University of Alberta

Comparison of Tooth Loss between Intensity Modulated and Non-Intensity Modulated Radiotherapy in Head and Neck Cancer Patients

by

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Dedication

To my family: for their patience, understanding and devotion. I am very grateful and blessed with your love and encouragement.

Abstract

Advanced radiotherapy systems are used to treat cancers involving the head and neck. Amongst these systems intensity modulated radiotherapy is widely used to treat cancers of the head and neck. Organ preservation techniques using intensity modulated radiotherapy (IMRT) have the potential to preserve functional salivary tissues that are vital to oral-dental health. However, a combination of radiation and chemotherapy (chemoradiation) potentially increases toxicity as well as oral and dental complications.

In the present study, tooth loss was retrospectively assessed using oral cavity, oropharyngeal and nasopharyngeal cancer patients. Clinical photographs were used to determine differences between subjects treated with conventional (non-intensity modulated, nonIMRT) and advanced (intensity modulated, IMRT) radiotherapy. Additionally, risk factors related to tooth loss were also explored between both treatment groups. Subject data were collected pre -postradiotherapy using the functional assessment data from The Institute for Reconstructive Sciences in Medicine (iRSM) in Edmonton, Alberta, Canada. Available subject data was included from 2000 – 2010. Due to the paucity in the data, data beyond the second year after radiotherapy could not be included in the final analysis.

Ultimately, while the number of teeth lost in both groups was shown to be similar with more subjects losing teeth in the nonIMRT group, statistically there were no between group differences up to two years after radiotherapy. Further investigations are necessary to increase the sample size and timeframe after radiotherapy treatment to determine the clinical implications of these dental changes.

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Chapter 1: Introduction and Statement of the Problem

Introduction and Statement of the Problem

Advanced radiotherapy treatment has become a key approach in the management of head and neck cancer (HNC).[1] In the 1990s and into the new millennium, advanced radiotherapy (RT) technologies such as inverse treatment-planning systems with intensity modulation (intensity modulated radiotherapy, IMRT) were implemented worldwide to treat HNC.[2,3] The principle advantage of IMRT includes better target volume coverage and the avoidance of normal radiosensitive salivary tissues to protect salivary function.[2,4] However, a combination of radiation and chemotherapy (chemoradiation) potentially increases toxicity as well as oral and dental complications not encountered previously. The effects from radiation-induced xerostomia caused by salivary hypofunction demonstrate the critical role saliva has in the preservation of oral and dental health.[5] Conformal techniques such as IMRT have the potential to preserve salivary gland tissue, and thus preserve saliva functions vital to the health of teeth and oral functions such as speech, swallowing, and chewing. Head and neck radiotherapy side effects are often life-long and HNC survivors are likely to experience the effects of radiation-related xerostomia and its sequelae.[6-9] Over the past few decades, interest in the area of organ preservation has increased in head and neck cancer literature.[10] Studies have documented promising results in the preservation of normal salivary tissues using advanced radiotherapy techniques, as well as improved functional outcomes and quality of life scores, when compared to conventional RT techniques.[11-13]

In the past, teeth were extracted prior to the initiation of radiotherapy.[14-16] This was due to the risk of developing osteoradionecrosis (ORN), a radiation-induced, nonhealing wound of the jaw that is a well-documented complication of radiotherapy.[17-19] Later, only teeth within

the high dose radiation treatment volumes and teeth considered nonrestorable that were located outside of the treatment volumes were removed.[14] As a result of partial or complete loss of dentition after the commencement of RT, many HNC patients experienced difficulty with eating, chewing, and speaking.[15,16] Functional complications associated with tooth loss contributed to a movement aimed at maintaining and preserving as many teeth as possible before and after RT.[15,16] Preserving and restoring the teeth of RT patients is the current philosophy, and only "high-risk" or "unsalvageable" teeth are removed prior to RT.[17-19] Oral-dental evaluations before, during, and after RT, as well as daily home fluoride or remineralization programs, are now considered effective measures implemented to preserve teeth.[14]

The advent of advanced functional imaging modalities such as cone-beam computed tomography (CBCT), magnetic resonance imaging (MR), and positron emission tomography (PET) in combination with IMRT planning and delivery techniques allow the delivery of nonuniform beam intensities compared to conventional two-dimensional (2D) RT systems.[3] Three-dimensional (3D) IMRT delivers focused, high dose radiation to the tumour site while sparing normal tissues.[20] The ability to deliver lower radiation doses helps to protect nontarget tissues and reduces treatment side effects that contribute to oral and functional complications such as difficulty with speech and swallowing.[13,20] The use of parotid sparing IMRT has improved the scores of questionnaires that inquire about radiation-induced xerostomia and quality of life after RT. [1,13,21,22] However, a number of clinical questions about dentition breakdown and loss have not yet been fully investigated. It was the intent of this study to investigate the effects of these treatments on dental health as they related to IMRT and non-

IMRT for the treatment of head and neck cancer, with and without chemotherapy and with and without surgery.

Significance of the Study

Retrospective chart review data were utilized to explore the status of dental health in HNC patients treated with "intensity modulated" and "nonintensity modulated" radiotherapy +/- chemotherapy, +/- surgery. The information gleaned from this exploratory study was used to discuss the limitations of using archival data as well as to understand what data are necessary to collect within a prospective multisite research project.

Primary Objective: Specific Research Questions

1. How do the following factors—age, gender, smoking history, diabetes history, hyperbaric oxygen history, salivary gland sparing versus Salagen, radiation dose and number of days after radiotherapy—interact with the different radiotherapy systems to affect tooth loss?
2. Will there be an increased incidence in tooth loss in patients treated with IMRT +/- surgery and +/- chemotherapy compared to patients treated with nonintensity modulated radiotherapy +/- surgery and +/- chemotherapy?

Chapter 2: Background

Background

Head and neck cancer. An estimated 4,550 Canadians were diagnosed with head and neck cancer in 2010, which accounts for about 3-4% of new cancers.[23,24,25,26] Squamous cell carcinoma is the histologic type in over 90% of head and neck cancer tumours.[27] HNC is the term used for a group of cancers arising in the upper aerodigestive tract (lips, tongue, oral and nasal cavities, paranasal sinuses, pharynx and larynx).[27] The head and neck region contains delicate, organized organs that are vital for basic physiological functions as well as social interactions.[28] The primary etiologic factors associated with head and neck cancers have traditionally been associated with the use of tobacco and heavy alcohol consumption.[29] The concept of field cancerization proposes that epithelium injury can arise from prolonged carcinogen exposure depending on an individuals' genetic profile.[30] If such an individual develops and survives an upper aerodigestive cancer, he or she is at a higher risk of developing a second primary tumour (SPT) in the same anatomic region in subsequent years.[30,31] Results from studies in the area of field cancerization have shown that patients cured of their first HNC had more than 20% projected lifetime risk of developing an SPT, and a 4% to 6% risk of developing an annual SPT up to the first eight years after the first HNC diagnosis.[32,33] A study by Lippman et al.[34] described the development of an SPT as the leading cause of death in patients with early HNC. More recently, the role of viral-associated head and neck carcinogenesis such as human papillomavirus (HPV) infection (HPV positive) has attracted more attention as a risk factor for the development of SCC of the oropharynx.[28,31,35] Other factors associated with HNC include leukoplakia and erythroplakia, and mechanisms governing cellular and tissular responses (previous ionizing radiation) may carry an increased risk for transformation into a

head and neck carcinoma.[31] Despite basic and translational research efforts as well as advances in the treatment for head and neck cancer, the survival rate has remained largely unaltered with modest improvements over the past two to three decades.[28,31]

Mortality and morbidity rates associated with HNC may be higher compared to non head and neck cancers as a result of patients presenting with advanced stage tumours that have poor local-regional disease control rates and complex treatment regimens compared to early stage tumours.[29] In the United States and parts of the European Union, studies have documented a rise in the incidence of HPV related HNC involving the oropharnyx, and oral cavity, while the incidence of HPV negative (tobacco and alcohol related) HNC is on the decline[31,35,36] Interestingly, prospective and retrospective studies of clinical trials have indicated that patients with HPV positive cancers have better response to treatment and survival than to HPV negative tumours.[35] Although there have been improvements in surgical resection-reconstructive techniques and advances in radiotherapy planning and delivery methodology in the treatment of HNC, patients often suffer functional and possibly life-long complications related to their teeth.

Head and neck cancer treatment. Head and neck cancer oncologists are challenged to balance cancer cure and survival with the preservation of function, cosmesis, and patient quality of life.[37] The extent of disease, or stage at diagnosis guides the management of care as well as predicts the survival rates in patients with head and neck cancer.[35] The American Joint Committee on Cancer (AJCC)[38] staging classification is used for the National Comprehensive Cancer Network (NCCN)[35] treatment recommendation guidelines for head and neck cancer. For select HNC, treatments are predominately combined modality therapies consisting of a regimen

of surgery, radiotherapy, chemotherapy, or some combination thereof.[17,21,39,40] Integrated interdisciplinary collaborations among oncologists and oral health care providers is essential for the management and rehabilitation of HNC patients to be able to provide coordinated care in order to optimize cosmetic and dental functional outcomes. Currently, in the United States (US), many centres use primary radiotherapy in combination with chemotherapy for the treatment of localized head and neck cancer tumours.[20,41] Single-modality treatment with surgery or radiotherapy alone is generally recommended in approximately 30-40% of cases of patients presenting with early stage disease (stage I or stage II).[35] Combined modality therapy is generally recommended for approximately 60% of cases with locally or regionally advanced disease at diagnosis.[35] Treatment management approaches such as surgical procedure, radiation target (dose and fractionation) and indications for chemotherapy depends on the patient stage at diagnosis, site of the tumour, the nodal status, the patient's health, and the resources available, expertise and philosophies of the treatment institution involved in the management of the HNC patient.[42] The NCCN panel recommends "participation in clinical trials…in many situations" and has "tried to make the guidelines evidence-based while providing a statement of consensus as to the acceptable range of treatment options." (p.MS-3).[35]

In select cases, interest in organ preservation and the feasibility of using chemoradiation have led investigators to use a nonsurgical treatment approach in patients with advanced head and neck cancers of the pharynx and larynx.[13,42] In addition, in the 7th edition of the AJCC staging classification manual,[38] the words "resectable" and "unresectable" have been replaced

by the terms “moderately advanced” and “very advanced” (p. MS-2) since a large proportion of advanced stage head and neck malignancies are being treated non-surgically.[13,35]

Head and neck cancer radiotherapy. Radiotherapy for head and neck cancer has become increasing complex.[35] Over the past two decades, inverse treatment planning systems with intensity modulation or IMRT (including helical tomotherapy, HT) have become important in the management of head and neck cancer.[1] Innovations in the use of 3D imaging and delivery of external beam radiotherapy (using a multileaf collimator) allows the user to digitally define tumour target volumes and reduce radiation exposure to adjacent normal tissues and organs without compromising tumour control rates.[3] Limiting the radiation dose to nontargeted tissues and organs can reduce salivary dysfunction and the incidence, duration, and severity of treatment side effects such as xerostomia which is often associated with oral complications.[13,21] IMRT is widely used in head and neck cancer and is the predominant radiation technique used at NCCN centers.[35]

The largest difference between conventional radiotherapy and IMRT is the approach to treatment planning and delivery methodology. In conventional RT a forward planning approach uses CT and MR imaging to manually transfer the anatomic volumes onto standard radiographs. This approach is essential to evaluate the treatment volumes after the radiation treatment has been delivered. With 2D RT, radiation beam angles are aligned on conventional axial planes.[31] With inverse planning, or IMRT, the treatment is planned and evaluated using sophisticated computer software programs before the radiation treatment delivery. Before the evolution of IMRT, three-dimensional conformal radiotherapy (3D-CRT) was implemented using advances in the planning and delivery of RT as well as in computer driven 3D technology. 3D-CRT could

conform (or shape) the distribution of a prescribed radiation volume to a 3D target volume. The radiation beam intensity with 3D-CRT is typically uniform compared to IMRT; IMRT optimizes nonuniform beam intensities that are no longer limited to conventional axial planes and offers the ability to spare vital dose sensitive normal structures. Some of the disadvantages reported with IMRT include the front-end costs of the equipment and technology, the time required for radiation treatment planning and delivery, and the staff training necessary to implement the technology. Due to labour intensive, intricate treatment planning and delivery, IMRT has been reported to have a higher risk of error than conventional 2D treatment systems.[1,3] One method to reduce error is the use of immobilization techniques such as constructing an immobilization mask to be used for repeatable head positioning during IMRT treatment.[1]

The role of IMRT has been tested in randomized trials as well as retrospective studies in a number of centres.[11-13] These studies have demonstrated its superiority and potential to reduce side effects over conventional radiotherapy. In a study by Pow et al.,[13] the investigator noted that the highest level of evidence presently in the literature supporting reduced complications and improved quality of life after parotid-sparing IMRT for HNC patients is from prospective longitudinal and matched case-control studies. The study by Pow et al.[13] was a randomized controlled trial to compare salivary gland function and quality of life in nasopharyngeal cancer (NPC) patients treated with conformal RT (CRT) or IMRT. Results from this study suggested a significant improvement in quality of life and parotid sparing in patients with NPC randomized to the IMRT group compared with patients randomized to conventional radiotherapy.[13]

