The Effect of Radiation Therapy on Temporomandibular Joint and Its Function in Head and Neck Cancer Patients: A Prospective Study

Aia Naksho

Faculty of Dental Medicine and Oral Health Sciences

McGill University, Montreal

September 2024

A thesis submitted to McGill University in partial fulfillment of the requirements of the degree of

Master of Dental Sciences (Thesis)

Dedication

In the name of God Almighty, whose grace, guidance, and countless blessings have sustained me throughout my whole life, it is through His boundless mercy and grace that I have found the courage to persevere through challenges and the clarity to complete this work.

I would like to dedicate this work to my parents, Dr. Firas Naksho and Linda Sejary whose unwavering support has been my strength through all my life. Their love, encouragement, unlimited support and guidance have shaped who I am today. Those many years and nights of hard work was all to make them proud.

Also, I dedicate this thesis to my esteemed supervisor, Dr. Firoozeh Samim, with heartfelt gratitude for her unwavering belief in me and for her invaluable guidance and support throughout this journey, she has been truly an inspiration to me. Finally, I want to thank my dearest sisters, whose endless love, unwavering support, and constant encouragement have carried me through the toughest moments. Your belief in me has been my greatest source of strength and inspiration, and I couldn’t have done this without you by my side.

Table of contents

List of graphs and tables …….

List of abbreviations …….

Abstract …….....

Résumé ……

Preface …….

Contribution of the authors …….

Chapter 1. Introduction ……

Chapter 2. Comprehensive review of Literature …….

2.1 Head and neck cancer definitions …….

2.2 Head and neck cancer epidemiology ……

2.3 Risk Factors of Head and neck Cancer ……

2.4 Head and neck cancer treatment modalities ……

2.5 Radiation therapy description …….

2.6 Radiation therapy toxicities and side effects …….

2.7 Temporomandibular disorders ……

2.7.1 Temporomandibular disorders symptoms ……

2.7.2 Temporomandibular disorders detection …….

2.7.3 Frequency of Temporomandibular disorders in radiation treated cancer patients

2.8 Factors associated to radiation related Temporomandibular disorders ……..

2.8.1 Demographic factors ……

2.8.2 Type, stage and location of cancer ……..

2.8.3 Radiation dose …….

2.8.4 Radiation field …….

2.8.5 History of Temporomandibular disorders ……...

2.8.6 Exercise and speech therapy ……..

Chapter 3. Study objectives and hypotheses …….

3.1 objectives ……..……

3.2 hypothesis ……

Chapter 4. methodology ……..

4.1 study design ……

4.2 ethical approval , Consents and Patient confidentiality ……

4.3 Sample population and eligibility criteria…….……

4.4 Sample Size ……

4.5 Data collection ……

4.6 Data analysis …….……

Chapter 5. Manuscript ……

Chapter 6. Discussion…….

6.1 Summary of Results ……

6.2 Methodological considerations…….

6.2.1 Bias ……..

6.2.2 Strength of the study ……

6.2.3 Limitation of the study……

Chapter 7. conclusion ……..

Chapter 8. Clinical Implications ……

Chapter 9. Knowledge Translation ……

Chapter 10. References ……..

Appendix ……

Research Ethics Board Approval Letter……

Research Consent form ……

DC/TMD Examination Form ……

List of Graphs:

1. A pie chart with percentages for distribution of HNC subsites in Canada
2. Incidence and mortality rates of HND in Canada, Quebec and North America
3. Distribution of Risk Factors of HNCSS
4. Distribution of Risk Factors of HNC
5. Demographic of HNC by age and gender
6. Sample size flow chart
7. Baseline radiographic evaluation of participants.
8. Sample radiographic appearances of head and neck patients
9. TMJ range of motion
10. Pain on palpation in baseline, mid-treatment, 3 months follow up, and 6 months follow up.
11. Accompanying symptoms (clicking , crepitus, joint locking)

Tables:

1. Demographic and clinical data. n (%) for categorical data
2. Descriptives of mouth openings, lateral and protrusive movements.
3. Test of normalities
4. Mean (95% CI) change in pain free opening in millimeters and percent at each time-point compared to baseline
5. Mean (95% CI) change in maximum unassisted opening in millimeters and percent at each time-point compared to baseline.
6. Mean (95% CI) change in maximum assisted opening in millimeters and percent at each time-point compared to baseline.

7. Mean (95% CI) and change in right lateral movement at each time-point compared to baseline.
8. Mean (95% CI) and change in left lateral movement at each time-point compared to baseline.
9. Mean (95% CI) and change in protrusive movement at each time-point compared to baseline.
10. TMD symptoms among head and neck cancer patients at each time-point and compared to baseline.

List of abbreviations

DC/TMD:	Diagnostic Criteria for Temporomandibular Disorders
HPV:	Human Papilloma Virus
HNC:	Head and Neck Cancer
PTMD:	Pain-related temporomandibular disorder
SCC:	Squamous cell carcinoma
TMD:	Temporomandibular disorder

Abstract

The Effect of the Radiation Therapy on Temporomandibular Joint and Its Function in Head and Neck Cancer Patients : A Prospective Study

Background

Different multiple modalities can be used to treat head and neck cancers such as chemotherapy, surgery, and radiation therapy. While radiotherapy is considered a primary treatment for most head and neck cancers, it can cause debilitating side effects such as hyposalivation, mucositis, and limitation in the mouth opening. These side effects of radiation depend on several risk factors including the radiation dosage and field, tumor size and location, and the existence of temporomandibular disorders (TMD) in patients prior to their cancer diagnosis. Unfortunately, the quality of life of head and neck cancer patients drops dramatically due to TMD disorder symptoms, such as pain and limitation in mouth opening. The development of TMD disorders and hypofunction in oncology patients is due to the fibrosis and inflammation of the muscles of mastication and temporomandibular joint. The Temporomandibular joint (TMJ) and the masticatory muscles reveal delayed responses to radiation, distinguishing them as late-responding tissues when compared to other oral tissues. TMJ and masticatory muscles radiation induced changes are often noticed several months or even years after the end of the radiotherapy.

Objectives

The primary aim of this study is to determine the prevalence of TMD symptoms and effect of the radiation on TMJ structure in head and neck cancer patients, including those with squamous cell carcinoma SCC of the oral cavity and oropharyngeal areas. Additionally, this study aims to compare changes in potential risk factors over time.

Materials and methods

After the comprehensive literature review all patients with newly diagnosed head and neck cancers who referred to the oral oncology clinic located at Royal Victoria Hospital (Glenn site) prior to radiation therapy will be recruited. Patients who have undergone prior radiation therapy or surgical therapy with limitations in mouth opening will be excluded. Examinations will be conducted prior to, mid-treatment, and after radiotherapy, as well as at 3-month and 6-month follow-up appointments. Validated DC/TMD criteria and an Examination Form will be used to record our findings. All examinations will be performed by specialists, trained dentists, or residents who have been calibrated, and inter- and intra-examination reliability will be assessed.

Results

All patients with HNC were initially included in the study. The study composed a total of 44 participants, with an age range from 31 to 96 years. Majority of our patients had SCC and tumor locations varied across different anatomical sites, with oropharynx being the most common (18.2%), followed by tongue (13.6%) , larynx (11.4%), parotid gland, and tonsil, each (9.1%). All patients underwent radiation therapy with the minimum total dosage of 24 Gy and maximum of 70 Gy. The mean pain free opening before oncologic treatment was 40.12 (SD 8.328) mm, and the corresponding values at 3 and 6 months were 36.35 (SD 8.937) and 35.53 (SD 9.441) mm. The p Value Δ from baseline to the 6 months follow up on pain free opening is 0.53. Out of 44 patients undergoing RT, 24 (57.1%) showed no masticatory muscles pain pre-treatment. Then, 51.7% developed muscle pain on mid-treatment and 59.1% on 3 months post XRT.

Finally, 63.3% of our patient showed increased in both unilateral and bilateral muscle pain at the 6 months follow up. Most of our participants initially had a straight opening pattern that decreased at the mid treatment and 3 months but improved to 95.7% at 6 months. Although clicking and joint locking showed slight variations over time, no significant changes were observed when compared to baseline.

Conclusion:

We concluded that there is a modest reduction in pain-free mouth opening over a period of 6 months following oncologic treatment, indicating a potential impact of the treatment on oral function. Additionally, a significant proportion of patients who did not have masticatory muscle pain prior to radiotherapy developed unilateral muscle pain by the 6-month follow-up. This suggests that radiotherapy may be associated with the onset of muscle pain in a majority of cases, highlighting the need for proactive management strategies to address this complication.

Keywords: Head and neck cancer, SCC , Temporomandibular disorders, Orofacial pain, Radiation therapy

Résumé

Effet de la Radiothérapie sur l'Articulation Temporo-Mandibulaire et sa Fonction : une étude Prospective

Arrière-plan

Différentes modalités multiples peuvent être utilisées pour traiter les cancers de la tête et du cou, comme la chimiothérapie, la chirurgie et la radiothérapie. Bien que la radiothérapie soit considérée comme le traitement principal de la plupart des cancers de la tête et du cou, elle peut provoquer des effets secondaires débilitants tels qu'une hyposalivation, une mucite et une limitation de l'ouverture de la bouche. Ces effets secondaires des radiations dépendent de plusieurs facteurs de risque, notamment la dose et le champ de radiation, la taille et l'emplacement de la tumeur, ainsi que l'existence de troubles temporo-mandibulaires (TMD) chez les patients avant leur diagnostic de cancer. Malheureusement, la qualité de vie des patients atteints d'un cancer de la tête et du cou diminue considérablement en raison des symptômes du trouble TMD, tels que la douleur et la limitation de l'ouverture de la bouche. Le développement de troubles du TMD et d'hypofonctionnement chez les patients en oncologie est dû à la fibrose et à l'inflammation des muscles de la mastication et de l'articulation temporo-mandibulaire. L'articulation temporo-mandibulaire (ATM) et les muscles masticateurs révèlent des réponses retardées aux radiations, ce qui les distingue comme des tissus à réponse tardive par rapport aux autres tissus buccaux. Les modifications induites par la radiothérapie des ATM et des muscles masticateurs sont souvent constatées plusieurs mois, voire plusieurs années après la fin de la radiothérapie.

Objectifs

L'objectif principal de cette étude est de déterminer la prévalence des symptômes du TMD et l'effet du rayonnement sur la structure de l'ATM chez les patients atteints d'un cancer de la tête et du cou, y compris ceux atteints d'un carcinome épidermoïde SCC de la cavité buccale et des zones oropharyngées. De plus, cette étude vise à comparer l'évolution des facteurs de risque potentiels au fil du temps.

Matériels et méthodes

Après une revue complète de la littérature, tous les patients atteints d'un cancer de la tête et du cou nouvellement diagnostiqué qui ont été référés à la clinique d'oncologie buccale située à l'hôpital Royal Victoria (site Glenn) avant la radiothérapie seront recrutés. Les patients ayant déjà subi une radiothérapie ou une thérapie chirurgicale avec des limitations d'ouverture de la bouche seront exclus. Des examens seront effectués avant, à mi-traitement et après la radiothérapie, ainsi qu'aux rendez-vous de suivi à 3 et 6 mois. Des critères DC/TMD validés et un formulaire d'examen seront utilisés pour enregistrer nos résultats. Tous les examens seront effectués par des spécialistes, des dentistes qualifiés ou des résidents calibrés, et la fiabilité inter et intra-examen sera évaluée.

Résultats

Tous les patients atteints de HNC ont été initialement inclus dans l'étude. L'étude comprenait un total de 44 participants, âgés de 31 à 96 ans. La majorité de nos patients présentaient un CEC et la localisation des tumeurs variait selon les différents sites anatomiques, l'oropharynx étant le plus fréquent (18,2 %), suivi de la langue (13,6 %), du larynx (11,4 %), de la glande parotide et de l'amygdale, chacun (9,1 %).). Tous les patients ont subi une radiothérapie avec une dose totale minimale de 24 Gy et maximale de 70 Gy. L'ouverture moyenne sans douleur avant le

traitement oncologique était de 40,12 (SD 8,328) mm, et les valeurs correspondantes à 3 et 6 mois étaient de 36,35 (SD 8,937) et 35,53 (SD 9,441) mm. La valeur p Δ entre le départ et le suivi de 6 mois sur l'ouverture sans douleur est de 0,53. Sur 44 patients soumis à une RT, 24 (57,1 %) ne présentaient aucune douleur des muscles masticateurs avant le traitement. Ensuite, 51,7 % ont développé des douleurs musculaires à mi-traitement et 59,1 % 3 mois après XRT. Enfin, 63,3 % de nos patients ont présenté une augmentation des douleurs musculaires unilatérales et bilatérales au suivi à 6 mois. La plupart de nos participants avaient initialement un schéma d'ouverture droite qui diminuait à mi-traitement et à 3 mois, mais s'améliorait à 95,7 % à 6 mois. Bien que les clics et le verrouillage des articulations aient montré de légères variations au fil du temps, aucun changement significatif n'a été observé par rapport à la ligne de base.

Conclusion:

Nous avons conclu qu'il existe une légère réduction de l'ouverture buccale sans douleur sur une période de 6 mois après un traitement oncologique, indiquant un impact potentiel du traitement sur la fonction buccale. De plus, une proportion significative de patients qui ne souffraient pas de douleurs musculaires masticatoires avant la radiothérapie ont développé des douleurs musculaires unilatérales au bout de 6 mois de suivi. Ceci suggère que la radiothérapie pourrait être associée à l'apparition de douleurs musculaires dans la majorité des cas, soulignant la nécessité de stratégies de gestion proactives pour traiter cette complication.

Mots-clés : Cancer de la tête et du cou, CSC, Troubles temporo-mandibulaires, Douleur orofaciale, Radiothérapie

Preface

This thesis fulfills the requirements for the degree of Master's in Dental Sciences, and its objectives stem from the authors' strong interest in unraveling the effect of radiation therapy on Temporomandibular disorders and orofacial pain. Following the ethical approval mandated by the Research Ethics board of the Graduate and Postdoctoral Studies at McGill University, this thesis aspire to expand by both an existing literature review and data collection from cancer patients following up at the oral medicine clinic at Royal Victoria hospital glen site. Firstly, a compendious table of content and abstract summarize the research. Then, Chapter one sets the stage with an introduction to the thesis, followed by a chapter exploring the existing literature on head and neck cancers, their treatments, toxicity of radiation therapy, and finally the relation of temporomandibular disorders to radiotherapy. Chapter three delineates the objectives and hypotheses, setting the stage for a thorough examination of the methodology and statistical analysis in Chapter Four. Chapter 5 covers the manuscript containing the results leading to both discussion and conclusion chapters. The following chapter introduces the clinical implications then translation of knowledge that was produced from this thesis finalized with the references used.

In the sections that follow, due acknowledgment is explicitly given to each contributor's valuable role to this thesis.

Contribution of the authors

1. Aia Naksho: Main author, Master's thesis student, patient recruiter, data collector

2. Firoozeh Samim: Master's supervisor, manuscript main author, hospital attending, reviewer

3. Ali abdolrahmani: data analyst

4. Nour Karra: Master's degree committee member, hospital attending

Chapter 1: Introduction

Head and neck cancer is globally ranked as the seventh most prevalent form of cancer and are becoming common due to the dramatic increase of carcinogens exposure . [1, 2] Long standing evidence links alcohol and tobacco to be predominant causative factors in oral cavity, hypopharynx, larynx, and HPV-unrelated oropharynx cancers. Given that these carcinogens can affect the entire epithelium of the aerodigestive tract, individuals with head and neck cancers face the potential of having simultaneous primary tumors and developing secondary neoplasms in the head and neck region, lungs, esophagus, and breasts. Additionally, there has been a sudden rise in the incidence of oropharyngeal cancers due to escalating of human papillomavirus (HPV) infection. In the United States and certain parts of the European Union, the estimated attributable fraction for HPV in newly diagnosed oropharyngeal cancer is between 60% and 70%. [3-7] Unlike head and neck cancers associated with alcohol and smoking, HPV positive oropharyngeal cancer affects a younger demographic, often comprising individuals who are actively employed and showing interestingly better prognosis .[8, 9] Nevertheless, this devastating disease can be treated using various therapeutic approaches, including chemotherapy, surgery, and radiation therapy. In addition to surgery, radiation therapy stands as a primary treatment approach for most of head and neck cancers, applicable to both early and advanced stages. Radiation doses typically range from 54 to 70 Gy, delivered using a standard fractionation regimen of 2 Gy per fraction,

administered once daily, five fractions per week. [10] The aim of radiation therapy is to eliminate cancer cells. Given that cancer cells tend to proliferate and multiply more rapidly than normal cells, they are more susceptible to destruction by radiation. Nonetheless, radiotherapy is known to be associated with acute and chronic debilitating effects. The probability and intensity of the side effects vary based on several factors, such as radiation dose, the duration over which it was administered, and the specific regions of the head and neck subjected to radiotherapy. [11] Acute side effects arise during the treatment course and shortly 2-3 weeks after treatment cessation. Conversely, late effects may emerge at any point, thereafter, ranging from weeks to years later. The immediate effects of radiotherapy include mucositis, thick secretions, infections, sensory changes and pain. On the other hand, the enduring consequences of head and neck radiation therapy involve xerostomia, fibrosis, heightened vulnerability to mucosal infections, neuropathic pain, altered sensory perception, an elevated risk of dental caries, periodontitis and Temporomandibular disorders and jaw hypomobility. [12]

Temporomandibular disorders can be defined as any pain and functional disturbance in the temporomandibular joint and the muscles responsible for its movement which are masticatory muscles, including the masseter muscle, temporalis muscle, lateral and medial pterygoid.[13] This disturbance can result in noticeable signs and symptoms such as joint and muscle pain, clicking and crepitus noises, and restricted painful mouth opening and mandibular lateral and protrusive movements . [14] Recently, studies have suggested that the prevalence of TMD in the general population is between 40-60%, and only 10% of the population seeks treatment because they experience severe symptoms[13, 14].

Temporomandibular joint disorders and fibrosis in the head and neck structures can lead to restriction of the function of the lips and tongue. These effects may occur due to radiation exposure to the masticatory muscles (such as the masseter, temporalis, medial, and lateral pterygoids) and the Temporomandibular joint (TMJ).[15] Jaw hypomobility is a well-known consequence of radiation therapy that is dependent on several risk factors, including the radiation therapy dose, tumor size and location, and prior existence of temporomandibular disorders (TMD) in patients before their cancer diagnosis. Recent evidence had revealed that head and neck cancer treatments is now known as one of the causes of TMD symptoms. Reduction in mouth opening have been documented in a range of 6% to 86% among patients who underwent radiation therapy targeting the temporomandibular joint and masticatory muscles such as the masseter and pterygoid muscles. [16] In 2005, a study discussed that among their participants who didn't have a prior history of limitation in mouth opening before radiotherapy, there was noted to be a mere 1.3% reduction in maximum incisal distance per month. However, notable progression of symptoms occurred within the first nine months post-radiotherapy followed by a stabilization period. Thereafter, resulting in an average decrease in interincisal opening of 32% after four years of radiotherapy.[17]

Causes of jaw hypomobility can also be due to muscular dysfunction, temporomandibular joint disorders, oral submucous fibrosis, fracture of the jaws, mucositis , and restricted stretching of the oral mucosa.[18] This occurrence is thought to be attributable to several factors. This include radiation-induced fibrosis, a gradual decline in vascularity, and denervation of the joint muscles, along with injury to the mandible and temporomandibular joint (TMJ). Fibrosis is known to be triggered by ischemia due to endarteritis obliterans, referring to the inflammation and narrowing of arteries leading to decreased blood flow. [19] Reduced range of movement and masticatory

muscle pain resulting from radiation therapy (RT) is primarily associated with muscle damage and fibrosis, often initiated by abnormal fibroblast proliferation. This condition may also involve scar tissue from radiation or surgery with neuropathy leading to both muscle and temporomandibular joint degeneration. Brief periods of muscle immobilization can trigger muscle atrophy, while joint immobilization can rapidly induce degenerative changes such as synovial fluid thickening and cartilage thinning, as evidenced by studies. [20] A cross sectional study has shown that in post-radiotherapy nasopharyngeal carcinoma patients, the temporomandibular joint exhibited decreased disc thickness, increased condyle irregularity and joint vascularity.[21]

Moreover, some research have indicated that the extent of radiation-induced TMD is linked to the location and dosage of the radiation field administered. [22] Jaw hypomobility may worsen following several radiotherapy sessions. [18, 19] A prospective study observed the effect of irradiation on mandibular opening and mobility in 58 cancer patients. The results revealed that the higher is the dosage of radiation given to the temporomandibular joint and pterygoid muscles, the lower is the maximal jaw opening. [15] Another major factor related to temporomandibular disorder symptoms is the delivery technique of radiation. Radiation induced limitation in mouth opening incidence is 25% in patients receiving conventional radiotherapy when compared to intensity modulated radiation therapy (IMRT) with only 5%. It has shown that IMRT decrease the dose received by the TMJ, consequently reducing the side effects. [23] [24] Also, increasing the dose to masticatory muscles to above 55 Gy, can evidently decrease the range of motion of the jaw and increased facial pain. [25] Hypomobility of the jaw have been documented in 6% to 86% of the patients who underwent radiotherapy that target the

temporomandibular joint (TMJ) and/or masticatory muscles, especially the pterygoid muscles.[15] [26]

It has been suggested as well that the variations in the T allele at position -509 of the transforming growth factor beta 1 (TGF-β1) gene have been correlated with mouth opening issues during late tissue reactions due to radiation induced fibroatrohpic activity. This genetic variant has been proposed as a potential genetic factor associated with the development of mandibular limited range of motion. [27]

Because restricted mouth opening often leads to compromised nutritional intake, it can cause substantial weight loss and nutritional deficiencies among affected individuals. [28] Limited mouth opening can also hinder proper chewing and airway clearance, potentially leading to aspiration of food due to compromised mastication, poor bolus organization, and increased residue. Additionally, restricted mouth opening can compromise oral hygiene, particularly in patients who have undergone radiation affecting the salivary glands, necessitating meticulous oral care for caries prevention [20] Also, it has been proved that temporomandibular disorders including limitation in mouth opening after cancer treatment can have a psychosocial and economic impact on survived patients affecting daily life activity and social interactions. [29, 30]

Temporomandibular disorder pain and discomfort can decrease quality of life and may ultimately affect the patient's chances of recovery.[31] Therefore, it is essential to identify the prevalence and risk factors of TMD symptoms in head and neck cancer patients before starting their radiotherapy. It is also important to develop effective preventive strategies to avoid or minimize the debilitating side effects of radiation therapy. This can include early interventions such as jaw exercises, massage therapy, and occlusal appliances to improve jaw movements and minimize

the symptoms of TMD disorders.[32] Hence, future prospective studies are essential to identify the potential sociodemographic risk factors and effective preventive strategies to avoid radiotherapy complications in both short and long term, ultimately improving the quality of life for head and neck cancer patients.

There are hardly any prospective studies that track TMDs developments and symptoms in oral and oropharyngeal cancer patients before, during, and after cancer treatment. The purpose of our study is to determine the prevalence of TMD symptoms in head and neck cancer patients, including SCC of the oral cavity and oropharyngeal areas, and to identify risk factors of radiation-related hypomobility prior to the start of treatment. Obtaining this information will help health professionals in the future to develop therapeutic targets aimed at minimizing the long-term TMD side effects of radiation therapy in cancer patients and implementing preventive strategies.

