average Income				0.019
< 45,000	292 (9.6%)	40 (7.8%)	332 (9.4%)	
45,000-75,000	1,310 (43.1%)	250 (48.7%)	1,560 (44.0%)	
>75,000	1,433 (47.2%)	216 (42.1%)	1,649 (46.5%)	
No data available[a]	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	1,147 (37.8%)	184 (35.9%)	1,331 (37.5%)	
Central Alberta	384 (12.6%)	69 (13.5%)	453 (12.8%)	
Edmonton	959 (31.6%)	157 (30.6%)	1,116 (31.4%)	
Northern Alberta	317 (10.4%)	54 (10.5%)	371 (10.5%)	
No data available[a]	0 (0.0%)	5 (1.0%)	5 (0.1%)	

chi-square test or Fisher Exact test were used whichever was appropriate.
[a] Category for No Data Available was not considered while applying chi-square or Fisher Exact Test.
BMI: Body Mass Index
MPT: Multiple Primary Tumor

3.2.2 Clinical Characteristics

3.2.2.1 Occurrence of MPTs

Out of 513 MPT patients, 82.8% (n= 425) were diagnosed with one SPT, 15.6% (n=80) with two MPTs and 1.6% (n=8) with more than two MPTs (*Figure 3-2*). It was observed that 77.9% of the MPTs were metachronous and 22.03% were synchronous (*Figure 3-3*). The average duration until occurrence of MPT was 4.2±3.8 years after the occurrence of POC.

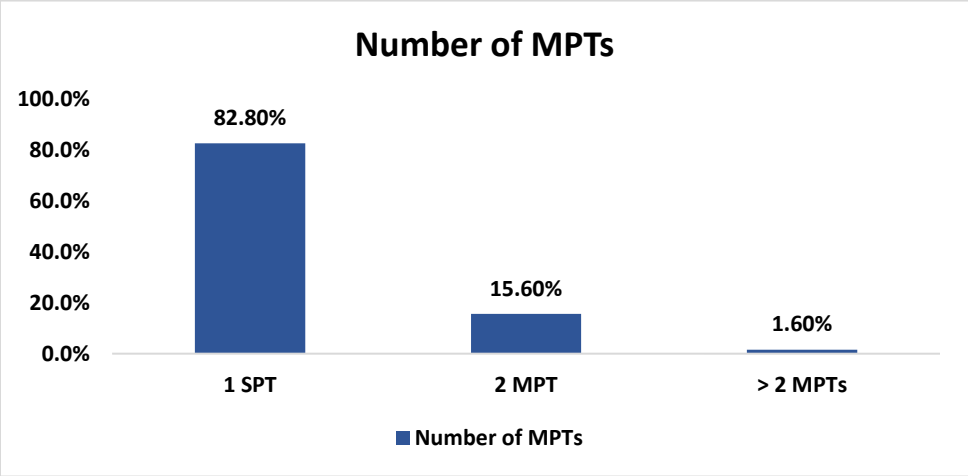

Figure 3-2 Number of MPTs

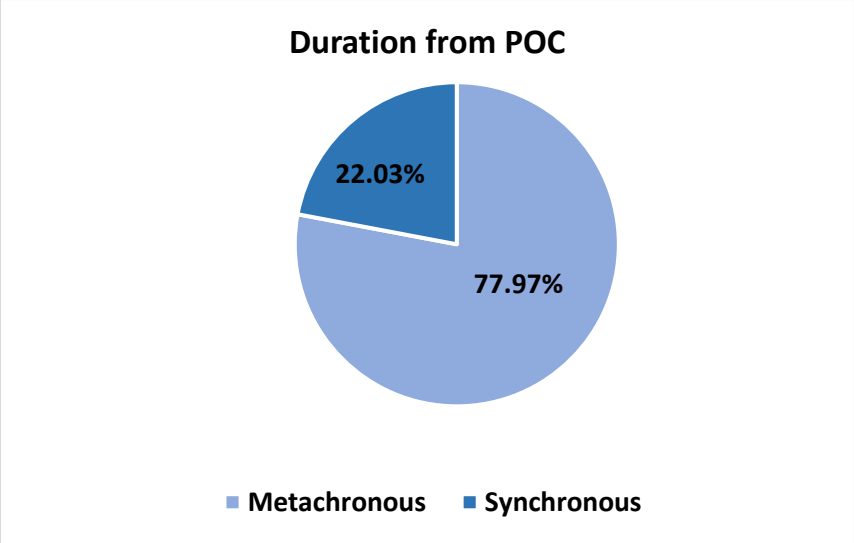

Figure 3-3 Distribution of metachronous and synchronous tumors

3.2.2.2 Site Distribution

Of 3,549 primary oral cancer patients, 1,712 (48.2%) were classified as OCC, while 1837 (51.8%) were classified as OPC. The proportion of POC patients with OCC who later developed MPTs (53.4%) was found to be slightly higher than OPC patients who developed MPTs (46.6%). Of the primary OCC subsites in the study, tongue tumors (37.6%) showed a higher probability of developing MPTs followed by floor of mouth (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 oral region (31.8%) followed by lung/bronchus (19.1%), digestive system (12.3%) and head & neck sites other than oral region (11.3%). A similar pattern was observed for 3rd, 4th and 5th primary tumors. Sites and distribution of tumors are presented in *Table 3-2* and *Table 3-3*.

Table 3-2 Subsites of primary oral cancer tumors developing MPTs

Type of Oral Cancer	Without MPT	MPT	Total	p-value
	N=3,036	N=513	N=3,549	
OCC	**1,438 (47.4%)**	**274 (53.4%)**	**1,712 (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 & unspecified	236 (16.4%)	49 (17.8%)	285 (16.7%)	
Palate	136 (9.5%)	22 (8.0%)	158 (9.2%)	
Tongue, other & unspecified	700 (48.7%)	103(37.6%)	803 (47.0%)	
OPC	**1,598 (52.6%)**	**239 (46.6%)**	**1,837 (51.8%)**	0.011
Base of Tongue	591 (37.0%)	90 (37.6%)	681 (37.0%)	
Lip, Oral Cavity & Pharynx, other & 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%)	

Table 3-3 Distribution of 2nd, 3rd, 4th and 5th primary tumor or MPTs by site

Sites	Second Primary Tumor		Third Primary Tumor		Fourth Primary Tumor		Fifth Primary Tumor	
	N	%	N	%	N	%	N	%
Oral cancer	163	31.8	27	33.8	3	50.0		
H&N	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				
Total	513	100	80	100	6	100	2	100

3.2.2.3 History of medical conditions

The proportion of any comorbid condition was found to be higher in MPT patients (51.0%) as compared to non-MPT patients (40.0%) as illustrated in *Figure 3-4*. The most prevalent and statistically significant comorbid conditions in MPT patients were chronic obstructive pulmonary disease (24.6%, $p < 0.001$)), diabetes (18.7%, $p < 0.001$)) and cardiovascular disease (11.5%, $p = 0.040$) as depicted in *Table 3-4.*

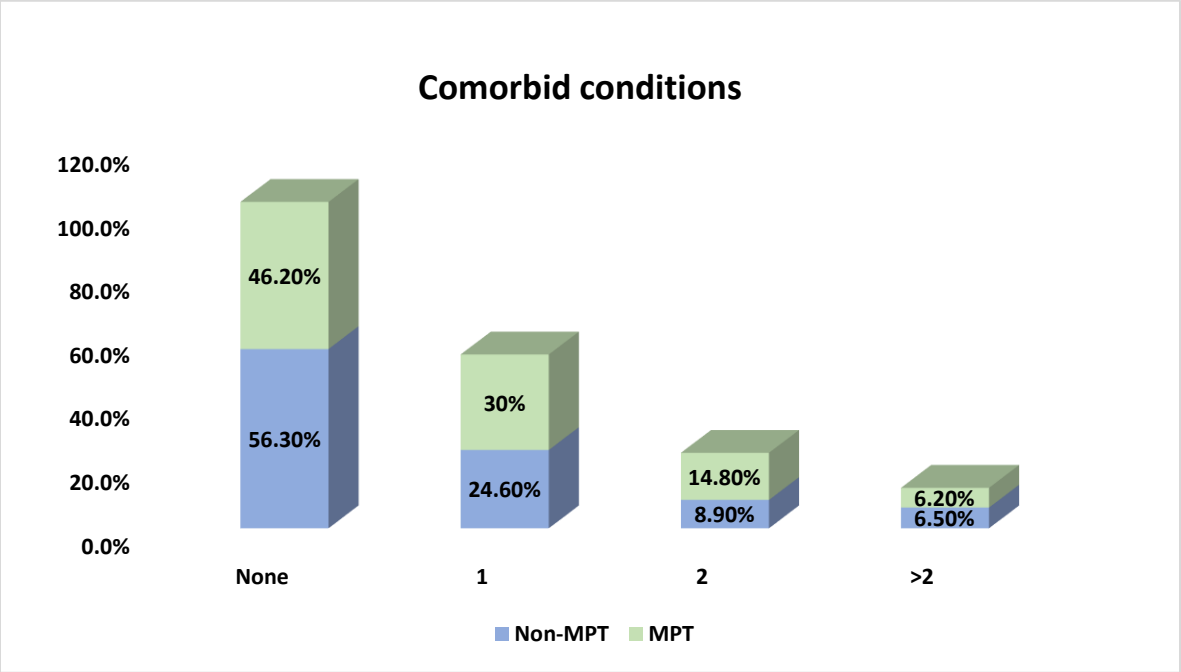

Figure 3-4 Incidence of co-morbid conditions in MPT and non-MPT patients

Table 3-4 Co-morbidities in MPT and non-MPT patients

Medical Conditions	Without MPT	MPT	Total	p-value
	N=3,036	N=513	N=3,549	
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
COPD	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