Other studies also showed that parotid sparing IMRT may lead to improved salivary flow rates and quality of life scores compared to conventional RT.[22,44] One study by Reddy et al.[44] compared parotid sparing radiation with conventional 2D techniques in oral cavity cancer patients. Results from this study found that there were improvements in xerostomia and nutritional intake in those who received parotid sparing RT. Chao et al.[11] conducted a prospective clinical study to determine whether parotid-sparing techniques (inverse-planning IMRT and forward-planning 3D RT) resulted in objective and subjective improvement in xerostomia. Results from this study found stimulated salivary flow six months after RT was reduced exponentially for each gland at a rate of approximately 4% per Gy (gray) of mean parotid dose.[11] Quality of Life (QOL) scores related to eating and speaking functions were also significantly correlated with salivary flow. In a retrospective study by Chao et al.,[12] acute and late toxicity and tumour control were compared using conventional beam arrangement RT or IMRT in patients with cancers of the oropharynx. Results from this study showed a significant reduction of late toxicity and no adverse impact on tumour control or disease-free survival in the IMRT group.[12]

Parliament et al.[45] conducted a phase I–II trial using IMRT on head and neck cancer patients with the goal of at least one parotid gland being spared by receiving a median dose less than 2000 cGy (centigray). The mean dose to each spared parotid volume was 2280 and 2090 cGy for the right and left glands, respectively. In this study, 11% of the patients experienced grade 2 xerostomia during the 3-month period after RT and 13% experienced chronic xerostomia using the Radiation Therapy Oncology Group (RTOG) grading system.[45] Results from this study revealed that the stimulated and unstimulated whole-mouth saliva flow

rates were variably preserved and were inversely correlated with combined mean parotid doses after IMRT.[45] Scrimger et al.[4]observed that parotid flow rates resulted in improvement between six and 12 months after IMRT as well as a strong correlation between the mean parotid gland dose and relative flow reduction from these glands.

In HNC, radiation dose usually varies from 5000 cGy for microscopic disease to greater than 7000 cGy for gross disease.[31] New radiobiologic concepts have led to altered fractionation regimes (hyperfractionation) and accelerated fractionation schedules for the treatment of HNC.[31] The European Organization for Research on Treatment of Cancer (EORTC)[47] showed a moderate but consistent improvement (10% to 15%) in the local control of a moderate-to-advanced subset of HNC patients who received hyperfractionation. In addition, the late toxicity of a 10% to 15% increment in total RT dose delivered in smaller than the standard fraction sizes, which were given twice a day, was comparable with the results observed with conventional schedules.[31] Accelerated fractionation (delivery of six fractions per week) and a concomitant boost yielded significantly improved local tumour control rates relative to standard fractionation.[31] Considerations related to cost, resource utilization, patient convenience, institutional philosophy, and practitioner expertise are taken into consideration when implementing radiotherapy practices such as the type of fractionation schedules used to treat HNC patients. Many centres have adopted the relatively simple concomitant boost regimen as the standard radiotherapy treatment for patients receiving RT alone for intermediate-stage HNC.[31] Other factors related to RT treatment include the tumour type and location and the treatment modality used.[42] Certain subsets of head and neck cancers such as oral cavity (O), oropharynx (OP), and nasopharynx (NP) will have comprehensive bilateral neck irradiation as

part of their RT treatment. This has been associated with grade 2 or even higher degrees of xerostomia in 60–80% of patients treated with bilateral neck irradiation.[48] Efficacy of treatment is potentially compromised by reductions in radiation dosage and treatment interruptions due to acute adverse effects such as mucositis and sequelae from xerostomia.[20] In select cases, or more commonly in Europe, radiotherapy is delivered preoperatively to reduce the size of the tumour. Radiotherapy is predominately delivered postoperatively in North America either alone or in combination with chemotherapy to control residual disease.

Radiotherapy for oral cavity, oropharngeal, and nasopharngeal carcinomas. Cancers of the oral cavity include tumours involving the lip, floor of mouth, oral tongue, retromolar trigone, anterior faucial pillar, buccal mucosa, hard palate, and upper alveolar ridge. Cancers of the oropharynx include tumours involving the soft palate, tonsillar fossa, base of tongue, and posterior oropharyngeal wall. For cancers involving the oral cavity, a combination of surgical resection as well as postoperative radiation is generally preferred in medically operable patients and is frequently required for advanced stage lesions involving the bone, nerves, or nodes.[31] In recent years, adjuvant chemotherapy has been implemented in addition to the surgery and RT (chemoradiation). Primary radiotherapy is generally reserved for patients who refuse surgery or who are inoperable.[31] Postoperative external beam radiotherapy for cancers of the oral cavity include the entire surgical bed, site of the neck dissection, and dissected draining lymphatics. In areas of the original tumour and involved nodes, an additional boost dose may be delivered to the region carrying the highest risk of recurrence such as the sites of extracapsular nodal disease or positive margins.[31] For cancers involving the oropharynx, chemoradiation is generally the treatment modality at most centres in the US, however,

institutions in Edmonton, Alberta, Canada predominately use a combination of surgical resection as well as postoperative chemoradiation in medically operable patients.

It is desirable to commence postoperative radiotherapy as soon as healing has occurred or roughly three to four weeks after surgery. When delayed wound healing postpones postoperative radiotherapy beyond five to six weeks, accelerated fractionation such as a concomitant boost given twice a day for one week can be delivered to reduce the potential hazard of prolonged cumulative treatment time.[31]

Due to the inoperable as well as anatomically challenging location of nasopharyngeal tumours, standard treatment for stage I and II NPC is primary radiotherapy. For stage III and IV NPC, a combination radiotherapy and chemotherapy is preferred.[31] RT treatment regimes vary depending on the RT delivery systems used. For example, with the conventional RT technique, 5000 cGy (25 fractions) is delivered to regions at risk for harbouring subclinical disease, followed by a boost dose of 1600 to 2000 cGy (eight to ten fractions) to the primary tumour site and involved node(s), depending on the size of the tumour.[31] With IMRT, 6600 to 7040 cGy is delivered to the primary tumour and involved node(s) and 5400 to 5760 cGy (given in 30 to 32 fractions) is delivered to regions at risk for harbouring subclinical disease. The fraction size varies from 180 cGy to the subclinical region to 220 cGy to the region of gross disease.[31]

In regard to organ preservation and the preservation of salivary function, primary radiotherapy or radiation in combination with surgery and/or chemotherapy are potential treatment interventions for cancers involving the oral cavity, oropharynx and nasopharynx. Unfortunately, as a result of hypofunction of the minor and major salivary glands located within the RT treatment volumes, the health, maintenance and integrity of the teeth may be affected.

Chemotherapy and radiation combined with chemotherapy. Treatment of head and neck cancer was once the realm of surgeons and radiation oncologists.[7,49] Over the past 20 years, medical oncologists have become an integral part of a multidisciplinary team approach.[49] New knowledge such as viral-induced changes in cellular behaviour and new concepts such as the multistep tumour progression model and field cancerization have contributed to the expanding role of cancer chemoprevention.[31] Chemotherapeutics agents are used to destroy or deactivate rapidly dividing cancer cells. Rapidly proliferating normal cells are susceptible to suppression by chemotherapeutic agents and often contribute to oral complications. According to the NCCN guidelines,[35] the choice of chemotherapy should be individualized based on patient characteristics such as performance status and goals of thearapy. Chemotherapy-induced oral complications such as oral mucositis and xerostomia are suggested to be caused by the cytotoxic effects of chemotherapy on oral tissues.[50] The severity of the oral complications is relative to the dosage and duration of the chemotherapy drug administered and to the patient's systemic and oral health status.[50]

Sequelae of HNC radiation and chemotherapy. Acute or immediate effects on the oral cavity after irradiation typically include oral mucositis, tooth root sensitivity, and difficulty opening the jaw (trismus).[17,51] Late or long-term effects from RT include xerostomia, rampant dental caries, soft tissue necrosis, and ORN.[17] The extent of oral sequelae is variable depending on the type, dosage, and location of the radiotherapy delivered; the complication rates of combined modality regimes are higher than those of RT alone.[15,31]

Xerostomia, or the subjective complaint of dry mouth, is a well-documented complication of radiation and of chemotherapy.[20,50] Radiation-induced xerostomia as a result of

the loss of saliva after HNC irradiation has significant clinical implications on the oral environment.[40] When the salivary glands are included in the field of radiation, damage to the salivary glands results in reduced salivary flow and changes in the composition of saliva.[42] Saliva plays a vital role in the maintenance of oral and dental health. When saliva flow is reduced or altered in composition, oral-dental health may deteriorate.[20] Alterations in saliva have been associated with an increase in oral mucositis, periodontal disease, tooth decay, difficulty in wearing dentures, and difficulty in chewing and swallowing.[40] The severity of glandular damage and salivary dysfunction is directly related to the total dose of radiation to the salivary glands.[42] The major salivary glands include the parotid, submandibular, and sublingual glands; these glands are serous, mixed serous and mucous, and mucous, respectively.[51,52] Serous secretions produced by the parotid and partially by the submandibular glands contain more water than the viscous saliva produced by the submandibular and sublingual glands. In the head and neck region, the major salivary glands occur in pairs, with one of each gland located on either side of the head.[51] The major salivary glands produce up to 90% of stimulated and unstimulated salivary flow, while the minor salivary glands (mucous glands) lining the mouth and throat, produce the remaining 10%.[42,51,52,53] In the stimulated state such as eating and chewing, the parotid glands become dominant and produce the majority of the salivary flow, approximately 50%.[51,52] In the unstimulated or resting state, the submandibular glands contribute approximately 65% of the total salivary flow, compared to the parotid glands (20%) and sublingual glands (7–8%).[20] The average daily salivary output is approximately 1000–1500 ml/per day, and it is produced predominately by the parotid glands under stimulated conditions. From the daily salivary output, 200–300 ml is from the submandibular glands during

the resting state. The resting salivary flow from the submandibular gland is important in preventing xerostomia and plays a role in the health, maintenance, and integrity of the teeth.

Since the salivary glands are highly sensitive to the effects of irradiation, oral sequelae often occur during the first week of radiation.[54] A profound decrease in parotid and submandibular salivary flow of 60–70% from baseline occurs soon after delivery of 1000–1500 cGy of radiation.[53] Eishbruch et al.[41] found parotid gland mean dose RT thresholds below 2400 cGy for unstimulated glands and 2600 cGy for stimulated glands could compare with preradiotherapy salivary output levels. Other studies suggested a threshold dose of 3200 cGy could compare to preradiotherapy salivary levels.[12] Irreversible hypofunction, hyposalivation, and life-long xerostomia have been established after radiation doses greater than 4000–5000 cGy to most of the glands.[41,52,55] Other studies suggest there is a modest recovery of salivary function over time following irradiation of the parotid glands, even with mean parotid doses of 4000–5000 cGy.[53] Although reports in the literature vary in estimation of the exact mechanism of radiation induced salivary dysfunction and the extent of damage, there is agreement that there is a relationship between the salivary gland mean dose and residual salivary output.[41,42,52,56] A study by Stephens et al.[48] reported that acute degeneration and necrosis of serous cells in irradiated parotid and submandibular glands occurred in a dose-related fashion. From this study it was found that the mucous cells were less damaged compared to the sensitive serous cells in the same glands after receiving radiation doses up to 1500 cGy.[48] The authors observed that late atrophy was a direct result of acute loss of serous acini and a lack of regeneration of these cells after receiving acute injury postirradiation.[48]

Discrepancies in correlating mean RT dose thresholds with glandular functional deficits could be explained by the use of different methodologies to assess salivary output or function. Further research in this area will help guide the treatment for HNC and lead to improved outcomes for the HNC survivor.[1,41,42]