Chapter 2: Comprehensive literature review

2.1 HEAD AND NECK CANCER DEFINITIONS:

The meaning of cancer has changed a lot over the centuries mainly due to the progress in medical science and technology. Back in 460-370 BC , the term cancer was first used by Hippocrates who had given the Greek words carcinos and carcinoma to describe the non-ulcer-forming and ulcer-forming tumor [33]. Hippocrates believed an overabundance of black bile was the reason for these tumours. [34]

In the 18th century, the meaning of the term cancer started to change towards the modern concept as autopsies became more common and thus, more anatomical study of tumours was possible. From year 1728-1793, John Hunter a Scottish surgeon, who proposed that some cancers could be cured by surgery if they were caught before they spread to other tissues thus introducing the concept of metastasis. [35]

The 19th century was the time when the microscope in medicine appeared and as a result, we had the great progress in the knowledge about cancer. Rudolf Virchow who is usually called “the father of the modern pathology” had created the theory of cellular pathology which states that the diseases like cancer are the results of the abnormalities in the cells not in the organs or the tissues as the previous thought. [36]

By the 20th century we saw that the molecular basis of cancer began to unravel with the discovery of oncogenes in the 1970s. [37] This discovery changed the way the term cancer was looked at from the anatomical to the genetic that was necessary in the understanding that mutations in genes could cause cells to proliferate uncontrollably.

Nowadays, cancer is defined not only by the uncontrollable cell growth but also by its ability to evade the immune system, the vascular growth, the resistance to cell death and the invasion of other tissues.[38] The definition keeps on changing as time goes by and as more and more research is done on genetic, epigenetic and molecular pathways.

Head and neck cancers (HNCs) encompass a diverse group of malignancies originating from the squamous epithelial cells lining the mucosal surfaces of the head and neck region. [39] This includes the oral cavity, nasal cavity, paranasal sinuses, pharynx, larynx, and glands of salivation. Predominantly, these malignancies are classified as head and neck squamous cell carcinomas (HNSCC), accounting for over 90% of cases. [40]

Anatomical and Histological Classification

Oral Cavity: Cancers of the oral cavity involve the lips, anterior two-thirds of the tongue, gums, floor of the mouth, hard palate, and buccal mucosa. These cancers typically present as non-healing ulcers or masses that may cause pain, bleeding, and dysphagia.[41]

Pharynx: The pharynx is divided into three regions: nasopharynx, oropharynx, and hypopharynx. Nasopharyngeal carcinoma (NPC) is distinct due to its strong association with Epstein-Barr virus (EBV) infection Oropharyngeal cancers often involve the tonsils and base of the tongue and are increasingly linked to human papillomavirus (HPV) infection, particularly HPV-16. [42] Hypopharyngeal cancers are typically diagnosed at an advanced stage due to late symptom presentation, such as sore throat and referred otalgia. [43]

Larynx: Laryngeal cancer can occur in the glottic (vocal cords), supraglottic, or subglottic regions. Glottic cancers are usually detected early due to changes in voice quality (dysphonia), whereas supraglottic and subglottic cancers may present with symptoms like throat pain, dysphagia, and airway obstruction. [44]

Nasal Cavity and Paranasal Sinuses: These cancers are relatively rare and often present with symptoms such as nasal obstruction, epistaxis, and facial pain or swelling. [45] Due to their location, they are frequently diagnosed at a later stage.

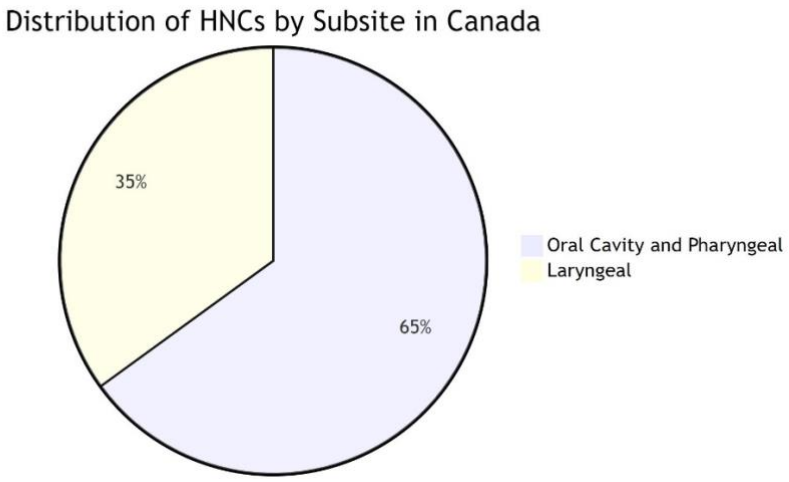
Salivary Glands: Salivary gland tumors can be benign or malignant, with the latter often presenting as painless masses. Malignant cases, such as mucoepidermoid carcinoma and adenoid cystic carcinoma, may exhibit rapid growth, facial nerve involvement, and pain. [45]

2.2 HEAD AND NECK CANCER EPIDEMIOLOGY:

Head and neck cancers (HNCs) represent approximately 4% of all cancers globally, with an estimated incidence of 550,000 new cases and 300,000 deaths annually. [46] The majority of HNCs are squamous cell carcinomas (HNSCC) associated with risk factors including tobacco use, alcohol consumption, and human papillomavirus (HPV) infection, particularly HPV-16. The incidence of HPV-positive oropharyngeal cancers has been increasing, especially in high-income countries. Epidemiologically, there is a higher prevalence in males and individuals over the age of 50. [47]

Epidemiology of Head and Neck Cancer in Canada, Quebec, and North America

Canada



A majority of HNC usually take up 3-5% percentages of all cancer in Canada, and cancer is the second position of causes for the death in the Canada. [47] In numbers that are quite unsettling, as per Canadian Cancer Society, around 5000 cases, every year, are diagnosed. [48]The rate of incidence varies by subsite where oral cavity and pharyngeal cancers are the most frequent, and phalangeal cancers come second to laryngeal cancers. As regards HNCs overall, there have any been no significant changes during the last decade; nevertheless, the cases of HPV-related oropharyngeal cancers which number has been increasing, according to global patterns. [42]

The mortality in the cases of HNCs in Canada is 1. 3 per 100,000 people per year that is equivalent to 1 in every 75,000 individuals. [48] The 5-year relative survival rate for HNC sited (depending on the localization and the stage at the diagnosis, early-staged presentation has a better prognosis than others). It may be explored with the example of Stage 5-year survival rate for localized oral cavity cancer which is about 75%. But this decreases significantly if it is advanced Stage. [49]

Quebec

The relationships between HNC incidence and mortality in the Quebec's population follow the national trends but inconsistency of these figures in the various regions of the province can be confirmed. The INSPQ cites data which shows a 1,000 new cases of having HNCs annually. [50] The Quebec rate of pituitary adenoma is 12 per 100 000 people, which is more than the national average. A higher incidence rate in Quebec can be accounted for by life characteristics of its

people, as they exhibit higher cleavages of tobacco and alcohol, which are main risk factors for HNCs.

Cancers related to human papilloma virus (HPV) of the oropharynx in Quebec has shown an incline, comparable to rate that has been happening across North America. Public health to role which emphasis on HPV vaccination is a must practice in direction to diminish this growing tendency. In the span of 5 years the survival rates in Quebec have been set at the national level, with early detection and improvement of treatment protocol being the reason for the better outcome. [51]

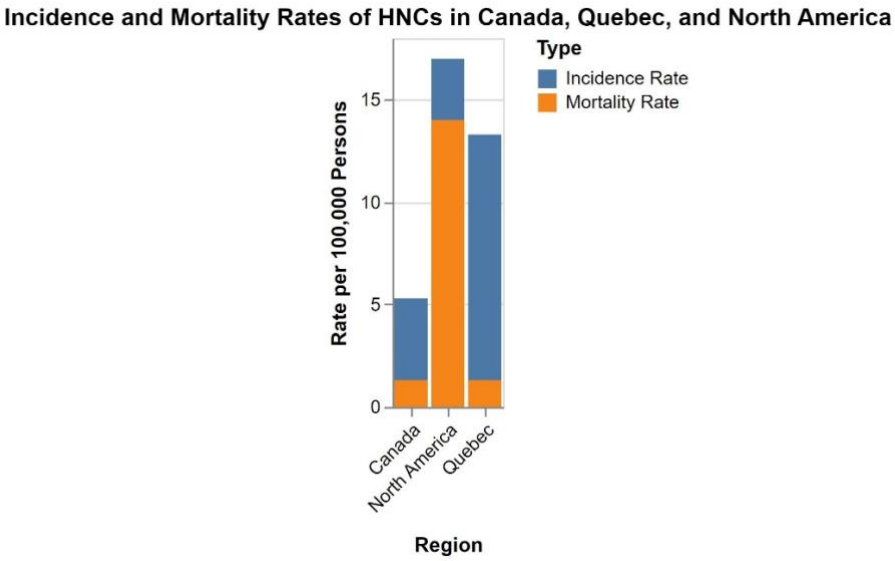
North America

As for the North American cancer statistics, head and neck cancers comprise about 3% of new cases. According to the American Cancer Society, 66,000 annual cases of head and neck cancers are diagnosed and more than 14,000 deaths occur. [52] From the time trend perspective, the HNC incidence rates have been relatively stable for the past decades, but, unknowingly, we have observed likewise tendencies in Canada: a surge of HPV-related oropharyngeal cancer. These men aged 35-64 years notice an increasing trend. [53]

The HNC cases across North America are more variable geographically whereby people in regions with a high proportion of smokers and drinkers tend to have higher rates of the cancer. HPV-caused oropharyngeal cancers in the people of high socioeconomic status are more frequently diagnosed and, almost certainly, this is a result of their varied sexual behavior and exposure to HPV. [54]

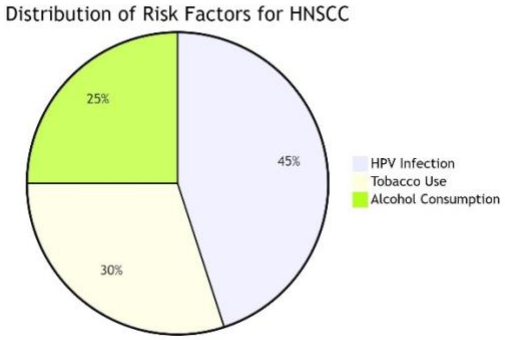
Cancer mortality rates among the head and neck cancers in North American continent have been in a sustained decline and it is thought that this is due to progress in therapeutic modalities and early detection. In the United States about 5-year survival rate of the head and neck cancers reaches

up to 66%, and it can be influenced by subsite and stage of the disease. [55] The statistics of HPV-positive oropharyngeal cancer survival rate is much more optimistic as it is 80% for HPV-positive cases compared to HPV-negative cases which is just 40% in 5-year period after the diagnosis. [56]



2.3 RISK FACTORS OF HEAD AND NECK CANCER:

The cancer of the oral cavity, pharynx and larynx (the head and neck cancer or head and neck cancers, short form of HNC) which is by the complex interaction of environmental and genetic risk factors affected. Tobacco use has always been the biggest risk of getting this cancer, and accounts for about 75% of cases every where in the world. [53] An irrefutable evidence that has been strongly found in the literature is that these cancers develop if smoking cigarettes or chewing tobacco are the main habits to during the period of production of the HNC.

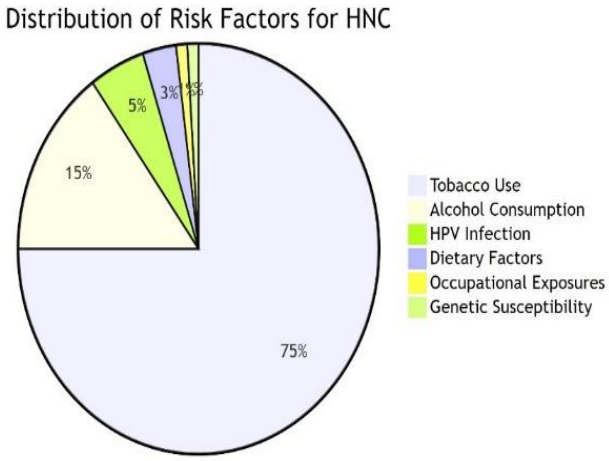


The metabolite of alcohol, acetaldehyde, has carcinogenic properties that increase the mutagenic potential of tobacco, consequently, the cancer risk is significantly increased, especially for the oral cavity and oropharynx. Moreover, not having enough fruits and vegetables, which are good for you, has been linked to the higher risk of HNC, thus the importance of dietary antioxidants and other phytochemicals.

Besides, the other vital risk factor is the infection with high-risk HPV type 16. This is the main reason for oropharyngeal cancers, its incidence is increasing in many parts of the world, especially in men in developed countries. [51]Contrary to HNCs caused by tobacco, HPV-positive oropharyngeal cancers usually affect the younger people and have a better prognosis and response to treatment. [57]

Occupational exposures to wood dust, asbestos and chemicals used in the textile, painting and construction industries are also responsible for the HNC risk, especially cancers of the nasopharynx and larynx.[46]

The fact of genetic susceptibility is also considered, with several genetic polymorphisms linked to the increased HNC risk, which makes the genetic factors in the modulation of the individual susceptibility to the environmental carcinogens. [46]



2.4 HEAD AND NECK CANCER TREATMENT MODALITIES:

The treatment is a multidisciplinary approach which is designed according to the tumour type, location and stage, and the patient's overall health. The key modalities are surgery, radiation therapy, chemotherapy, targeted therapy, and immunotherapy, which are usually used in combination to achieve the best results. [58]

Surgical resection is still the main method for HNC treatment, intending to take out the tumor completely but at the same time, to save important functions like speech and swallowing [59]. New surgical techniques has been developed recently like transoral robotic surgery (TORS) and laser microsurgery which made the surgical process more precise and less morbid compared to the traditional open surgeries. [60]

Radiation therapy is usually the second option in the surgery or the last resort treatment, especially for the patients who cannot have surgery. Nowadays, IMRT is the standard, since it is able to deliver the higher doses to the tumor with less side effects by shielding the healthy tissue around it. [61]

Chemotherapy is mainly employed as a concurrent treatment to radiation in local advanced diseases to boost the tumoricidal effects, or as a palliative treatment in metastatic cases. The typical agents that are used are cisplatin, carboplatin and 5-fluorouracil. [58]

Targeted therapy and immunotherapy of HNC has been made by the targeted therapy and immunotherapy, especially the patients with the relapse or the metastatic cases. Medicines like cetuximab, a monoclonal antibody that targets the EGFR pathway, are either alone or in combination with radiation. On the other hand, immunotherapy agents such as pembrolizumab and nivolumab, which are the PD-1/PD-L1 pathway inhibitors, have been proved to be useful in increasing the survival rates of HNC patients, mainly those with recurrent disease. [62]

Each treatment plan is designed individually after a thorough investigation of the tumor's genetic and molecular features, thus, the precision and the efficiency of the treatment are improved and at the same time the quality of life is maintained.

2.5 RADIATION THERAPY DESCRIPTION:

Radiation therapy is a significant treatment for various cancers including the head and neck, breast, prostate, and brain cancers. This technique includes the use of ionizing radiation to the DNA of cancerous cells, which after that leads to the disturbance of their reproduction and the eventual cell death. [63] Radiation therapy can be the cure for the localized tumor, the curative in the advanced cancer stages or the additive to other treatments like surgery and chemotherapy.

There are a lot of radiation therapy methods, and each one is meant for a certain type of cancer and also the needs of the individual patients. The most common technique of radiation therapy, which is the external beam radiation therapy (EBRT), is when the rays are aimed from outside the body onto the tumor through the machine. [64] The latest methods including intensity-modulated radiation therapy (IMRT) and the volumetric modulated arc therapy (VMAT), have brought a

possibility to accurately target the tumor and, at the same time, to lessen the damage to the healthy tissue. [65]

Brachytherapy is also an alternative radiation therapy, which is the one that involves putting radioactive sources inside or close to the tumor area. The technique is mostly used in the treatment of prostate cancer and cervical cancer and it is the best one for the two diseases treatment of the diseases since it delivers a high dose of radiation to the tumor but also reduces the exposure to the normal tissues.

In the recent years, proton beam therapy has become a modern replacement for the conventional photon-based therapy. [66] Protons are the main source of energy which is deposited at a certain depth (known as the Bragg peak), so, the tumor is killed with the highest effect and the exit dose is the lowest, thus, the side effects are reduced and the outcomes in cancers which are close to the critical structures like the brain and spinal cord are improved.

The efficacy of radiation therapy is determined by the total dose of the radiation, the fractionation schedule, and the type of the tumor. [64] The latest technological innovations have paved the way for the creation of treatment planning systems that are capable of optimizing the dose distribution, thus, improving both the tumor control and the quality of life of the patients.

2.6 RADIATION THERAPY TOXICITIES AND SIDE EFFECTS:

Radiation therapy, which is a very important part of cancer treatment, is the application of ionizing radiation to cancer cells destruction. Although it is effective, this treatment does have side effects which may differ from one to another depending on the treatment area, dose and the patient's health. [64] The short-term side effects are usually temporary but they can greatly affect the quality of life, while the late effects are usually permanent and more severe.

Acute toxicities These are the side effects that appear during or directly after the treatment and usually go away in a few weeks. Head and neck cancer patients are usually prone to acute reactions such as mucositis, dermatitis and xerostomia (dry mouth) that can result in swallowing problems, changes in taste and nutritional challenges. Radiation dermatitis is a skin disorder that goes from slight redness to severe ulceration. [67]

Late toxicities The problems that may occur even after the therapy may appear months or years later and can be permanent. To name a few, radiation fibrosis, which can be any organ that is exposed to radiation, causes chronic pain and functional impairments. [68] In the case of head and neck cancers, the jaw osteoradionecrosis and hypothyroidism are the typical late effects. [69] Moreover, radiation-induced secondary cancers can also take place, but not very often, because of the carcinogenic nature of the ionizing radiation. [70]

The latest advancements in radiation technology, for instance, IMRT and proton beam therapy, have been developed to reduce these side effects by maximizing the dose to the tumor and sparing the surrounding healthy tissue at the same time. [61] , [66] Nevertheless, despite the existence of these technologies, the management of the side effects of radiation therapy is still important for the enhancement of the patient's outcome and quality of life.

2.7 TEMPOROMANDIBULAR DISORDERS:

TMDs are a kind of several musculoskeletal conditions that involve the temporomandibular joint (TMJ), the muscles of mastication and the related structures. [71] The TMDs are usually indicated by pain in the jaw joint and the tissues surrounding it plus the restrictions in the jaw movements, which include the limitation in the mouth opening. These situations can either be a cause or a result of the oral function and the life quality.

TMDs can be classified into three main categories: The oral pain condition's cause can be the myofascial pain, joints' degeneration (such as disc displacement), and degenerative joint disease (TMJ osteoarthritis) among others. [72] The myofascial pain is the most frequent type of jaw pain, which is a pain or discomfort in the jaw's muscles, and the neck's and the shoulder's muscles.

The TMDs can be caused by many factors and they can be explained as a combination of (macrotrauma of the jaw), (microtrauma as a result of parafunctional habits like bruxism), and (psychological factors like stress) which in turn can make the muscle tension and the pain worse. [72] Moreover to these factors which are the mechanics of the jaw and the teeth alignment, they also contribute to the formation of these diseases.

TMD diagnostics is usually the result of a complete clinical exam which consists of the patient's history, the jaw movement evaluation and the palpation of the jaw and the surrounding muscles. Besides, the radiograph, MRI, and CT scans are also the tools which are used to acquire the detail view of the TMJ anatomy and to check the structural abnormalities in the joint. [73]

The treatment modes for TMDs are designed in a way to eradicate the pain, to enhance the function and to restrict the mouth opening. These are the treatments that can be used for TMD patients that include patient education, pharmacotherapy, physical therapy, and use of occupying devices, and in the case of a more complicated TMD, surgical interventions. [73] The conservative, non-invasive treatments that are the first choice of the disease management system are the first step of the process.

2.7.1 TEMPOROMANDIBULAR DISORDERS SYMPTOMS:

TMDs are the most prevalent of the orofacial pain causes not related to the teeth and therefore, they can significantly affect the quality of life. [74] It is the reason why the symptoms of the TMDs are varying many, so, it is difficult to diagnose and manage the condition.

Pain The most noticeable symptom of TMDs is jaw, temporomandibular joint area, or muscles of mastication pain, which usually occurs in these areas. Moreover, it can also come to the ear, cheek, and temples. [75] This pain, frequently, becomes worse during jaw activities such as chewing, speaking, or yawning.

Limitation in mouth opening The pain in the jaw is the other cardinal symptom of TMDs. Patients may be faced with a limited jaw motion or a feeling of stiffness in the jaw muscles, which will make their life more difficult in terms of eating and talking. In some cases, the limitation is also accompanied by the deviation or the deflection of the jaw path when the jaw opens or closes. [76]

Joint sounds The pain in the jaw is the other cardinal symptom of TMDs. Patients may be faced with a limited jaw motion or a feeling of stiffness in the jaw muscles, which will make their life more difficult in terms of eating and talking. [72] In some cases, the limitation is also accompanied by the deviation or the deflection of the jaw path when the jaw opens or closes. [75]

Other symptoms Headaches, neck pain, and dizziness are among the many symptoms of the linkage between TMDs and other musculoskeletal systems. Besides, patients with TMD usually complain of bruxism (teeth grinding or clenching), which not only aggravates the joint and muscle strain but also causes the dental wear and the increased sensitivity.

The cause of TMDs is believed to be a result of various factors such as biological, behavioral, and environmental ones. Stress is usually considered as the main factor that causes the problem because of its function in the creation of muscle tension and parafunctional jaw activities. [77]

The diagnosis is mainly clinical, it is based on the patient's history and the detailed physical examination of the jaw and the related structures. The imaging techniques like MRI or CT scans that are used to evaluate the anatomical status of the TMJs and to exclude the other conditions that could imitate TMD symptoms are the complementary ones. [72]

The management plans for TMDs are to lessen the pain, to repair the function and to improve the patient's life. Treatment of this disorder is usually conservative, which includes the patient education about the disorder, pharmacological interventions (the drugs to be taken) and also the drugs to be taken). g. Besides that, the treatments could be: , analgesics, muscle relaxants, physical therapy, and occlusal appliances to reduce the teeth grinding and jaw clenching. [77]The conservative methods are the first choice after the other methods fail and the anatomical integrity of the TMJ is considered.

2.7.2 TEMPOROMANDUBULAR DISORDERS DETECTION:

The diagnosis and the detection of TMDs are the most crucial for the successful management but at the same time, they are the most difficult to detect and diagnose due to the complexity and variability of the symptoms. The diagnosis procedure generally involves the clinical evaluation and imaging techniques at the same time, besides the patient history, which will give the complete picture of the disorders. [72]

Clinical Evaluation: The initial step of TMD diagnosis is a thorough clinical examination. This entails the analysis of the jaw motion range and the determination of the limitations in the mouth opening. Patients may also display jaw movements that are away from the normal or that are deflected, which are the significant diagnostic indicators. The masseter and temporomandibular

joints are palpated to find the areas of the pain or discomfort. Besides, the doctors also listen for joint sounds, like clicking, popping, or crepitus, which are the sign of the joint derangements. [77]

Patient History: A complete history of a patient is needed to know the beginning, the time of the onset, and the intensity of the symptoms, and also to find out the factors that may have caused the symptoms, e. g. injuries, dental history, or systemic health issues. Patients are frequently asked to describe the pain patterns, joint noises, headaches, neck pain, and the behaviors that worsen the symptoms like chewing or stress. [78] This history is the main reason why TMDs are not the same as other orofacial pain disorders.