p-value using Chi-square test

3.2.2.4 Treatment Modalities

There was no significant difference between the type of treatment received for primary oral cancer and development of MPT (p=0.22). Surgery alone (57.0%) was the most common type of treatment seen in the entire cohort followed by chemotherapy+radiotherapy for both MPT and non-MPT patients, accounting for 20.5% and 20.1%, respectively *(Figure 3-5).* Most patients received their first treatments within three months after being diagnosed with primary oral cancer (58.1%). However, the mean duration from diagnosis to treatment was slightly higher for MPT patients as compared to non-MPT patients (2.27 *vs*. 2.19 months, p = 0.090)

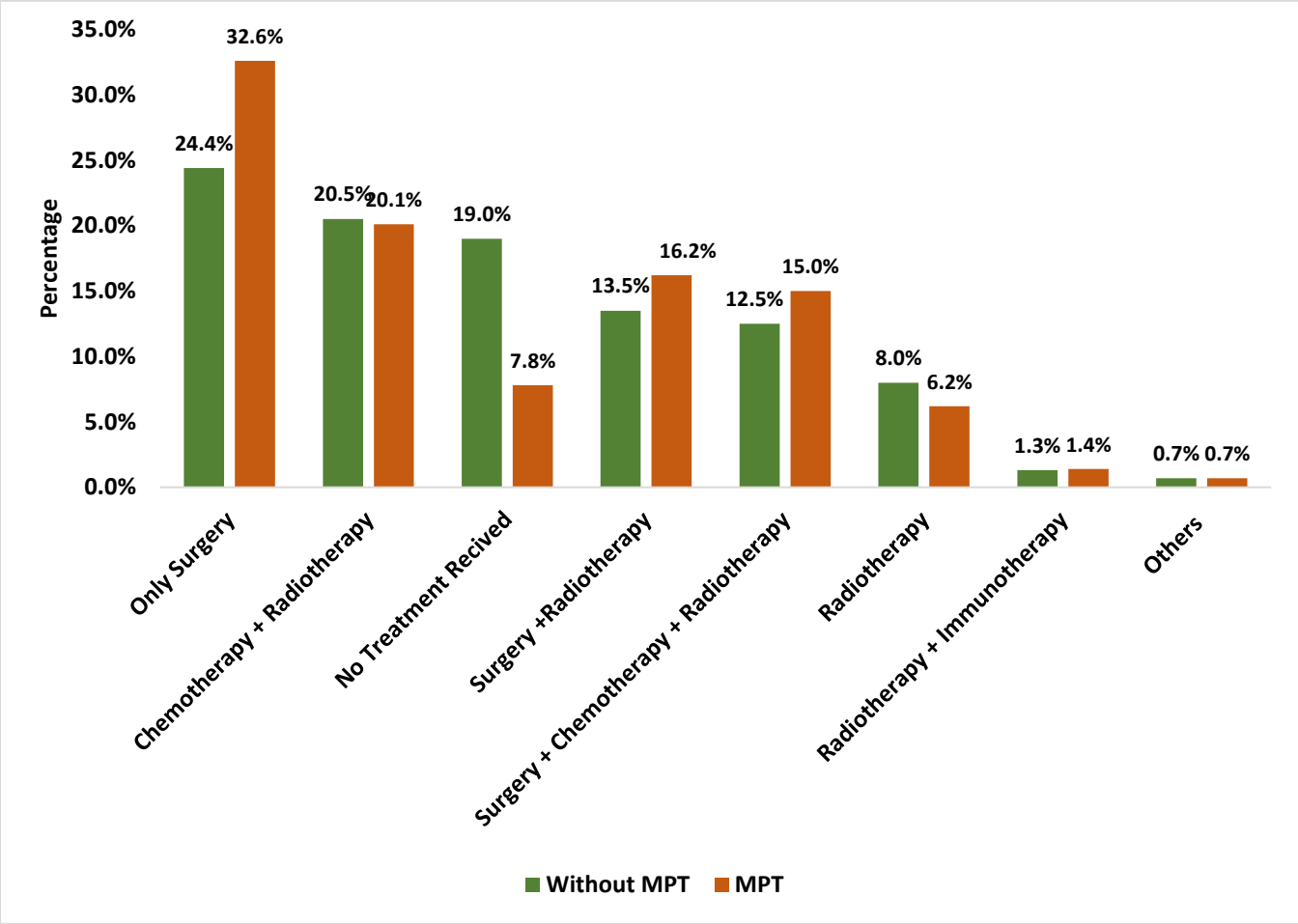

Figure 3-5 Treatment modalities for primary oral cancer patients who developed MPTs

3.2.2.5 Staging of Oral Cancer

According to ajcc7 tumor classification, the majority of POC patients were diagnosed at stage IV regardless of developing or not developing MPT (51.6% and 61% respectively). According to

ajcc8 tumor classification, no significant difference was found between the two groups (p = 0.535).

Table 3-5 Pathological Staging of Oral Cancer

Cancer Stage	Without MPT	MPT	p-value
	N=3,036	N=513	
Staging Ajcc7			**0.005**
I	315 (12.9%)	80 (17.2%)	
II	178 (7.3%)	41 (8.8%)	
III	212 (8.7%)	48 (10.3%)	
IV	1,482 (61.0%)	240 (51.6%)	
UNK	241 (9.9%)	56 (12.0%)	
Staging Ajcc8			**0.535**
I	177 (29.1%)	14 (29.2%)	
II	86 (14.1%)	10 (20.8%)	
III	90 (14.8%)	9 (18.7%)	
IV	130 (21.3%)	7 (14.6%)	
UNK	125 (20.5%)	8 (16.7%)	

3.3 Regression Analysis

The univariate analysis identified the following factors to be significantly associated with an increased risk of MPT development: age > 45 years (p < 0.001), average income between 45,000 – 75,000 (p = 0.019), POC with 2 co-morbid conditions (p < 0.001) including cardiovascular disease (p = 0.022), diabetes (p < 0.001) and COPD (p < 0.001) and increasing duration from diagnosis to treatment (p < 0.001). 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 univariate analysis in the multivariate model, all these variables retained their independent prognostic significance in the multivariate model (*Table 3-6*).

Table 3-6 Risk factors associated with MPT development

Variable	Risk Ratio (95% CI)	P-value	Adjusted Risk Ratio (95% CI)	P-value
Age at Diagnosis				
46-65 Years	2.4(1.5-3.7)	<0.001	2.3(1.4-3.9)	< 0.001
> 65 Years	2.6(1.7-4.1)	<0.001	2.4(1.4-4)	< 0.001
Average 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
Duration Diagnosis to Treatment				
3-6 Months	2.4(1.8-3.3)	<0.001	3.7(2.1-6.7)	< 0.001
6-12 Months	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

3.4 Survival Analysis

Out of 3,549 oral cancer patients, 1,963 (55.3%) patients survived, and 1,586 (44.7%) patients died. In the entire cohort, 5-year disease specific survival rate (DSS) was 71%. The mean (SD) years of survival for MPT patients was 5.7 (3.8) years as compared to 3.0 (4.7) years in non-MPT patients. However, the 5- year DSS rate was found to be approximately similar in both MPT and non-MPT patients (71% vs. 70%, $p < 0.260$; *Figure 3-6*).