The etiology of radiation caries and dental destruction is multifactorial.[19] One of the risk factors for radiation caries is an indirect effect from hypofunction of the salivary glands.[19] In the oral cavity, dental caries may arise in teeth outside of the radiation treatment volumes as a result of alterations in salivary production.[52] Radiotherapy results in a qualitative and quantitative alteration of salivary gland function.[16] Changes in salivary flow and composition contribute to changes in salivary pH, immunoproteins (IgA, IgG), enzymes, minerals, and buffering capacity which are vital in preserving teeth.[16,55] Saliva promotes mineralization of the teeth; severe loss of salivary flow may cause the teeth to become demineralized leading to rampant dental caries.[5] Alterations in saliva composition may lead to an increase in plaque accumulation, tooth demineralization, and an increase in acidogenic and cariogenic micro-organisms such as *Streptococcus mutans* and *Lactobacillus.*[19] These changes in the oral flora and saliva may increase the risk of dental caries after radiotherapy.[19] Radiation caries can begin as early as three to six months after RT and progress to complete destruction of the dentition over three to five years.[55] Radiation caries usually start on the front, smooth surfaces of the cervical areas of the teeth and progress to encircle the entire cervical area. A black-brown discolouration will occur in this area and lead to amputation of the tooth crowns and potential complete loss of the dentition (Figures 1, 2).[19] Other RT-related dental complications include a risk of odontogenic abscess and periodontal disease due to the potential disruption in

cellularity and vascularity of the periodontal ligament supporting the tooth root.[6,16,17,19,41] The periodontium contains specialized connective tissue fibres that provide a bond between the cervical margin of the roots of the teeth and the alveolus of the jaws.[6] Long-term survival of the teeth requires a periodontal attachment between the soft and hard tissues of the jaws. Blood vessels in the soft and hard tissues supporting the teeth are sensitive to the effects of radiation. High doses of radiation lead to changes in the soft and hard tissues supporting the teeth such as widening of the periodontal ligament space and destruction of the supporting bone.[6] In a study by Epstein et al.,[5] investigators found an increase in periodontal involvement and subsequent tooth loss in teeth located in the high dose radiation treatment volumes compared to teeth outside the treatment volumes. The increase in periodontal involvement may have resulted from an impaired capacity for bone remodeling and soft tissue healing after radiotherapy.[6,52]

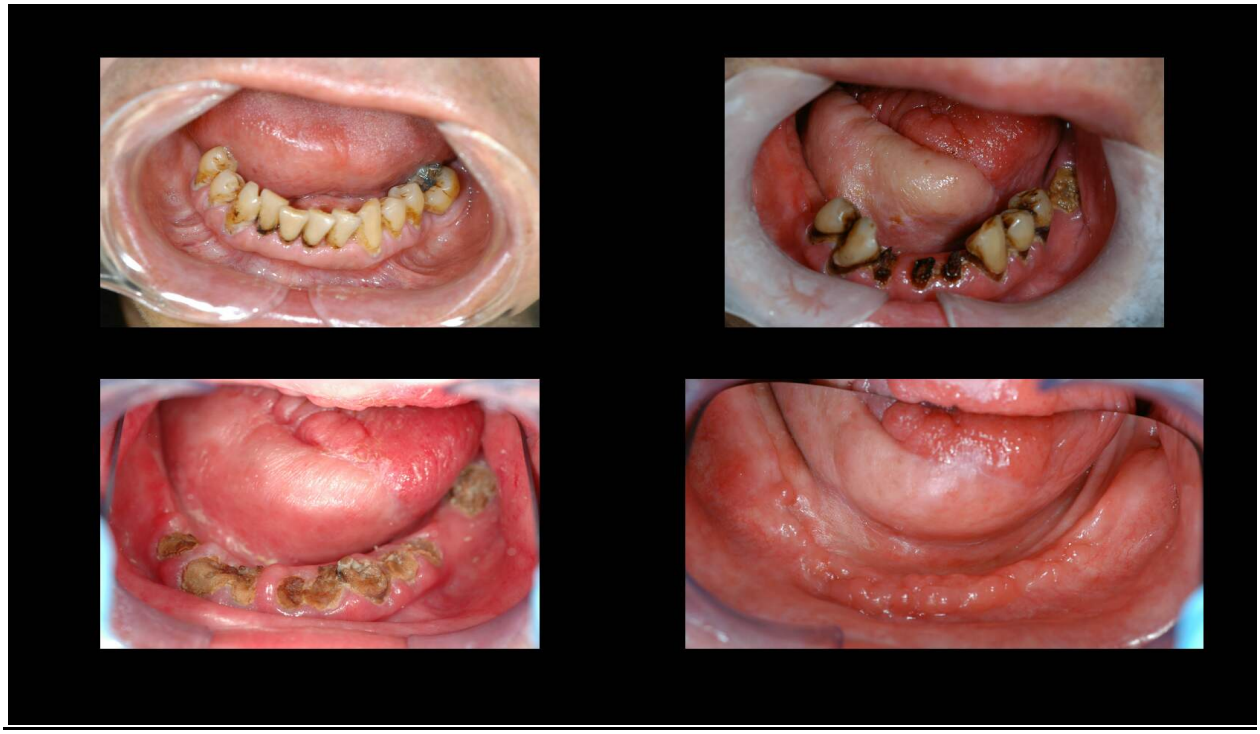

Figure 1. Progression of radiation related caries

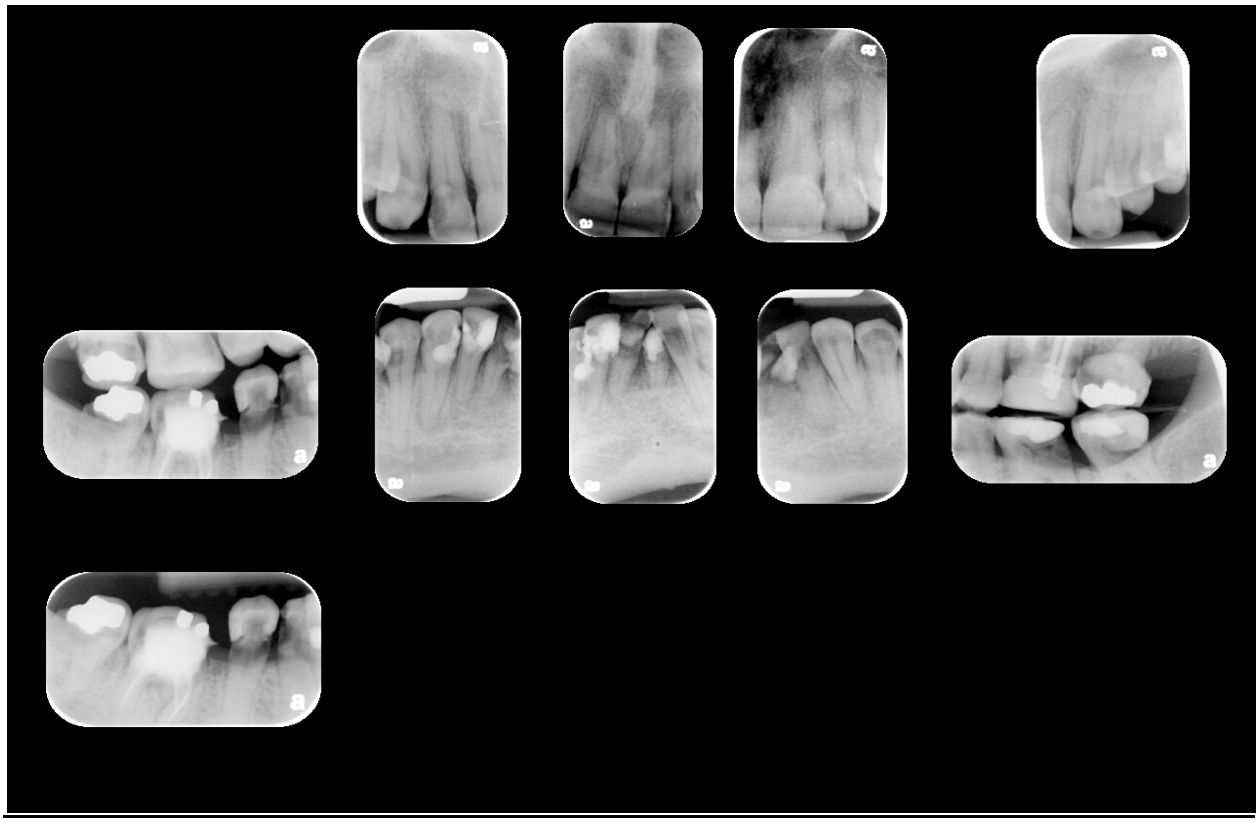

Figure 2. Radiographic findings of radiation related caries

Health economic considerations. The time and cost of maintaining and restoring the teeth following radiation-induced xerostomia can be "tremendous."[5] (p. 1494) Recently reported costs of replacing missing teeth in the United States (US) are between $1000–1200 per arch, and greater than $10,000 for an implant retained overdenture prosthesis.[5]

Radiation related effects on dentition. Radiotherapy damages tumour cells as well as normal tissues such as the mucosa, blood vessels, muscle, bone, and salivary glands located within RT treatment volumes.[42,57] Radiation-related caries are the most common dental complication associated with head and neck cancer irradiation.[8,58] This was reported as early as 1939, and since then studies have been performed on the histological, physical, and chemical changes in irradiated teeth.[8,19,57-60] Radiation caries begin soon after radiation and progress

rapidly; dental changes can occur within a short period of time.[8,17,19,55] Destruction of dental hard tissues evolve as a direct result of irradiation as well as an indirect consequence of reduced salivary flow and changes to salivary composition.[8,16,41,57,58,60] In addition, radiation induced oral mucositis, characterized by inflammation, ulcerations, and discomfort to the oral mucosa, has been associated with an increase in radiation-related caries formation due to the difficulties with oral hygiene and a diet that is soft and rich in cariogenic carbohydrates.[8,19,60-63]

Studies have been performed to determine if there is direct radiogenic damage to the dentition.[8,19,41,58,61] These studies have investigated patterns of demineralization (loss of minerals from tooth enamel) and microhardness of the dentition in irradiated teeth.[8,19,41,58,61] Al-Nawas et al.[58]used ultrasound transmission velocity (UTV) to analyze the mechanical properties of teeth after in vitro, in situ, and in vivo irradiation. Data from this study revealed direct radiation-induced damage on the enamel crystalline structure.[58] In another study, Franzel et al.[54] studied the effects of X-ray energy and high energy electrons on the mechanical properties, hardness, and elasticity, of human dental tissues. Tooth defects resulting in cracks and increased roughness were identified after the first fraction of head and neck irradiation. Results from this study found a decrease in enamel and dentin hardness and elasticity after 50 cGy radiation.[54] Therapeutic irradiation for HNC starts at 200 cGy, at which point the enamel is nearly completely damaged.[54] The mineral-organic interaction between apatite crystals and collagen is reduced and potentially induces microfractures in the tooth enamel leading to microbial colonization and dental caries.[19,54]

Radiation therapy hot spots. Hot spots in the radiation field due to target dose inhomogeneity have been documented in advanced radiation systems.[64] Radiation in hot spots

is 15% to 20% higher than the prescribed dose and may be delivered to localized regions of the oral mucosa, teeth, or bones. Limited research exists on this topic, but it is probable that hot spots can be minimized with careful planning of the treatment.[64] Long-term follow up of patients treated with IMRT is required to monitor oral and dental complications related to the delivery of high dose radiation systems.

HNC and poor oral health. Few studies have compared the frequency of dental care for HNC patients before, during, and after RT.[20] There is little standardization in preventative oral hygiene protocols.[19,20] Randomized controlled trials in the area of oral health prevention are lacking and oral health recommendations are mainly based on clinical experience and empirical evidence.[19] An interesting finding in a study by Duke et al.[65]was that HNC survivors often have poor dentition and dental health prior to radiotherapy. The objective of Duke's study was to analyze the dental status of long-term (5 years after treatment) HNC patients and evaluate the effect of their dental status on their subjective quality of life. In addition to subjective QOL questionnaires, the investigators performed dental examinations and radiographs to determine which teeth were decayed, missing, and filled before and after treatment. Studies by Lockhart et al.[66]and Maier et al.[67]also found that HNC patients were noncompliant with routine dental care and had poor oral hygiene. The authors found a high incidence of decayed teeth and bone loss and reported that most of the patients required dental care pre-RT treatment but seldom followed through with the recommended dental care.[48,55] In the head and neck cancer literature, preexisting dental status and dental health outcomes are often underreported, limiting the use of data from patient records. Randomized clinical trials and research on the preservation of dentition after RT are lacking in this area. More research is needed in this area

to understand the complexity of the problem and to create programs aimed at preserving the teeth of HNC patients.[19]

Trismus. Trismus results in a loss of function and range of mandibular motion.[68,69] It is a well-known complication of head and neck cancer treatment and a late complication following radiotherapy.[68] Normal mouth opening is described as 45 +/- 7 mm compared to 20 to 40 mm mouth opening for trismus in a review by Dijkstra et al.[70] Radiotherapy causes a loss of function by inducing fibrosis when the muscles of mastication (temporalis, masseter, and pterygoid muscles) and the temporomandibular joint are within high dose RT treatment volumes.[69,70] The incidence of radiation-induced trismus depends on factors such as location of the tumour, radiation treatment volumes, radiation dose, fractionation, and radiation treatment technique.[69] In a study by Weber et al.[69] half of the HNC patients presented with mouth openings of less than 36 mm. In that study, 65% of oral and oropharyngeal cancer patients showed a limited mouth opening compared to 44% of hypopharyngeal and 31% of laryngeal cancer patients.[69] Restrictions and difficulty opening the mouth can interfere with oral and dental health as well as function and quality of life (Figure 3). Complications with proper oral hygiene, eating, speaking and difficulty wearing dentures have been associated with trismus.[28,50,63,69] Supportive aftercare management or trismus therapy is recommended for the HNC survivor, as oral complications and poor dental status persist after the completion of treatment.[65,68,69] In a study by Graff et al.,[71] fewer oral complications with oral discomfort such as pain in the jaw and difficulties in opening the mouth, swallowing, and eating were reported among HNC survivors who received bilateral neck RT using intensity-modulation (IMRT) compared to conventional radiotherapy. More research is needed to determine if oral

complications such as trismus can be reduced using focused RT systems (IMRT) with an ability to shield the temporomandibular joint and masticatory muscles.