Imaging Techniques: Imaging, although not always needed, can be useful in giving details about the anatomical features of the TMJ and the structures around it. The most common imaging techniques are the conventional radiographs, MRI and CT. MRI is a good tool for detecting soft tissue abnormalities like disc displacement, on the other hand, CT scans are excellent for showing the bony structures [79]. Besides the traditional methods, the ultrasound and cone-beam computed tomography (CBCT) are also becoming more popular because they are more convenient and they have less radiation exposure than the traditional methods. [80]

Diagnostic Criteria: The Diagnostic Criteria for Temporomandibular Disorders (DC/TMD) sets the clinical and research protocols for the diagnosis of TMD in a standardized way. [81] This tool is vital in the differentiation of various subtypes of TMDs by specific criteria, such as pain-related disorders and degenerative joint conditions. The DC/TMD has been proven in recent years and is now the most accepted method for both the clinical and research fields. [82]

Adjunctive Tests: Sometimes, the doctors will use the arthrography or the joint vibration analysis to check the TMJ more thoroughly. [83]Nevertheless, these are mostly utilized for difficult cases when the usual diagnostic methods do not produce clear results.

Management Implications: The correct identification of TMDs is the key to successful management. The data collected from the clinical evaluation, patient history, and imaging aids in the creation of a personalized treatment plan, which may include pain management, physical therapy, behavioral interventions, and sometimes surgical options. [81]

2.7.3 INCIDENCE OF TEMPOROMANDIBULAR DISORDERS IN RADIATION TREATED CANCER PATIENTS:

TMDs in patients who have undergone radiation therapy for head and neck cancers are a significant concern since radiation has an effect on the bones, muscles, and joints that are involved in the jaw function. The ratio of TMDs in this population is significantly higher than the general population, mainly because of the radiation-induced fibrosis and damage to the temporomandibular joint and masticatory muscles. [68]

Incidence and Risk Factors: The research has proven that the patients who get radiation therapy, especially when the TMJ region is in the radiation field, are at a high risk of developing TMDs. [84] The number of TMD symptoms, such as pain and limitation in mouth opening, can be different but in some studies it has been reported as many as 25-30% of patients after radiation therapy. This risk is increased by the higher radiation doses and the bigger areas of radiation.

Pathophysiology: Radiation can cause degenerative changes in the TMJ, which are marked by the fibrosis of the nearby tissues and muscles. This fibrosis can make the normal sliding motion of the TMJ restricted thus, the mouth opening will be stiff and limited. [68] Moreover, radiation-induced osteoradionecrosis can be a reason for the deterioration of the joint structure, which in turn, will make the patient's life even more difficult, since he/she will not be able to perform even the basic oral functions such as speaking and eating. [69]

Clinical Manifestations: Patients usually have the pain that starts slowly and is located around the TMJ (lateral pole) and at the same time, they have the increasing difficulty in opening their mouths. The symptoms can be worsened by eating, talking or any other jaw movement. Besides the short-term effects, the long-term radiation effects also involve the changes in the bone density and quality, which can lead to fractures and reduction in the joint mobility. [74]

Diagnosis and Management: The diagnosis of radiation-induced TMDs constitutes a thorough clinical evaluation, which involves the patient history related to the radiation therapy, the physical examination of the jaw movement and the imaging studies such as the panoramic radiographs or MRI to check the degree of the joint and muscular damage. [[81],[82] The management tactics are focused on the mouth opening and the pain decrease. [71] The normal types of treatments for knee pain are holding physical therapy exercises, drugs for pain management and some times, the interventions like the intra-articular injections or surgery for the severe cases. [77]

Preventive Measures: The huge number of the TMDs cases and the extreme effect that they have on the quality of life turn them into a must to be prevented. [74] There are some ways to shield the TMJ from radiation that include the use of the stents during the radiation therapy to reduce the radiation exposure to the TMJ and the physical therapy before and after the radiation to keep the muscles flexible and the joints mobile. [33] In addition to that, the patients should realize the significance of the exercises for the jaw that they should perform after the treatment to reduce their symptoms [85].

2.8 FACTORS ASSOCIATED TO RADIATION RELATED TEMPOROMANDIBULAR DISORDERS:

That TMDs which are a consequence of radiation therapy in head and neck cancer patients is one of the complex and multi-faceted problems show how complex and how highly intertwined this process is. There are a number of factors that increase the risk of the patients with dental problems from having TMDs, among which are the radiation dose, field of exposure, and the individual characteristics of the patients, are the reasons behind that.

Radiation Dose and Field: The most crucial factors that determine the total dose of radiation and the volume of the TMJ that is exposed to radiation are the ones that have an effect on the development.of TMDs. The greater doses of radiation are associated with the rise of fibrosis and osteoradionecrosis which consequently result in the joint stiffness and the limitation of mouth opening. [68]One study proved that the probability of TMDs is very high when the radiation dose is more than 60 Gy. [86]

Timing of Radiation: The TMDs risk also varies as the radiation dose timing changes. Fractionated doses that are administered in several sessions, can give the tissues some time to heal between treatments, thus, cutting down the intensity of TMD symptoms. [33] On the other hand, the effect of the numerous exposures can still lead to the joint and muscular damage.

Patient-Specific Factors: Factors which leads to the risk and severity of radiation related TMDs are genetics, dental or TMJ problems that are already present, and the overall health of a person. The patients who have a history of TMDs or the connective tissue disorders are the ones who are more likely to have severe symptoms after the radiation. [86]

Radiation Technique: The creation of the new radiation therapy techniques, i. e. the intensity-modulated radiation therapy (IMRT) and proton beam therapy, has been the main goal to reduce

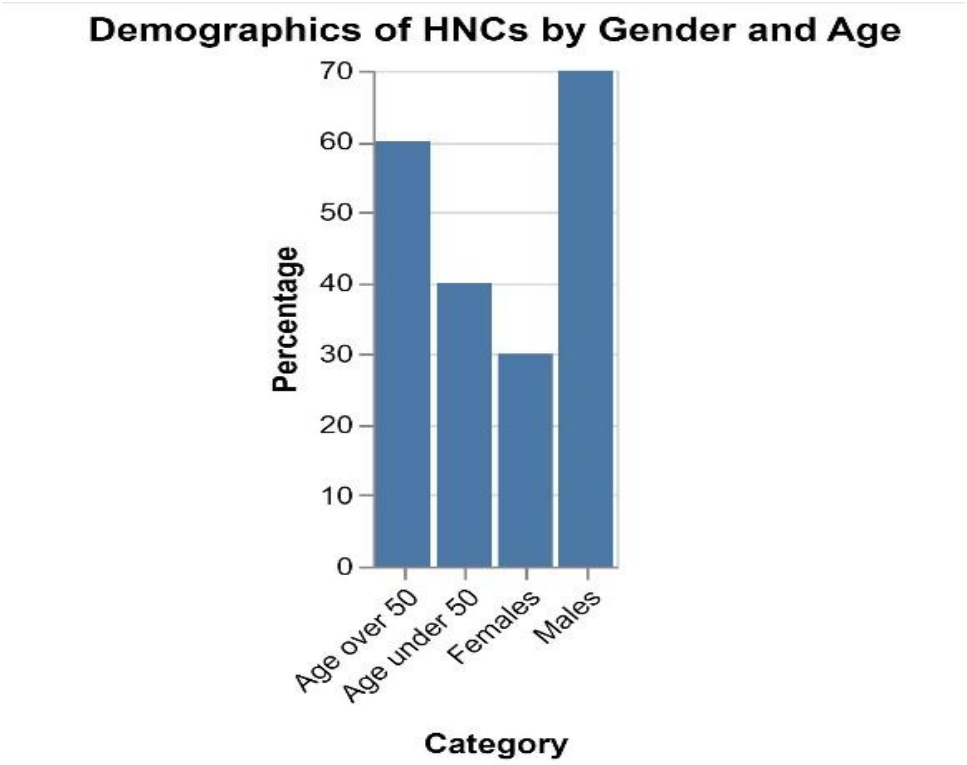
the radiation exposure to the healthy tissues. [61] [66], The mentioned methods can have a considerable effect on the decrease of the TMDs occurrence and seriousness by more accurately striking the tumor and limiting the radiation dose to the TMJ and those around it.

Preventive Measures and Early Intervention: The measures of the prevention, which are the pre-treatment dental evaluation, the use of protective stents and the patient education on the jaw exercises can greatly reduce the risk of the TMDs development. The initial stage of the process is the early intervention strategies which are the physical therapy and the pharmacological management that are very crucial for the regulation of the symptoms and the enhancement of the outcomes for those who are affected. [33],[72],[75]

2.8.1 DEMOGRAPHIC FACTORS:

The TMDs, which are related to the radiation, in the patients who are undergoing the radiation therapy for the head and neck cancers are influenced by the variety of demographic factors. These factors can be the primary cause of the TMDs occurrence and the severity of the symptoms like the pain and mouth opening limitation. By knowing the demographic groups that are at most risk for the disease, we can design the most efficient prevention and management strategies for them.

Age: Age is a primary demographic trait. Older patients invariably have a greater baseline risk of degenerative joint diseases, which in turn aggravates the severity of radiation-induced



temporomandibular disorders. Besides, the seniors are usually more prone to shoulder injuries and a slow healing process and hence they are more likely to have comorbidities which can be a barrier to their treatment and recovery. Scary is it that researches have demonstrated that the patients above the age of 60 are more at risk to be seriously handicapped in mouth opening after radiation treatment. [13]

Gender: The occurrence of TMDs in the two genders has been shown, and females have a higher probability of TMDs than males. This habit may be due to the hormonal differences that affect the pain perception and inflammation in men and women differently. The study that has been conducted has demonstrated that the female patients who have had the head and neck radiation are higher risk of having more severe symptoms and a higher rate of chronic pain associated with TMDs [87].

Ethnicity and Genetic Background: The ethnicity and genetic factors can be the reason behind the development of radiation-related TMDs. The genetic factors that make a person have a greater chance of getting collagen vascular diseases or other connective tissue disorders might be the reason for the fibrosis and thus TMDs after the radiation therapy. [86]The genetic structure can also be an influential factor which is the metabolic processing of radiation, and thus, the tissue sensitivity and recovery rates are different among different ethnic groups.

Socioeconomic Status:The socioeconomic factors are the indirectly connecting factors with the development and the management of the radiation-related TMDs. Patients from the less privileged social and economic backgrounds may not have the access to healthcare resources, for instance the specialized care for TMDs and cancer treatment follow-up. [13], [14] The restriction of the capacity to diagnose TMDs at the beginning can result in the impairment the diagnosis and the management of TMDs, which in turn causes the complications that are more severe and the outcomes that are poorer.

Lifestyle Factors: The lifestyle choices, such as smoking and alcohol usage, are the most known risk factors for head and neck cancers and they also have the effect of the incidence and the severity of TMDs. Smoking is an example of the factors that can hinder the oxygenation of tissue and healing, which in turn, escalates the fibrotic processes that are started by radiation. [88] Alcohol use, as well as other habits, can be the cause of the development of osteoradionecrosis, which, in turn, can lead to the restriction of jaw mobility. [13]

Preexisting Health Conditions: The already existing conditions like the diabetes and autoimmune disorders can also be the cause of the intensity and the frequency of the radiation-related TMDs. [46] These factors may modify the body’s inflammatory response and healing abilities,

consequently, such factors will affect the formation and the progression of TMD symptoms after radiation therapy.

2.8.2 TYPE, STAGE AND LOCATION OF CANCER:

Radiation-related TMDs are especially common among the head and neck cancer patients who are subjected to radiation therapy. The kind, the stage, and the location of the cancer in the body play a major role in the possibility and the seriousness of these complications. The connection between these two fields is very important for the planning of the treatment modalities and for the prediction and management of the possible side effects such as the limitation of the mouth opening, the pain, and the TMJ dysfunction.

Type of Cancer: The cancers that are directly related to or located near the TMJ and the masticatory muscles, for example, the oral cavity and the oropharyngeal cancers, are more likely to be the ones that are related to the TMDs caused by radiation. [72] The cancers that are associated with radiation fields that include the TMJ, thus, they require radiation fields that cover the TMJ, which in turn, leads to the higher exposure and subsequently the higher risk of complications.

Cancer Stage: The stage of cancer at the time of diagnosis is also a factor that determines the risk of TMDs after the radiation therapy. Cancers with advanced stages usually need more aggressive treatment methods, such as higher doses of radiation and larger radiation fields, which in turn, increase the chances of TMDs. Besides, the higher-stage tumors may require the same time as the chemotherapy, which can make the symptoms of TMD worse because of the radiation's effects on the bone and the soft tissues. [89]

Location of Cancer: The close location of the tumor to the TMJ and the muscles of mastication is an important factor. Tumors that are situated in places like the base of the tongue, nasopharynx, or

the parotid gland usually need radiation therapy which involves the TMJ area as a part of the treatment field. Radiation in these areas can cause direct damage to the joint and the nearby muscles, thus, leading to stiffness, inflammation, and limitation of mouth opening. [90]The degree of the radiation overlap with the TMJ area is the same as the frequency and the intensity of TMDs. Radiation Dose and Technique: The amount of radiation and the particular technique used are also responsible for the incidence of TMDs. The Intensity-modulated radiation therapy (IMRT) is capable of better preserving of healthy tissues than the traditional techniques. [61] Nevertheless, even with the sophisticated techniques, the high-dose radiation that affects the TMJ area can cause major structural changes, including fibrosis and osteoradionecrosis, which are the main reasons for TMDs.

Preventive and Management Strategies: Thus, oncologists and radiation therapists are trying to design radiation treatment plans that are as little as possible in the TMJ and masticatory muscles. The use of protective measures such as the custom-fitted dental stents or the limitation of the radiation dose to the TMJ will be able to decrease the risk. The earlier and more the management is done, the more effective it is in reducing the severity of TMDs if they do develop. [46]

2.8.3 RADIATION DOSE:

Radiation dose management is one of the main factors in the treatment of head and neck cancers, and it has a great impact on the patient outcomes including the chance of getting temporomandibular disorders (TMDs) which is the condition that is characterized by the limitation in mouth opening. The intake and distribution of radiation are carefully designed to be the most efficient in the control of the tumor and at the same time the least exposure of the nearby normal tissues, including the temporomandibular joint (TMJ) and the masticatory muscles.

Radiation Dose Considerations: The general radiation dose for head and neck cancers is between 60 and 70 Gy, which is given over several weeks. [91] Higher doses are typically required for the curative treatments, which consequently increase the risk of side effects, in particular the TMDs. The TMJ-dose is a serious concern as it can lead to fibrosis and osteoradionecrosis, which are the joint stiffness and limited mouth opening. [92]

Technological Advancements: The new radiation methods such as intensity-modulated radiation therapy (IMRT) and volumetric modulated arc therapy (VMAT) have enabled the sparing of healthy tissues to a great extent. [61]These methods can precisely target the tumor and at the same time, reduce the dose delivered to the TMJ, thereby, the occurrence and severity of the radiation-induced TMDs will be decreased.

Dosimetric Studies: Studies have proved that the mean dose to the TMJ should not be more than 50 Gy, and thus the risk of TMDs will be considerably reduced. [93],[94] Dosimetric studies reveal that the planning and technique adjustment can be done in a way that the dose to the critical structures will be minimized and at the same time, the oncologic outcomes will be effective.

Clinical Implications: Dose delivery must be accurate, as even small deviations can cause toxicity to increase. Doctors have to find a way to achieve both the effective cancer control and the preservation of function and quality of life, which is the dose optimization that is the basis of the treatment planning for head and neck cancer patients. [45]

2.8.4 RADIATION FIELD:

In radiation therapy for head and neck cancers, the definition and optimization of the radiation field are the key factors for the successful treatment and at the same time the reduction of the adverse effects including temporomandibular disorders (TMDs), which can be manifested as the

limitation of mouth opening. The radiation field is the area and volume of tissue that is exposed to radiation during the treatment, which is meticulously planned to cover all the known cancerous tissue while at the same time, avoiding the normal tissue to the maximum extent possible.

Definition of Radiation Field: The radiation field is figured out on the basis of the type, location, and the extent of the tumor, which is informed by the imaging studies such as the CT, MRI and PET scans. This field usually comprises the main tumor site and any neighboring areas that are prone to the microscopic disease spread like lymph nodes. [44] The exactness in the definition of this field is the most important thing to make sure that the tumor gets a good dose for control or eradication and at the same time, the exposure of the critical structures such as the temporomandibular joint (TMJ) and salivary glands is minimized.

Techniques to Optimize the Field The development of progress in radiation planning and delivery technologies has greatly increased the accuracy of radiation fields. Methods such as intensity-modulated radiation therapy (IMRT) and volumetric modulated arc therapy (VMAT) allow the dose intensity within the field to be modulated, which results in the higher doses to the tumor and lower doses to the healthy tissues. [34] This modulation is very important for the decrease of the risk of TMDs caused by radiation, that are the ones with fibrosis and limited mouth opening.

Impact of Field Size and Location: The radiation field's size and location are the two factors that can either increase or decrease the side effects' frequency. To mention, when the field is related to TMJ or the mastication muscles, patients are more likely to suffer from TMDs. [44]The field size or its boundaries can be either diminished or relocated away from the sensitive areas, if it is oncologic-ally safe, thus, the risk is decreased. Nevertheless, these changes have to be made very carefully so as not to not treat the cancer in a superficial way.

Dosimetric Considerations: The dosimetry is a study that is really important in the planning and the checking of the radiation field. The researches give us the opportunity to analyze the radiation field distribution and the dose that the tumor and the normal tissues get. The new dosimetric methods have the capability to produce the 3D images of the dose distribution that assists in the reduction of the non-target tissue exposure. [95]

Field Verification and Adjustment: The process of radiation treatment is a lengthy one and during the whole time it needs to be verified many times. The verification of the radiation delivered to the target area is for the purpose of making sure that the actual radiation is the same as the intended distribution, taking into account the patient movement and the change of the tumor size. IGRT, for example, is a method that enables real-time adjustments to the radiation field, thus, the target area is accurately treated in each session, hence, the risk of radiation-induced complications such as limitation in mouth opening is reduced. [96]

2.8.5 HISTORY OF TEMPOROMANDIBULAR DISORDERS:

TMDs are the disorders of the temporomandibular joint (TMJ), the muscles that are responsible for the jaw movement, and the other structures that are connected to it. In the past ten years, the researchers have been studying for a while the causes, diagnosis, and management of TMDs. Finally, they have found that TMDs are a multifactorial problem which involves anatomical, physiological, psychological and environmental factors. This narrative is about the history of the mouth opening limitation and the study of this limitation called TMD, as well as the clinical implications of this field in the last decade. [97]

Historical Perspective and Evolution: In the past, the TMDs were seen from a mechanical aspect, and the problems were mainly caused by the dental malocclusions and physical trauma. [98]

However, the last ten years have made the mindset to change, which now the holistic view is being accepted. These days, the TMDs are formed and continued by the mechanical and the psychosocial factors together. This general approach has made the treatment more whole, because both the physical and the psychological therapies are taken into consideration. [99]

Recent Advances in Etiology:Numerous recent studies have proved that the cause of TMDs is not solely the dental occlusion or trauma but also the systemic and psychological conditions. For example, it is known that such as the chronic stress, anxiety, and other psychological factors, which are the major factors that are linked to the muscle tension and dysfunction that are typical of TMDs. [46] Besides that, the role of inflammation and neural sensitization in TMD pain pathways has been the main research area, which, as a result, the focus of the study shifted on the possible pharmaceutical interventions.

Diagnostic Developments: The RDC/TMD (Research Diagnostic Criteria for Temporomandibular Disorders) has been of great importance in defining the diagnosis of the disorder. Nevertheless, in the last ten years, the criteria have been improved to be more clinically useful and to make them cover the complex nature of TMDs. [100]The DC/TMD, a revision of the initial criteria, has been widely accepted and is based on a dual-axis model, which includes both the physical diagnosis and the psychosocial assessment, that is, the key for a holistic treatment strategy. [82]

Management and Treatment Innovations: Treatment techniques have undergone great transformations. Although the earlier treatments mostly concentrated on the invasive procedures like surgery or the extensive dental work, the recent trends are now based on the less invasive management strategies. The aforementioned are the therapies that are used for the treatment of the problems such as physical therapy, behavioral therapy, and pharmacological treatments that are directed at the pain and dysfunction management. [33],[77],[78]. Lately, the awareness of the

significance of patient education and self-management techniques has increased, thus, patients could reduce the behaviors that worsen symptoms. [99]

Focus on Limitation in Mouth Opening: The restriction of the mouth opening, which is the most important and the most debilitating symptom of TMDs, has been the focus of the researchers for a long time. Studies have proven that the preventive measures, like not doing excessive jaw movements and the management of the underlying risk factors like bruxism, are really important in the management of this symptom. [43] Besides, the exercises that are designed to enhance the jaw mobility have also been proved to be efficient in the improvement of mouth opening and the total joint function.

The emphasis for the future TMD studies and the clinical practice is probably going to be on the multidisciplinary approaches which will combine the dental, medical and psychological therapies. The study of the genetic and molecular bases of TMDs also is a new area that could result in more focused and efficient treatments.

2.8.6 EXERCISE AND SPEECH THERAPY:

The treatment of temporomandibular disorders (TMDs) in head and neck cancer patients who have undergone radiotherapy usually includes the therapies of exercises and speech therapy. These interventions are very significant in the treatment of the functional impairments, for example, the problems with the mouth opening, which are frequent after the radiation therapy. The major strides in the modification of these therapeutic strategies in the last ten years has led to the improvement of their effectiveness and patient compliance.

Exercise Therapy: Physical therapy exercises are the key element in the treatment of radiation-induced TMDs. These activities are designed to keep or improve the jaw mobility, decrease muscle

stiffness, and to reduce pain. Therapeutic exercises are usually composed of mild stretching and strengthening of the chewing muscles that eventually enhance the range of motion and function. Studies have found out that a program of daily exercises, which include controlled jaw opening, lateral movements, and neck stretches, can greatly improve the symptoms of limited mouth opening in patients after radiotherapy. [101]

Protocols and Efficacy: Current research has been mainly on the creation of the standard exercise programs. For example, the load is gradually increased during the training which is proved to be advantageous. This method slowly raises the intensity and frequency of exercises, which lets the body to adapt and thus, the risk of worsening the condition is minimized. [101]Such methods have been proved to be effective in not only the improvement of the jaw mobility but also in the enhancement of the general quality of life by the reduction of pain and discomfort which are the symptoms of TMDs. [102]

Speech Therapy: Speech therapy is also an essential part of the TMDs management in post-radiotherapy patients. Radiation can influence speech by limiting the movement of the jaw, tongue, and lips due to fibrosis and muscular restrictions. Speech therapists help patients to learn techniques that will assist them to improve the articulation and speech clarity. [103] The techniques usually consist of exercises that are aimed at the improvement of the flexibility and the strength of the orofacial muscles, which are the key features of the speech and swallowing.

Integration with Other Treatments The combination of physical activity and speech therapy with other treatments like medication for pain and inflammation or the use of assistive devices like jaw motion rehabilitation systems has been proved to be the best way to improve the results. [104]These integrated methods tackle the multi-dimensional nature of TMD symptoms after

radiation therapy, thus they provide a holistic management strategy that deals with both the physical and functional aspects of the disorder.