3.4.1 Kaplan-Meier Analyses

Kaplan-Meier analysis showed that patients whose survival time was longer than 5 years had a sharp decrease in 5-year DSS if they developed MPT (from 70% to 47%, p = 0.004; *Figure 3-6*). Furthermore, patients with MPT located in the oral region had better DSS than MPT located in digestive system (oral vs. digestive system: 68% vs. 52%, p = 0.001; *Figure 3-8*). We further analyzed the prognosis of MPT patients with synchronous and metachronous tumors. Interestingly, we found out that MPT patients with metachronous tumors had significantly higher survival rate than synchronous tumors (75% vs. 45%, p < 0.001; *Figure 3-9*).

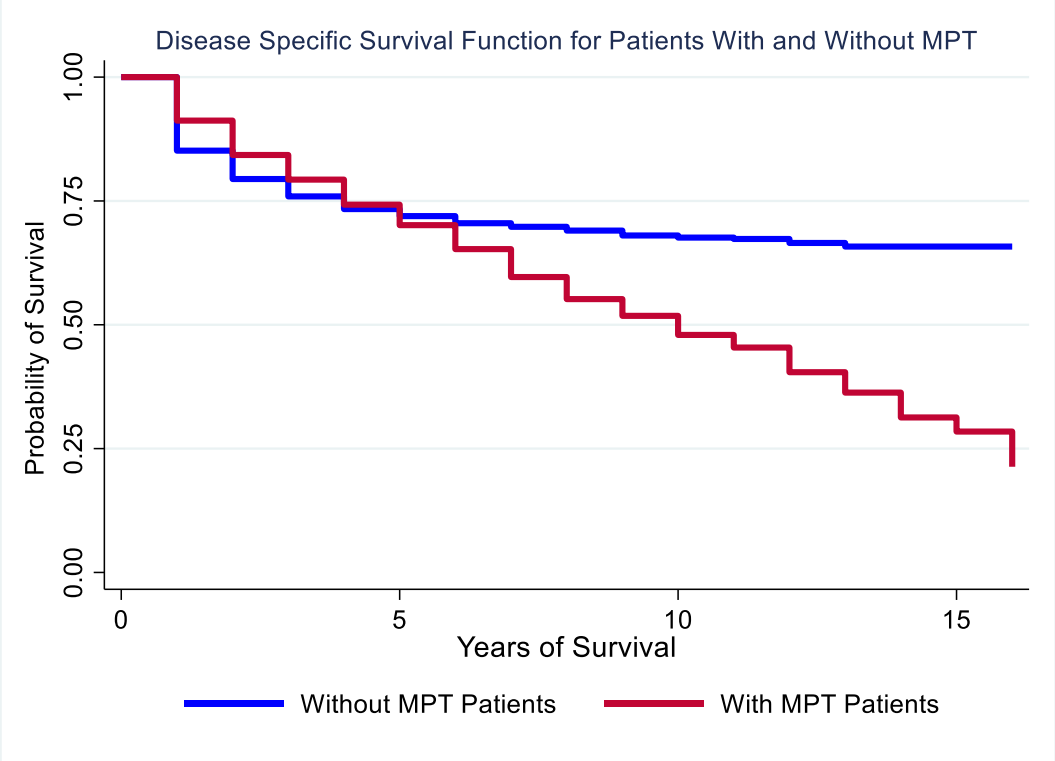

Figure 3-6 Survival curves of MPT and non-MPT patients

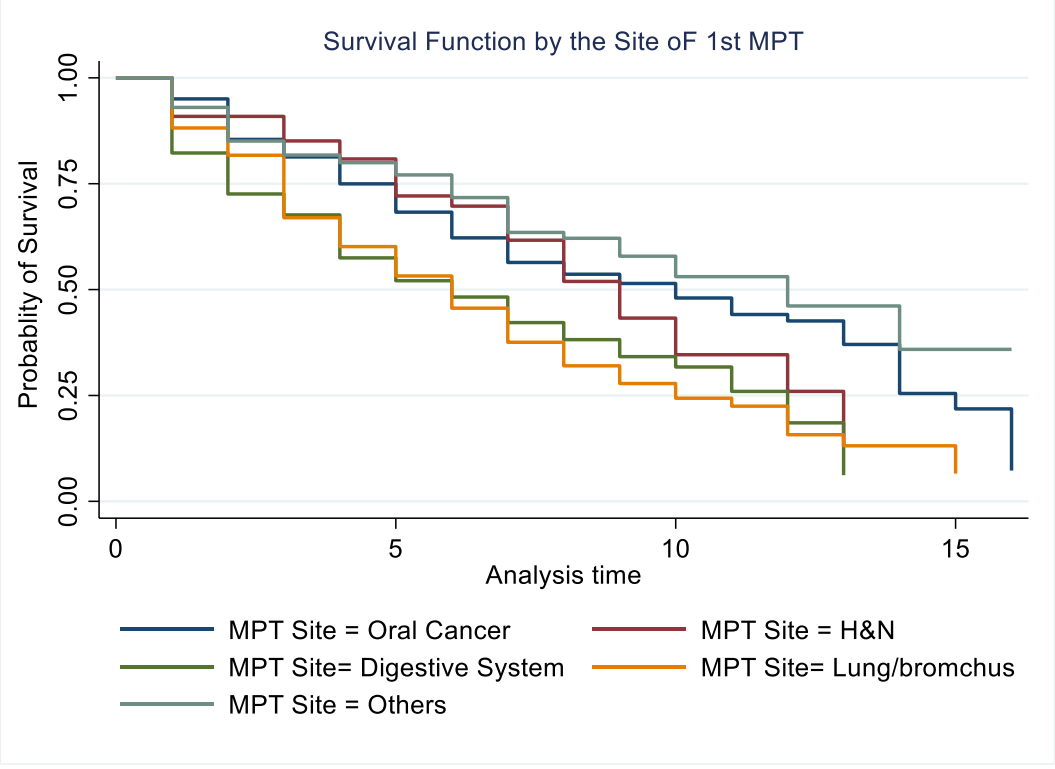

Figure 3-7 Survival analysis by site of MPT

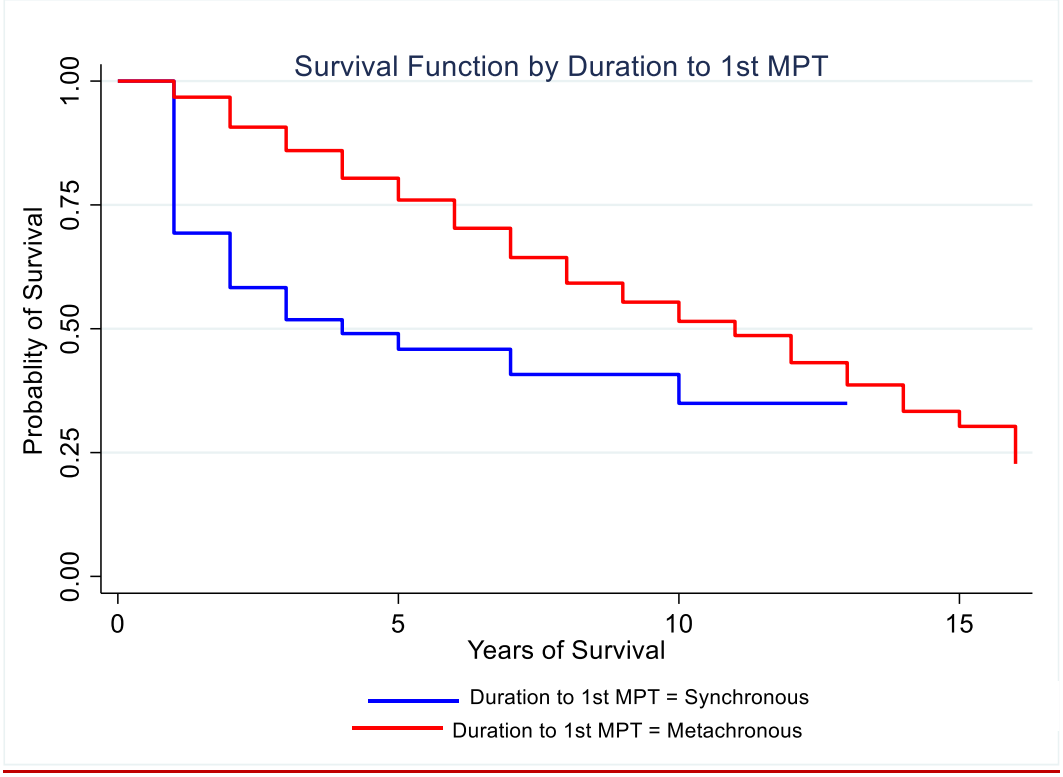

Figure 3-8 Survival by duration to 1st MPT

3.4.2 Cox regression model

To further investigate the high-risk factors for poor prognosis of MPT patients, the baseline data served as covariates and were analyzed using Cox regression hazard models.