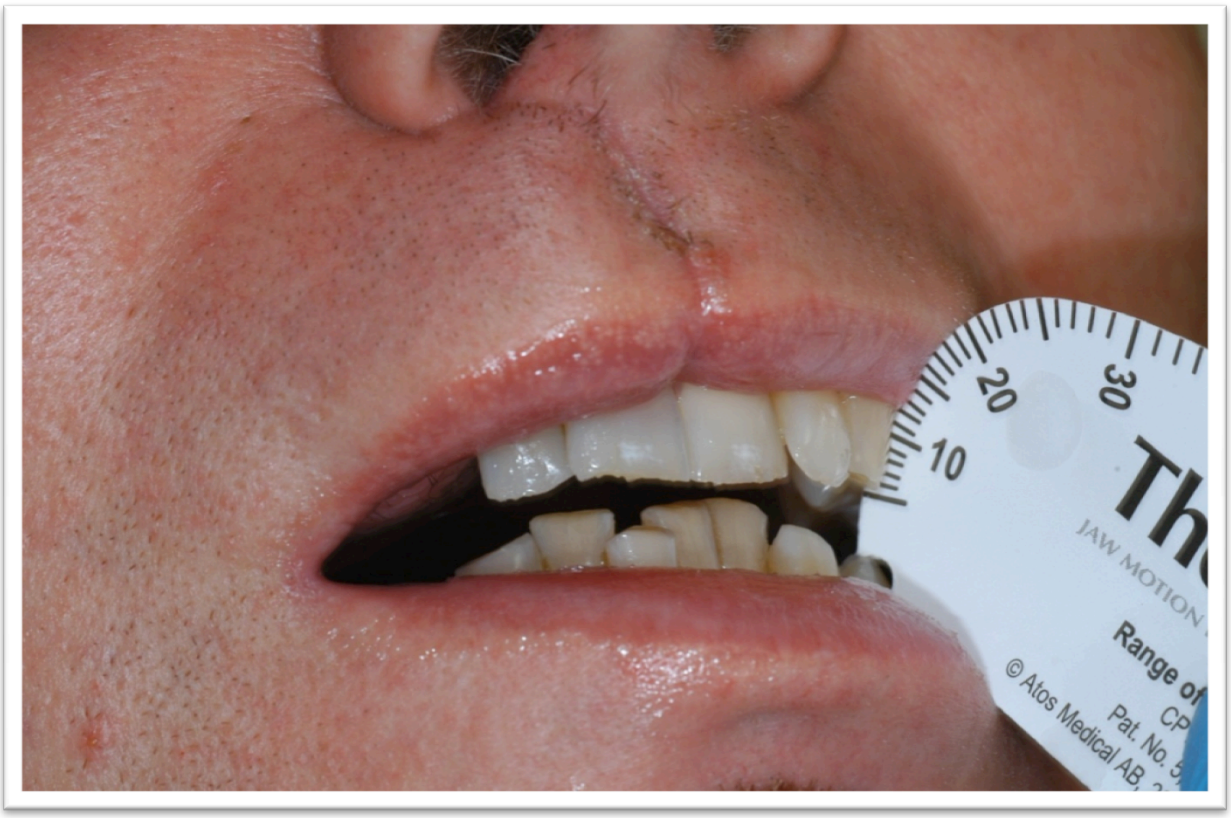

Figure 3. Limited maximal mouth opening (trismus)

Osteoradionecrosis (ORN). Soft tissue injury or trauma after tooth extraction in an area previously irradiated has been reported as a predisposing factor in the development of ORN.[18] High radiation doses delivered to the mandible increase the risk of developing ORN.[21] In a study by Parliament et al.,[21] patients receiving mandibular dose distributions in IMRT were compared to patients treated with conventional RT. The investigators concluded that IMRT offers a dosimetric advantage if sparing the mandible is included in the plan optimization.[21] This is clinically important as the mandible (especially the molar region) is at a greater risk of ORN

compared to the maxilla, especially after a total dose greater than 5000–6000 cGy. To reduce the risk of osteoradionecrosis and to improve bone healing, some investigators have implemented a protocol for using hyperbaric oxygen (HBO).[72-75] In an article by Larsen,[75] inclusion of hyperbaric oxygen was described to exert a beneficial effect on osteogenesis through the stimulation of fibroblastic proliferation, collagen synthesis, and the formation of capillaries. HBO treatment typically involves many treatments before and after the removal of any teeth or the installation of osseointegrated dental implants in patients that have been irradiated.[75]

Management of Radiation and Chemotherapy Sequelae

Strategies to manage radiation-induced oral and dental complications are discussed in the following sections.

Preventive care programs. Preventive oral-dental care regimes before, during, and after RT are incorporated with the intention of reducing sequelae.[20] Prior to the start of radiation, a thorough dental evaluation should be performed and prophylactic intervention should be recommended to address any source of irritation or infection involving the soft and hard tissues in the mouth.[20] Supportive and preventive oral-dental care is recommended for dentate as well as edentulous HNC patients. Management of oral health can be optimized through a combination of interventions. This includes routine dental evaluations, meticulous oral hygiene regimes, daily home fluoride applications (1% sodium fluoride gel or 0.4% stannous fluoride used daily for 5–10 minutes), routine dental restorations for teeth that are restorable or

extractions for patients with unsalvageable teeth, and pharmacologic therapy to alleviate oral symptoms and trismus rehabilitation.

Parotid and submandibular gland sparing IMRT protocols. Parotid-sparing IMRT has been associated with preserved salivary function, improved radiation-induced xerostomia, and improved quality of life scores compared to conventional RT.[51] Attempts to spare submandibular gland function by excluding the contralateral submandibular gland from the planned target volume in patients with HNC receiving parotid-sparing IMRT have been described by Saarilahti and colleagues.[76] This procedure requires extensive planning and is more demanding than the parotid sparing IMRT technique.[20] In Saarilahti's study, sparing of at least one parotid gland was possible in all patients but the submandibular gland could be spared in only six of the 17 patients.

The submandibular radiation dose in Saarilahti et al.'s[76]study was 2750 cGy compared to 700–1400 cGy in a study by Jha et al.[77] that involved a surgical procedure to reposition one of the submandibular glands into the submental space where it could be shielded from radiation. Shielding of the submandibular gland is clinically important as the gland is responsible for the majority of unstimulated or resting saliva vital to the maintenance of dental health. In a phase II study, Jha et al.[78] reported that of the HNC patients who underwent gland transfer, 81 % directly after RT and 71% at the 6 months follow up reported no or minimal xerostomia. In comparison, of the HNC patients who did not undergo gland transfer, 48% directly after RT and 71% at the 6 month follow up reported moderate to severe xerostomia. Results were measured using the University of Washington Quality of Life Questionnaire.[78,80] Two year follow up results for this study showed a significant difference in both stimulated and unstimulated

salivary flow rates between the two treatment groups.[81] Eighty-three percent of the patients who had undergone gland transfer reported normal amounts of saliva compared to none (0%) of the patients in the nontransferred gland group.[55] In addition, the improvement in xerostomia was accompanied by a better swallowing function in the gland transferred group compared to the nontransferred gland group.[40] A prospective phase III multicenter randomized study by Jha et al.[76] compared the submandibular salivary gland transfer procedure followed by RT with pilocarpine medication during RT and for three months after RT. Results from this study showed significantly higher median salivary flow rates and stimulated salivary flow rates in the SGT group compared to the pilocarpine group.[77] The QOL scores were also reported to be significantly higher in the SGT group compared to the pilocarpine group. The authors concluded that the SGT procedure is superior to administration of pilocarpine in the management of radiation-induced xerostomia.[77] In a planning study by Saibishkumar et al.,[82] authors set out to understand the consequences of sparing both the surgically transferred submandibular glands as well as the parotid glands using parotid sparing IMRT. Results from that study showed that sparing the salivary glands did not result in underdosing of the planning target volume (PTV). The authors concluded that by combining the gland transfer procedure and IMRT, the mean dose to the total parotid volume and transferred gland could be reduced to less than 2600 cGy.[41] This is clinically important since parotid gland mean dose RT thresholds below 3200 - 2600 cGy for stimulated glands could compare with preradiotherapy salivary output levels.[12,82]

Salivary stimulants. The use of salivary stimulants may reduce xerostomia related to salivary gland dysfunction.[51] Sialogogic agents such as pilocarpine hydrochloride may be used in select patients to reduce radiation-induced xerostomia during and after RT. Several randomized

studies have shown pilocarpine to be beneficial in the management of radiation-induced xerostomia. However, pilocarpine treatment produces adverse effects such as sweating, flushing, increased urination, blurred vision, and rapid heartbeat.[42,51] Treatment is based on clinical judgment and may offer improvement in the preservation of salivary function to select HNC patients.[42]

Chemoprotectants. Organ-sparing radiotherapy and chemotherapy protectant agents (chemoprotectants) have been used to reduce toxicities associated with chemoradiation. Amifostine prevents xerostomia by selectively protecting salivary function and normal tissues from damage induced by cisplatin-based chemoradiation.[42] In 1999, the American Society of Clinical Oncology[83] published guidelines that indicated amifostine could be considered in patients treated with RT to decrease acute and late xerostomia. However, other publications have recommended this drug be used experimentally until further studies establish a positive therapeutic index.[42]

Alternative treatment modalities. Alternative therapies to manage oral sequelae of RT treatment currently in the early stages of investigation include acupuncture, electrostimulation, and salivary gland gene transfer.[51] Other treatment modalities used to reduce oral-dental sequelae include the use of bite blocks, dental stents, and radiation guards. The adjuncts can be used to open the mouth and limit the number of teeth in the treatment volumes and to reduce electron backscatter off metallic dental restorations to adjacent soft tissues.[18]

Oral Rehabilitation After RT and Chemotherapy

HNC patients have been reported to have poor dentition and dental health before and after their cancer diagnosis.[65] HNC patients have been reported to have higher prevalence and

incidence of dental disease as well as poor compliance with dental care compared to the general population.[49,50,84] Difficulties opening the jaw or discomfort with the oral soft or hard tissues after HNC treatment often decrease compliance with dental care. Oral and dental complications may be exacerbated by preexisting dental conditions and may progress to partial or entire loss of the dentition. Changes in salivary secretions following therapeutic doses of radiotherapy have significant bearing on the use, comfort, and safety of wearing dental prostheses.[52] With minimal saliva present, less lubricant and more friction is produced at the denture-mucosal interface during function. In addition, the vestibule plays an important role in oral function and the ability to wear conventional dentures.[85] When the vestibule is lost or altered after HNC treatment, there may be limited vertical opening of the mouth or changes in the depth of the vestibule that result in poor retention and decreased stability of conventional dentures. Unstable dentures can cause difficulties in mastication which can lead to mucosal alterations.[85] The intricate interdigitation of the teeth of a dentate patient is lost in the partially or fully edentulous patient.[85] When teeth are lost there is resorption of the supporting trabeculated alveolar bone. Alveolar bone resorption results in a pseudoprominent chin or "overclosure" of the mandible which may impact conventional or future prosthetic stability and oral rehabilitation.[85] These changes further compromise retention of oral prosthesis leading to an unknown factor of risk for irradiated patients wearing conventional dentures.[85]

Over the last 20 years, endosseous dental implants have improved dental rehabilitation in the HNC patient by increasing stability, retention, and function (Figure 4).[74,85] However, practical limitations such as cost incurred for dental rehabilitation may place a considerable burden on many patients.[85] According to the American Academy of Osseointegration[86]

therapeutic tumoricidal irradiation remains a potential contraindication to implant therapy due to the risk of developing ORN and a risk of implant failure. As previously described, the risk of ORN is relatively low, about 4% in irradiated patients receiving an osseointegrated implant, and such implants are successful prosthetic alternatives to conventional dentures. Even in irradiated tissues, success rates as high as 90% to 95% retention after 10 years has been reported.[85] In addition to radiotherapy, other risk factors associated with implant failure or peri-implantitis include poor oral hygiene, periodontal disease, history of smoking, history of diabetes, and bisphosphonate-related osteonecrosis of the jaw.[85]