Recent Clinical Trials and Studies: The clinical trials conducted in the last ten years have given the proof that these therapies should be used. For instance, the randomized controlled trials that compare the different intensities and frequencies of the therapeutic exercises have contributed to the identification of the optimal treatment regimens that can be customized according to the individual patient needs and response to therapy. [105]

Patient Education and Self-Management: The patient's education on the significance of the self-management and the following of the therapy regimens is the key. Patients who are given the knowledge and the skills to manage their condition can achieve better long-term outcomes. [106]Besides, the way to doctors and other health care professionals regularly is to check on the patient's progress and to make changes to the therapy accordingly. [107]

Chapter 3. Study objectives and hypotheses

3.1 Objectives:

After our comprehensive literature review, no recent prospective study has been conducted within Canada/Quebec demonstrating development of Temporomandibular Disorders in head and neck cancer patients using the DC/TMD diagnostic criteria.
Therefore, the two main aims of this study are;

1- The primary aim of this study is to determine the prevalence and frequency of temporomandibular disorders (TMD) symptoms in head and neck cancer patients who are undergoing radiation therapy with and without chemotherapy, including those diagnosed with SCC in the oral cavity, and oropharyngeal areas.
2- The second aim of this study is to compare changes in potential risk factors over time.

3.2 Hypothesis:

Our hypothesis is that radiation therapy would increase TMD signs and symptoms including myofascial pain and jaw hypomobility in patients with oral and oropharyngeal cancer.

Chapter 4. Methodology

This section aims to overview the methodology used to accomplish the objectives of the study and to prove our hypothesis.

4.1 Study design

Our study was a prospective, observational study that was conducted after a comprehensive literature review that was done using multiple databases. In this comprehensive literature search, conducted through the McGill library's Ovid platform and Google Scholar, a total of 35 articles were initially identified using a combination of relevant keywords, including "radiation," "radiotherapy," "TMJ," "temporomandibular joint," "TMD," "myofascial pain," "SCC," and "head and neck cancer." The search results were filtered and refined. Initially, 35 articles were retrieved, which were subsequently deduplicated resulting in 33 abstracts. The selection criteria were narrowed down to include articles in the English language published between the year 2000 and the current date, resulting in a total of 27 articles for detailed evaluation. After a meticulous review of related abstracts, 9 articles were directly relevant to the research topic.
Additionally, a complementary search on Google Scholar resulted in some more relevant articles, enhancing the scope of the review.

As for our prospective study, we started collecting data from patients since March 2023 to March 2024 at the Royal Victoria Hospital Glenn site Cedar cancer, oral medicine clinic in Montreal, QC. After obtaining their consent and explaining the purpose of the study, we followed all newly diagnosed head and neck cancer patients who were referred to the oral medicine clinic for at least four appointments.

4.2 Ethical approval, Consents and Patient confidentiality

On March 2023, we submitted the study protocol to seek ethical approval from the Research Ethics Board (REB) of McGill University Health Center (MUHC).

The ethical approval for both prospective and retrospective study was obtained (2024-9879 - HNCguideline) and the approval confirmation is attached in the Appendix 1. This was done in order to ensure we achieve the highest ethical standards and ensure patient confidentiality.

All the patients seeking treatment and follow up at Royal Victoria Hospital , Glenn site oral medicine clinic were requested to fill out general and specific research consent forms during their visits. The general consents forms indicate if the patients are willing to share their clinical records for any research purposes.

Patients' information that was collected from both clinical examination and reviewing their medical record from our medical systems Medesync and Oasis were entered into an excel sheet by assigning randomly generated codes to patient names to ensure anonymity. Patient codes were kept by the principle investigator in a password protected digital file behind the MUHC firewall in case we need to re-access patient records for any missing or follow-up information. Only the authors had access to the collected data. In case of sharing collected data among the authors, the files were always transferred through secured links and password protected files. The data collected will be stored in a password protected computer for 7 years following the completion of the study as per the hospital protocol, then the digital files will be destroyed.

4.3 Sample Population and Eligibility criteria

All head and neck cancer patients regardless of their diagnosis who were referred to the Oral Medicine clinic in Royal Victoria Hospital (RVH) between March 2023 and March 2024 were considered as our sample population. All these patients were covered by Quebec accepting Régie de l'assurance Maladie du Québec (RAMQ) for dental pre-assessment prior the start of radiation therapy. Our patients were cleared dentally to start radiotherapy with and without chemotherapy ,

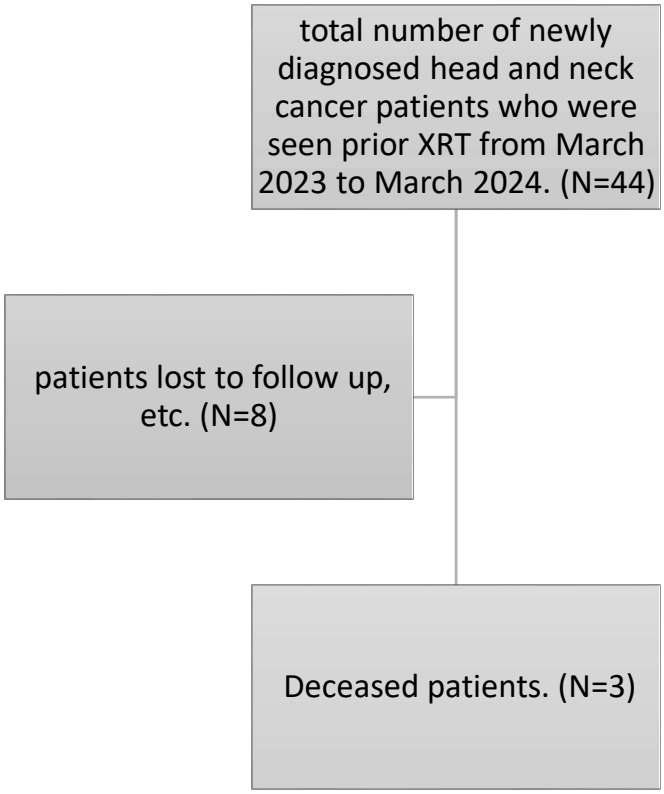
then followed up biweekly during treatment. They were also followed up for 3 , 6 , and 12 months post XRT for dental treatments and TMD both at Royal Victoria Hospital and Montreal General Hospital.

All patients who are above 18 years old and able to sign the consent form were included. However, we excluded all patients who underwent surgery in and near the temporomandibular joint. We also excluded all incomplete records including those who did not show up for the pre-assessment prior XRT, patients who followed up with their private dentists, and patients who did not agree to participate in our study and didn't sign the consent form.

4.4 Sample Size

Initially, we collected clinical records from 44 patients who visited the Oral Medicine Clinic in Royal Victoria Hospital , Cedar Cancer department for the primary dental evaluation for dental clearance to begin radiotherapy. We excluded 8 records that did not meet the study's eligibility criteria including missing information, unavailability of complete dentures to record mandible movements, prior presence of head and neck cancer, and those who refused to participate. Also, we excluded 3 patients who were deceased mid study. One patient had recurrence of cancer at his 6 months post radiation , and his visit was excluded from the excluded from our results. Ultimately, we included 44 clinical records for the study analysis.

Sample size flow chart:



4.5 Data Collection

After signing both the clinic and the research consent forms, the research objectives were explained to each participant. Data were collected directly from patients at their first visits upon their diagnosis of head and neck cancer and through Medesync TELUS portal and OASIS that were used to collect demographic and tumour/patient information such as cancer diagnosis, stage and location, medical and medication history, treatment suggested by the oncologist, oral and dental health, history of previous hospitalizations and surgeries, history of trauma to the head and neck area, history of smoking, alcohol, and drug use, self-reported symptoms, and triggering and alleviating factors.

Clinically, master students or general dentistry practice residents who were trained previously by an orofacial specialist at the Montreal General hospital, orofacial pain clinic, examined the

patients in the presence and confirmation of these examination findings by the attending. Data were collected using the DC/TMD validated form from 44 patients on 4 appointments (prior XRT, mid-treatment, post XRT in 3 months, post XRT in 6 months). This form included direct question to the patient if they experienced pain or headaches in the last 30 days and the location of the pain mentioned using their own finger.

Using a medical sterile ruler, measurements of the overjet, overlap, midline deviation were recorded. Opening pattern was also documented to detect any corrected and uncorrected deviation.

The pain free, maximum assisted, unassisted opening, lateral and protrusive movements was measured for all patients. For edentulous patients, this measurement was taken while they were wearing their dental prostheses.

Clicking and crepitus in both opening and lateral movements were also detected and recorded.

Finally, 1 kg was applied by the examiner's digital compression to the masticatory muscles temporalis (anterior, middle, posterior) ,masseter (origin, body, insertion) and TMJ including the (lateral pole 0.5 kg, around lateral pole, posterior mandibular region, submandibular region, lateral pterygoid area, and temporalis tendon) to record any pain with palpation.

In addition to the data collected directly from patients using the Validated DC/TMD criteria, Medesync TELUS portal and OASIS was used to collect demographic and tumour/patient information such as cancer diagnosis, stage and location, medical and medication history, treatment suggested by the oncologist, oral and dental health, history of previous hospitalizations and surgeries, history of trauma to the head and neck area, history of smoking, alcohol, and drug use, self-reported symptoms, and triggering and alleviating factors.

With the help of a physicist, the radiotherapy planning protocol for each patient's CT scan was retrieved in the Royal Victoria hospital, Glenn site. After contouring both of the condyles on the scan, a new structure with the name z_TMJ was documented and saved for each of the 35 patients in the planning platform. Subsequently, the total dosage in Gy, number of sessions given, and the mean dosage for both the right and the left TMJ were calculated and added to the excel sheet.

Each patient's panoramic X-ray was taken prior the beginning of the treatment and was carefully calibrated for any flattening or remodelling of the condyles, calcifications of the stylohyoid ligaments, osteophytes, irregular bone changes of the angle of the mandible and recorded in the excel sheet.

4.6 Data analysis

The collected data were organized and entered with anonymous patients numbering system for confidentiality into multiple spreadsheets in Excel 2024. For descriptive purposes, categorical variables were reported as numbers and percentages, and continuous variables as mean, standard deviation (SD), minimum, maximum. To compare changes over time, the sign test was used for categorical variables. The Shapiro-Wilk test, along with P-P and Q-Q plots, were utilized to assess the normality of quantitative data. To compare changes over time, the paired t-test was used for continuous variables with a normal distribution, and the Wilcoxon signed-rank test was used for continuous variables with a non-normal distribution. All tests were two-tailed and conducted at a 5% significance level. The data were processed in SPSS 29.0.1.1.

Chapter 5: manuscript

The Effect of Radiation Therapy on Temporomandibular Joint and Its Function in Head and Neck Cancer Patients: A Prospective Study

Manuscript draft

Aia Naksho[1,2], Ali Abdolrahmani, Nour Karra[1,2], Firoozeh Samim[1,2]

[1]Faculty of Dental Medicine and Oral Health Science, McGill University, Montreal, Quebec, Canada

[2]Oral medicine Clinic, Royal Victoria Hospital glenn site, Montreal, Quebec, Canada

Correspondence should be addressed to:

Dr. Firoozeh Samim, DMD, M.Sc., FRCD ©, DIP. ABOMP

Oral Medicine/Oral & Maxillofacial Pathologist

Chair, Equity, Diversity, and Inclusion.

Faculty of Dental Medicine and Oral Health Sciences / Faculté de médecine dentaire et des sciences de la santé orale | Université McGill University

2001, McGill College, # 500 Room 518

Montréal (Québec) Canada H3A 1G1

Tel: (514) 398 7203

Email: firoozeh.samim@mcgill.ca

Abstract

Aim:

The primary aim of this study is to determine the prevalence of TMD symptoms in head and neck cancer patients including SCC of oral cavity, and oropharyngeal areas. Additionally, this study aims to compare changes in potential risk factors over time.

Methodology

The initial phase of this project was a comprehensive literature review. The second phase of the study was to prospectively follow up 44 newly diagnosed patients with Head and neck cancer who were referred to the oral oncology clinic located at Royal Victoria hospital (Glenn site) prior to the initiation of radiation therapy. Patient with prior radiation therapy or surgical therapy with limitation in the mouth opening consequently were excluded. The examinations were performed prior, mid- treatment and after radiotherapy in 3-months and 6-months follow up. Validated DC/TMD criteria and Examination Form was used to record our findings. Panoramic X-rays and CT scans were calibrated for any degenerative changes in the TMJ. All examination was performed by a specialist or a dentist or resident who have been calibrated. Inter and intra-examination liability was performed.

Results

All patients with HNC were initially included in the study. The study composed a total of 44 participants, with an age range from 31 to 96 years and a mean age of 63.30 years. Majority of our patients had SCC with a percentage of 81.8%. Tumor locations varied across different

anatomical sites, with oropharynx being the most common (18.2%), followed by tongue (13.6%) , larynx (11.4%), parotid gland, and tonsil, each (9.1%). All patients underwent radiation therapy with the minimum total dosage of 24 Gy and maximum of 70 Gy. The mean pain free opening before oncologic treatment was 40.12 (SD 8.328) mm, and the corresponding values at 3 and 6 months were 36.35 (SD 8.937) and 35.53 (SD 9.441) mm. The p Value Δ from baseline to the 6 months follow up on pain free opening is 0.53. Out of 44 patients undergoing RT, 24 (57.1%)showed no masticatory muscles pain pre-treatment. Then, 51.7% developed muscle pain on mid-treatment and 59.1% on 3 months post XRT. Finally, 63.3% of our patient showed increased in both unilateral and bilateral muscle pain at the 6 months follow up.

Conclusion

Based on these results, it can be concluded that there is a modest reduction in pain-free mouth opening over a period of 6 months following oncologic treatment, indicating a potential impact of the treatment on oral function. Additionally, a significant proportion of patients who did not have masticatory muscle pain prior to radiotherapy developed unilateral muscle pain by the 6-month follow-up. This suggests that radiotherapy may be associated with the onset of muscle pain in a majority of cases, highlighting the need for proactive management strategies to address this complication.

This prospective study marks a significant step towards understanding the prevalence and risk factors of TMD in HNC patients undergoing RT. We aim to unravel crucial insights into the trajectory of TMD development and its association with radiation-related hypomobility. By elucidating the prevalence and underlying factors contributing to TMD symptoms, this study endeavors to pave the way for the formulation of effective preventive strategies and therapeutic

interventions aimed at mitigating the long-term adverse effects of radiation therapy on patient well-being.

Keywords: Head and neck cancer, SCC, Temporomandibular disorders, Orofacial pain, Radiation therapy

List of abbreviations

TMD:	Temporomandibular disorder
PTMD:	Pain-related temporomandibular disorder
HNC:	Head and Neck Cancer
SCC:	Squamous cell carcinoma
DC/TMD:	Diagnostic Criteria for Temporomandibular Disorders
HPV:	Human Papilloma Virus

Introduction:

Head and neck cancer ranks as the seventh most prevalent form of cancer globally and are becoming common due to the dramatic increase of carcinogens exposure . [1, 2] Long standing evidence links alcohol and tobacco to be predominant causative factors in oral cavity, hypopharynx, larynx, and HPV-unrelated oropharynx cancers. Given that these carcinogens can affect the entire epithelium of the aerodigestive tract, individuals with head and neck cancers face the potential of having simultaneous primary tumors and developing secondary neoplasms

in the head and neck region, lungs, esophagus, and other areas sharing similar risk factors. Additionally, there has been a sudden rise in the incidence of oropharyngeal cancers due to increasing rates of human papillomavirus (HPV) infection. In the United States and certain parts of the European Union, the estimated attributable fraction for HPV in newly diagnosed oropharyngeal cancer is between 60% and 70%. [3-7] Unlike head and neck cancers associated with alcohol and smoking, HPV positive oropharyngeal cancer affects a younger demographic, often comprising individuals who are actively employed and showing interestingly better prognosis .[8, 9] Nevertheless, this devastating disease can be treated using various therapeutic approaches, including chemotherapy, surgery, and radiation therapy. In addition to surgery, radiation therapy stands as a primary treatment approach for most of head and neck cancers, applicable to both early and advanced stages. Radiation doses typically range from 54 to 70 Gy, delivered using a standard fractionation regimen of 2 Gy per fraction, administered once daily, five fractions per week. [10] The aim of radiation therapy is to eliminate cancer cells. Given that cancer cells tend to proliferate and multiply more rapidly than normal cells, they are more susceptible to destruction by radiation. Nonetheless, radiotherapy is known to be associated with acute and chronic debilitating effects. The probability and intensity of the side effects vary based on several factors, such as radiation dose, the duration over which it was administered, and the specific regions of the head and neck subjected to radiotherapy. [11] Acute side effects arise during the treatment course and shortly 2-3 weeks after treatment cessation. Conversely, late effects may emerge at any point, thereafter, ranging from weeks to years later. The immediate effects of radiotherapy include mucositis, thickened secretions, mucosal infections, pain, and sensory changes. On the other hand, the enduring consequences of head and neck radiation therapy involve xerostomia, fibrosis, heightened vulnerability to mucosal infections, neuropathic

pain, altered sensory perception, an elevated risk of dental caries, periodontitis and Temporomandibular disorders and jaw hypomobility. [12]

Temporomandibular disorders can be defined as any pain and functional disturbance in the temporomandibular joint and the muscles responsible for its movement which are masticatory muscles, including the masseter muscle, temporalis muscle, lateral and medial pterygoid.[13] This disturbance can result in noticeable signs and symptoms such as joint and muscle pain, clicking and crepitus noises, and restricted painful mouth opening and mandibular lateral and protrusive movements . [14] Recently, studies have suggested that the prevalence of TMD in the general population is between 40-60%, and only 10% of the population seeks treatment because they experience severe symptoms[13, 14].

Temporomandibular joint disorders and fibrosis in the head and neck structures can lead to restriction of the function of the lips and tongue. These effects may occur due to radiation exposure to the masticatory muscles (such as the masseter, temporalis, medial, and lateral pterygoids) and the Temporomandibular joint (TMJ).[15] Jaw hypomobility is a well-known consequence of radiation therapy that is dependent on several risk factors, including the radiation therapy dose, tumor size and location, and prior existence of temporomandibular disorders (TMD) in patients before their cancer diagnosis. Recent evidence had revealed that head and neck cancer treatments is now known as one of the causes of TMD symptoms. Reduction in mouth opening have been documented in a range of 6% to 86% among patients who underwent radiation therapy targeting the temporomandibular joint and/or the masseter and pterygoid muscles. [16] In 2005, a study discussed that among their participants who didn’t have a prior history of limitation in mouth opening before radiotherapy, there was noted to be a mere 1.3%

reduction in maximum incisal distance (MID) per month. However, notable progression of symptoms occurred within the first nine months post-radiotherapy followed by a stabilization period. Thereafter, resulting in an average decrease in interincisal opening of 32% after four years of radiotherapy.[17]

Causes of jaw hypomobility can also be due to muscular dysfunction, temporomandibular joint disorders, oral submucous fibrosis, fracture of the jaws, mucositis , and restricted stretching of the oral mucosa.[18] This occurrence is thought to be attributable to several factors. This includes radiation-induced fibrosis, a gradual decline in vascularity, and denervation atrophy of the joint muscles, along with injury to the mandible and temporomandibular joint (TMJ). Fibrosis is known to be triggered by ischemia due to endarteritis obliterans, referring to the inflammation and narrowing of arteries leading to decreased blood flow. [19] Reduced range of movement and masticatory muscle pain resulting from radiation therapy (RT) is primarily associated with muscle damage and fibrosis, often initiated by abnormal fibroblast proliferation. This condition may also involve scar tissue from radiation or surgery, nerve damage, or a combination thereof, leading to both muscle and temporomandibular joint degeneration. Brief periods of muscle immobilization can trigger muscle atrophy, while joint immobilization can rapidly induce degenerative changes such as synovial fluid thickening and cartilage thinning, as evidenced by studies. [20] A cross sectional study has shown that in post-radiotherapy nasopharyngeal carcinoma patients, the temporomandibular joint exhibited decreased disc thickness, increased condyle irregularity and joint vascularity.[21]

Moreover, some research have indicated that the extent of radiation-induced TMD is linked to the location and dosage of the radiation field administered. [22] Jaw hypomobility may worsen

following several radiotherapy sessions. [18, 19] A prospective study observed the effect of irradiation on mandibular opening and mobility in 58 cancer patients. The results revealed that the higher is the dosage of radiation given to the temporomandibular joint and pterygoid muscles, the lower is the maximal jaw opening. [15] Another major factor related to temporomandibular disorder symptoms is the delivery technique of radiation. Radiation induced limitation in mouth opening incidence is 25% in patients receiving conventional radiotherapy when compared to intensity modulated radiation therapy (IMRT) with only 5%. It has shown that IMRT decrease the dose received by the TMJ, consequently reducing the side effects. [23] [24] Also, increasing the dose to masticatory muscles to above 55 Gy, can evidently decrease the range of motion of the jaw and increased facial pain. [25] Hypomobility of the jaw have been documented in 6% to 86% of the patients who underwent radiotherapy that target the temporomandibular joint (TMJ) and/or masticatory muscles, especially the pterygoid muscles.[15] [26]

It has been suggested as well that the variations in the T allele at position -509 of the transforming growth factor beta 1 (TGF-β1) gene have been correlated significantly with mouth opening issues during late tissue reactions due to radiation induced fibroatrohpic activity . This genetic variant has been proposed as a potential genetic factor associated with the development of mandibular limited range of motion. [27]

Because restricted mouth opening often leads to compromised nutritional intake, it can cause substantial weight loss and nutritional deficiencies among affected individuals. [28] Limited mouth opening can also hinder proper chewing and airway clearance, potentially leading to aspiration of food due to compromised mastication, poor bolus organization, and increased

residue. Additionally, restricted mouth opening can compromise oral hygiene, particularly in patients who have undergone radiation affecting the salivary glands, necessitating meticulous oral care to prevent dental caries.[20] Also, it has been proved that temporomandibular disorders including limitation in mouth opening after cancer treatment can have a psychosocial and economic impact on survived patients affecting daily life activity and social interactions. [29, 30]

Temporomandibular disorder pain and discomfort can decrease quality of life and may ultimately affect the patient's chances of recovery.[31] Therefore, it is essential to identify the prevalence and risk factors of TMD symptoms in head and neck cancer patients before starting their radiotherapy. It is also important to develop effective preventive strategies to avoid or minimize the debilitating side effects of radiation therapy. This can include early interventions such as jaw exercises, massage therapy, and occlusal appliances to improve jaw movements and minimize the symptoms of TMD disorders.[32] Hence, future prospective studies are essential to identify the potential sociodemographic risk factors and effective preventive strategies to avoid radiotherapy complications in both short and long term, ultimately improving the quality of life for head and neck cancer patients.

There are hardly any prospective studies that track TMDs developments and symptoms in oral and oropharyngeal cancer patients before, during, and after cancer treatment. The purpose of our study is to determine the prevalence of TMD symptoms in head and neck cancer patients, including SCC of the oral cavity and oropharyngeal areas, and to identify risk factors of radiation-related hypomobility prior to the start of treatment. Obtaining this information will help health professionals in the future to develop therapeutic targets aimed at minimizing the long-

term TMD side effects of radiation therapy in cancer patients and implementing preventive strategies.

Hypothesis:

Our hypothesis is that radiation therapy would increase TMD signs and symptoms including myofascial pain and jaw hypomobility in patients with oral and oropharyngeal cancer.

Materials and methods:

Ethical approval

The ethical approval for both prospective and retrospective study was obtained from the research ethics board of McGill University Health Centre **(2024-9879 - HNCguideline).**

Study design

This is a prospective, observational study that was conducted after a comprehensive literature review. We collected data from patients starting from March 2023 to March 2024 at the Royal Victoria Hospital Glenn site Cedar cancer clinic in Montreal, QC. After obtaining their consent and explaining the purpose of the study, we followed all newly diagnosed head and neck cancer patients in the oral medicine clinic for at least four appointments: prior treatment, mid-treatment, and after treatment at 3- and 6-months interval. Information were collected by a specialist, trained dentist, or resident using the validated DC/TMD criteria and examination form after

signing the consent form. All examiners were calibrated and intra- and inter examination liability assessment was conducted.