3.4.2.1 Univariate Analysis

The univariate analysis showed that patients with demographic characteristics including age above 45 years ($p < 0.001$), BMI < 18.5 ($p < 0.001$), income below 75,000 ($p < 0.001$) were significantly associated with high risk of death. The hazard of death was found to be 2-fold higher in patients older than 65 years with reference to the patients of the age ≤ 45 years [HR; 2.9, CI; 1.9-3.7, $p < 0.001$]. In addition, the increasing number of comorbid conditions was also found to be significantly associated with increasing hazard of death. The hazard ratio for each comorbid condition was separately determined and it showed that comorbidities such as COPD, diabetes, cardiovascular disease and renal failure were found to be significantly associated with an increased risk of death at univariate analysis. Furthermore, synchronous tumors ($p < 0.001$), site of primary oral cancer ($p = 0.002$) and site of 1st MPT ($p < 0.001$) were high risk prognostic factors for DSS of MPT patients. The hazard ratio of MPT cancer stage III and IV were found to be significantly higher and reported as [HR; 1.9, CI; 1.1-3.3, $p = 0.027$] & [HR; 2.3, CI; 1.5-3.7, $p < 0.001$] respectively, as depicted in *Table 3-5*.

3.4.2.2 Multivariate analysis

A further multivariate analysis showed that age above 45 years and BMI < 18.5 remained significant prognostic factors for fatal outcome. Patients who had more than two comorbid conditions along with MPT had a three-fold increased risk of death compared to those who did not have any comorbid conditions [HR; 4.3, CI; 0.9-20.8, $p = 0.048$]. Similarly, patients with synchronous tumors remained more susceptible to death as compared to patients with metachronous tumors [HR; 2.6, CI; 1.7-4.1, $p < 0.001$]. None of the POC site remained significant

in multivariate model for the prediction hazard associated with MPT. However, only digestive system as MPT site remained significant in multivariate model [HR; 2.1, CI; 1.3-3.5, p = 0.040]. Additionally, Stage III and IV of MPT Cancer also remained highly significant as the predictor of death with hazard ratios [HR; 2.1, CI; 1.09-3.9, p = 0.025] and [HR; 2.6, CI; 1.5-4.3, p < 0.001] respectively, as demonstrated in *Table 3-7*.

Table 3-7 High risk factors for disease specific survival among POC patients who developed MPTs

Variable	Hazard Ratio	95% CI	p-value	AHR (95% CI)	p-value
Age at Diagnosis					
46-65 Years	1.8	1.3-2.5	<0.001	1.6 (1.2- 2.2)	<0.001
> 65 Years	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 Income					
< 45,000	1.8	1.5-2.3	<0.001		
45,000-75,000	1.4	1.2-1.6	<0.001		
Number of 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		
Duration 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	2.07(1.09-3.9)	0.025
IV	2.3	1.5-3.7	<0.001	2.6(1.5-4.3)	<0.001
UNK	1.9	1.1-3.2	0.016	2.5(1.3-4.6)	0.003

3.5 Summary of the Results

- ✓ A total of 513 patients developed MPTs with an incidence rate of 14.5%. Among them, 82.8% were diagnosed with one MPT, 15.6% with two MPTs and 1.6% with more than two MPTs with oral region as the most prevalent site.
- ✓ The average duration until occurrence of 1st MPT was 4.2 years after occurrence of POC.
- ✓ 77.97% of MPTs were metachronous tumors and 22.03% were identified as synchronous.
- ✓ POC patients with OCC compared to OPC had a higher probability of developing MPT. The most common site for MPT development was the oral region followed by lungs and digestive system.
- ✓ Oral cancer patients with COPD, diabetes and cardiovascular disease were found to develop more MPTs.
- ✓ Advanced age, average income, co-morbidities including COPD, diabetes and cardiovascular disease and increased duration from diagnosis to treatment were found to be potential risk factors for MPT development in POC patients.
- ✓ Survival analysis depicted that oral cancer patients who survived more than 5 years showed a sharp decrease in survival rate if they developed MPTs (from 70% to 47%). DSS was worse for patients with synchronous tumors, age >45 years, BMI <18.5, >2 co-morbid conditions and stage III and IV oral cancer.

4 Chapter Four: Discussion

In this chapter, I will be analyzing, interpreting, and discussing my findings and relating it with the other studies. I will also explain the significance of the results and citing relevant resources to place them in the context.

This retrospective population-based study was the first study focusing on MPTs in oral cancer patients in Alberta and included not only the oral cavity, but other distant sites. The objective of the present study was to investigate the sociodemographic and clinicopathological characteristics of oral cancer patients with and without MPTs and their associations with survival rate. Data from this study showed that oral cancer patients with MPTs had a poor disease specific survival rate and 20% higher mortality rate than non-MPT patients.

4.1 Study Population

The retrospective chart analysis revealed that out of 3,549 OC patients reviewed, 513 (14.5%) patients developed MPTs. The incidence of MPTs in previous studies has been reported from 11 to as high as 27% retrieved from different population databases, which is comparable to this study (Ko et al., 2016; Lai et al., 2013; Lubek & Clayman, 2012; Rennemo et al., 2010). We identified that the majority of the patients in our study developed one SPT (82.8%) with an average duration of 4.04 years after the occurrence of primary oral cancer. This finding is similar to the previous studies that reported an average duration of 4.5 and 4.7 years until the development of MPTs (Feng et al., 2017; Rogers et al., 2019). It is apparent that the patients at risk may develop secondary tumors long after the presentation of primary tumors, thus supporting the significance of long-term

follow-up and continuous monitoring even after treatment to improve the prognosis of the disease. (Mochizuki et al., 2015).

4.2 Socio-demographic Characteristics

A comparative analysis between MPT and non-MPT patients was carried out to study if any relation existed between development of MPT and the sociodemographic factors. While no significant association was found between gender and development of MPT, a stronger male predilection was seen in both groups with a mean age of 61 years. This finding is consistent with other reports in the literature (Choi & Thomson, 2020). However, there are other studies documented from USA population database reporting older females to be more affected with multiple primaries. This could be due to smaller number of patients in the studies (20 and 40 individuals, respectively) (Qaisi et al., 2014; Wiseman et al., 2003).

Among other sociodemographic characteristics that were considered, advanced age and average income were found to be potential risk factors associated with the development of MPT. Since the incidence of cancer increases with age, it was not surprising to see a positive association between increasing age and MPT development.

4.3 Clinico-pathologic features

In this study, among all the different primary subsites of oral cavity, higher number of MPTs were seen in patients with tongue and tonsil tumors. Moreover, MPTs were found to be predominant in the oral region involving tongue and floor of the mouth, accounting for the common clinical presentation followed by lungs and digestive system. These findings may have supported the concept of ‘field cancerization’ which explains that the susceptibility to cancer in the regional

sites, most probably due to environmental carcinogens (Jovanoic et al., 1994). Previous studies have reported smoking and/or drinking alcohol increases the development of MPT, by 25 times or higher, indicating that patients exposed to these host factors may be more vulnerable (Schantz et al., 1990). However, there are studies that have found little or no relation between smoking or alcohol and MPT development. Mochizuki et al. reported that MPTs were more frequently observed in non-smokers, suggesting a genetic or other underlying association (Mochizuki et al., 2015). Due to limited information related to smoking and alcohol habits in patients' charts in the registry, the causal relationship could not be established in this study and the question of personal habits needs to be further clarified in future studies.

The findings showed that the entire cohort belonged to an advanced stage of POC. Stage IV was found to be the most predominant type of stage at the time of POC diagnosis. The regression analysis showed stage IV to be inversely associated with MPT development. This could be due to poor survival of oral cancer patients with an advanced stage of the disease and therefore not leading to further tumor development.

Furthermore, this study showed a positive correlation between development of MPTs and existing co-morbid conditions including COPD and diabetes. Different epidemiological and clinical studies have reported a correlation between increased incidence of oral cancer and diabetes mellitus (Giovannucci et al., 2010). It has been suggested that long-term exposure to high glucose concentrations predisposes to upregulation of oncogenic pathways leading to malignancy (Vander Heiden et al., 2009). The experimental studies on mice also supported that diabetes mellitus facilitated oral tumorigenesis due to various underlying cellular and molecular mechanisms (Vairaktaris et al., 2007). It is therefore important that oral cancer patients who also have an

associated co-morbid condition specifically diabetes mellitus, should be closely monitored to diagnose development of any secondary tumors in due time.