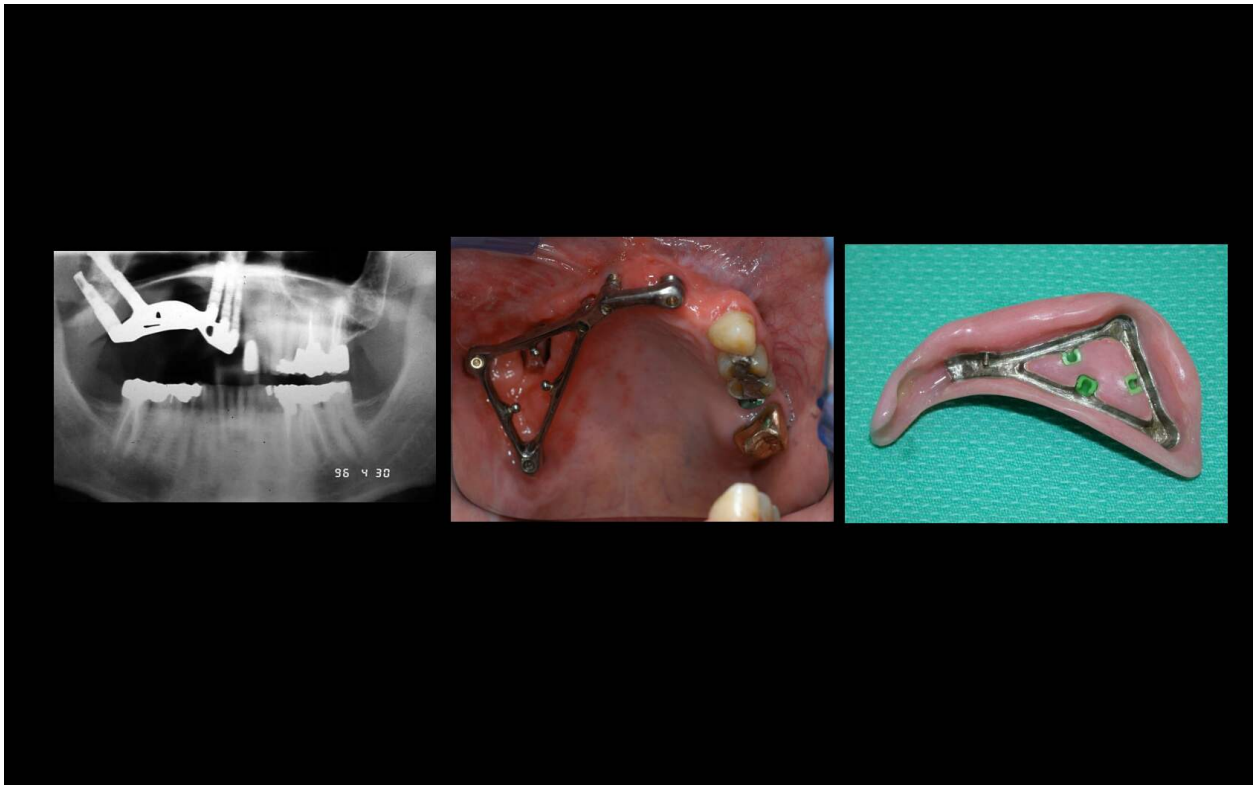

Figure 4. Implant retained prosthesis

Incidence of and Risk Factors for Tooth Loss

Periodontal risk assessment, or the weighing of the relative strengths of all risk factors present in order to quantify the risk for development or progression of periodontal disease, is a critical component of evidence-based dentistry.[87] Assessment of risk associated with dental disease and utilization of the results of risk assessment are important components of prevention, diagnosis, and treatment of oral-dental diseases.[88] Although risk assessment is relatively new in dentistry, several risk assessment tools have been described.[88] For example, the periodontal risk calculator[89] uses a weighted mathematical algorithm to classify risk (from lowest risk 1 to highest risk 5) based on the following nine factors: age, smoking history, diagnosis of diabetes, history of periodontal surgery, pocket depth, furcation involvement, restorations or calculus below the gingival margin, radiographic bone height, vertical bone lesions. Currently, risk assessment in the HNC dental literature is assessed by subjective evaluation such as practitioner or institutional philosophies regarding guidelines for pre-RT extraction criteria and oral health prevention programs; this can lead to variable outcomes for the HNC survivor.

A literature search was conducted on the incidence and risk factors of tooth loss in the general Canadian and United States as well as HNC population. In Canada, there has been a significant decline in the rate of tooth loss and edentulism over the past 20 years.[90] From 2007 to 2009, 93.6% of Canadian adults aged 20 to 79 reported having some natural teeth and 6.4% reported being edentulous, a significant decline over the last 20 years compared to 17% of the population who reported having no natural teeth in 1999. Among Canadian adults aged 20 to 39, less than 1% of the population had lost all of their teeth compared to 4.4% aged 40 to 59

and 21–22% aged 60 to 79. In the general population, a three-year longitudinal study of 491 subjects was designed to estimate the incidence as well as risk factors of tooth loss in older Canadians.[91] During the three-year follow up, 23.2% (114 subjects) lost one or more teeth. A total of 233 teeth were lost over the three-year period constituting 2.5% of the teeth present in the baseline data. Of 114 subjects who reported tooth loss, 69 subjects lost one tooth, 21 subjects lost two teeth, and 24 subjects lost three or more teeth. The annual tooth loss rate (tooth loss per subject, per year) was 0.9. The rate of edentulism was reported as low with six subjects (1.2%) who became edentulous after three years. These results were comparable to other studies reported in the United States.[92-95] The long-term decline in the rate of tooth loss in Canada corresponds with the improved access to dental care as well as use of fluorides.[90]

In the United States, as a result of improved tooth retention, the rate of edentulism has declined over the past few decades.[95] Principle findings from a longitudinal analysis of national data found the number of remaining teeth at baseline was strongly associated as a stable predictor of edentulism.[95] For example, nearly 42% of the subjects with only 1-7 teeth remaining at baseline were edentulous after 10 years compared to 2% of subjects with 24 or more teeth at baseline.[95] In a study by Hunt et al,[93] tooth loss was investigated over 18 months in a population of North Carolina adults aged 65 years and older. Results from this study were comparable to that of an Iowa study which investigated a similar cohort of subjects in an 18-month period. In these two studies, both cohorts mean tooth loss rate (tooth loss per subject, per year) among older white adults was 0.4.[93,94] In addition, the proportion of subjects losing at least one tooth was similar in both cohorts, 21% of the Iowans and 19% of the North Carolinians lost teeth within the follow up period.[93,94] The long-term decline in the rate of tooth loss in the

United States has been attributed to improved access to dental care as well as the benefits of modern preventive dentistry.[95]

Research on the incidence and progression of periodontal factors and tooth loss has been reported in the untreated and treated periodontal disease population.[88,94,95] In an article by Martin et al.,[88] the variation in tooth loss was reported in the "periodontitis-affected" and "untreated population" (p.202).[88,96-101] For subjects without periodontal therapy, the mean tooth loss (tooth loss per subject) ranged from 0.70 to 3.80, and the mean tooth loss rate (MTLR; number of teeth lost per subject per year) ranged from 0.14 to 0.38. In addition to time as a predictor of tooth loss, research has shown that the severity of periodontal disease is a strong predictor of tooth loss.[88, 102] In a longitudinal study by Loe et al,[96] the incidence of tooth loss was assessed in a sample of untreated periodontal population of Sri Lankan labourers. Results from this study showed that the rapidly progressing periodontal disease group had the highest incidence of tooth loss. In this group, tooth loss already occurred by 20 years of age and steadily increased over the next 25 years. By age 40 to 45, nearly all teeth were lost in the rapid periodontitis group.

In the head and neck cancer literature, one study was located that used tooth loss as an outcome measures to assess dental status before and after HNC RT.[103] Bruins et al.[103]conducted a clinical survey involving a five-year retrospective and follow up evaluation of 209 patients treated for cancer of the head and neck. The main objective was to investigate the association of tooth loss with the patients' dental status (baseline number of teeth), dental risk factors, and radiation-related risk factors. Results from this study showed that tooth loss was greater in the HNC population compared to the general population. The incidence of tooth loss in the 98

dentate patients preintervention (65 subjects postintervention) was 602 teeth lost. 441 (31% of the total number of teeth at baseline) teeth were lost prior to radiation and 161 (11%) were lost after radiation. The mean tooth loss (tooth loss per subject) was 1.64 for the remaining 65 subjects postintervention and 0.55 for the mean tooth loss rate during the 3 year follow up. Of those patients, 7% (7 patients) became edentulous in the follow up period after radiotherapy. At the follow up evaluation, 45% of the dentate patients were reported to have one or more teeth affected by radiation caries requiring extensive dental treatment or extraction. The authors concluded that tooth loss in the HNC patients in this study was considerably higher than tooth loss in similar age groups in the general population in the United States, Canada, and Europe.[91-95] The findings of this clinical survey also indicated that when a HNC patient presents with reduced dentition or poor dental health prior to the initiation of RT, there is a potential risk of substantial tooth loss due to extensive dental treatment subsequent to RT.[103] Estimates of the incidence of tooth loss in the HNC North American population have not been previously reported.

In a study by Guggenheimer et al.,[104] a comparison between patients with squamous cell carcinoma (SCC) of the oral cavity and a survey of the U.S. population of comparable age and socioeconomic status found that the prevalence of edentulism was 1.5 to 4.5 times greater in the oral cancer group compared to the comparable U.S. population.

Mean tooth loss and annualized tooth loss rates for the general and HNC population are reported in Table 1 and 1a, respecitvely. Mean tooth loss and annualized tooth loss rates for subjects in the untreated periodontal therapy population are reported in Table 2.

Researcher (Country/Year)	Length of Study (years)	N	Age (mean)	Mean Tooth Loss (number of tooth lost per subject)	Mean Tooth Loss Rate (number of tooth lost per subject per year)	Rate of Edentulism (%)
Locker et al Canada/1996	3	491	NA	0.48	0.16	1.2
Drake et al USA/1996	3	228	> 65	NA	0.9	NA
Hunt et al USA/1988	1.5	451	> 65	NA	0.4	NA
Hunt et al USA/1995	1.5	284	> 65	NA	0.4	1.8
Martin et al USA/2009	15	523	47.3 (mean)	2.39	0.16	NA

Abbreviations: N, sample size; NA, not available

Table 1: Tooth Loss for Subjects in General population

Researcher (Country)	Length of Study (years)	N	Age	Mean Tooth Loss (number of tooth lost per subject)	Mean Tooth Loss Rate (number of tooth lost per subject per year)	Rate of Edentulism (%)
Bruins et al Netherlands/1999	1 - 5 (3 year median)	65	60 (mean)	1.64	0.55 (3 year median)	7

Abbreviations: N, sample size

Table 1a: Tooth Loss for Subjects in HNC population

Researcher (Country)	Length of Study (years)	N	Age	Mean Tooth Loss (number of tooth lost per subject)	Mean Tooth Loss Rate (number of tooth lost per subject per year)
Papapanou et al Sweden/1989	10	191	25-80 (range)	3.80	0.38
Becker et al USA/1979	3.72	29	NA	1.24	0.36
Harris et al USA/2003	2.1	30	50 (mean)	0.70	0.33
Gilbert et al USA/2002	4	687	>45	1.12	0.28
Buckley and Crowley USA/1984	10	1016	27 (mean)	2.50	0.25
Loe et al Sri Lanka/1986	15	480 -	14-46 (range) 40-44 (range)	2.07 2.33	0.14 NA

Abbreviations: N, sample size; NA, not available

Table 2: Tooth Loss in Untreated Periodontal Population (adapted from Martin et al 2009)

In the HNC literature, the most common indices used to assess dental status include the indices decayed, missing, filled surfaces (DMFS) and periodontal probing depths (PD). Other assessments include the qualitative assessments using various QOL questionnaires (Appendix A).[65,102]

Tooth loss is a complex outcome with many risk factors associated with it such as age, oral health habits, periodontal and medical diseases, social-demographic status, general health, personal philosophy, and behavioural variables.[87-89] These variables reflect aspects of a complex process whose outcome may contribute to the loss of one or more teeth. For example, a dentist or patient may decide to extract a tooth that is fractured or has a poor prognosis instead of restoring it because it is too expensive to restore or replace. Individuals participating in government-funded programs may receive medical and dental treatment such as dental extractions, tooth restorations, or implant supported prosthesis that they would not be able to afford if they had to pay for it personally. No studies were located related to dental status in HNC patients treated with RT that compared government funded programs and the private sector.

Clinical and functional implications of tooth loss. Another issue that is important for future research is the limited longitudinal studies available reporting functional and social outcome data of tooth loss. Partial or complete loss of the dentition can lead to many clinical and functional implications. In a study by Miller and Locker,[105] subjects who reported losing one or more teeth in the previous year were reported to have poorer outcomes relating to function, social, and psychological problems than subjects who reported no tooth loss. In an article by Loewen et al.,[106] the state of an individual's natural dentition related to factors associated with

chewing efficiency; the more natural dentition a patient had the more efficient the patient was at breaking down a bolus. As many side effects of HNC treatment have been reported to resolve within a few years after treatment, problems related to the teeth, dry mouth and oral quality of life issues affect many facets of life for the long-term cancer survivor.[65,107,108]

Summary

Evolving treatment strategies such as advanced radiotherapy have changed from conventional two-dimensional systems to three-dimensional conformational systems. IMRT has the ability to deliver different dose distributions to a target compared to conventional two-dimensional RT. The use of organ sparing IMRT and chemoradiation in advanced head and neck cancer is increasing in popularity as sparing vital organs has the potential to spare function. Research related to dental outcomes after conventional RT versus IMRT is limited in HNC and dental literature.