Selection criteria

Our study included all newly diagnosed head and neck cancer patients referred to the oral medicine clinic with no history of previous cancer or surgery that has caused limitation in mouth opening. We included all individuals above 18 years of age who can sign a consent form, regardless of gender, who are receiving radiation therapy or brachytherapy with or without chemotherapy. Edentulous patients who do not wear dentures and patients diagnosed with metastasis of the tumor to the temporomandibular joint (TMJ) area will be excluded from this study. All necessary data based on the DC/TMD criteria for the one-year interval were directly from patients.

Data collection

Data were collected using the DC/TMD validated form from 44 patients on 4 appointments (prior XRT, mid-treatment, post XRT in 3 months, post XRT in 6 months). This form included direct question to the patient if they experienced pain or headaches in the last 30 days and the location of the pain mentioned using their own finger.

Using a medical sterile ruler, measurements of the overjet, overlap, midline deviation were recorded. Opening pattern was also documented to detect any corrected and uncorrected deviation.

The pain free, maximum assisted, unassisted opening, lateral and protrusive movements was measured for all patients. For edentulous patients, this measurement was taken while they were wearing their dental prostheses.

Clicking and crepitus in both opening and lateral movements were also detected and recorded.

Finally, 1 kg was applied by the examiner's digital compression to the masticatory muscles temporalis (anterior, middle, posterior) ,masseter (origin, body, insertion) and TMJ including the (lateral pole 0.5 kg, around lateral pole, posterior mandibular region, submandibular region, lateral pterygoid area, and temporalis tendon) to record any pain with palpation.

In addition to the data collected directly from patients using the Validated DC/TMD criteria, Medesync TELUS portal and OASIS was used to collect demographic and tumour/patient information such as cancer diagnosis, stage and location, medical and medication history, treatment suggested by the oncologist, oral and dental health, history of previous hospitalizations and surgeries, history of trauma to the head and neck area, history of smoking, alcohol, and drug use, self-reported symptoms, and triggering and alleviating factors.

With the help of a physicist, the radiotherapy planning protocol for each patient's CT scan was retrieved in the Royal Victoria hospital, Glenn site. After contouring both of the condyles on the scan, a new structure with the name **z_TMJ** was documented and saved for each of the 44 patients in the planning platform. Subsequently, the total dosage in Gy, number of sessions given, and the mean dosage for both the right and the left TMJ were calculated and added to the excel sheet.

Each patient's panoramic X-ray was taken prior the beginning of the treatment and was carefully calibrated for any flattening or remodelling of the condyles, calcifications of the stylohyoid ligaments, osteophytes, irregular bone changes of the angle of the mandible and recorded in the excel sheet.

Oncologic treatment

Curative radiotherapy was administered following regional protocols. Most of our patient underwent radiation therapy on 35 sessions delivering 70 Gy daily, five days per week with a mean of 62.46 Gy , minimum of 24 Gy and maximum of 70 Gy. After contouring the TMJ in the radiotherapy planning , we found out the amount of radiation absorbed by the TMJ with a mean of 18.12 Gy.

63.6% of the participants had combined concurrent or induction chemotherapy/brachytherapy with radiation therapy. Surgical intervention, in accordance with the Oral maxillofacial surgery and tumor board, was utilized in conjunction with radiotherapy and chemotherapy for certain tumor sites for 16 (36.4%) of our patients.

Statistical analysis

For descriptive purposes, categorical variables were reported as numbers and percentages, and continuous variables as mean, standard deviation (SD), minimum, maximum. To compare changes over time, the sign test was used for categorical variables. The Shapiro-Wilk test, along with P-P and Q-Q plots, were utilized to assess the normality of quantitative data. To compare changes over time, the paired t-test was used for continuous variables with a normal distribution,

and the Wilcoxon signed-rank test was used for continuous variables with a non-normal distribution. All tests were two-tailed and conducted at a 5% significance level. The data were processed in SPSS 29.0.1.1.

Results:

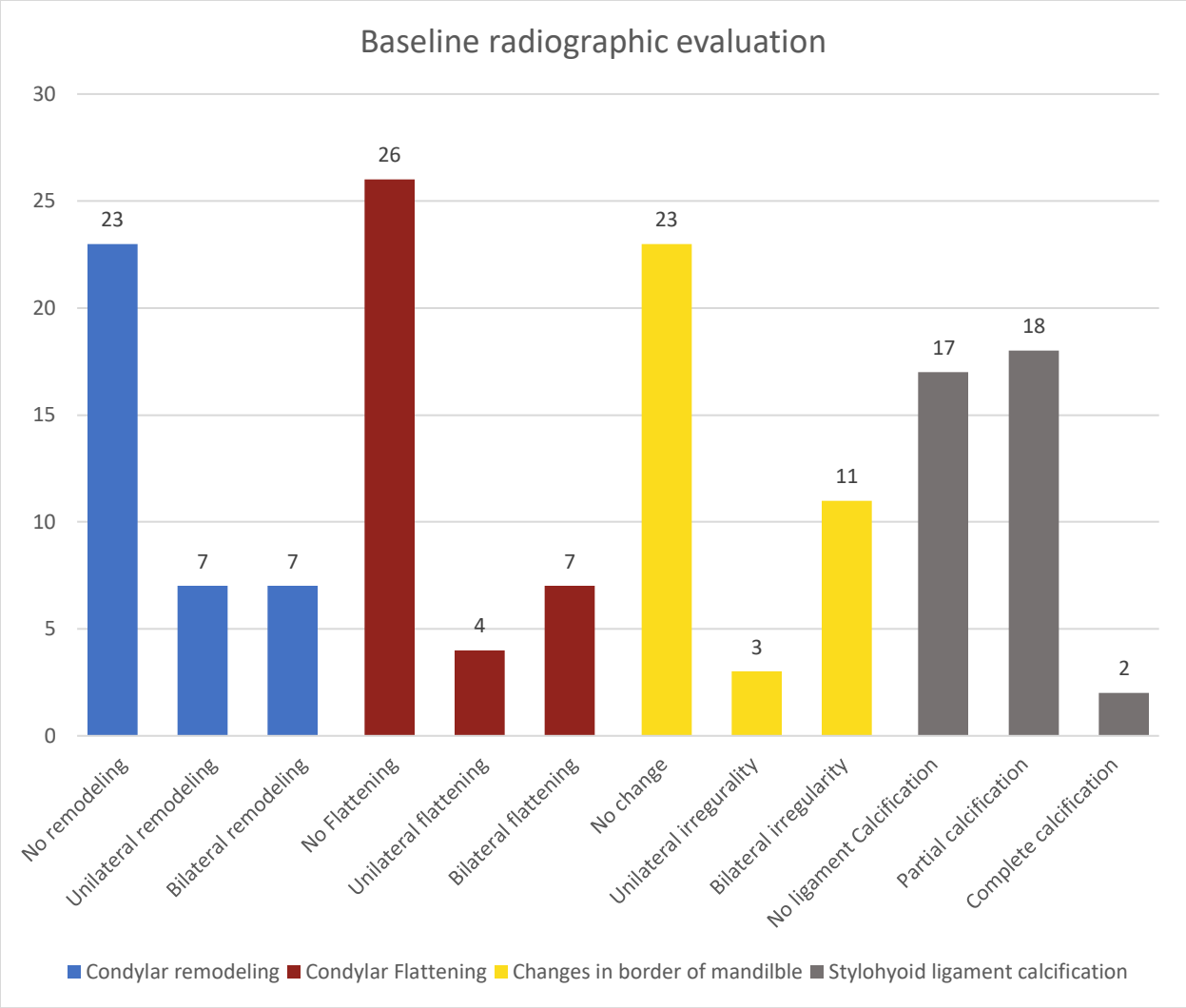
Demographic and clinical data

44 patients with HNC were initially included in the study. 3 patients deceased before undergoing the full examination and 8 patients didn't show up for the rest of follow up sessions and were excluded from the analysis. Demographic data such as gender, age, as well as treatment regimen are detailed in Table 1. The study composed a total of 44 participants, with an age range from 31 to 96 years and a mean age of 63.30 (SD 14.626). Of the 44 participants, 32 (72.7%) were male, and 12 (27.3%) were female. Regarding lifestyle factors, 14 (31.8%) participants reported smoking habits, while 23 (52.3%) reported alcohol consumption. Tumor diagnosis majority is (81.8%) having SCC. The presence of EBER was positive in 3 cases (6.8%) and HPV was detected in 10 cases (22.7%). Tumor locations varied across different anatomical sites, with oropharynx being the most common (18.2%), followed by the tongue 6 (13.6%), larynx (11.4%) , parotid gland, and tonsil, each (9.1%). Squamous cell carcinoma (SCC) was the primary diagnosis for our patients, however, other diagnosis such as Adenoid cystic carcinoma, Hodgkin and Non-hodgkin's lymphoma, and small cell carcinoma were also documented.

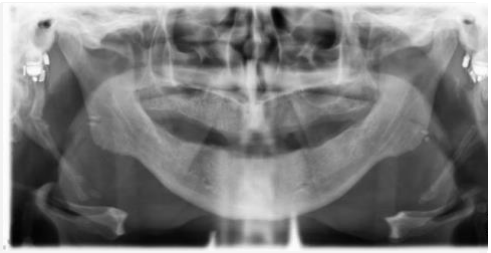
Our patients underwent radiation therapy with the mean XRT sessions number of 30.44 (SD 7.115) with minimum of 5 sessions only and maximum of 35 sessions. The mean total dosage of radiation is 62.46 (SD 11.765) with the mean dosage received by the Temporomandibular joint of 18.12 (SD 13.193) As for other oncologic adjunctive therapies, 28 (63.6%) patients received chemotherapy along with radiotherapy and 16 (36.4%) underwent surgical treatment.

Radiographic assessment

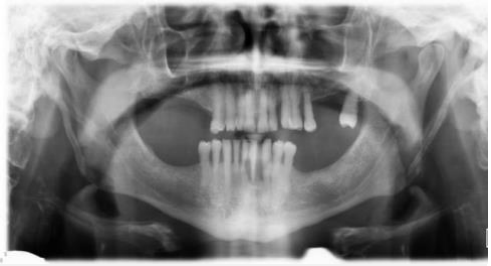
The radiographic assessment of the panoramic X-rays showed interesting findings. As per chart 1, prior XRT, 6 patients showed unilateral remodelling and 6 showed bilateral remodelling of the condyles. 3 patients revealed unilateral flattening and 7 with bilateral flattening. Also, 11 panoramic X-rays indicated bilateral irregularity of the border of the mandible revealing the presence of bruxism and parafunctional habits. Interestingly, 17 patients were found to have partial calcification of the stylohyoid ligament and 2 patients with complete calcification.



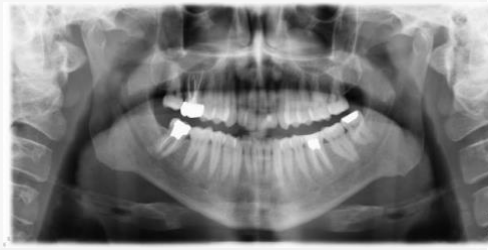
Graph 7. Baseline radiographic evaluation of participants.



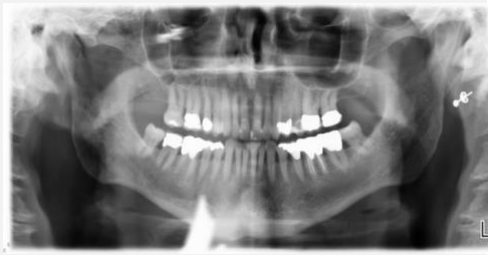
a-X-ray of a complete bilateral calcification of stylohyoid ligament



b-X-ray of bilateral condyle remodeling



c-X-ray of bilateral irregularity of the angle of mandible



d-X-ray of right condyle flattening

Graph 8: sample radiographic appearances of head and neck patients:

- a- Panoramic X-ray showing complete bilateral calcification of stylohyoid ligament
- b- Panoramic X-ray showing bilateral condyle remodelling
- c- Panoramic X-ray of bilateral irregularity of the angle of mandible.
- d- Panoramic X-ray showing right condyle

Table1 Demographic and clinical data. n (%) for categorical data

	n = 44
Age (mean, [min-max])	(63.30, 31-96)
Gender n (%)	
Male	32 (72.7%)
Female	12 (27.3 %)
Total	44 (100%)
Smoking n (%)	14 (31.8%)
Alcohol n (%)	23 (52.3%)
Tumor Diagnosis n (%)	
Adenoid cystic carcinoma (ACC)	1 (2.3%)
Ameloblastic carcinoma	1 (2.3%)
Hodgkin lymphoma	1 (2.3%)
Nasal adenoid cystic carcinoma	1 (2.3%)
Non Hodgkin's lymphoma, plasmacytoma	1 (2.3%)
Squamous cell carcinoma (SCC)	36 (81.8%)
Small cell carcinoma	1 (2.3%)
Merkel cell carcinoma	1 (2.3%)
Kimura disease	1 (2.3%)
Total	44(100%)
EBER (positive , negative n - %)	(3-6.8% , 41-93.2%)
HPV (positive , negative n - %)	(10-22.7% , 34-77.3%)
Tumor location n (%)	
Buccal mucosa	1 (2.3%)
Gingiva	3 (6.8%)
Larynx	5 (11.4%)
Maxilla	2 (4.5%)
Nasopharynx	4 (9.1%)
Nose	1 (2.3%)
Oropharynx	8 (18.2%)
Parotid gland	4 (9.1%)
Soft palate & neck	1 (2.3%)
Submandibular gland	1 (2.3%)
Tongue	6 (13.6%)
Tonsil	4 (9.1%)
Neck	1 (2.3%)
Total	44 (100%)
Dentition	
Normal	26 (59.1%)
Missing more than 6 teeth	14 (31.8%)
Edentulous	4 (9.1%)
total	44 (100%)
XRT sessions (mean, [min-max])	30.44 (5-35)
XRT Total dosage (mean, [min-max])	62.46 (24-70)

XRT mean dosage received by TMJ (mean, [min-max])	18.12 (0.15-50.78)
XRT + Chemotherapy n (%)	28 (63.6%)
XRT + Surgery n (%)	16 (36.4%)

Table 2. Tests of Normality. All p values are more than 0.05. Thus, all variables here are normally distributed.

	Shapiro-Wilk		
	Statistic	df	p value
Pain free opening baseline	.976	17	.909
pain free opening mid treatment	.973	17	.873
Pain free opening 3 months	.956	17	.557
Pain free opening 6 months	.944	17	.367
Maximum Unassisted Opening baseline	.969	17	.806
Maximum Unassisted Opening mid treatment	.974	17	.878
Maximum Unassisted Opening 3 months	.933	17	.246
Maximum Unassisted Opening 6 months	.949	17	.444
Maximum Assisted Opening baseline	.969	17	.801
Maximum Assisted Opening mid treatment	.978	17	.940
Maximum Assisted Opening 3 months	.941	17	.332
Maximum Assisted Opening 6months	.950	17	.458
Right lateral baseline	.803	17	.002
Right lateral mid treatment	.907	17	.088
Right lateral 3 months	.953	17	.502
Right lateral 6 months	.922	17	.158
Left Lateral baseline	.894	17	.054
Left Lateral mid treatment	.926	17	.187
Left Lateral 3 months	.970	17	.816

Left Lateral 6 months	.920	17	.147
Protrusion baseline	.795	17	.002
Protrusion mid treatment	.854	17	.012
Protrusion 3 months	.894	17	.054
Protrusion 6 months	.843	17	.008
*. This is a lower bound of the true significance.			
a. Lilliefors Significance Correction			

Table 3. Descriptives of mouth openings, lateral and protrusive movements

			Statistic	Std. Error
Pain free opening baseline	Mean		40.12	2.020
	95% Confidence Interval for Mean	Lower Bound	35.84	
		Upper Bound	44.40	
	5% Trimmed Mean		40.13	
	Median		40.00	
	Variance		69.360	
	Std. Deviation		8.328	
	Minimum		25	
	Maximum		55	
	Range		30	
	Interquartile Range		12	
	Skewness		-.103	.550
	Kurtosis		-.337	1.063
pain free opening mid treatment	Mean		37.94	2.530
	95% Confidence Interval for Mean	Lower Bound	32.58	
		Upper Bound	43.30	
	5% Trimmed Mean		38.27	
	Median		37.00	
	Variance		108.809	
	Std. Deviation		10.431	
	Minimum		15	

	Maximum		55	
	Range		40	
	Interquartile Range		13	
	Skewness		-.406	.550
	Kurtosis		.315	1.063
Pain free opening 3 months	Mean		36.35	2.168
	95% Confidence Interval for Mean	Lower Bound	31.76	
		Upper Bound	40.95	
	5% Trimmed Mean		36.34	
	Median		37.00	
	Variance		79.868	
	Std. Deviation		8.937	
	Minimum		21	
	Maximum		52	
	Range		31	
	Interquartile Range		15	
	Skewness		-.284	.550
	Kurtosis		-.754	1.063
Pain free opening 6 months	Mean		35.53	2.290
	95% Confidence Interval for Mean	Lower Bound	30.68	
		Upper Bound	40.38	
	5% Trimmed Mean		35.98	
	Median		36.00	
	Variance		89.140	
	Std. Deviation		9.441	
	Minimum		12	
	Maximum		51	
	Range		39	
	Interquartile Range		12	
	Skewness		-.851	.550
	Kurtosis		1.188	1.063
Maximum Unassisted Opening baseline	Mean		43.35	2.044
	95% Confidence Interval for Mean	Lower Bound	39.02	
		Upper Bound	47.69	
	5% Trimmed Mean		43.45	
	Median		44.00	

	Variance		70.993	
	Std. Deviation		8.426	
	Minimum		28	
	Maximum		57	
	Range		29	
	Interquartile Range		14	
	Skewness		-.263	.550
	Kurtosis		-.629	1.063
Maximum Unassisted Opening mid treatment	Mean		41.71	2.098
	95% Confidence Interval for Mean	Lower Bound	37.26	
		Upper Bound	46.15	
	5% Trimmed Mean		41.84	
	Median		42.00	
	Variance		74.846	
	Std. Deviation		8.651	
	Minimum		24	
	Maximum		57	
	Range		33	
	Interquartile Range		11	
	Skewness		-.067	.550
	Kurtosis		.038	1.063
Maximum Unassisted Opening 3 months	Mean		40.47	2.295
	95% Confidence Interval for Mean	Lower Bound	35.61	
		Upper Bound	45.34	
	5% Trimmed Mean		40.69	
	Median		43.00	
	Variance		89.515	
	Std. Deviation		9.461	
	Minimum		22	
	Maximum		55	
	Range		33	
	Interquartile Range		14	
	Skewness		-.495	.550
	Kurtosis		-.374	1.063
Maximum Unassisted Opening 6 months	Mean		40.12	2.081
	95% Confidence Interval for Mean	Lower Bound	35.71	

		Upper Bound	44.53	
	5% Trimmed Mean		40.19	
	Median		41.00	
	Variance		73.610	
	Std. Deviation		8.580	
	Minimum		24	
	Maximum		55	
	Range		31	
	Interquartile Range		13	
	Skewness		-.144	.550
	Kurtosis		-.339	1.063
Maximum Assisted Opening baseline	Mean		45.06	1.977
	95% Confidence Interval for Mean	Lower Bound	40.87	
		Upper Bound	49.25	
	5% Trimmed Mean		45.18	
	Median		46.00	
	Variance		66.434	
	Std. Deviation		8.151	
	Minimum		30	
	Maximum		58	
	Range		28	
	Interquartile Range		13	
	Skewness		-.361	.550
	Kurtosis		-.684	1.063
Maximum Assisted Opening mid treatment	Mean		43.29	2.034
	95% Confidence Interval for Mean	Lower Bound	38.98	
		Upper Bound	47.61	
	5% Trimmed Mean		43.49	
	Median		44.00	
	Variance		70.346	
	Std. Deviation		8.387	
	Minimum		25	
	Maximum		58	
	Range		33	
	Interquartile Range		11	
	Skewness		-.195	.550
	Kurtosis		.249	1.063

Maximum Assisted Opening 3 months	Mean		42.06	2.321
	95% Confidence Interval for Mean	Lower Bound	37.14	
		Upper Bound	46.98	
	5% Trimmed Mean		42.29	
	Median		44.00	
	Variance		91.559	
	Std. Deviation		9.569	
	Minimum		23	
	Maximum		57	
	Range		34	
	Interquartile Range		16	
	Skewness		-.490	.550
	Kurtosis		-.445	1.063
Maximum Assisted Opening 6months	Mean		41.71	2.025
	95% Confidence Interval for Mean	Lower Bound	37.41	
		Upper Bound	46.00	
	5% Trimmed Mean		41.84	
	Median		43.00	
	Variance		69.721	
	Std. Deviation		8.350	
	Minimum		25	
	Maximum		56	
	Range		31	
	Interquartile Range		13	
	Skewness		-.257	.550
	Kurtosis		-.191	1.063

Pain free opening

The mean pain free opening before oncologic treatment was 40.12 (SD 8.328) mm, then decreased to 37.94 (SD 10.431) at mid-treatment. The corresponding values at 3 and 6 months were 36.35 (SD 8.937) and 35.53 (SD 9.441) mm. The maximum unassisted and assisted opening started with mean of 43.35 (SD 8.426) and 45.06 (SD 8.151) prior XRT and decreased to 40.12 (SD8.580) and 41.71 (SD 8.350) at the 6 months post XRT appointment.

*Table 4. Mean (95% CI) change in **pain free opening** in millimeters and percent at each time-point compared to baseline.*

Time-point	***Δ in % mm from baseline***	***Δ in % from baseline***	***p Value Δ from baseline***	***p Value Δ from preceding follow-up***
Mid-treatment	*–1.44 (–4.48, +1.58)*	*–3.54 (–11.01, +3.88)*	*0.33*	*-*
3 months follow up	*–2.91 (–5.47, –0.35)*	*–7.05 (–13.25, –0.84)*	*0.02*	*0.29*
6 months follow up	*–1.26 (–5.40, +2.87)*	*–3.34 (–14.34, +7.62)*	*0.53*	*0.63*

Maximum unassisted opening

The maximum unassisted opening at baseline had the mean of 43.35 (SD 8.426) and decreased at mid-treatment to 41.71(SD 8.651) with a p value from baseline of 0.33. It kept slightly decreasing at the 3 and 6 months follow up with a mean of 40.47 (SD 9.461) and 40.12 (SD 8.580) as shown in Table 5.

*Table 5. Mean (95% CI) change in **maximum unassisted opening** in millimeters and percent at each time-point compared to baseline.*

Time-point	***Δ in % mm from baseline***	***Δ in % from baseline***	***p Value Δ from baseline***	***p Value Δ from preceding follow-up***
Mid-treatment	*–0.79 (–2.44, +0.80)*	*–1.81 (–5.61, +1.83)*	*0.33*	*-*
3 months follow up	*–2.43 (–4.33, –0.53)*	*–5.45 (–9.72, –1.19)*	*0.01*	*0.12*
6 months follow up	*+0.13 (–3.78, +4.04)*	*+0.32 (–9.31, +9.95)*	*0.94*	*0.99*

Maximum assisted opening

Similarly to the maximum unassisted opening, the assisted opening statistical analysis has observed a decrease from baseline appointments of 45.06 (SD 8.151) to the 6 months post XRT with the mean of 41.71 (SD 8.350). The least p value was recorded of 0.01 of change from baseline to the 3 months follow up.