In our study, no significant association was found between the type of treatment received for primary oral cancer and development of MPT. Surgery alone was the most common type of treatment recorded in the entire cohort followed by chemotherapy+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 the cases followed by the chemotherapy+radiotherapy regime (Mochizuki et al., 2015). Kramer et al in his study also reported that more than 50% of all examined patients were treated by surgery only (Kramer et al., 2004). Although, surgery is the most common type of treatment for oral cancer patients, the significance of including negative surgical margins is less important in preventing development of MPTs (González-García et al., 2009; Tabor et al., 2001). This further supports the concept of field cancerization of oral mucosa, in that even after complete excision of the primary tumor, new multiple primary carcinomas may develop in the condemned mucosa due to genetically altered epithelial cells distant from the surgical site (van Houten et al., 2004).

4.4 Clinical Outcome

In this study, the five-year survival rate for MPT patients was 71% as compared to non-MPT patients (70%). The approximately similar survival rate in MPT and non-MPT patients could be due to the measurement of survival years from the primary oral cancer. We, therefore, conducted the survival analysis for MPT patients separately to determine the survival time after developing second primary tumor. We found a comparatively lower survival rate of 45% in MPT patients. We also found out that oral cancer patients who had a survival rate longer than 5 years, showed a sharp

decrease in DSS after developing MPTs. Similarly, a significant decrease has been reported in the survival rate after developing MPTs in oral cancer patients by other studies. It is well documented that patients who develop MPTs have increased morbidity and mortality rates (Cianfriglia et al., 1999; Ellison, 2010; Mochizuki et al., 2015). It has been suggested that the reduced survival of patients with MPTs could be due to challenges in diagnosing and treating an additional malignancy due to scar formation from the previous surgical treatment of POC (Kramer et al., 2004).

To study the prognostic factors for poor DSS, we ran a regression analysis. Our results showed that the patients with an advanced age > 45 years and BMI < 18.5 had an increased hazard ratio of death. These findings are similar to previous studies reported in the literature (Badri et al., 2021). However, it is noteworthy to mention that the BMI was recorded at the time of initial treatment of POC and not at the time of diagnosis of cancer. Furthermore, synchronous tumors had an increase hazard of death as compared to metachronous tumors. Previous studies have also documented that synchronous tumors have a relatively poor survival rate as compared to metachronous tumors (Bugter et al., 2019; Di Martino et al., 2002). This could be due to presentation of synchronous tumors with more advanced stage (III and IV) as compared to the metachronous tumors or due to limited treatment options for additional malignancy (Bugter et al., 2019). Panosetti et al. in his study also documented that the prognosis of synchronous tumors worsens if the treatment plan has to be modified due to occurrence of second primary tumor (Panosetti et al., 1990).

We also found a 3-fold increased risk of death in MPT patients who had other associated co-morbid conditions. Previous studies focusing on breast, lung, and colorectal cancer reported similar trends of decreasing survival rates in cancer patients with comorbidities (Cronin-Fenton et al., 2007; Iversen et al., 2009; Lüchtenborg et al., 2012). Suboptimal treatment employed among cancer

patients with comorbidities along with chances of development of postoperative complications may be some of the causes of decreased survival rates in such patients (Søgaard et al., 2013).

The site of SPT was also found to play a significant role in survival. Although the incidence of SPTs was higher in the oral region than the other distant sites, the survival rate was found to be 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. (Chen et al., 2010) and Dequanter et al. (Dequanter et al., 2011b). 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 results also showed that higher pathological stage of oral cancer was closely associated with lower DSS. These findings are consistent with previous literature showing that advanced stage of oral cancer has proven to be the poor prognostic factor and one of the major causes of poor survival rate (Tsou et al. 2007). Therefore, an early detection of a developing tumor is very important in order to improve the prognosis of the disease.

4.5 Study Limitations and Future Directions

4.5.1 Limitations

Some of the study limitations are listed as follows:

1. Retrospective study design: As the study was conducted based on the past patient records, some of the baseline information was missing that would have been informative. There was lack of information regarding tobacco and alcohol use, which could have help understand the concept of field cancerization in MPT patients.

2. There was incomplete information about TNM staging, which as well could help understand the differences in the clinical profile and disease outcome of both groups.
3. Since the data was retrieved from an administrative database, there is a possibility of data omission and inaccuracy in data entry due to human error.

4.5.2 Future directions:

1. Ideally, it would be beneficial to conduct another study by merging multiple databases which could include the associated risk factors and help understand the development of MPT with field cancerization.
2. Future studies are recommended to include the clinical staging of the disease to understand the differences between the POC and MPT staging and its effect on survival.
3. Experimental studies should be conducted to understand the genetic profile of POC and MPTs and find out if there is any association between both the mucosal profiles.

4. This study was limited to only the Alberta Cancer registry database. A nation-wide study involving existing provincial databases could be conducted to understand the development of MPT and oral cancer in the Canadian population.

4.5.3 Policy & practice implications

This study showed an increased incidence and poor survival of primary oral cancer patients who developed MPTs. This challenge could be addressed through the following strategies:

- Educating dentists, physicians, nurses and patients about development of MPTs in oral and other distant sites after treatment of primary oral cancer.
- Close monitoring and regular follow-up of oral cancer patients' post-treatment with a focus on at risk groups, such as older patients, patients with co-morbid conditions, and users of alcohol or/and tobacco to improve the prognosis of disease.

5 Chapter Five: Conclusions

Our results suggest that about 5 in every 30 patients with primary oral cancer developed MPTs in Alberta. The comparative analyses also demonstrated that the oral cancer patients with advanced age, associated co-morbid conditions, and those who survived longer after the treatment of primary tumors developed more MPTs. This showed a negative impact on disease specific survival rate, which was more predominant in patients with MPTs. The hazard ratio of death was higher in patients with synchronous tumors, associated co-morbid conditions and who developed MPTs in esophagus. To enhance the survival in cancer patients and to reduce the financial, emotional, and physical burden of further treatment and dysfunction, early detection of a second primary tumor is of key importance. Patients should be provided with adequate information and awareness of likelihood of second primary tumors after the treatment of primary oral cancer. Additionally, close monitoring and follow up should be executed for patients treated for primary cancers.

6 Chapter Six: References

Ang, K. K., Harris, J., Wheeler, R., Weber, R., Rosenthal, D. I., Nguyen-Tân, P. F., Westra, W. H., Chung, C. H., Jordan, R. C., Lu, C., Kim, H., Axelrod, R., Silverman, C. C., Redmond, K. P., & Gillison, M. L. (2010). Human papillomavirus and survival of patients with oropharyngeal cancer. *N Engl J Med*, *363*(1), 24-35. https://doi.org/10.1056/NEJMoa0912217

Ang, K. K., & Sturgis, E. M. (2012). Human papillomavirus as a marker of the natural history and response to therapy of head and neck squamous cell carcinoma. *Semin Radiat Oncol*, *22*(2), 128-142. https://doi.org/10.1016/j.semradonc.2011.12.004

Badri, P., Ganatra, S., Baracos, V., Lai, H., & Amin, M. (2021). Oral Cavity and Oropharyngeal Cancer Surveillance and Control in Alberta: A Scoping Review. *JOURNAL OF THE CANADIAN DENTAL ASSOCIATION*, *87*. https://login.ezproxy.library.ualberta.ca/login?url=https://search.ebscohost.com/login.aspx?direct=true&db=edswsc&AN=000634855100001&site=eds-live&scope=site

Bedi, G. C., Westra, W. H., Gabrielson, E., Koch, W., & Sidransky, D. (1996). Multiple head and neck tumors: evidence for a common clonal origin. *Cancer Res*, *56*(11), 2484-2487.

Blot, W. J., McLaughlin, J. K., Winn, D. M., Austin, D. F., Greenberg, R. S., Preston-Martin, S., Bernstein, L., Schoenberg, J. B., Stemhagen, A., & Fraumeni, J. F., Jr. (1988). Smoking and drinking in relation to oral and pharyngeal cancer. *Cancer Res*, *48*(11), 3282-3287.