Advances in the treatment of head and neck cancer and the goal of better survival rates increase the importance of improved dental outcomes for the head and neck cancer survivor. Early and late dental sequelae after radiotherapy can have long-term effects on oral function, cosmesis, and quality of life. Although parotid sparing IMRT shows promise in decreasing certain radiation-induced complications compared to conventional 2-D radiation, a number of clinical questions and challenges have yet to be fully explored.[1] Previous research has mainly focused on subjective measures using validated quality of life and xerostomia-related quality of life questionnaires after head and neck cancer irradiation. Other studies have focused on objective measures to quantify salivary function before and after RT using conventional or

conformal RT, while little research has been reported on the status of dental health after HNC treatment. It has been expressed at international conferences and through personal communications that there is a growing concern related to the failure of dentition within a few years of receiving IMRT.[109] A review of available literature in the present study found no evidence of this perception. More research and clinical interventions are needed to evaluate the impact preventive oral hygiene care regimens have on the health and longevity of dentition. The purpose of this study was to determine whether IMRT contributed to the failure of dentition years after IMRT.

Chapter 3: Research Methods

Research Methods

Study design. A retrospective chart review was implemented in a one-way, between subjects, causal-comparative design. Information from patient charts was analyzed to compare tooth loss among the different RT systems (IMRT vs. non-IMRT) used to treat oral cavity, oropharyngeal, and nasopharyngeal cancer. Since this study utilized archival data, the only meaningful and objective comparison of dental status that could be made pre- and post-treatment was to measure the number of missing teeth.[14,110] A retrospective approach had important advantages. It enabled the investigator to review patient records that spanned many years yielding data for a relatively large number of patients. Many studies in the current literature focus on the early failure of dentition by examining radiation-induced caries up to one year after radiotherapy.[8,110] Since the breakdown of cancer patients' dentition tends to start the first year after treatment and becomes more severe with increasing time, a prospective study would have been time-consuming and not feasible for a master's level thesis.

Research hypothesis. A nondirectional hypothesis was used for the dependent measure.

H_0: There is no difference in tooth loss (after surgery) following radiation therapy +/- chemotherapy for head and neck cancer patients compared to treatment without radiation therapy +/- chemotherapy.

Materials and Methods

Review by a research ethics board was required for the secondary use of data. This study was conducted under approval of the Health Research Ethics Board (REB panel B) at the University of Alberta and the Alberta Cancer Research Ethics Committee (ACREC).

Participants. The subjects of this study included adult (over 18) patients who had undergone functional assessment at the Institute for Reconstructive Sciences in Medicine (iRSM) at the Misericordia Community Hospital in Edmonton, Alberta, Canada. A convenience sample was used, and included data over a 11 year period from January 1, 2000, to December 31, 2010. Patients with a history of oral cavity (O), oropharyngeal (OP), and nasopharyngeal (NP) cancer were included in the study. These subgroups (O, OP, and NP) of HNC were selected for the study since RT treatment typically includes bilateral neck irradiation as well as radiation to the tumour bed. Since 2000, the Cross Cancer Institute in Edmonton, Alberta, Canada has had an IMRT and Helical Tomotherapy unit (in 2002) at its disposal in addition to conventional 2D RT units for treating head and neck cancer patients. Subjects in this study received RT and chemotherapy treatment at the Cross Cancer Institute.

Subjects in this study had previously participated in functional outcomes assessments at iRSM. From the functional outcomes database, there were approximately 663 charts available to be reviewed for the study. The advantage of using data from the functional outcomes assessments was the standardized subject demographic information and clinical photographs available from these appointments. In addition, the functional outcomes assessments included data presurgery, 1 month after surgery (pre-RT, prechemotherapy), 6 months after surgery (approximately 5 months after RT and chemotherapy), and 12 months after surgery

(approximately 11 months after RT and chemotherapy). From the potential 663 subjects eligible for this study, 86 subjects met the inclusion criteria and were included in the study. The remaining 577 subjects were excluded for the following reasons:

1. 330 subjects did not have pre- or postintervention data to compare tooth loss over time;
2. 105 subjects were edentulous prior to the initiation of HNC treatment;
3. 72 subjects did not receive RT as part of the HNC treatment modality;
4. 70 subjects had a recurrence or received a second HNC intervention such as surgery, chemotherapy, or RT after the initiation of RT.

The primary loss of data was due to missing pre- or postintervention data which may be attributed to subject mortality, illness such as a cancer recurrence, or a combination of logistic, financial, and demographic reasons. Rationale for the missing data was not always documented in the subjects' charts, but many subjects were recorded as deceased when reviewing the HNSFAL database.

Power and sample size. In order to have a 0.05 alpha level with a study power of 80% and "effect size" of 0.05, approximately 60 subjects were needed for the study. To reach this sample size, N=30 subjects divided by 1 is 30 for each cell (1 X 2 = 2 cells/levels, 30 X 2 = 60) subjects required.

Inclusion criteria:

1. A history of oral cavity cancer, oropharyngeal cancer, or nasopharyngeal cancer;
2. Treatment included radiotherapy and/or chemotherapy alone or in combination with surgery;

3. Radiotherapy and/or chemotherapy was received at the Cross Cancer Institute (CCI), Edmonton, Alberta, Canada.

Exclusion criteria:

1. History of carcinoma outside the head and neck region involving chemotherapy or radiotherapy;
2. History of head and neck cancer recurrence or second primary tumour involving reirradiation, surgery, or chemotherapy;
3. Patient was edentulous before treatment intervention. Edentulous patients were excluded from the primary analysis of the study;
4. History of salivary gland disease, e.g., Sjorgren's syndrome.

Independent variable. The independent variable was radiation treatment *group* having 2 levels (IMRT, non-IMRT).

Dependent variable. The dependent variable was *tooth loss*.

Co-factor variables. The following factors were chosen as risk factors of tooth loss - age, gender, smoking history, diabetes history, salivary gland transfer versus Salagen, hyperbaric oxygen, radiotherapy total dose, number of days after radiotherapy.

Data collection. The data on patient characteristics and information regarding their medical and dental history were retrieved from iRSM patient charts. Radiation related data such as RT dose, RT treatment dates, and RT delivery that were missing from the iRSM patient charts were retrieved from the Cross Cancer Institute patient charts. Patient demographics and tooth loss data were obtained by one examiner, a dental hygienist, and recorded on a spreadsheet using Microsoft Office Excel 2003 version 11.0 (Microsoft Office Excel, Redmond,

WA, USA) as described in Appendix B. The study intended to capture data from patient charts who attended functional assessments at iRSM from January 1, 2000, to December 31, 2010.

Archival clinical photographs were the primary modality used to determine the number of teeth present prior to the initiation of RT and annually after RT. Clinical photographs offered the most consistent method to measure tooth loss for this retrospective study. Clinical photographs consisted of digital images and analog images depending on the year the images were taken. Clinical photographs from 2000 to 2003 were in analog form and viewed on a slide projector. Images from 2004 to 2010 were digital and stored within the software program Image FX® (Scican Inc, Toronto, ON, Canada) available on iRSM clinical computers. As iRSM operates under a quality management system, standardized clinical photographs were collected for the functional assessment appointments. Appendix C is the clinic work instruction number 9.4 for the intra-oral digital images. The purpose of the work instructions is to ensure consistent and accurate patient intraoral images. If clinical photographs were not available or the number of teeth could not be determined from the photograph, alternative modalities such as archived radiographs (full mouth series, panoramic image, CBCT), dental charting records, or correspondence were used. The addition of sending out a questionnaire to the patients was not considered for this study as it would be difficult for individuals to remember their dental history over the past few years. Digital photographs were used for 80 subjects (93%), analog slides were used in two cases (2%), and data from a combination of digital photographs, radiographs, and dental charting were used for four subjects (5%).

Data were collected on dentate patients, that is, subjects with at least one tooth present at baseline. Tooth loss was defined as complete loss of the tooth or a retained root tip

(nonfunctional tooth). All teeth counted, including wisdom teeth. Collection of tooth loss data for all subjects occurred at the following time points: Time 1: approximately 1 month after HNC surgery, before initiation of radiotherapy (baseline, or "pre-RT time"); Time 2: approximately 1 year after surgery, and approximately 6 to 9 months after completion of radiotherapy ("up to 1 year post-RT time"); and annually thereafter (Time 3 through Time 10 if data were available). To avoid potential bias in the number of teeth lost prior to the initiation of RT, baseline data were recorded before initiation of RT but after HNC surgery to avoid inclusion of teeth sacrificed during the resection-reconstruction surgery (i.e., maxillectomy, hemimandibulectomy).

Tooth loss was used as the dependent variable and calculated by taking the difference in the total number of teeth at baseline and at each time point data where available annually after RT. Tooth loss data were recorded on a spreadsheet using Microsoft Office Excel 2003 version 11.0 (Microsoft Office Excel, Redmond, WA, USA).

To confirm acceptable levels of intra and interexaminer reliability, 20% (17 of the 86 subjects at baseline) of the clinical records were reanalyzed by a the primary investigator and clinical assistant from iRSM, respectively. The clinical assistant was trained and experienced with the iRSM quality management system regarding the collection of subject demographics as well as the clinical work instruction for taking clinical photographs. The following demographic data was reanalyzed:

1. Subject demographic: age, site of disease;
2. Clinical photographs: baseline number of teeth, tooth loss year 1, tooth loss year 2;
3. Dependent variable demographics: difference from baseline and year 1 and 2 data.

There were 110 subject and dependent variable demographics reanalysed by the two examiners with 99% agreement using the following calculation: (% agreement = number of agreements/numbers of codes compared) X 100% = 99/100 x 100%.

Statistical data analysis and data management.

Preliminary Analysis of the Data

The statistical analyses were performed using IBM Predictive Analytical Software (PASW) statistical software version 19.0 (PASW Inc., Chicago, IL, USA), using a personal computer. The distribution of the data were analyzed using descriptive statistics (mean, median, skewness, kurtosis) to investigate the normality prior to using nonparametric and parametrical statistical procedures. The dependent variable, tooth loss is a continuous variable that yields ratio-level data.

Box plots were used to illustrate the data and visually inspect the distribution of the data, central tendency, and outliers. Since the data did not follow a normal distribution, box plots were chosen as the most appropriate graphical analysis to illustrate the data. Within a box plot, the top of the box represents the 75^{th} percentile, the bottom of the box represents the 25^{th} percentile, and the line in the middle of the box represents the 50^{th} percentile. The central box represents 50% of the data, or data that fall between the upper and lower quartiles. The bold black line within the box represents the median of the distribution. If the placement of the median value within the box is toward the upper or lower quartile, the data are positively or negatively skewed, respectively. The whiskers are the lines extending out the top and bottom of the box (range where the data fall) that represent the highest and lowest values that are not

outliers or extreme values. The outliers are values that are between 1.5 and 3 times the interquartile range, illustrated by asterisks. Extreme outliers are values that are more than 3 times the interquartile range, and are represented by open circles beyond the whiskers.

Preliminary Data Analysis—Covariates

The study employed a correlational design using parametric and nonparametric tests to measure the degree of relationship between the predictor variables (covariates or factors) and the criterion variable, tooth loss. Since the criterion variable did not follow a normal distribution and the predictor variables were not measured on an interval or ratio level scale, a nonparametric measure of correlation, Spearmans's rho (rho), was used in the analyses.

Multiple regression analysis was not used to answer this research question due to the small sample size and the large number of predictor variables (factors) used in the regression. Since some of the nominal predictor variables (i.e. history of smoking, diabetes) were not dichotomous (having two variables) they would need to be recoded so that you would create different variables each with two categories. Since year one had a sample size of 82 and year two had a sample size of 28, the subject to variable ratio would be less than 5:1. When using multiple regression, the number of subjects must considerably exceed the number of predictor variables to maintain a minimum ratio of 5:1. More acceptable ratios such as 10:1 or as high as 40:1 have been recommended using multiple regression analysis.[113]

Chapter 4: Results

Results

Subject demographics. Eighty-six subjects, 71 (83%) male, and 15 (17%) female fulfilled the inclusion criteria for the study. The mean age was 57.1 (median 56.6; range 82) for the 86 subjects. Age, gender, tumour stage (T = tumour size, and N = nodal involvement, T 1 - 2 = early tumour stage, T 3 - 4 = advanced tumour stage) and mean follow up time did not differ significantly between the two treatment groups ($p > 0.05$) using an independent t-test. The prevalence of the tumour site (OP, O, NP) was significantly different between groups since there were limited nasopharynx subjects in the study compared to the oral cavity and oropharynx group, and no nasopharynx in the IMRT groups as a result of the overall small NP samples in the study (Table 3).