*Table 6. Mean (95% CI) change in **maximum assisted opening** in millimeters and percent at each time-point compared to baseline.*

Time-point	*Δ in % mm from baseline*	*Δ in % from baseline*	*p Value Δ from baseline*	*p Value Δ from preceding follow-up*
Mid-treatment	*–0.69 (–2.51, +1.13)*	*–1.53 (–5.59, +2.51)*	*0.44*	-
3 months follow up	*–2.30 (–4.13, –0.47)*	*–5.00 (–8.97, –1.02)*	*0.01*	*0.18*
6 months follow up	*–0.43 (–4.01, +3.91)*	*–1.02 (–9.51, +9.28)*	*0.98*	*0.82*

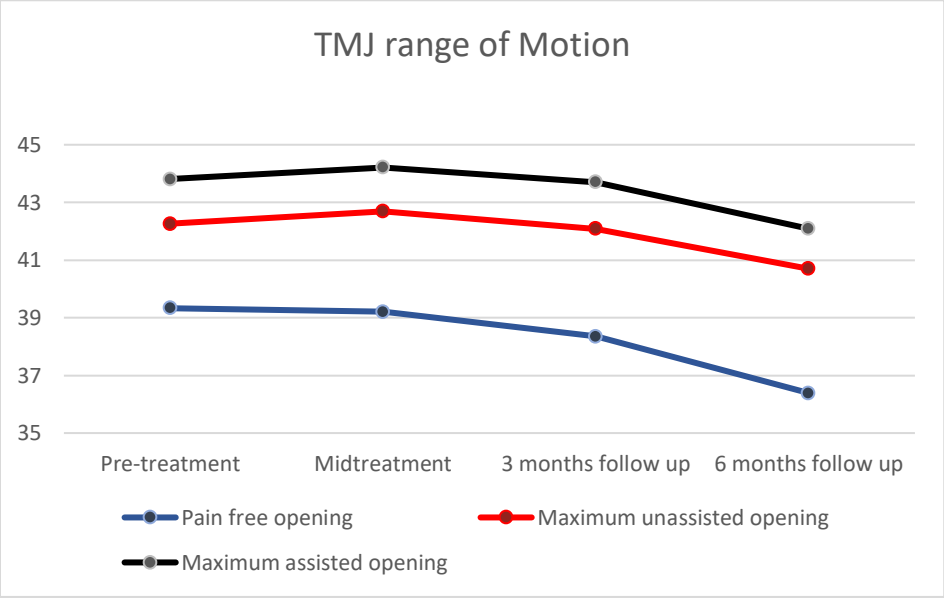


Chart 9. TMJ range of motion

TMJ range of motion (extrusive movement)

We compared each appointment to both the baseline visit and preceding follow up . The mean (95% CI) for excursive movements during the baseline visit for right lateral movement is 7.44 (6.30-8.58), left lateral movement 8.28 (7.09-9.50), and protrusive movement: 4.37 (3.61-5.12) The right lateral and protrusive movements remained fairly stable over time during before, during and after treatment. However , the left lateral movement showed a slight increase during and after treatment from baseline into mean of 8.69 (6.89-10.50) mid-treatment, 9.00 (7.46-10.54) 3 months post XRT, and after 6 month post-XRT 8.48 (7.34-9.63). The range and standard deviations suggest some variability in the data, with larger spreads observed during mid-treatment and 6 months for both lateral movements and protrusion.

*Table7 . Mean (95% CI) and change in **right lateral movement** at each time-point compared to baseline.*

Time-point	***Mean (95% CI)***	***Z*** ***Δ from baseline***	***P value*** ***Δ from baseline***	***Z*** ***Δ from preceding follow-up***	***p Value*** ***Δ from preceding follow-up***
Mid-treatment	*7.38 (5.80- 8.97)*	*–0.21*	*0.82*	-	-
3 months follow up	*7.24 (6.09- 8.39)*	*–0.20*	*0.84*	*–0.17*	*0.86*
6 months follow up	*7.28 (5.84- 8.71)*	*–0.34*	*0.73*	*–0.70*	*0.48*

*Table 8. Mean (95% CI) and change in **left lateral movement** at each time-point compared to baseline.*

Time-point	***Mean (95% CI)***	***Z*** ***Δ from baseline***	***P value*** ***Δ from baseline***	***Z*** ***Δ from preceding follow-up***	***p Value*** ***Δ from preceding follow-up***
Mid-treatment	*8.69 (6.89- 10.50)*	*–0.78*	*0.43*	-	-
3 months follow up	*9.00 (7.46- 10.54)*	*–1.52*	*0.12*	*–0.50*	*0.62*
6 months follow up	*8.48 (7.34- 9.63)*	*–1.35*	*0.18*	*–0.81*	*0.42*

*Table 9. Mean (95% CI) and change in **protrusive movement** at each time-point compared to baseline.*

Time-point	***Mean (95% CI)***	***Z*** ***Δ from baseline***	***P value*** ***Δ from baseline***	***Z*** ***Δ from preceding follow-up***	***p Value*** ***Δ from preceding follow-up***
Mid-treatment	*4.15 (3.12- 5.19)*	*–0.12*	*0.90*	-	-
3 months follow up	*4.19 (3.23- 5.15)*	*–0.67*	*0.50*	*–0.01*	*0.99*
6 months follow up	*4.31 (3.03- 5.59)*	*–0.62*	*0.54*	*–0.31*	*0.76*

Opening pattern

The analysis of the opening pattern at various time points revealed notable trends. Initially, 83.3% of patients exhibited a straight opening pattern. This proportion slightly decreased to 79.3% mid-treatment and 73.9% at three months, suggesting some deviation during and shortly after treatment. However, by the six-month mark, the percentage of patients with a straight opening pattern increased to 95.7%, suggesting a potential improvement over time. Conversely, the occurrence of corrected or uncorrected deviation in opening patterns was 16.7% at baseline, increased during mid-treatment (20.7%) and three months (26.1%), then significantly dropped to 4.3% at six months.

Clicking/crepitus and joint locking

Our research findings indicate that there wasn't a notable change in the occurrences of clicking/crepitus starting with a 12 (28.6%) showing sounds on the pre-treatment appointment and ending on a 12 (40%) showing clicking/crepitus at the 6 months post XRT. The same was noticed for joint locking among our patients in before 36 (85.7%) no incidence and after 26 (86.7%) undergoing radiation therapy.

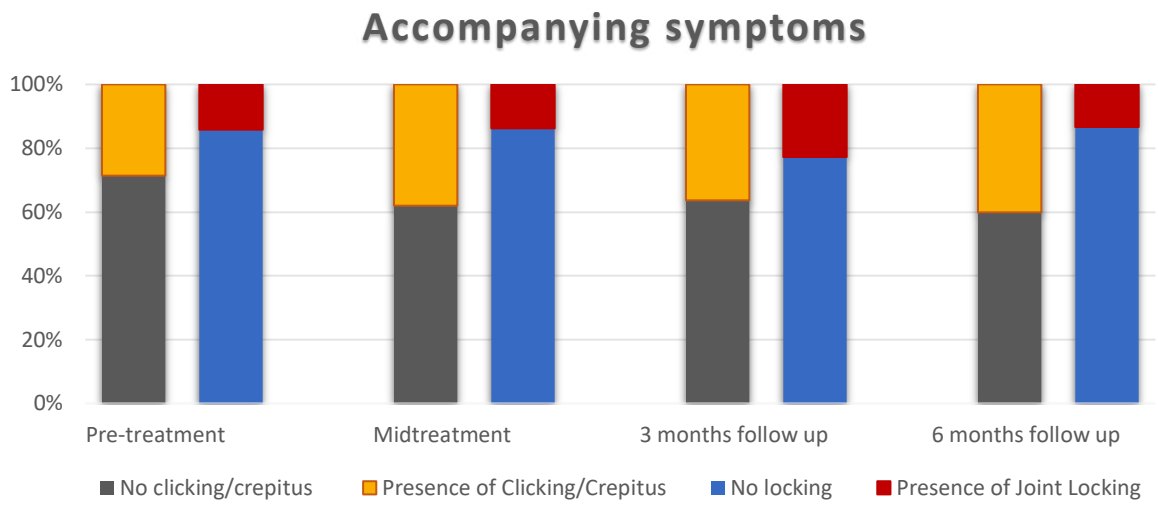


Chart 11. Accompanying symptoms, clicking, crepitus, joint locking.

Pain on palpation

Initially, 42.9% of our patients showed masticatory muscle pain at baseline. This percentage has continued to rise through treatment reaching to 63.3% at 6 months post-radiation follow-up showed masticatory muscles pain both unilaterally and bilaterally when compared to baseline**.** Our patients consistently reported experiencing more pain in the masticatory muscles on the side undergoing radiation therapy compared to the contralateral side. This unilateral manifestation of pain in the masticatory muscles was a notable observation in our research.

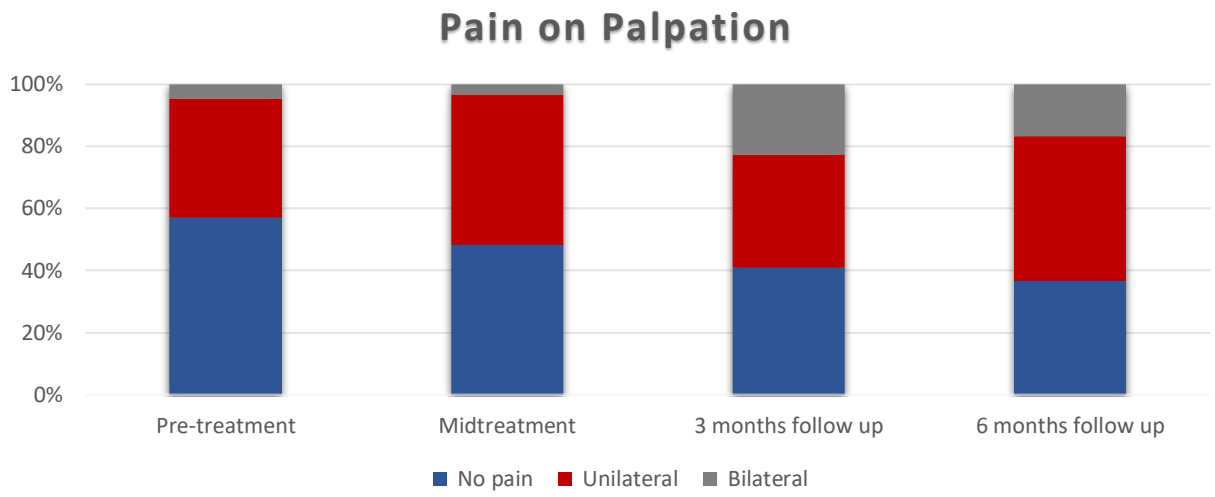


Chart 10. Pain on palpation in baseline, mid-treatment, 3 months follow up, and 6 months follow up.

Table 10. TMD symptoms among head and neck cancer patients at each time-point and compared to baseline.

	Baseline n (%)	***Mid-treatment n (%)***	***3 months n (%)***	***6 months n (%)***	***p Value Δ baseline to mid-treatment***	***p Value Δ baseline to 3 months***	***p Value Δ baseline to 6 months***
Opening pattern						-	
Straight	*35 (83.3%)*	*23 (79.3%)*	*17 (73.9%)*	*22 (95.7%)*	*0.99*	*0.25*	*0.99*
Corrected/uncorrected deviation	*7 (16.7%)*	*6 (20.7%)*	*6 (26.1%)*	*1 (4.3%)*			
TMJ sound							
None	*30 (71.4%)*	*18 (62.1%)*	*14 (63.6%)*	*18 (60.0%)*	*0.68*	*0.37*	*0.50*
Clicking/crepitus	*12 (28.6%)*	*11 (37.9%)*	*8 (36.4%)*	*12 (40.0%)*			
Joint locking							
No incidence	*36 (85.7%)*	*25 (86.2%)*	*17 (77.3%)*	*26 (86.7%)*	*0.99*	*0.62*	*0.99*
Occurred	*6 (14.3%)*	*4 (13.8%)*	*5 (22.7%)*	*4 (13.3%)*			
Pain on palpation							
None	*24 (57.1%)*	*14 (48.3%)*	*9 (40.9%)*	*11 (36.7%)*	*0.99*	*0.22*	*0.18*

Unilateral/bilateral	*18 (42.9%)*	*15 (51.7%)*	*13 (59.1%)*	*19 (63.3%)*

Discussion

Radiation-induced orofacial pain represents a significant global health concern. Temporomandibular disorders and orofacial pain frequency is steadily rising in head and neck cancer patient due to increased use of radiation therapy as a main modality to kill tumor cells. Our study focused on understanding the prevalence and impact of radiation therapy on TMJ function in HNC patients, specifically those with squamous cell carcinoma (SCC). These cancer types were chosen due to their susceptibility to radiation therapy without the confounding influence of surgery. Jaw hypomobility and masticatory muscles pain, a common consequence of radiation therapy, progress slowly over time. The effect on masticatory muscles is usually reported 9 months after completion of treatment and can keep progressing up to 9 months post treatment. [25] This can be mainly explained by the acceleration of fibrogenic response in the cellular level observed within the first six months post-treatment. This finding aligns with previous studies on radiation-induced tissue damage, highlighting the need for early intervention strategies to mitigate fibrosis and preserve TMJ function prior, during, and after radiation therapy. Restricted mouth opening and temporomandibular disorder is often encountered in cancer care, significantly impacting cancer patients' quality of life and depression rates. [15] Common problems associated with limited mouth opening include speech difficulties, chewing

impairments, malnutrition, compromised oral hygiene . Proper evaluation of temporomandibular disorders is crucial, involving measurements of mouth opening and visual assessment, especially in cancer patients undergoing treatment, where limitation of mouth opening or orofacial pain can result from tumor invasion or therapy-induced effects.

Many research have showed promises in preventing and managing strategies including pharmacological interventions such as pentoxifylline, physiotherapy, and supportive measures such as hot compresses, warm saline rinsing, and pain management. Exercise therapy by the use of stabilizing devices like TheraBite and Dynasplint, are recommended in literature to increase pain free mouth opening. [19] Some drugs, such as Pentoxifylline, has shown promise in increasing mandibular range of motion, while surgical interventions may be considered in severe cases refractory to conservative treatments, although guidelines for surgical management are currently lacking. A pilot study investigated the effect of pentoxifylline in the treatment of radiation induced trismus and limitation in mouth opening suggesting it to be a modest therapy in increasing mouth opening after radiation therapy. [108] Recently, low level laser therapy has been introduced to manage cancer therapy side effects. A case control in Brazil with oropharyngeal cancer, showed improvement in mouth opening from 20mm to 30mm after only one month of administering laser. Also, they found out that muscle pain was reduced significantly and the patient even gained weight at his 1 year post-radiation follow up appointment. [109] Overall, a multimodal approach involving pharmacotherapy, physiotherapy,supportive measures and photobiomodulation is essential in effectively managing the limitation in mouth opening and masticatory muscle pain in cancer patients, thereby improving their quality of life. [19]

Our study underscores the significance of addressing TMJ disorders and jaw hypomobility in HNC patients undergoing radiation therapy. Notably, we observed a unilateral manifestation of masticatory muscle pain in patients' post-treatment, indicating a potential side effect specific to the irradiated side. This observation emphasizes the importance of targeted interventions to alleviate pain and improve TMJ function in affected individuals.

While our study did not observe significant changes in clicking/crepitus and joint locking before and after radiation therapy, further research is warranted to comprehensively understand the impact of radiation therapy on the condyle, disc health, and vascularity and the symptoms associated with it.

Future studies should explore preventive strategies and early interventions to minimize the long-term effects of radiation therapy on TMJ function, ultimately improving the quality of life for HNC patients. Additionally, advancements in radiotherapy technology, such as three-dimensional conformal or intensity-modulated radiation therapy (IMRT), may offer promising avenues for reducing treatment-related complications, including TMJ disorders and jaw hypomobility.

Clinical implications

These findings suggest that oncologic treatment may lead to a modest decrease in pain-free mouth opening within the 6-month period post radiation therapy. Moreover, a considerable number of patients who did not experience masticatory muscle pain prior to radiotherapy developed unilateral muscle pain by the 3 and 6-months follow-up, indicating a potential association between radiotherapy and the onset of Temporomandibular joint disorders. This underscores the importance of proactive management strategies to address this complication.

This prospective study represents a significant advancement in understanding temporomandibular disorders (TMD) prevalence and risk factors in Head and Neck Cancer (HNC) patients undergoing radiotherapy. It seeks to uncover critical insights into the development trajectory of TMD and its correlation with radiation-induced hypomobility. By shedding light on the underlying factors contributing to TMD symptoms, this research aims to lay the groundwork for the development of effective preventive measures and therapeutic interventions. This helps us as dentists and oral medicine specialists to better alleviate the long-term adverse effects of radiation therapy on patient well-being. This information helped us to better understand the cancer patients' complains and how to manage them. Using our data, patients who reported masticatory muscle pain when palpating at their 6 months post-XRT appointment, were referred to our orofacial pain clinic and treated accordingly.

Strength and limitations

The strengths of our study lie in its prospective cohort design and the utilization of objective measurements using the DC-TMD validated form for assessing TMD symptoms. Additionally, the low rate of patient attrition is noteworthy. Notably, there is a gap in the existing literature regarding investigations into the radiation effects on the Temporomandibular joint disorders in Head and Neck Cancer (HNC) patients. The consistency ensured by having the same individual administer the examination form is advantageous for maintaining continuity. However, there is a possibility of bias. While our study comprehensively investigated the impact of radiation therapy on temporomandibular disorders (TMD) and limitation in mouth opening among head and neck

cancer patients, it is important to acknowledge certain limitations. One notable limitation is the lack of assessment of the effect of chemotherapy on TMD and myalgia. Chemotherapy, particularly agents like capecitabine, has been associated with neuromuscular symptoms, including trismus, which could contribute to TMD symptoms. Reports suggest that discontinuation of capecitabine resulted in the resolution of symptoms, indicating a potential causal relationship.[110, 111] Additionally, certain medications such as succinylcholine and tricyclic antidepressants have been identified as capable of causing restriction of mouth opening as a secondary effect. [112, 113] Another limitation to be considered is the small sample that was restricted by limitation of time provided to finish this study and missing data due to the loss of follow up of some of our patients . Also, the difference between the effects on TMJ by conventional RT and IMRT was not put into consideration in our study.

Conclusions

In conclusion, our study contributes valuable insights into the prevalence and impact of radiation therapy on TMJ function in HNC patients. By identifying key risk factors and outcomes associated with TMJ disorders, we aim to inform clinical practice and guide the development of targeted interventions to optimize patient care and outcomes.

Disclosure statement

No potential conflict of interest was reported by the author(s).

Funding

No external funding was provided for this study.

1. Pezzuto, F., et al., *Update on head and neck cancer: current knowledge on epidemiology, risk factors, molecular features and novel therapies.* Oncology, 2015. **89**(3): p. 125-136.
2. Mehanna, H., et al., *Head and neck cancer—Part 1: Epidemiology, presentation, and prevention.* Bmj, 2010. **341**.
3. Chaturvedi, A., E. Engels, and R. Pfeiffer, *Human papillomavirus and rising oropharyngeal cancer incidence in the United States.* J Clin Oncol, 2011. **29**: p. 4294-4301.
4. Gillison, M., T. Broutian, and R. Pickard, *Prevalence of oral HPV infection in the United States, 2009-2010.* JAMA, 2012. **307**: p. 693-703.
5. Chaturvedi, A., E. Engels, and W. Anderson, *Incidence trends for human papillomavirus-related and -unrelated oral squamous cell carcinomas in the United States.* J Clin Oncol, 2008. **26**: p. 612-619.
6. Näsman, A., P. Attner, and L. Hammarstedt, *Incidence of human papillomavirus (HPV) positive tonsillar carcinoma in Stockholm, Sweden: an epidemic of viral-induced carcinoma?* Int J Cancer, 2009. **125**: p. 362-366.
7. Mehanna, H., T. Beech, and T. Nicholson, *Prevalence of human papillomavirus in oropharyngeal and nonoropharyngeal head and neck cancer--systematic review and meta-analysis of trends by time and region.* Head Neck, 2013. **35**: p. 747-755.
8. El-Mofty, S.K., *Human papillomavirus (HPV) related carcinomas of the upper aerodigestive tract*. 2007, Springer.
9. Ang, K.K., et al., *Human papillomavirus and survival of patients with oropharyngeal cancer.* New England Journal of Medicine, 2010. **363**(1): p. 24-35.
10. Marta, G.N., et al., *Intensity-modulated radiation therapy for head and neck cancer: systematic review and meta-analysis.* Radiother Oncol, 2014. **110**(1): p. 9-15.
11. Brook, I., *Early side effects of radiation treatment for head and neck cancer.* Cancer Radiother, 2021. **25**(5): p. 507-513.
12. Sroussi, H.Y., et al., *Common oral complications of head and neck cancer radiation therapy: mucositis, infections, saliva change, fibrosis, sensory dysfunctions, dental caries, periodontal disease, and osteoradionecrosis.* Cancer Med, 2017. **6**(12): p. 2918-2931.
13. Saghafi, E., L. Tuomi, and G. Kjeller, *The prevalence and symptoms of temporomandibular disorders in head and neck cancer patients.* Acta Odontologica Scandinavica, 2022. **80**(4): p. 252-257.
14. Pauli, N., et al., *Temporomandibular disorder in head and neck cancer patients undergoing radiotherapy: Clinical findings and patient-reported symptoms.* Head & Neck, 2019. **41**(10): p. 3570-3576.

15. Goldstein, M., et al., *The effects of antitumor irradiation on mandibular opening and mobility: a prospective study of 58 patients.* Oral Surg Oral Med Oral Pathol Oral Radiol Endod, 1999. **88**(3): p. 365-73.
16. Louise Kent, M., et al., *Radiation-induced trismus in head and neck cancer patients.* Supportive Care in Cancer, 2008. **16**(3): p. 305-9.
17. Wang, C.J., et al., *The degree and time-course assessment of radiation-induced trismus occurring after radiotherapy for nasopharyngeal cancer.* The Laryngoscope, 2005. **115**(8): p. 1458-1460.
18. Stubblefield, M.D., L. Manfield, and E.R. Riedel, *A preliminary report on the efficacy of a dynamic jaw opening device (dynasplint trismus system) as part of the multimodal treatment of trismus in patients with head and neck cancer.* Arch Phys Med Rehabil, 2010. **91**(8): p. 1278-82.
19. Satheeshkumar, P.S., M.P. Mohan, and J. Jacob, *Restricted mouth opening and trismus in oral oncology.* Oral Surg Oral Med Oral Pathol Oral Radiol, 2014. **117**(6): p. 709-15.
20. Bensadoun, R.J., et al., *A systematic review of trismus induced by cancer therapies in head and neck cancer patients.* Support Care Cancer, 2010. **18**(8): p. 1033-8.
21. Wu, V.W., M.T. Ying, and D.L. Kwong, *A study on the post-radiotherapy changes of temporomandibular joint in nasopharyngeal carcinoma patients.* Br J Radiol, 2017. **90**(1080): p. 20170375.
22. Wu, V.W. and Y.N. Lam, *Radiation-induced temporo-mandibular joint disorder in post-radiotherapy nasopharyngeal carcinoma patients: assessment and treatment.* Journal of Medical Radiation Sciences, 2016. **63**(2): p. 124-132.
23. van der Molen, L., et al., *Dysphagia and trismus after concomitant chemo-Intensity-Modulated Radiation Therapy (chemo-IMRT) in advanced head and neck cancer; dose-effect relationships for swallowing and mastication structures.* Radiother Oncol, 2013. **106**(3): p. 364-9.
24. Chen, Y.Y., et al., *Intensity-modulated radiation therapy reduces radiation-induced trismus in patients with nasopharyngeal carcinoma: a prospective study with >5 years of follow-up.* Cancer, 2011. **117**(13): p. 2910-6.
25. Louise Kent, M., et al., *Radiation-induced trismus in head and neck cancer patients.* Support Care Cancer, 2008. **16**(3): p. 305-9.
26. Whitmyer, C.C., J.C. Waskowski, and H. Iffland, *Radiotherapy and oral sequelae: preventive and management protocols.* Journal of Dental Hygiene: JDH, 1997. **71**(1): p. 23-29.
27. Lyons, A.J., S. Crichton, and T. Pezier, *Trismus following radiotherapy to the head and neck is likely to have distinct genotype dependent cause.* Oral Oncol, 2013. **49**(9): p. 932-936.
28. Hsiung, C.Y., et al., *Intensity-modulated radiotherapy for nasopharyngeal carcinoma: the reduction of radiation-induced trismus.* Br J Radiol, 2008. **81**(970): p. 809-14.
29. Pauli, N., et al., *The incidence of trismus and long-term impact on health-related quality of life in patients with head and neck cancer.* Acta Oncol, 2013. **52**(6): p. 1137-45.
30. Lee, L.Y., et al., *Postradiation trismus and its impact on quality of life in patients with head and neck cancer.* Oral Surg Oral Med Oral Pathol Oral Radiol, 2015. **119**(2): p. 187-95.