Brands, M. T., Brennan, P. A., Verbeek, A. L. M., Merkx, M. A. W., & Geurts, S. M. E. (2018). Follow-up after curative treatment for oral squamous cell carcinoma. A critical appraisal

of the guidelines and a review of the literature. *Eur J Surg Oncol*, *44*(5), 559-565. https://doi.org/10.1016/j.ejso.2018.01.004

Bugter, O., van Iwaarden, D. L. P., Dronkers, E. A. C., de Herdt, M. J., Wieringa, M. H., Verduijn, G. M., Mureau, M. A. M., Ten Hove, I., van Meerten, E., Hardillo, J. A., & Baatenburg de Jong, R. J. (2019). Survival of patients with head and neck cancer with metachronous multiple primary tumors is surprisingly favorable. *Head Neck*, *41*(6), 1648-1655. https://doi.org/10.1002/hed.25595

Califano, J., Leong, P. L., Koch, W. M., Eisenberger, C. F., Sidransky, D., & Westra, W. H. (1999). Second esophageal tumors in patients with head and neck squamous cell carcinoma: an assessment of clonal relationships. *Clin Cancer Res*, *5*(7), 1862-1867.

Canadian Cancer Society. (2022a). *Canadian Cancer Statistics*. Retrieved May 12 from https://cancer.ca/en/research/cancer-statistics

Canadian Cancer Society. (2022b, May 12). *Canadian Cancer Statistics*. https://cancer.ca/en/research/cancer-statistics/canadian-cancer-statistics

Cancer Centre. (2018). *ICD-0-3 Topographical Codes*. Retrieved May 1st from https://cancercenter.ai/icd-o-pathology-codes/topographical-codes-icd-o-3/

Chen, M. C., Huang, W. C., Chan, C. H., Chen, P. T., & Lee, K. D. (2010). Impact of second primary esophageal or lung cancer on survival of patients with head and neck cancer. *Oral Oncol*, *46*(4), 249-254. https://doi.org/10.1016/j.oraloncology.2010.01.002

Choi, S. W., & Thomson, P. (2020). Multiple oral cancer development-Clinico-pathological features in the Hong Kong population. *J Oral Pathol Med*, *49*(2), 145-149. https://doi.org/10.1111/jop.12962

Chow, L. Q. M. (2020). Head and Neck Cancer. *New England Journal of Medicine*, *382*(1), 60-72. https://doi.org/10.1056/NEJMra1715715

Cianfriglia, F., Di Gregorio, D. A., & Manieri, A. (1999). Multiple primary tumours in patients with oral squamous cell carcinoma. *Oral Oncol*, *35*(2), 157-163. https://doi.org/10.1016/s1368-8375(98)00105-5

Coyte, A., Morrison, D. S., & McLoone, P. (2014). Second primary cancer risk - the impact of applying different definitions of multiple primaries: results from a retrospective population-based cancer registry study. *BMC Cancer*, *14*, 272. https://doi.org/10.1186/1471-2407-14-272

Cronin-Fenton, D. P., Nørgaard, M., Jacobsen, J., Garne, J. P., Ewertz, M., Lash, T. L., & Sørensen, H. T. (2007). Comorbidity and survival of Danish breast cancer patients from 1995 to 2005. *British Journal of Cancer*, *96*(9), 1462-1468. https://doi.org/10.1038/sj.bjc.6603717

Dequanter, D., Shahla, M., Lardinois, I., Gilbert, O., Hanquet, O., Tragas, G., Van Meerhæghe, A., & Lothaire, P. (2011a). Second primary lung malignancy in head and neck cancer patients. *European Annals of Otorhinolaryngology, Head and Neck Diseases*, *128*(1), 11-13. https://doi.org/https://doi.org/10.1016/j.anorl.2010.06.004

Dequanter, D., Shahla, M., Lardinois, I., Gilbert, O., Hanquet, O., Tragas, G., Van Meerhæghe, A., & Lothaire, P. (2011b). Second primary lung malignancy in head and neck cancer patients. *Eur Ann Otorhinolaryngol Head Neck Dis*, *128*(1), 11-13. https://doi.org/10.1016/j.anorl.2010.06.004

Di Martino, E., Sellhaus, B., Hausmann, R., Minkenberg, R., Lohmann, M., & Esthofen, M. W. (2002). Survival in second primary malignancies of patients with head and neck cancer. *J Laryngol Otol*, *116*(10), 831-838. https://doi.org/10.1258/00222150260293664

Ellison, L. F. (2010). Measuring the effect of including multiple cancers in survival analyses using data from the Canadian Cancer Registry. *Cancer Epidemiol*, *34*(5), 550-555. https://doi.org/10.1016/j.canep.2010.06.015

Feng, Z., Xu, Q. S., Qin, L. Z., Li, H., Huang, X., Su, M., & Han, Z. (2017). Second primary cancer after index head and neck squamous cell carcinoma in Northern China. *Oral Surgery, Oral Medicine, Oral Pathology & Oral Radiology*, *123*(1), 95-102. https://doi.org/10.1016/j.oooo.2016.08.013

Ferlay, J., Steliarova-Foucher, E., Lortet-Tieulent, J., Rosso, S., Coebergh, J. W., Comber, H., Forman, D., & Bray, F. (2013). Cancer incidence and mortality patterns in Europe: estimates for 40 countries in 2012. *Eur J Cancer*, *49*(6), 1374-1403. https://doi.org/10.1016/j.ejca.2012.12.027

Giovannucci, E., Harlan, D. M., Archer, M. C., Bergenstal, R. M., Gapstur, S. M., Habel, L. A., Pollak, M., Regensteiner, J. G., & Yee, D. (2010). Diabetes and cancer: a consensus report. *Diabetes care*, *33*(7), 1674-1685. https://doi.org/10.2337/dc10-0666

Glicksman, A. S., & Fulton, J. P. (2013). Metachronous cancer. *R I Med J (2013)*, *96*(4), 41-44.

González-García, R., Naval-Gías, L., Sastre-Pérez, J., Rodríguez-Campo, F. J., & Román-Romero, L. (2009). Local recurrences and second primary tumors from squamous cell carcinoma of the oral cavity: A retrospective analytic study of 500 patients [Article]. *Head and Neck*, *31*(9), 1168-1180. https://doi.org/10.1002/hed.21088

Ha, P. K., & Califano, J. A. (2003). The molecular biology of mucosal field cancerization of the head and neck. *Crit Rev Oral Biol Med*, *14*(5), 363-369. https://doi.org/10.1177/154411130301400506

Hamadah, O., Goodson, M. L., & Thomson, P. J. (2010). Clinicopathological behaviour of multiple oral dysplastic lesions compared with that of single lesions. *Br J Oral Maxillofac Surg*, *48*(7), 503-506. https://doi.org/10.1016/j.bjoms.2009.08.027

Hashibe, M., Brennan, P., Benhamou, S., Castellsague, X., Chen, C., Curado, M. P., Dal Maso, L., Daudt, A. W., Fabianova, E., Fernandez, L., Wünsch-Filho, V., Franceschi, S., Hayes, R. B., Herrero, R., Koifman, S., La Vecchia, C., Lazarus, P., Levi, F., Mates, D., . . . Boffetta, P. (2007). Alcohol drinking in never users of tobacco, cigarette smoking in never drinkers, and the risk of head and neck cancer: pooled analysis in the International Head and Neck Cancer Epidemiology Consortium. *J Natl Cancer Inst*, *99*(10), 777-789. https://doi.org/10.1093/jnci/djk179

Heroiu Cataloiu, A.-D., Danciu, C. E., & Popescu, C. R. (2013). Multiple cancers of the head and neck. *Maedica*, *8*(1), 80-85. https://pubmed.ncbi.nlm.nih.gov/24023604

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3749768/

Hong, W. K., Lippman, S. M., Itri, L. M., Karp, D. D., Lee, J. S., Byers, R. M., Schantz, S. P., Kramer, A. M., Lotan, R., Peters, L. J., & et al. (1990). Prevention of second primary tumors with isotretinoin in squamous-cell carcinoma of the head and neck. *N Engl J Med*, *323*(12), 795-801. https://doi.org/10.1056/nejm199009203231205

International rules for multiple primary cancers. (2005). *Asian Pac J Cancer Prev*, *6*(1), 104-106.

Ishimori, T., Patel, P. V., & Wahl, R. L. (2005). Detection of unexpected additional primary malignancies with PET/CT. *J Nucl Med*, *46*(5), 752-757.