Category	IMRT (n=44)	Non-IMRT (n=42)	P Value (independent t-test) (Between groups)
Age, mean, y	55.9	58.3	0.838
Sex, No. (%) Male Female	 37 (84) 7 (16)	 34 (81) 8 (19)	0.577
Site of disease, No. (%) Oropharynx Oral cavity Nasopharynx	 36 (82) 8 (18) 0 (0)	 29 (51) 6 (15) 7 (16)	0.000
T stage, No. (%) 1 and 2 3 and 4	 21 (48) 23 (52)	 23 (55) 18 (40)	0.064
N stage, No. (%) 0 and 1 2 and 3	 19 (43) 25 (57)	 16 (38) 25 (60)	0.064
Months after initiation of RT Year 1 Year 2	 11 19	 10 21	 0.690 0.167

Table 3: Subject Demographics using full data set

Dependent variable demographics. The first year after the initiation of RT yielded the most data (n=82) and could be used in the final analysis. The second year yielded the next most inclusive data set (n=28) and could be compared to the first year in the statistical analysis. Descriptive statistics for the dependent variable, tooth loss, are described in Tables 4 and 5 up to two years after RT. The intentions of this study were to collect data from 2000 – 2010, but due to the lack of available subject data after the second year postinitiation of RT, data points from the third year onward were not included in the final analysis. In addition, due to the small samples after the second year after RT, it would be difficult to make between group comparisons as described in the research hypothesis. Descriptive statistics illustrating the small samples beyond the third year after RT are shown in Table 6.

Since the data did not follow a normal distribution the first year after RT, the median, quartile range (Q_u, Q_L), and skewness were used as the best estimate of central tendency (Tables 4, 5). At year one, the median of the distribution value for the dependent variable was zero and was positively skewed in both groups. The upper and lower quartiles (Q_U, Q_L) are the medians of the upper and lower halves of the data; in Table 4, Q_U and Q_L were zero for both groups. Since the interquartile range deals with only the middle 50% of the data, it is less affected by extreme scores.

At year two, the data distribution was close to normal and was less skewed compared to the first year after RT (Table 5). In both groups, the median of the distribution was zero but there was more variability in the data for the second year after RT compared to data for the first year after RT, as described by the mean and upper quartile range in Table 5.

	Mean	Median	N	Variance	Skewness	Q_L	Q_U
IMRT	.41	0	41	1.60	3.60	0	0
Non-IMRT	1.15	0	41	11.79	3.75	0	0

Abbreviations: N, number of subjects; Q_L, lower quartiles, Q_U; upper quartiles

Table 4: Descriptive Statistics for the Dependent Variable, Tooth Loss, up to one year after RT using the full data set

	Mean	Median	N	Variance	Skewness	Q_L	Q_U
IMRT	1.35	0	17	6.37	2.17	0	2
Non-IMRT	5.55	0	11	91.48	1.49	0	12

Abbreviations: N, number of subjects; Q_L, lower quartiles; Q_U, upper quartiles

Table 5: Descriptive Statistics for the Dependent Variable, Tooth Loss, up to two years after RT using the full data set

Descriptive Statistics						
RT Treatment Group		Tooth Loss year 3	Tooth Loss year 4	Tooth loss year 5	Tooth Loss year 6	Tooth Loss year 7-10
IMRT	N	8	1	0	1	0
	Mean	7.75	4.00	NA	1.00	NA
	Median	6.00	4.00	NA	1.00	NA
Non-IMRT	N	3	2	0	1	0
	Mean	11.00	7.00	NA	24.00	NA
	Median	10.00	7.00	NA	24.00	NA

Abbreviations: N, number of subjects; NA, not applicable

Table 6: Descriptive Statistics for the Dependent Variable beyond Two Years after RT

In the first year post-RT, tooth loss data in both groups did not follow a normal distribution (Figure 5). Visual inspection of the box plots showed that the medians of the distribution values were zero for both groups. As illustrated in Figure 5, there is no central box to illustrate the upper and lower quartiles due to the limited range of scores and small variability of the data. The skewness of the data cannot be seen in the box plot since there is no box around the median value. Tooth loss data in both groups were positively skewed as described in Table 3. Since the majority of the data set values were zero, the data did not follow a normal distribution. As illustrated in Figure 5, there was no box or interquartile range, whiskers, or inner fence that could be calculated due to the distribution of the data. In Figure 5,

there were more outliers, as illustrated by the asterisks, in the non-IMRT group than in the IMRT group.

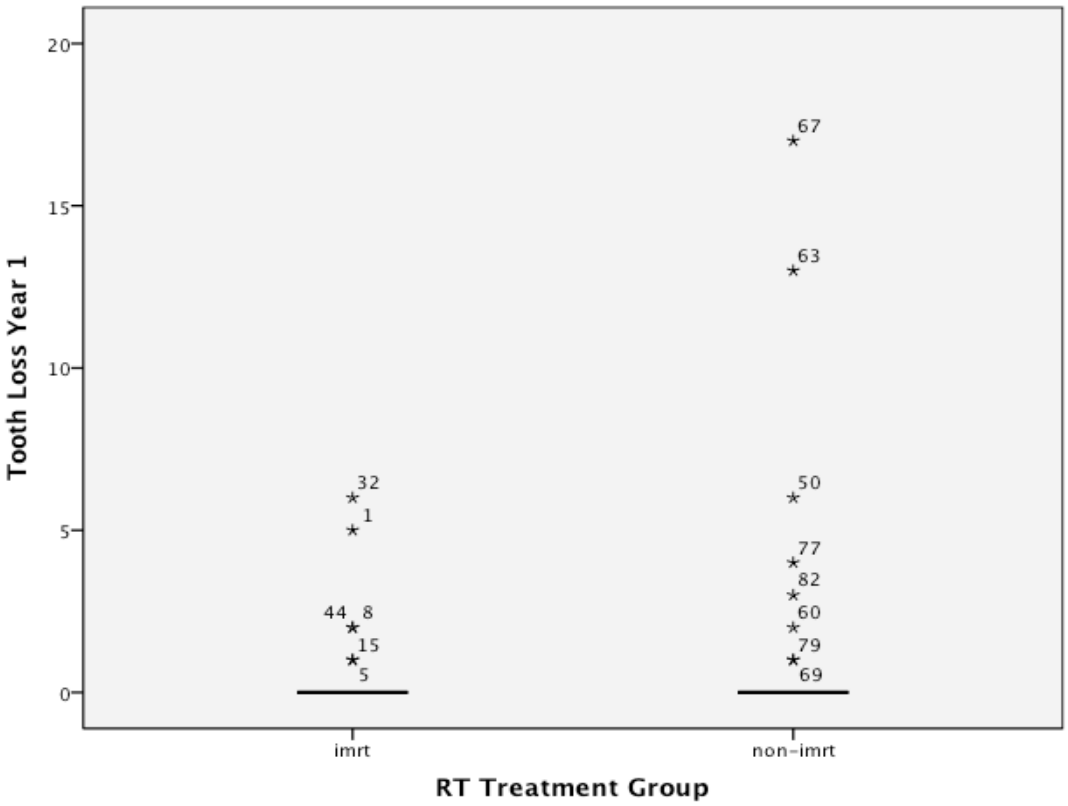

Figure 5: Box plots depicting tooth loss at year one for each RT treatment group using the full data set. The bold black line represents the median of the distribution. The outliers are illustrated by the asterisks and the numbers represent the subject data points.

At year two, tooth loss for both groups was close to a normal distribution (Figure 6). Visual inspection of the box plots showed that there was some overlap between the two groups. The median of the distribution is illustrated by the bold black line within the box. In Figure 6, the median of the distribution is zero for both groups with more variability of the data

in the non-IMRT group than in the IMRT group. In both groups, the distribution of the data falls within the upper quartile range as shown in the box. There are no whiskers extending from the IMRT box and one line (whisker) coming from the upper end of the non-IMRT box since there is no distribution of the data below the median value. There are more outliers in the IMRT group than in the non-IMRT group as illustrated by the asterisks and open circles. As illustrated in Figures 5 and 6, there was more data distribution, or variability of data, toward the upper quartile in the non-IMRT group than in the IMRT group the second year after RT compared to the first year. The second year after RT yielded more outliers in the IMRT group than in the non-IMRT group; these results were different from results from the first year after RT where there were more outliers seen in the non-IMRT group (Figures 5, and 6).

Tooth Loss Comparison Between Group up to Two Years After RT

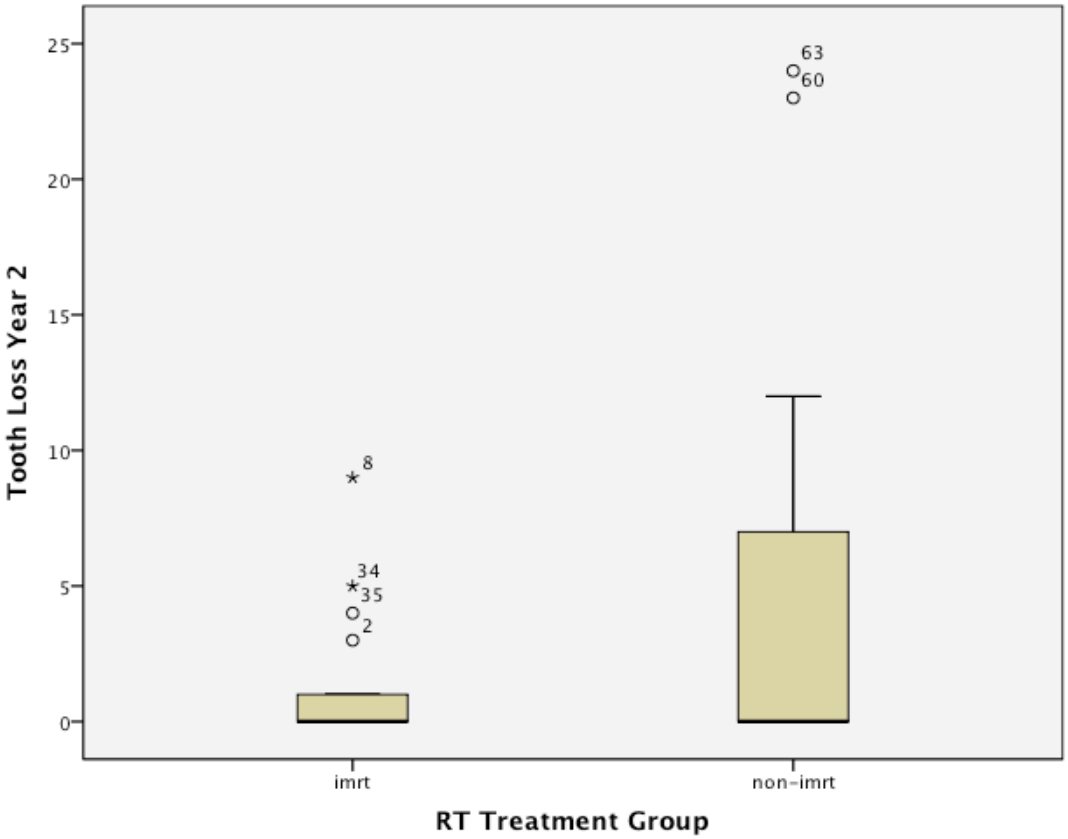

Figure 6: Box plots depicting tooth loss at year two between RT treatment groups using the full data set. The bold black line within the box represents the median, the gray box represents the interquartile range, and the whiskers extend to extreme values. The numbers represent subject data points. The asterisks represent the outliers and the open circles represent the extreme values.

Covariates and tooth loss. This section pertains to research question 1: How do the following factors—age, gender, smoking history, diabetes history, salivary gland transfer versus Salagen, hyperbaric oxygen, radiotherapy total dose, number of days after radiotherapy—interact with the different RT systems to affect tooth loss?

There were no significant correlations between the factors and tooth loss up to two years after radiotherapy (Tables 7, 8).