31. van der Geer, S.J., et al., *Prevalence and prediction of trismus in patients with head and neck cancer: A cross-sectional study.* Head Neck, 2019. **41**(1): p. 64-71.
32. Aghajanzadeh, S., et al., *The effect of jaw exercises on anxiety and depression in patients with head and neck cancer receiving radiotherapy: Prospective 2-year follow-up study.* Head Neck, 2020. **42**(2): p. 330-335.
33. Chua, D.T.T., et al., *A Pilot Study of Pentoxifylline in the Treatment of Radiation-Induced Trismus.* American Journal of Clinical Oncology, 2001. **24**(4): p. 366-369.
34. Bernal Rodriguez, C.G., et al., *Photobiomodulation with Low-Level Laser in the Treatment of Trismus After Radiotherapy: A Case Report.* Photobiomodul Photomed Laser Surg, 2019. **37**(4): p. 240-243.
35. Couch, L.S., et al., *Capecitabine-related neurotoxicity presenting as trismus.* Clin Colorectal Cancer, 2003. **3**(2): p. 121-3.
36. Cunningham, P.A. and R.W. Kendrick, *Trismus as a result of metoclopramide therapy.* J Ir Dent Assoc, 1988. **34**(4): p. 128-9.
37. Filho, A.S., et al., *Trismus induced by fluoxetine.* J Clin Psychopharmacol, 2009. **29**(3): p. 306-7.
38. Fitzpatrick, L.R., *Masseter muscle rigidity, elevated creatine kinase, and rhabdomyolysis following succinylcholine administration: a case report.* Aana j, 2008. **76**(5): p. 349-54.

Chapter 6: Discussion

6.1 Summary of Results

After our comprehensive literature review, we found out that there aren't enough studies done prospectively on the effect of radiation therapy on temporomandibular disorders, especially in Canada and North America. Our prospective clinical results highlighted the importance of examining the temporomandibular joint through the radiation therapy journey. Our findings will be crucial in shaping effective prevention strategies for temporomandibular disorders to assess clinicians in alleviating any orofacial pain that could increase post treatment.

It was noted that the mean age of our participants is 63.30 years and that approximately 72.7 % were male. Lifestyle factors that contributed to head and neck cancer diagnosis included

smoking, alcohol consumption, and previous infections of HPV and EBER virus. The most frequent tumor diagnosis is squamous cell carcinoma (SCC) . The pain free opening in radiotherapy receiving patients marked a significant decrease in the 3rd and 6th month interval. While pain on palpation is the most reported temporomandibular disorder symptom with both unilateral and bilateral facial pain especially at the 6 months appointment. The most reported affected side was the radiated side with some radiated pain to the head and neck at the same side. Clicking and crepitus complains are reported but have not remarkably changed prior and post radiation therapy. The opening pattern also showed an interesting results, the findings imply that while treatment may temporarily affect the opening patterns of patients, there is a substantial return to normalcy or even improvement by 6 months post-treatment.

Our results are in line with some other studies that followed similar objective and research questions. Pauli and Finizia reported similar results with peak of reduced mouth opening and more stiffness and pain in the jaw at the 6 months post radiation therapy. [14] Pauli et al. also stated in other study that temporomandibular disorders are prevalent among head and neck cancer patients. Among their 83 participants, they came with the conclusion that those who experience temporomandibular disorders prior radiation therapy are at greater risk of developing mandibular hypomobility 6 months post radiation.[86] Similar results were found in our study where patients whose pain free mouth opening measurements were low at their pre-radiation assessment accompanied with painful clicking, developed even lower measurements and exaggerated pain at touch at their 6 months appointment. Also, although we did find that the radiated masticatory muscles showed more pain and stiffness, our study did not find association between increased clicking and crepitus noises and increased radiation dosage.

However, Goldstein has mentioned that as the radiation dose to the masticatory muscles and the temporomandibular joint increased, the maximum unassisted opening was reduced in a linear fashion. Also, he stated that the higher radiation dose the pterygoid muscles received, the worsen mandibular dysfunction was. [15]

6.2 Methodological considerations

6.2.1 Bias

Any epidemiological study is susceptible to bias due to inaccuracies or errors in study results or conclusions caused by the unability of the researcher from impartially answering a research question. Bias can be introduced at all stages of research such as study design, data collection, analysing the data and the publication process. Thus, evaluating and reporting potential biases in any study is crucial. Additionally, it's essential to design studies carefully and anticipate potential sources of bias to minimize their occurrence. The expected types of bias in this study and the measures taken to prevent them are discussed below.

6.2.1.1 Selection Bias

The way the participants were selected for the study can result in selection bias. Factors such as diagnosis can lead to selection bias. To minimize this, we included patients referred to our oral medicine clinic regardless of their diagnosis and whether they have TMD symptoms or not in the first visit.

6.2.1.2 Information Bias

All patients clinical TMD symptoms were recorded using the DC/TMD clinical examination protocol. Thus, the chances of misdiagnosis were minimized as all of them followed the same protocol and were confirmed by the attending on site. Moreover, although most patients were seen by one researcher, many other residents, specialists, and master students participated in the data collection and all results were compared and approved by the orofacial pain specialist.

Also, the patients might have failed to report certain events that contributed to their location and severity of pain.

Detection bias arises when the examiner's prior knowledge about the effect of exposure on the outcome influences their assessment. In our case, clinicians' previous experience with patients and existing literature on the association between radiation therapy and TMD may have affected the final diagnosis.

6.2.2 Strength of the study

Our research has multiple strengths starting with the prospective design that allows us to have control on the methodology collecting the needed data. Another strength noted is that we used one standardized examination (DC/TMD criteria) to all patients which minimized the possibility of misdiagnosing. Also, all data from the medical portals including OASCIS and Medesync were extracted by a single person.

6.2.3 Limitation of the study

Due to restricted time of the master’s program, we were not able to recruit more patients. Thus, one of our limitations is our small sample size and short time follow up of up to 6 months post radiation therapy. Also, many patients failed to show up for the follow up appointments due to

multiple other medical appointments at the same time when treated for cancer. The use of medications that some patients used such as statins, may have contributed to myalgia and masticatory muscle pain may also have affected the pain on palpation results. We did not account for potential confounding factors such as exercises and some appliances used during the treatment, when measuring the association between radiation and TMD, which may have impacted the accuracy of the study results.

Chapter 7: Conclusion

As a result of our prospective study, we concluded the following points:

- Reduction in pain-free mouth opening was noticed over a 6-month period following radiation therapy suggesting an impact on oral function such as speaking, eating, and swallowing.
- A significant proportion of patients developed unilateral masticatory muscle pain by the 6-month follow-up when palpated, despite not having such pain prior to radiotherapy, indicating a potential association between radiotherapy and masticatory muscles pain.
- Our findings emphasize on the importance for proactive management strategies prior and during the oncologic treatment to address muscle pain and improve patient outcomes.
- This prospective study provides an understanding on the prevalence and risk factors of TMD in HNC patients undergoing radiotherapy.
- The higher dosage the TMJ receives can lead into increased TMD symptoms and radiation-induced hypomobility.
- By identifying the prevalence and underlying factors of TMD symptoms, the study seeks to inform the creation of effective preventive and therapeutic measures for dentists and

clinicians to alleviate the long-term adverse effects of radiation therapy on patient well-being and improve their quality of life after survival.

- Future investigations into radiotherapy delivery techniques and confounders elimination may reduce head and neck radiation induced TMD symptoms.

Chapter 8: Clinical Implications

TMD symptoms have become a known common and frequent side effect of radiation therapy in head and neck cancer patients. Although much previous research suggested that muscles fibrosis can be hard to manage after oncological treatment, its prevention is evidently possible. Due to our results, we have referred many patients who had masticatory pain after their 6 months post radiation last follow up appointment to our orofacial pain clinic at the Montreal General hospital. Knowing what we studied in the last years, we now are able to alleviate many cancer patients' facial pain using appliances and trigger points injections. We also started investigating on some prevention strategies and early interventions that can be applied to our oral medicine clinic such as exercises that might help lessen reduced pain free opening and muscle fibrosis on the long term.

Chapter 9: Knowledge Translation

To translate our knowledge to the dental and research society, we have presented our research in multiple events through North America. Our research was presented in form of poster presentation at the 2024 The International Association for Dental, Oral, and Craniofacial

Research IADR/AADOCR/CADR General Session and Exhibition in New Orleans, LA, USA. We also presented at the McGill University Research Day (2023, 2024). We submitted a video presentation to the Network of Oral and Bone Health Research (RSBO) (submitted for 2023). Moreover, we presented our poster research at the Journées dentaires internationales du Québec, JDIQ, Montreal, QC in May 2024.

Chapter 10: References

1. Pezzuto, F., et al., *Update on head and neck cancer: current knowledge on epidemiology, risk factors, molecular features and novel therapies.* Oncology, 2015. **89**(3): p. 125-136.
2. Mehanna, H., et al., *Head and neck cancer—Part 1: Epidemiology, presentation, and prevention.* Bmj, 2010. **341**.
3. Chaturvedi, A., E. Engels, and R. Pfeiffer, *Human papillomavirus and rising oropharyngeal cancer incidence in the United States.* J Clin Oncol, 2011. **29**: p. 4294-4301.
4. Gillison, M., T. Broutian, and R. Pickard, *Prevalence of oral HPV infection in the United States, 2009-2010.* JAMA, 2012. **307**: p. 693-703.
5. Chaturvedi, A., E. Engels, and W. Anderson, *Incidence trends for human papillomavirus-related and -unrelated oral squamous cell carcinomas in the United States.* J Clin Oncol, 2008. **26**: p. 612-619.
6. Näsman, A., P. Attner, and L. Hammarstedt, *Incidence of human papillomavirus (HPV) positive tonsillar carcinoma in Stockholm, Sweden: an epidemic of viral-induced carcinoma?* Int J Cancer, 2009. **125**: p. 362-366.
7. Mehanna, H., T. Beech, and T. Nicholson, *Prevalence of human papillomavirus in oropharyngeal and nonoropharyngeal head and neck cancer--systematic review and meta-analysis of trends by time and region.* Head Neck, 2013. **35**: p. 747-755.
8. El-Mofty, S.K., *Human papillomavirus (HPV) related carcinomas of the upper aerodigestive tract*. 2007, Springer.
9. Ang, K.K., et al., *Human papillomavirus and survival of patients with oropharyngeal cancer.* New England Journal of Medicine, 2010. **363**(1): p. 24-35.
10. Marta, G.N., et al., *Intensity-modulated radiation therapy for head and neck cancer: systematic review and meta-analysis.* Radiother Oncol, 2014. **110**(1): p. 9-15.
11. Brook, I., *Early side effects of radiation treatment for head and neck cancer.* Cancer Radiother, 2021. **25**(5): p. 507-513.
12. Sroussi, H.Y., et al., *Common oral complications of head and neck cancer radiation therapy: mucositis, infections, saliva change, fibrosis, sensory dysfunctions, dental caries, periodontal disease, and osteoradionecrosis.* Cancer Med, 2017. **6**(12): p. 2918-2931.

13. Saghafi, E., L. Tuomi, and G. Kjeller, *The prevalence and symptoms of temporomandibular disorders in head and neck cancer patients.* Acta Odontologica Scandinavica, 2022. **80**(4): p. 252-257.
14. Pauli, N., et al., *Temporomandibular disorder in head and neck cancer patients undergoing radiotherapy: Clinical findings and patient-reported symptoms.* Head & Neck, 2019. **41**(10): p. 3570-3576.
15. Goldstein, M., et al., *The effects of antitumor irradiation on mandibular opening and mobility: a prospective study of 58 patients.* Oral Surg Oral Med Oral Pathol Oral Radiol Endod, 1999. **88**(3): p. 365-73.
16. Louise Kent, M., et al., *Radiation-induced trismus in head and neck cancer patients.* Supportive Care in Cancer, 2008. **16**(3): p. 305-9.
17. Wang, C.J., et al., *The degree and time-course assessment of radiation-induced trismus occurring after radiotherapy for nasopharyngeal cancer.* The Laryngoscope, 2005. **115**(8): p. 1458-1460.
18. Stubblefield, M.D., L. Manfield, and E.R. Riedel, *A preliminary report on the efficacy of a dynamic jaw opening device (dynasplint trismus system) as part of the multimodal treatment of trismus in patients with head and neck cancer.* Arch Phys Med Rehabil, 2010. **91**(8): p. 1278-82.
19. Satheeshkumar, P.S., M.P. Mohan, and J. Jacob, *Restricted mouth opening and trismus in oral oncology.* Oral Surg Oral Med Oral Pathol Oral Radiol, 2014. **117**(6): p. 709-15.
20. Bensadoun, R.J., et al., *A systematic review of trismus induced by cancer therapies in head and neck cancer patients.* Support Care Cancer, 2010. **18**(8): p. 1033-8.
21. Wu, V.W., M.T. Ying, and D.L. Kwong, *A study on the post-radiotherapy changes of temporomandibular joint in nasopharyngeal carcinoma patients.* Br J Radiol, 2017. **90**(1080): p. 20170375.
22. Wu, V.W. and Y.N. Lam, *Radiation-induced temporo-mandibular joint disorder in post-radiotherapy nasopharyngeal carcinoma patients: assessment and treatment.* Journal of Medical Radiation Sciences, 2016. **63**(2): p. 124-132.
23. van der Molen, L., et al., *Dysphagia and trismus after concomitant chemo-Intensity-Modulated Radiation Therapy (chemo-IMRT) in advanced head and neck cancer; dose-effect relationships for swallowing and mastication structures.* Radiother Oncol, 2013. **106**(3): p. 364-9.
24. Chen, Y.Y., et al., *Intensity-modulated radiation therapy reduces radiation-induced trismus in patients with nasopharyngeal carcinoma: a prospective study with >5 years of follow-up.* Cancer, 2011. **117**(13): p. 2910-6.
25. Louise Kent, M., et al., *Radiation-induced trismus in head and neck cancer patients.* Support Care Cancer, 2008. **16**(3): p. 305-9.
26. Whitmyer, C.C., J.C. Waskowski, and H. Iffland, *Radiotherapy and oral sequelae: preventive and management protocols.* Journal of Dental Hygiene: JDH, 1997. **71**(1): p. 23-29.
27. Lyons, A.J., S. Crichton, and T. Pezier, *Trismus following radiotherapy to the head and neck is likely to have distinct genotype dependent cause.* Oral Oncol, 2013. **49**(9): p. 932-936.

28. Hsiung, C.Y., et al., *Intensity-modulated radiotherapy for nasopharyngeal carcinoma: the reduction of radiation-induced trismus.* Br J Radiol, 2008. **81**(970): p. 809-14.
29. Pauli, N., et al., *The incidence of trismus and long-term impact on health-related quality of life in patients with head and neck cancer.* Acta Oncol, 2013. **52**(6): p. 1137-45.
30. Lee, L.Y., et al., *Postradiation trismus and its impact on quality of life in patients with head and neck cancer.* Oral Surg Oral Med Oral Pathol Oral Radiol, 2015. **119**(2): p. 187-95.
31. van der Geer, S.J., et al., *Prevalence and prediction of trismus in patients with head and neck cancer: A cross-sectional study.* Head Neck, 2019. **41**(1): p. 64-71.
32. Aghajanzadeh, S., et al., *The effect of jaw exercises on anxiety and depression in patients with head and neck cancer receiving radiotherapy: Prospective 2-year follow-up study.* Head Neck, 2020. **42**(2): p. 330-335.
33. Abboud, W.A., et al., *Restricted mouth opening in head and neck cancer: etiology, prevention, and treatment.* JCO Oncology Practice, 2020. **16**(10): p. 643-653.
34. Feinberg, A.P. and B. Tycko, *The history of cancer epigenetics.* Nature Reviews Cancer, 2004. **4**(2): p. 143-153.
35. Cohen, B., *John Hunter, pathologist.* Journal of the Royal Society of Medicine, 1993. **86**(10): p. 587-592.
36. David, H., *Rudolf Virchow and modern aspects of tumor pathology.* Pathology-Research and Practice, 1988. **183**(3): p. 356-364.
37. Bister, K., *Discovery of oncogenes: The advent of molecular cancer research.* Proceedings of the National Academy of Sciences, 2015. **112**(50): p. 15259-15260.
38. Brown, J.S., et al., *Updating the definition of cancer.* Molecular Cancer Research, 2023. **21**(11): p. 1142-1147.
39. Pfister, D.G., et al., *Head and neck cancers.* Journal of the National Comprehensive Cancer Network, 2011. **9**(6): p. 596-650.
40. Bhatia, A. and B. Burtness, *Treating head and neck cancer in the age of immunotherapy: a 2023 update.* Drugs, 2023. **83**(3): p. 217-248.
41. Tran, Q., et al., *Oral cavity cancer in young, non-smoking, and non-drinking patients: A contemporary review.* Critical Reviews in Oncology/Hematology, 2023: p. 104112.
42. Huang, J., et al., *Disease burden, risk factors, and trends of lip, oral cavity, pharyngeal cancers: A global analysis.* Cancer Medicine, 2023. **12**(17): p. 18153-18164.
43. Wehner, B.L. and R. Calla, *An osteopathic approach for a patient with sequela after treatment for a cheek squamous cell carcinoma.* AAO Journal, 2024. **34**(1): p. 37-42.
44. Kearney, M., M. Coffey, and A. Leong, *A review of Image Guided Radiation Therapy in head and neck cancer from 2009–2019–Best Practice Recommendations for RTTs in the Clinic.* Technical Innovations & Patient Support in Radiation Oncology, 2020. **14**: p. 43-50.
45. Thompson, L.D. and J.A. Bishop, *Update from the 5th Edition of the World Health Organization classification of head and neck tumors: nasal cavity, paranasal sinuses and skull base.* Head and Neck Pathology, 2022. **16**(1): p. 1-18.
46. Barsouk, A., et al., *Epidemiology, risk factors, and prevention of head and neck squamous cell carcinoma.* Medical Sciences, 2023. **11**(2): p. 42.

47. Da Cunha, A.R., et al., *The global, regional, and national burden of adult lip, oral, and pharyngeal cancer in 204 countries and territories: A systematic analysis for the global burden of disease study 2019.* JAMA oncology, 2023. **9**(10): p. 1401-1416.
48. Levy, B.B., et al., *A scoping assessment of dental services at designated head and neck cancer centres in Ontario, Canada.* BMC Oral Health, 2024. **24**(1): p. 232.
49. Al-Soneidar, W.A., et al., *Prevalence of Alpha, Beta, and Gamma Human Papillomaviruses in Patients With Head and Neck Cancer and Noncancer Controls and Relation to Behavioral Factors.* The Journal of Infectious Diseases, 2024. **229**(4): p. 1088-1096.
50. Goggin, P., *Guidelines on cervical cancer screening in Québec: Lignes directrices sur le dépistage du cancer du col utérin au Québec*. 2011: desLibris.
51. Gamelin, R., et al., *Ethnographic study of the barriers and facilitators to implementing human papillomavirus (HPV) self-sampling as a primary screening strategy for cervical cancer among Inuit women of Nunavik, Northern Quebec.* International Journal of Circumpolar Health, 2022. **81**(1): p. 2032930.
52. Siegel, R.L., et al., *Cancer statistics, 2022.* CA: a cancer journal for clinicians, 2022. **72**(1).
53. Gormley, M., et al., *Reviewing the epidemiology of head and neck cancer: definitions, trends and risk factors.* British Dental Journal, 2022. **233**(9): p. 780-786.
54. Aupérin, A., *Epidemiology of head and neck cancers: an update.* Current opinion in oncology, 2020. **32**(3): p. 178-186.
55. Siegel, R.L., A.N. Giaquinto, and A. Jemal, *Cancer statistics, 2024.* CA: a cancer journal for clinicians, 2024. **74**(1): p. 12-49.
56. Siegel, R.L., et al., *Cancer statistics, 2023.* Ca Cancer J Clin, 2023. **73**(1): p. 17-48.
57. Jordan, K.H., et al., *Factors Related to Human Papillomavirus Positivity among Oral Cavity and Pharynx Cancers from Surveillance, Epidemiology and End Results (SEER) Program Data.* Cancer Epidemiology, Biomarkers & Prevention, 2023. **32**(3): p. 452-462.
58. Ferrari, D., et al., *The slippery role of induction chemotherapy in head and neck cancer: myth and reality.* Frontiers in oncology, 2020. **10**: p. 7.
59. Rygalski, C.J., et al., *Time to surgery and survival in head and neck cancer.* Annals of surgical oncology, 2021. **28**: p. 877-885.
60. Garas, G., et al., *Novel strategies for managing retropharyngeal lymph node metastases in head and neck and thyroid cancer with transoral robotic surgery (TORS).* Annals of Surgical Oncology, 2022. **29**(12): p. 7881-7890.
61. Evers, C., et al., *Benefit from surgery with additional radiotherapy in N1 head and neck cancer at the time of IMRT: A population-based study on recent developments.* PLoS One, 2020. **15**(2): p. e0229266.
62. Al Qaraghuli, M.M., *Biotherapeutic antibodies for the treatment of head and neck cancer: Current approaches and future considerations of photothermal therapies.* Frontiers in Oncology, 2020. **10**: p. 559596.
63. Chen, H.H. and M.T. Kuo, *Improving radiotherapy in cancer treatment: Promises and challenges.* Oncotarget, 2017. **8**(37): p. 62742.
64. Koka, K., et al., *Technological advancements in external beam radiation therapy (EBRT): An indispensable tool for cancer treatment.* Cancer Management and Research, 2022: p. 1421-1429.