Iversen, L. H., Nørgaard, M., Jacobsen, J., Laurberg, S., & Sørensen, H. T. (2009). The impact of comorbidity on survival of Danish colorectal cancer patients from 1995 to 2006--a

population-based cohort study. *Dis Colon Rectum*, *52*(1), 71-78. https://doi.org/10.1007/DCR.0b013e3181974384

Jovanoic, A., van der Tol, I. G. H., Schulten, E. A. J. M., van der Waal, I., Kostense, P. J., de Vries, N., & Snow, G. B. (1994). Risk of multiple primary tumors following oral squamous-cell carcinoma [Article]. *International Journal of Cancer*, *56*(3), 320-323. https://doi.org/10.1002/ijc.2910560304

Ko, H. H., Chen, H. M., Cheng, S. J., Kok, S. H., Lee, J. J., Cheng, S. L., & Wang, C. W. (2016). Factors influencing the incidence and prognosis of second primary tumors in patients with oral squamous cell carcinoma [Article]. *Head and Neck*, *38*(10), 1459-1466. https://doi.org/10.1002/hed.24457

Kramer, F. J., Janssen, M., & Eckardt, A. (2004). Second primary tumours in oropharyngeal squamous cell carcinoma. *Clin Oral Investig*, *8*(2), 56-62. https://doi.org/10.1007/s00784-003-0246-z

Lai, W.-M., Chen, C.-C., Lee, J.-H., Chen, C.-J., Wang, J.-S., Hou, Y.-Y., Liou, H.-H., Chen, H.-C., Fu, T.-Y., Lee, Y.-C., & Ger, L.-P. (2013). Second primary tumors and myeloperoxidase expression in buccal mucosal squamous cell carcinoma. *Oral Surgery, Oral Medicine, Oral Pathology and Oral Radiology*, *116*(4), 464-473. https://doi.org/https://doi.org/10.1016/j.oooo.2013.06.018

Leong, P. P., Rezai, B., Koch, W. M., Reed, A., Eisele, D., Lee, D. J., Sidransky, D., Jen, J., & Westra, W. H. (1998). Distinguishing second primary tumors from lung metastases in patients with head and neck squamous cell carcinoma. *J Natl Cancer Inst*, *90*(13), 972-977. https://doi.org/10.1093/jnci/90.13.972

Liu, C. H., Chen, H. J., Wang, P. C., Chen, H. S., & Chang, Y. L. (2013). Patterns of recurrence and second primary tumors in oral squamous cell carcinoma treated with surgery alone. *Kaohsiung J Med Sci*, *29*(10), 554-559. https://doi.org/10.1016/j.kjms.2013.03.001

Lubek, J. E., & Clayman, L. (2012). An Update on Squamous Carcinoma of the Oral Cavity, Oropharynx, and Maxillary Sinus. *Oral and Maxillofacial Surgery Clinics of North America*, *24*(2), 307-316. https://doi.org/https://doi.org/10.1016/j.coms.2012.01.003

Lüchtenborg, M., Jakobsen, E., Krasnik, M., Linklater, K. M., Mellemgaard, A., & Møller, H. (2012). The effect of comorbidity on stage-specific survival in resected non-small cell lung cancer patients. *Eur J Cancer*, *48*(18), 3386-3395. https://doi.org/10.1016/j.ejca.2012.06.012

Lydiatt, W., O'Sullivan, B., & Patel, S. (2018). Major Changes in Head and Neck Staging for 2018. *Am Soc Clin Oncol Educ Book*, *38*, 505-514. https://doi.org/10.1200/edbk_199697

Madani, M., Berardi, T., & Stoopler, E. T. (2014). Anatomic and Examination Considerations of the Oral Cavity. *MEDICAL CLINICS OF NORTH AMERICA*, *98*(6), 1225-+. https://doi.org/10.1016/j.mcna.2014.08.001

Mariotto, A. B., Noone, A.-M., Howlader, N., Cho, H., Keel, G. E., Garshell, J., Woloshin, S., & Schwartz, L. M. (2014). Cancer survival: an overview of measures, uses, and interpretation. *Journal of the National Cancer Institute. Monographs*, *2014*(49), 145-186. https://doi.org/10.1093/jncimonographs/lgu024

Mochizuki, Y., Harada, H., Ikuta, M., Shimamoto, H., Tomioka, H., Tanaka, K., Hirai, H., & Omura, K. (2015). Clinical characteristics of multiple primary carcinomas of the oral cavity. *Oral Oncol*, *51*(2), 182-189. https://doi.org/10.1016/j.oraloncology.2014.11.013

Mohan, M., & Jagannathan, N. (2014). Oral field cancerization: an update on current concepts. *Oncology reviews*, *8*(1), 244-244. https://doi.org/10.4081/oncol.2014.244

National Cancer Institute. (2021). *SEER Program Coding and Staging Manual 2021* Retrieved May 12 from https://seer.cancer.gov/archive/manuals/2021/SPCSM_2021_MainDoc.pdf

Panosetti, E., Arnold, W., & Müller, W. (1990). [Site and incidence of multiple cancers in patients with squamous cell carcinomas of the upper aerodigestive tract]. *Laryngorhinootologie*, *69*(9), 449-453. https://doi.org/10.1055/s-2007-998228 (Lokalisation und Frequenz von Mehrfachkarzinomen bei Patienten mit Plattenepithelkarzinomen des oberen Aerodigestivtraktes.)

Qaisi, M., Vorrasi, J., Lubek, J., & Ord, R. (2014). Multiple Primary Squamous Cell Carcinomas of the Oral Cavity. *Journal of Oral and Maxillofacial Surgery*, *72*(8), 1511-1516. https://doi.org/https://doi.org/10.1016/j.joms.2014.03.012

Rennemo, E., Zätterström, U., & Boysen, M. (2010). Outcome of local failures after oral cancer - recurrence vs. second primary. *Journal of Oral Pathology & Medicine*, *39*(9), 657-661. https://doi.org/10.1111/j.1600-0714.2010.00905.x

Rogers, S. N., Swain, A., Carroll, C., & Lowe, D. (2019). Incidence, timing, presentation, treatment, and outcomes of second primary head and neck squamous cell carcinoma after oral cancer. *British Journal of Oral and Maxillofacial Surgery*, *57*(10), 1074-1080. https://doi.org/https://doi.org/10.1016/j.bjoms.2019.09.018

Schantz, S. P., Spitz, M. R., & Hsu, T. C. (1990). Mutagen sensitivity in patients with head and neck cancers: a biologic marker for risk of multiple primary malignancies. *J Natl Cancer Inst*, *82*(22), 1773-1775. https://doi.org/10.1093/jnci/82.22.1773

Scholes, A. G., Woolgar, J. A., Boyle, M. A., Brown, J. S., Vaughan, E. D., Hart, C. A., Jones, A. S., & Field, J. K. (1998). Synchronous oral carcinomas: independent or common clonal origin? *Cancer Res*, *58*(9), 2003-2006.

Secretan, B., Straif, K., Baan, R., Grosse, Y., El Ghissassi, F., Bouvard, V., Benbrahim-Tallaa, L., Guha, N., Freeman, C., Galichet, L., & Cogliano, V. (2009). A review of human carcinogens--Part E: tobacco, areca nut, alcohol, coal smoke, and salted fish. *Lancet Oncol*, *10*(11), 1033-1034. https://doi.org/10.1016/s1470-2045(09)70326-2

Slaughter, D. P., Southwick, H. W., & Smejkal, W. (1953). Field cancerization in oral stratified squamous epithelium; clinical implications of multicentric origin. *Cancer*, *6*(5), 963-968. https://doi.org/10.1002/1097-0142(195309)6:5<963::aid-cncr2820060515>3.0.co;2-q

Søgaard, M., Thomsen, R. W., Bossen, K. S., Sørensen, H. T., & Nørgaard, M. (2013). The impact of comorbidity on cancer survival: a review. *Clin Epidemiol*, *5*(Suppl 1), 3-29. https://doi.org/10.2147/clep.S47150

Statistics Canada. (2022). *Conditional survival analysis across cancer sites*. Retrieved April 10 from https://www150.statcan.gc.ca/n1/pub/82-003-x/2011002/article/11425-eng.pdf

Sung, H., Ferlay, J., Siegel, R. L., Laversanne, M., Soerjomataram, I., Jemal, A., & Bray, F. (2021). Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. *CA: A Cancer Journal for Clinicians*, *71*(3), 209-249. https://doi.org/https://doi.org/10.3322/caac.21660

Surveillance System Branch. (2012). *SEER Program Coding and Staging Manual*. Retrieved May 12 from https://seer.cancer.gov/archive/manuals/2012/SPCSM_2012_maindoc.pdf

Tabor, M. P., Brakenhoff, R. H., Ruijter-Schippers, H. J., Van Der Wal, J. E., Snow, G. B., Leemans, C. R., & Braakhuis, B. J. M. (2002). Multiple head and neck tumors frequently originate from a single preneoplastic lesion. *The American journal of pathology*, *161*(3), 1051-1060. https://doi.org/10.1016/S0002-9440(10)64266-6

Tabor, M. P., Brakenhoff, R. H., van Houten, V. M., Kummer, J. A., Snel, M. H., Snijders, P. J., Snow, G. B., Leemans, C. R., & Braakhuis, B. J. (2001). Persistence of genetically altered

fields in head and neck cancer patients: biological and clinical implications. *Clin Cancer Res*, *7*(6), 1523-1532.

Thomson, P. J. (2002). Field change and oral cancer: new evidence for widespread carcinogenesis? *Int J Oral Maxillofac Surg*, *31*(3), 262-266. https://doi.org/10.1054/ijom.2002.0220

Tsou, Y., Hua, C., Tseng, H., Lin, M., & Tsai, M. (2007). Survival study and treatment strategy for second primary malignancies in patients with head and neck squamous cell carcinoma and nasopharyngeal carcinoma. *Acta Oto-Laryngologica*, *127*(6), 651-657. https://doi.org/10.1080/00016480600951517

Vairaktaris, E., Spyridonidou, S., Goutzanis, L., Vylliotis, A., Lazaris, A., Donta, I., Perrea, D., Yapijakis, C., & Patsouris, E. (2007). Diabetes and oral oncogenesis. *Anticancer Res*, *27*(6b), 4185-4193.

van Houten, V. M., Leemans, C. R., Kummer, J. A., Dijkstra, J., Kuik, D. J., van den Brekel, M. W., Snow, G. B., & Brakenhoff, R. H. (2004). Molecular diagnosis of surgical margins and local recurrence in head and neck cancer patients: a prospective study. *Clin Cancer Res*, *10*(11), 3614-3620. https://doi.org/10.1158/1078-0432.Ccr-03-0631

Vander Heiden, M. G., Cantley, L. C., & Thompson, C. B. (2009). Understanding the Warburg effect: the metabolic requirements of cell proliferation. *Science*, *324*(5930), 1029-1033. https://doi.org/10.1126/science.1160809

Vogt, A., Schmid, S., Heinimann, K., Frick, H., Herrmann, C., Cerny, T., & Omlin, A. (2017). Multiple primary tumours: challenges and approaches, a review. *ESMO open*, *2*(2), e000172-e000172. https://doi.org/10.1136/esmoopen-2017-000172

Warnakulasuriya, K. A., Robinson, D., & Evans, H. (2003). Multiple primary tumours following head and neck cancer in southern England during 1961-98. *J Oral Pathol Med*, *32*(8), 443-449. https://doi.org/10.1034/j.1600-0714.2003.00179.x

Warren S, G. O. (1932). Multiple primary malignant tumors. A survey of the literature and a statistical study. *Am J Cancer 16*, 13-58.

Wiseman, S. M., Swede, H., Stoler, D. L., Anderson, G. R., Rigual, N. R., Hicks, J. W. L., Douglas, W. G., Tan, D., & Loree, T. R. (2003). Squamous Cell Carcinoma of the Head and Neck in Nonsmokers and Nondrinkers: An Analysis of Clinicopathologic Characteristics and Treatment Outcomes [Original Paper]. *Annals of Surgical Oncology*, *10*(5), 551-557. https://doi.org/10.1245/aso.2003.09.010

World Health Organization. (2020). *International Agency for Research on Cancer*. Retrieved May 12 from https://gco.iarc.fr/today/data/factsheets/cancers/1-Lip-oral-cavity-fact-sheet.pdf

Yarbro, J. W., Page, D. L., Fielding, L. P., Partridge, E. E., & Murphy, G. P. (1999). American Joint Committee on Cancer prognostic factors consensus conference. *Cancer*, *86*(11), 2436-2446. https://doi.org/10.1002/(sici)1097-0142(19991201)86:11<2436::aid-cncr35>3.0.co;2-#

Zhai, C., Cai, Y., Lou, F., Liu, Z., Xie, J., Zhou, X., Wang, Z., Fang, Y., Pan, H., & Han, W. (2018). Multiple Primary Malignant Tumors - A Clinical Analysis of 15,321 Patients with Malignancies at a Single Center in China. *Journal of Cancer*, *9*(16), 2795-2801. https://doi.org/10.7150/jca.25482

Appendices

Appendix 1 Ethics Approval

HREBA Health Research Ethics Board of Alberta Cancer Committee

Health Research Ethics Board of Alberta
Cancer Committee
1500, 10104 - 103 Avenue NW
Edmonton, Alberta, T5J 0H8
Telephone: (780) 423-5727
Fax: (780) 429-3509
Email: cancer@hreba.ca

Modification of Ethics Approval

This is to acknowledge that the modification to the research indicated below has been reviewed and on behalf of the Health Research Ethics Board of Alberta (HREBA) – Cancer Committee (CC), I am pleased to advise that approval has been granted.

Ethics ID:	HREBA.CC-17-0370_MOD1
Principal Investigator:	Maryam Sharifzadeh-Amin
Co-Investigator(s):	Vickie Baracos Seema Ganatra Mohammadreza Pakseresht
Student Co-Investigator(s):	Parvaneh Badri Salma Asifali Sawani
Study Title:	Oral Cancer Surveillance and Control in Alberta: A Conceptual Framework
Sponsor:	

Effective: 31-Jul-2019 **Expires:** 30-Jul-2020

Modification reviewed by delegated review on 04 November 2019.

The following information was received and has been acknowledged:
-Salma Asifali Sawani has been added as a student Co-Investigator

This Committee is constituted and operates in accordance with the Alberta Health Information Act (HIA), the Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans (TCPS 2), Good Clinical Practice (GCP) Guidelines of the International Conference on Harmonization (ICH), Health Canada's *Food and Drug Regulations* (FDR), Part C, Division 5 and is registered with the U.S. Department of Health and Human Services (HHS), Office for Human Research Protections (OHRP), IRB # 0000968?.

Members of the HREBA-CC who are named as principal investigators or co-investigators in this research do not participate in discussions related to, nor vote on, such studies when they are presented to the Committee. The membership of this Committee is listed at www.hreba.ca.

Please note that the approval of this modification does not change the effective or expiry dates of this study as indicated above.

Please accept the Committee's best wishes for success in your research.

Approved on behalf of CC by, **Date:**

Raul Urtasun , HREBA-CC 6-Nov-2019

Note: This correspondence includes an electronic signature (validation and approval via an online system).

Appendix 2 Ethics Renewal I

HREBA | Health Research Ethics Board of Alberta Cancer Committee

Health Research Ethics Board of Alberta
Cancer Committee
1500, 10104 - 103 Avenue NW
Edmonton, Alberta, T5J 0H8
Telephone: (780) 423-5727
Fax: (780) 429-3509
Email: cancer@hreba.ca

Certification of Ethics Approval - Renewal

This is to acknowledge that the renewal to the research indicated below has been reviewed and on behalf of the Health Research Ethics Board of Alberta (HREBA) – Cancer Committee (CC), I am pleased to advise that approval has been granted.

Ethics ID:	HREBA.CC-17-0370_REN3
Principal Investigator:	Maryam Sharifzadeh-Amin
Co-Investigator(s):	Seema Ganatra Mohammadreza Pakseresht Vickie Baracos
Student Co-Investigator(s):	Salima Asifali Sawani Parvaneh Badri
Study Title:	Oral Cancer Surveillance and Control in Alberta: A Conceptual Framework
Sponsor:	

Effective: 8-Jul-2020 **Expires:** 7-Jul-2021

Appendix 3 Ethics Renewal III

HREBA | Health Research Ethics Board of Alberta Cancer Committee

Health Research Ethics Board of Alberta
Cancer Committee
1500, 10104 - 103 Avenue NW
Edmonton, Alberta, T5J 0H8
Telephone: (780) 423-5727
Fax: (780) 429-3509
Email: cancer@hreba.ca

Certification of Ethics Approval - Renewal

This is to acknowledge that the renewal to the research indicated below has been reviewed and on behalf of the Health Research Ethics Board of Alberta (HREBA) – Cancer Committee (CC), I am pleased to advise that approval has been granted.

Ethics ID:	HREBA.CC-17-0370_REN4
Principal Investigator:	Maryam Sharifzadeh-Amin
Co-Investigator(s):	Seema Ganatra Mohammadreza Pakseresht Vickie Baracos
Student Co-Investigator(s):	Salima Asifali Sawani Parvaneh Badri
Study Title:	Oral Cancer Surveillance and Control in Alberta: A Conceptual Framework
Sponsor:	

Effective: 15-Jun-2021 **Expires:** 14-Jun-2022