65. Ramos, M., *Emerging Technologies in Radiotherapy: Advances in Health Literacy and Healthcare Practice.* Transformative Approaches to Patient Literacy and Healthcare Innovation, 2024: p. 89-110.
66. Choi, J.I., et al. *Advances and challenges in conducting clinical trials with proton beam therapy*. in *Seminars in radiation oncology*. 2023. Elsevier.
67. Sourati, A., A. Ameri, and M. Malekzadeh, *Acute side effects of radiation therapy.* Cham: Springer, 2017.
68. Straub, J.M., et al., *Radiation-induced fibrosis: mechanisms and implications for therapy.* Journal of cancer research and clinical oncology, 2015. **141**: p. 1985-1994.
69. Ranta, P., et al., *Dysphagia, hypothyroidism, and osteoradionecrosis after radiation therapy for head and neck cancer.* Laryngoscope Investigative Otolaryngology, 2022. **7**(1): p. 108-116.
70. Dedović, S.J., et al., *Radiation-induced tumors and secondary malignancies following radiotherapy.* Vojnosanitetski pregled, 2022. **79**(7): p. 643-649.
71. Durham, J., T.R. Newton-John, and J.M. Zakrzewska, *Temporomandibular disorders.* Bmj, 2015. **350**.
72. Kapos, F.P., et al., *Temporomandibular disorders: a review of current concepts in aetiology, diagnosis and management.* Oral surgery, 2020. **13**(4): p. 321-334.
73. Nicot, R., et al., *Temporomandibular disorders in head and neck cancers: Overview of specific mechanisms and management.* Journal of Stomatology, Oral and Maxillofacial Surgery, 2020. **121**(5): p. 563-568.
74. Pigozzi, L.B., et al., *Quality of life in young and middle age adult temporomandibular disorders patients and asymptomatic subjects: a systematic review and meta-analysis.* Health and Quality of Life Outcomes, 2021. **19**: p. 1-22.
75. Ohrbach, R. and S. Sharma. *Temporomandibular disorders: Definition and etiology*. in *Seminars in Orthodontics*. 2023. Elsevier.
76. Greenbaum, T., et al., *The mouth-opening muscular performance in adults with and without temporomandibular disorders: A systematic review.* Journal of Oral Rehabilitation, 2022. **49**(4): p. 476-494.
77. Gauer, R.L. and M.J. Semidey, *Diagnosis and treatment of temporomandibular disorders.* American family physician, 2015. **91**(6): p. 378-386.
78. Jaeidah, S.H., *Treatment modalities for TMJ disorders: A literature review.* Journal of Medical Sciences, 2020. **15**(1): p. 1-7.
79. Pietra, L.C.F., et al., *Use of transcranial radiograph to detect morphological changes in mandibular condyles.* Revista CEFAC, 2017. **19**: p. 54-62.
80. Tamimi, D. and E. Jalali, *CBCT Evaluation of the TMJ.* Contemporary Management of Temporomandibular Disorders: Fundamentals and Pathway to Diagnosis, 2019: p. 143-172.
81. Schiffman, E., et al., *Diagnostic criteria for temporomandibular disorders (DC/TMD) for clinical and research applications: recommendations of the International RDC/TMD Consortium Network and Orofacial Pain Special Interest Group.* Journal of oral & facial pain and headache, 2014. **28**(1): p. 6.
82. Skeie, M.S., et al., *DC/TMD examiner protocol: longitudinal evaluation on interexaminer reliability.* Pain Research and Management, 2018. **2018**.

83. Ishigaki, S., et al., *Diagnostic accuracy of TMJ vibration analysis for internal derangement and/or degenerative joint disease.* CRANIO®, 1994. **12**(4): p. 241-246.
84. Pauli, N., et al., *Temporomandibular disorder as risk factor for radiation-induced trismus in patients with head and neck cancer.* Clinical and Experimental Dental Research, 2022. **8**(1): p. 123-129.
85. Bragante, K.C., et al., *Efficacy of exercise therapy during radiotherapy to prevent reduction in mouth opening in patients with head and neck cancer: A randomized controlled trial.* Oral surgery, oral medicine, oral pathology and oral radiology, 2020. **129**(1): p. 27-38.
86. Pauli, N., et al., *Temporomandibular disorder as risk factor for radiation-induced trismus in patients with head and neck cancer.* Clinical & Experimental Dental Research, 2022. **8**(1): p. 123-129.
87. Shinde, S., et al., *Estimation of temporomandibular joint dysfunction in oral cancer survivors.* Asian Pacific Journal of Cancer Prevention: APJCP, 2022. **23**(11): p. 3685.
88. Pauli, N., et al., *Risk structures for radiation-induced trismus in head and neck cancer.* Acta Oncologica, 2016. **55**(6): p. 788-792.
89. Jeon, K.J., et al., *Comparison of the Usefulness of CBCT and MRI in TMD Patients According to Clinical Symptoms and Age.* Applied Sciences, 2020. **10**(10): p. 3599.
90. Derwich, M., M. Mitus-Kenig, and E. Pawlowska, *Interdisciplinary approach to the temporomandibular joint osteoarthritis—review of the literature.* Medicina, 2020. **56**(5): p. 225.
91. Lowe, D., et al., *Radiation dose rate effects: what is new and what is needed?* Radiation and Environmental Biophysics, 2022. **61**(4): p. 507-543.
92. Deniz, Y., et al., *Comparison of CBCT radiation doses with conventional radiographs in TMJ imaging using Monte Carlo simulations.* Radiation and Environmental Biophysics, 2024: p. 1-7.
93. Anderson, G., et al., *An updated review on head and neck cancer treatment with radiation therapy.* Cancers, 2021. **13**(19): p. 4912.
94. Porceddu, S.V., et al., *Head and Neck Cancer International Group (HNCIG) consensus guidelines for the delivery of postoperative radiation therapy in complex cutaneous squamous cell carcinoma of the head and neck (cSCCHN).* International Journal of Radiation Oncology* Biology* Physics, 2020. **107**(4): p. 641-651.
95. Height, R., et al., *The dosimetric consequences of anatomic changes in head and neck radiotherapy patients.* Journal of Medical Imaging and Radiation Oncology, 2010. **54**(5): p. 497-504.
96. Stoiber, E.M., et al., *Analyzing human decisions in IGRT of head-and-neck cancer patients to teach image registration algorithms what experts know.* Radiation Oncology, 2017. **12**: p. 1-7.
97. Skármeta, N.P., et al., *Changes in understanding of painful temporomandibular disorders: the history of a transformation.* 2019.
98. Pullinger, A. and D. Seligman, *Trauma history in diagnostic groups of temporomandibular disorders.* Oral surgery, oral medicine, oral pathology, 1991. **71**(5): p. 529-534.

99. Palmer, J. and J. Durham, *Temporomandibular disorders.* BJA education, 2021. **21**(2): p. 44-50.
100. Hietaharju, M., et al., *Comparison of Axis II psychosocial assessment methods of RDC/TMD and DC/TMD as part of DC/TMD-FIN phase II validation studies in tertiary care Finnish TMD pain patients.* Journal of oral rehabilitation, 2021. **48**(12): p. 1295-1306.
101. Crane, P., et al., *TMD and Exercise Therapy Scoping Review Search Strategy.* 2024.
102. Ferrillo, M., et al., *Pain management and rehabilitation for central sensitization in temporomandibular disorders: a comprehensive review.* International Journal of Molecular Sciences, 2022. **23**(20): p. 12164.
103. Aslam, M.A., et al., *Interventions for the treatment of Radiotherapy Induced Trismus: A Systematic Review of the Literature.* Journal of the Pakistan Dental Association, 2022. **31**(3).
104. Parihar, U.S., et al., *Design of Jaw Rehabilitation Device for Patients with TMJ Disorder*, in *Recent Advances in Machines and Mechanisms: Select Proceedings of the iNaCoMM 2021*. 2022, Springer. p. 451-463.
105. van der Geer, S.J., et al., *The use of stretching devices for treatment of trismus in head and neck cancer patients: a randomized controlled trial.* Supportive Care in Cancer, 2020. **28**: p. 9-11.
106. Ryu, J.-W., *Considerations in the Diagnosis and Treatment of Temporomandibular Disorders in Children and Adolescents: A Review.* Journal of Oral Medicine and Pain, 2023. **48**(3): p. 75-80.
107. Bird, R. and E.V. Beecroft. *TMD diagnosis–What should general dentists and orthodontists know?* in *Seminars in Orthodontics*. 2024. Elsevier.
108. Chua, D.T.T., et al., *A Pilot Study of Pentoxifylline in the Treatment of Radiation-Induced Trismus.* American Journal of Clinical Oncology, 2001. **24**(4): p. 366-369.
109. Bernal Rodriguez, C.G., et al., *Photobiomodulation with Low-Level Laser in the Treatment of Trismus After Radiotherapy: A Case Report.* Photobiomodul Photomed Laser Surg, 2019. **37**(4): p. 240-243.
110. Couch, L.S., et al., *Capecitabine-related neurotoxicity presenting as trismus.* Clin Colorectal Cancer, 2003. **3**(2): p. 121-3.
111. Cunningham, P.A. and R.W. Kendrick, *Trismus as a result of metoclopramide therapy.* J Ir Dent Assoc, 1988. **34**(4): p. 128-9.
112. Filho, A.S., et al., *Trismus induced by fluoxetine.* J Clin Psychopharmacol, 2009. **29**(3): p. 306-7.
113. Fitzpatrick, L.R., *Masseter muscle rigidity, elevated creatine kinase, and rhabdomyolysis following succinylcholine administration: a case report.* Aana j, 2008. **76**(5): p. 349-54.

Appendix

Research Ethics Board Approval Letter

Centre universitaire de santé McGill | McGill University Health Centre

2023-08-03

Dr. Firoozeh Samim
Dept. of Oral and Maxillofacial Surgery Mouth Diseases and TMD & Orofacial Pain Clinic Room B3-131
MUHC-Montreal General Hospital

email: firoozeh.samim@mcgill.ca

RE: REB Conditional Approval of a New Research Project
Development of Evidence-Based Oral Care Guidelines for Pre-, interim-, and Post Radiation in Head and Neck Cancer Patients
(HNCguideline / 2024-9879)

MUHC REB Co-Chair for the CT1 panel: Vincent Lajoie

Dear Dr. Samim,

Thank you for the initial submission of the research project indicated above.

On 2023-08-03, a delegated review of the research project was provided by member(s) of the McGill University Health Centre (MUHC) Research Ethics Board (REB), more precisely its Clinical Trials 1 (CT1) panel.

The *Initial Submission Form* (F11H-NIR-115604) as well as the following documents were reviewed:

- **Research protocol**
  - (Prospective study.docx) [Date: 2023-04-01, Version: 1]
- **Informed Consent form**
  - (MUHC consent form final.doc) [Date: 2023-07-14, Version: 2023-07-14]

After reviewing the documents, **this research project was approved unanimously by the MUHC REB conditional upon the receipt of responses to the conditions listed in the *REB Conditions & PI Responses Form* (F20-117844) and documents attached to it.** This will be reported to the MUHC REB and will be entered accordingly into the minutes of the next CT1 meeting.

Corrected documents attached to the F20-117844 will have to be submitted in “track changes”.

We trust this will prove satisfactory to you. Thank you for your consideration in this matter.

Best Regards,

Research Consent form

Centre universitaire de santé McGill | McGill University Health Centre

INFORMED CONSENT FORM

Title of Study: Development of Evidence-Based Oral Care Guidelines for Pre-, interim-, and Post Radiation Head and Neck Cancer Patients

Principal Investigator: Dr. Firoozeh Samim, Dr. Noor Karra

Master students: Dr. Aia Naksho, Dr. Elahe Akbari

Introduction: You are being asked to participate in a research study. The purpose of this study is to develop evidence-based oral care guidelines for patients undergoing radiation therapy for head and neck cancer. The information gathered from this study will help healthcare professionals improve the care of patients with head and neck cancer who undergo radiation therapy.

Description of Study: This research study will take place at Royal Victoria (Glenn site) , Montreal, QC as well as Montreal General hospital of any treatment is necessary. You will be asked to attend five study visits

Risks:

There are minimal risks associated with participating in this study, including possible discomfort or minor pain during the examination.

Voluntary Participation:

Your participation in this research study is voluntary. Therefore, you may refuse to participate. You may also withdraw at any time, without giving any reasons, by informing the doctor in charge of this research or a member of the research team.

Your decision not to participate in the study, or to withdraw from it, will have no impact on the quality of care and services to which you are otherwise entitled, or on your relationship with the teams providing them.

The doctor in charge of this research study, the Research Ethics Board, the funding agency, or the sponsor may put an end to your participation without your consent. This may happen if new findings or information indicate that participation in this research study is no longer in your best interests, if you do not follow study instructions, or if there are administrative reasons to terminate the study.

However, before you withdraw from the study, we suggest that you take part in a final evaluation, for safety reasons.

If you withdraw or are withdrawn from the study, no further data or samples will be collected. However, the information , images and MRI already collected for the study will be stored, analyzed and used to ensure the integrity of the study, as described in this document.

Any new findings acquired during the course of the study that could influence your decision to continue your participation will be shared with you quickly.

Confidentiality:

During your participation in this study, the doctor in charge of the study and the research team will collect in a study file the information about you needed to meet the scientific objectives of the study.

The study file may include information from your medical charts including your choose: identity, such as your name, gender, date of birth, ethnicity, past and present health status, lifestyle, and the results of all tests, exams, and procedures that will be performed.

All study data collected during this research study (including personal information and samples) will remain confidential to the extent provided by law. You will be identified by a code number only. The key to the code linking your name to your study file will be kept by the doctor in charge of this research study.

Study data and samples will be stored for 7 years following the end of the study by the doctor in charge of this research study.

The study data may be published or shared at scientific meetings; however, it will not be possible to identify you.

For monitoring, control, safety, security, your study file as well as your medical charts may be examined by authorized representatives of the institution. All these individuals will have access to your personal data, but they adhere to a confidentiality policy.

You have the right to consult your study file in order to verify the information gathered and to have it corrected if necessary.

Compensation

You will not receive financial compensation for participating in this research study.

SHOULD YOU SUFFER ANY HARM

Should you suffer harm of any kind following administration of the study drug or any other procedure related to this research study, you will receive all the care and services required by your state of health.

By agreeing to participate in this research study, you are not waiving any of your rights nor discharging the doctor in charge of the study, the sponsor, or the institution of their civil and professional responsibilities.

Contact Information:

If you have any questions or concerns about this study, please contact the principal investigator at [Firoozeh.samim@mcgill.ca]. If you have any questions or concerns about your rights as a research participant, you may contact the MUHC Ombudsman at (514) 934-1934 ext 48306.

OVERVIEW OF ETHICAL ASPECTS OF THE RESEARCH:

The Research Ethics Board of the McGill University Health Centre has given ethics approval to this research study and is responsible for the ongoing ethics oversight of t

Research Study Title: Development of Evidence-Based Oral Care Guidelines for Pre-, interim-, and Post Radiation Head and Neck Cancer Patients

I have reviewed the Informed Consent form. Both the research study and the Informed Consent form were explained to me. My questions were answered, and I was given sufficient time to make a decision. After reflection, I consent to participate in this research study in accordance with the conditions stated above, including the use of all personal data and samples collected.

I authorize the study team to have access to my medical chart.
Signature: _____

Printed Name: _____

Date: _____

SIGNATURE OF PERSON OBTAINING CONSENT

I have explained the research study and the terms of this Informed Consent form to the research participant, and I answered all questions asked.

Name of the person obtaining consent	Signature	Date

DC/TMD Examination Form ……

DC/TMD Examination Form

Date filled out (mm-dd-yyyy) ___-___-_____

Patient _____ Examiner _____

1a. Location of Pain: Last 30 days (Select all that apply)

RIGHT PAIN				LEFT PAIN			
O None	O Temporalis	O Other m muscles	O Non-mast structures	O None	O Temporalis	O Other m muscles	O Non-mast structures
	O Masseter	O TMJ			O Masseter	O TMJ	

1b. Location of Headache: Last 30 days (Select all that apply)

O None	O Temporal	O Other	O None	O Temporal	O Other

2. Incisal Relationships Reference tooth O FDI #11 O FDI #21 O Other

Horizontal Incisal Overjet O If negative ___ mm

Vertical Incisal Overlap O If negative ___ mm

Midline Deviation Right O Left O N/A O ___ mm

3. Opening Pattern (Supplemental; Select all that apply)

O Straight O Corrected deviation

Uncorrected Deviation: O Right O Left

4. Opening Movements

A. Pain Free Opening ___ mm

B. Maximum Unassisted Opening ___ mm

C. Maximum Assisted Opening ___ mm

D. Terminated? (N) (Y)

	RIGHT SIDE				LEFT SIDE			
		Pain	Familiar Pain	Familiar Headache		Pain	Familiar Pain	Familiar Headache
B. Maximum Unassisted Opening	Temporalis	(N) (Y)	(N) (Y)	(N) (Y)	Temporalis	(N) (Y)	(N) (Y)	(N) (Y)
	Masseter	(N) (Y)	(N) (Y)		Masseter	(N) (Y)	(N) (Y)	
	TMJ	(N) (Y)	(N) (Y)		TMJ	(N) (Y)	(N) (Y)	
	Other M Musc	(N) (Y)	(N) (Y)		Other M Musc	(N) (Y)	(N) (Y)	
	Non-mast	(N) (Y)	(N) (Y)		Non-mast	(N) (Y)	(N) (Y)	
C. Maximum Assisted Opening	Temporalis	(N) (Y)	(N) (Y)	(N) (Y)	Temporalis	(N) (Y)	(N) (Y)	(N) (Y)
	Masseter	(N) (Y)	(N) (Y)		Masseter	(N) (Y)	(N) (Y)	
	TMJ	(N) (Y)	(N) (Y)		TMJ	(N) (Y)	(N) (Y)	
	Other M Musc	(N) (Y)	(N) (Y)		Other M Musc	(N) (Y)	(N) (Y)	
	Non-mast	(N) (Y)	(N) (Y)		Non-mast	(N) (Y)	(N) (Y)	

5. Lateral and Protrusive Movements

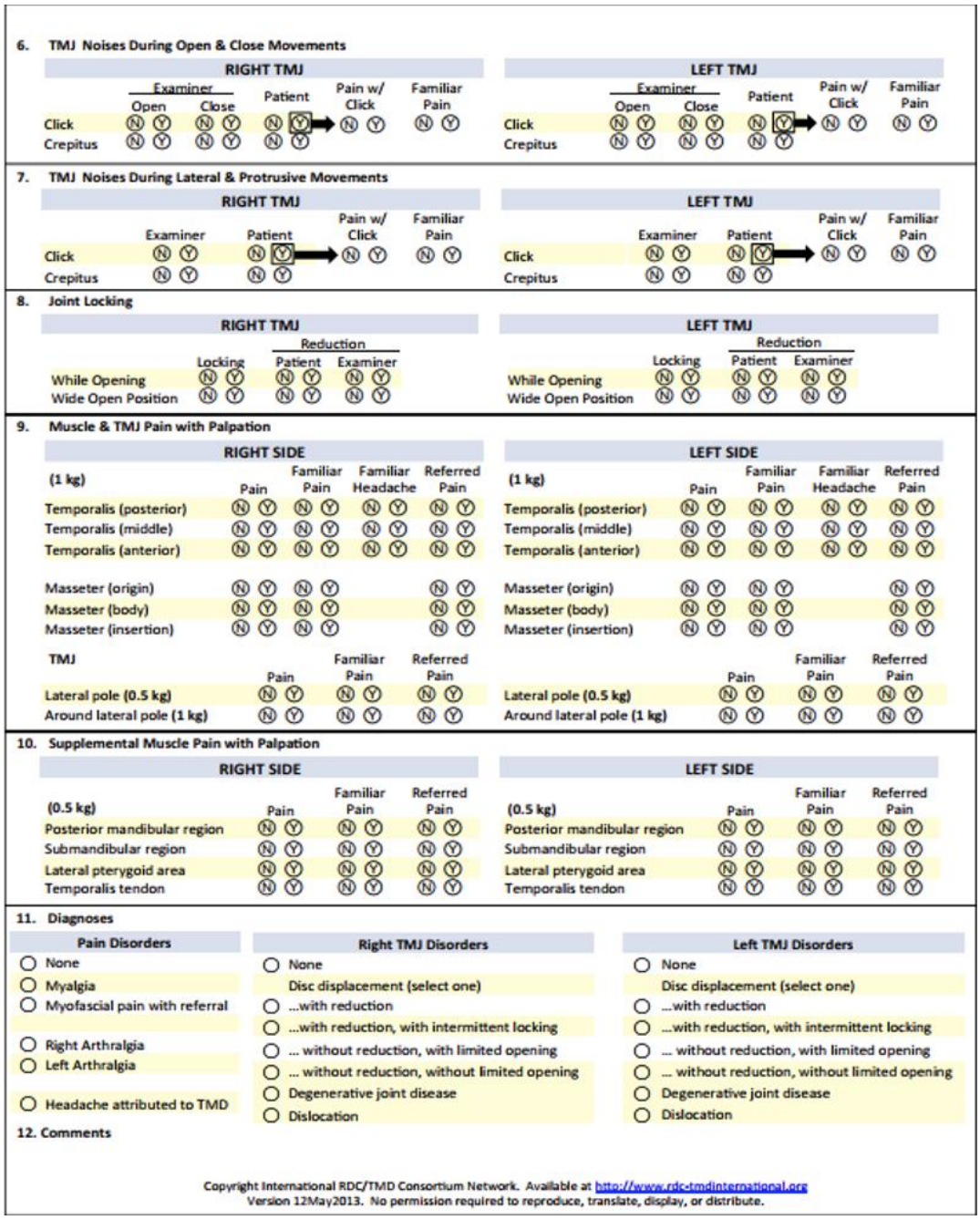
A. Right Lateral ___ mm

B. Left Lateral ___ mm

C. Protrusion ___ mm

O If negative

	RIGHT SIDE				LEFT SIDE			
		Pain	Familiar Pain	Familiar Headache		Pain	Familiar Pain	Familiar Headache
A. Right Lateral	Temporalis	(N) (Y)	(N) (Y)	(N) (Y)	Temporalis	(N) (Y)	(N) (Y)	(N) (Y)
	Masseter	(N) (Y)	(N) (Y)		Masseter	(N) (Y)	(N) (Y)	
	TMJ	(N) (Y)	(N) (Y)		TMJ	(N) (Y)	(N) (Y)	
	Other M Musc	(N) (Y)	(N) (Y)		Other M Musc	(N) (Y)	(N) (Y)	
	Non-mast	(N) (Y)	(N) (Y)		Non-mast	(N) (Y)	(N) (Y)	
B. Left Lateral	Temporalis	(N) (Y)	(N) (Y)	(N) (Y)	Temporalis	(N) (Y)	(N) (Y)	(N) (Y)
	Masseter	(N) (Y)	(N) (Y)		Masseter	(N) (Y)	(N) (Y)	
	TMJ	(N) (Y)	(N) (Y)		TMJ	(N) (Y)	(N) (Y)	
	Other M Musc	(N) (Y)	(N) (Y)		Other M Musc	(N) (Y)	(N) (Y)	
	Non-mast	(N) (Y)	(N) (Y)		Non-mast	(N) (Y)	(N) (Y)	
C. Protrusion	Temporalis	(N) (Y)	(N) (Y)	(N) (Y)	Temporalis	(N) (Y)	(N) (Y)	(N) (Y)
	Masseter	(N) (Y)	(N) (Y)		Masseter	(N) (Y)	(N) (Y)	
	TMJ	(N) (Y)	(N) (Y)		TMJ	(N) (Y)	(N) (Y)	
	Other M Musc	(N) (Y)	(N) (Y)		Other M Musc	(N) (Y)	(N) (Y)	
	Non-mast	(N) (Y)	(N) (Y)		Non-mast	(N) (Y)	(N) (Y)	



[1]Schiffman, Eric et al. "Diagnostic Criteria for Temporomandibular Disorders (DC/TMD) for Clinical and Research Applications: recommendations of the International RDC/TMD Consortium Network* and Orofacial Pain Special Interest Group†." Journal of oral & facial pain and headache vol. 28,1 (2014): 6-27. doi:10.11607/jop.1151