Covariate	IMRT (n=44)	Non-IMRT (n=42)	Statistical analysis, two tailed (up to one year after RT)
Age, mean (yr)	55.9	58.3	rho = 0.079, n = 82, p = 0.479
Gender (%) Male Female	 37 (84) 7 (16)	 34 (81) 8 (19)	rho = -0.008, n = 82, p = 0.941
History of diabetes, No. (%) 1) Type I 2) Type II 3) No history	 1 (2) 4 (9) 39 (87)	 4 (10) 3 (7) 34 (81)	rho = -0.008, n = 82, p = 0.940
History of smoking (%) 1) Never 2) Past 3) Current	 10 (23) 33 (75) 1 (2)	 7 (17) 28 (67) 3 (7)	rho = -0.108, n = 82, p = 0.336
Gland transfer (%) 1) Salivary gland transfer 2) Salagen 3) Neither	 19 (43) 1 (2) 24 (55)	 23 (55) 4 (10) 15 (36)	rho = -0.183, n = 82, p = 0.100
Radiation dose (cGy) (%) 1) Up to 5500 2) >5500–<6500 3) > 6500–7200	 2 (5) 33 (75) 6 (14)	 1 (2) 32 (76) 9 (15)	rho = 0.175, p = 0.116
Days after RT Year 1	 337	 326	r = -0.098, p = 0.422

Table 7: Subject Demographics—Covariates Analysis up to One Year After RT

Covariate	IMRT (n= 17)	Non-IMRT (n= 11)	Statistical analysis, two tailed (up to two years after RT)
Age, mean (yr)	55.9	58.3	rho = 0.081, p = 0.683
Gender (%) Male Female	 37 (84) 7 (16)	 34 (81) 8 (19)	rho = 0.081, p = 0.683
History of diabetes (%) 1) Type I 2) Type II 3) No history	 1 (2) 4 (9) 39 (87)	 4 (10) 3 (7) 34 (81)	rho = 0.250, p = 0.199
History of smoking, No. (%) 1) Never 2) Past 3) Current	 10 (23) 33 (75) 1 (2)	 7 (17) 28 (67) 3 (7)	rho = 0.250, p = 0.199
Gland transfer (%) 1) Salivary gland transfer 2) Salagen 3) Neither	 19 (43) 1 (2) 24 (55)	 23 (55) 4 (10) 15 (36)	rho = -0.021, p = 0.916
Radiation dose (cGy) (%) 1) Up to 5500 2) >5500–<6500 3) > 6500–7200	 2 (5) 33 (75) 6 (14)	 1 (2) 32 (76) 9 (15)	rho = 0.072, p = 0.716
Days after RT Year 2	 574	 645	r = 0.186, p = 0.374

Table 8: Subject Demographics—Covariates Analysis up to Two Years After RT

Preliminary Data Analyses (Dependent Variable)

Distributions of the outcome data were analyzed using descriptive statistics to investigate the normality of the data prior to using statistical procedures. An explanation of issues related to data management, data transformation, and choice of statistical procedures are described in this section.

Collapsed data. The initial proposal of this study included eight levels of the independent variable "group." Because of the relatively small numbers in each group, an analysis was undertaken to determine if it would be possible to collapse the data. Thus, a univariate analysis was completed to determine if there were significant differences between the subgroupings (+/- surgery, +/- chemotherapy) related to the IMRT and non-IMRT groups for the first and second years after RT. The results showed that there were no significant differences ($p>0.05$) between groups using univariate analysis. Thus, a decision was made to collapse the subgroups into two broad groups, IMRT and non-IMRT, in order to compare IMRT and non-IMRT according to the study's hypothesis and to increase the sample size within each group (Table 9).

IMRT treatment group	Number of subjects	Non-IMRT treatment group	Number of subjects
IMRT	2	Non-IMRT	1
IMRT + surgery	12	Non-IMRT + surgery	15
IMRT + chemotherapy	3	Non-IMRT + chemotherapy	6
IMRT + surgery + chemotherapy	27	Non-IMRT + surgery + chemotherapy	20
Total IMRT	44	Total non-IMRT	42

Table 9: Noncollapsed Radiotherapy Treatment Groups at Baseline

Normality of the data. To illustrate trends in the data, descriptive statistics and graphical analyses were used. The dependent variable, tooth loss, is a continuous variable that yields ratio-level data. Since the majority of the subjects did not lose teeth (zero or close to zero) the first two years after RT, the data set in research question 1 did not meet the criteria for a normal distribution (skewness values greater than ±2) (Tables 4, 5), (Figures 5, 6).

Transformation of the data. Since the data did not follow a normal distribution, a transformation procedure was employed in an attempt to normalize the data. The dependent variable (X) was transformed to a new variable (X') using the following techniques: arc sine transformation, square root transformation, and log transformation. These techniques were performed in order to conform the data to more closely satisfy necessary assumptions of normality.[111] Since the majority of the subjects had not lost any teeth one year after RT (equal or close to zero), the data continued to be positively skewed (> 2) after data transformation.

Covariates. Preliminary analysis revealed that age, gender, history of diabetes, history of smoking, RT-related factors, and the salivary gland were not influential on the outcomes related to tooth loss in this study. The factor, HBO was initially considered as a cofactor but was excluded from the final analysis since HBO is only administered prior to the removal of the dentition. In addition, the cofactor, salivary gland sparing technique (i.e., 1 parotid, 2 parotid, parotid + submandibular gland) was initially considered as a cofactor but due to lack of data, this cofactor could not be included as a potential covariate. The baseline number of teeth (i.e., teeth present before the initiation of radiotherapy) was found to be a significant covariate (rho = 0.986, N = 82, p = 0.022, two-tailed) and was entered into the analysis as such.

To check for homogeneity of regression, the covariate and the fixed independent variable (group) were analyzed to see if there was an interaction between the baseline number of teeth and the independent variable, group. The interaction between the covariate and the independent variable was nonsignificant (p = 0.420) and did not violate the assumption of homogeneity. In addition, graphical analyses were used to confirm a linear relationship between the covariate and the dependent variable prior to using RM-ANCOVA.

Rationale for RM-ANCOVA. After preliminary analysis of the data was completed, the between group variables, IMRT and non-IMRT, were analyzed using a repeated measures analysis of covariance (RM-ANCOVA). As described earlier, the tooth loss data did not follow a normal distribution, which violates one of the assumptions of using ANOVA designs.[111] After reviewing the literature and consulting with a statistical research consultant from the Centre for Research in Applied Measurement and Evaluation (CRAME), a repeated measures analysis of covariance was chosen as the most appropriate statistical method of analysis. The robustness

of using analysis of variance designs such as RM-ANCOVA is described in the literature. Some researchers theorize that if the measurement variable does not fit a normal distribution, there is a risk of a false positive result.[112] Some authors have tested this theory by performing simulation studies using a variety of nonnormal distributions and have concluded that violating this assumption did not increase the rate of obtaining a false positive result, since ANOVA is not very sensitive to moderate deviations from normality.[111,113] When using ANOVA designs, the normality assumption is not necessary for sample sizes over 10 to 20 (as described in the central limit theorem) and when there are balanced (equal or close to equal) samples in each group.[114]

It is not possible to control for all of the possible confounding variables. Analysis of covariance (ANCOVA) can achieve statistical control by measuring the confounding variables in addition to the dependent variable and account for variability in the analysis.[111] In the present study, the baseline number of teeth was handled as a covariate to correct for bias resulting from baseline differences in the number of teeth between groups. There was a significant negative (inverse) relationship between the baseline number of teeth and tooth loss at year one. That is, the larger the values at baseline, the smaller the values one year after treatment. For example, the more teeth the subjects had at baseline, the less likely they were to lose teeth over time.

ANCOVA was used to account for the effect of the baseline differences of the dependent variable since there were differences between the treatment groups at baseline.[102] Randomization of the retrospective data was not feasible in the present study, a convenience sample was used to increase the sample size and the statistical power of the final analysis.

Since the study recorded tooth loss over time, a repeated measures design (rather than an independent samples test) was recommended to reduce the error term in the analysis of variance, leading to a larger F-ratio and significance in the results.[111]

Dependent variable demographics—Repeated measures analysis. The repeated measures analysis yielded different descriptive statistics values compared to analysis of the full data set, as described in Tables 4 and 5. This is due to the fact that the repeated measures analysis excludes missing data points from the analysis. Thus, only year one and year two samples (n= 25, IMRT=14, non-IMRT=11) with contiguous data points were included in the final analysis (Tables 10, 11). Since the data did not follow a normal distribution the first year after RT, the median, quartile range (Q_u, Q_L), and skewness were used as the best estimate of central tendency to describe the data.

At year one, the median of the distribution value for the dependent variable was zero and was positively skewed in both groups the first year after RT. Q_L was 0 for both groups and Q_U was greater than 0 with more variability in the non-IMRT group as described in Table 10.

At year two, the median of the distribution for both groups were zero, but there was more variability in the data in the non-IMRT group the second year after RT compared to the first year as described by the mean and upper quartile range in Table 11.

	Mean	Median	N	Variance	Skewness	Q_L	Q_U
IMRT	0.14	0	14	.286	3.74	0	0
Non-IMRT	1.82	0	11	15.34	3.75	0	2

Abbreviations: N, number of subjects; Q_L, lower quartiles; Q_U, upper quartiles

Table 10: Descriptive Statistics for the Dependent Variable, Tooth Loss, up To One Year After RT using the 25 subjects from the RM-ANCOVA

	Mean	Median	N	Variance	Skewness	Q_L	Q_U
IMRT	1.07	0	14	7.0	2.65	0	0.25
Non-IMRT	5.55	0	11	91.43	1.49	0	12

Abbreviations: N, number of subjects; Q_L, lower quartiles; Q_U, upper quartiles

Table 11: Descriptive Statistics for the Dependent Variable, Tooth Loss, up to Two Years After RT using the 25 subjects from the RM-ANCOVA

Box plots were used to illustrate the data for the first two years after RT to visually inspect the distribution of the data, central tendency, and outliers. In the first year post-RT, tooth loss data in both groups did not follow a normal distribution (Figure 7). Visual inspection of the box plots showed that the medians of the distribution values were zero for both groups. As illustrated in Figure 7, in the IMRT group there was no central box to illustrate the upper and lower quartiles due to the limited range of scores and small variability of the data. The skewness of the data cannot be seen in the box plot since there was no box around the median value. Tooth loss data in both groups was positively skewed as described in Table 10. Since the majority of the data set values were zero, the data did not follow a normal distribution. As illustrated in Figure 7, in the IMRT group there was no box or interquartile range, whiskers, or inner fence that could be calculated due to the distribution of the data.

Tooth Loss Comparison Between Group up to One Year After RT Using Repeated Measures

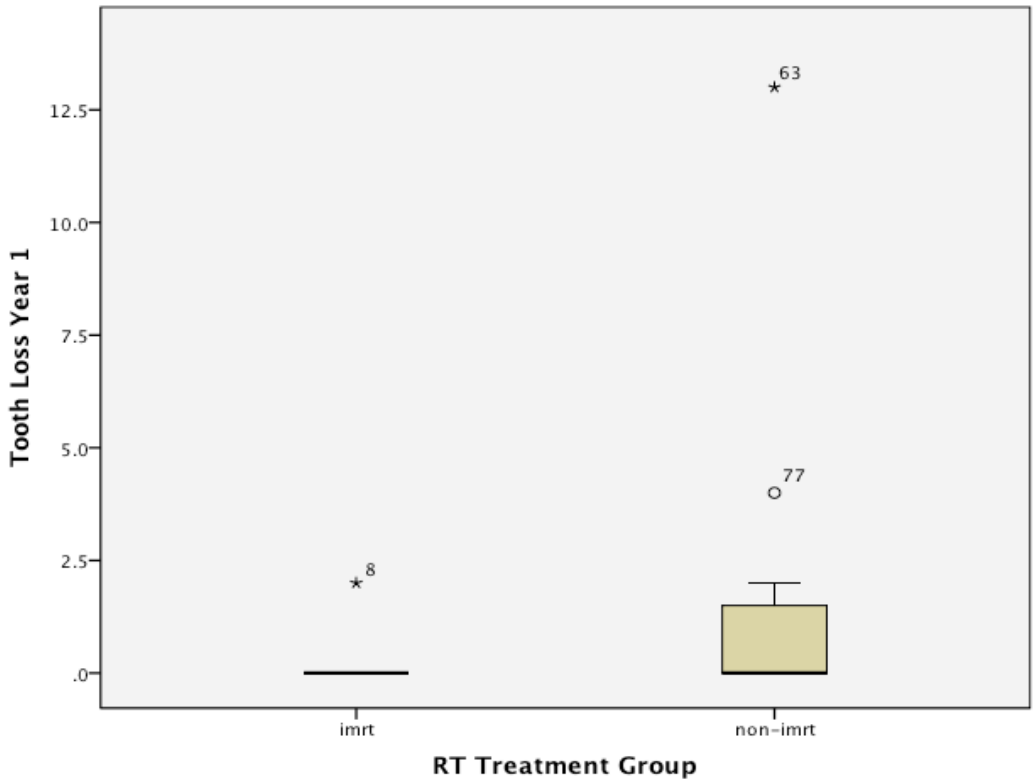

Figure 7: Box plots depicting tooth loss at year one for each RT treatment group. The bold black line within the box represents the median of the distribution. The outliers are illustrated by the asterisks and the extreme values are represented by open circles.

At year two, the median of the distribution illustrated by the bold black line was zero for both groups, with more variability of the data in the non-IMRT group than in the IMRT group. In the non-IMRT group, the distribution of the data fell within the upper quartile range as shown in the box. There are no whiskers extending from the IMRT box and one line (whisker) coming from the upper end of the non-IMRT box. There was no distribution of the data below the

median value. There were outliers in both groups as illustrated by the asterisks and open circles. As illustrated in Figures 7 and 8, there was more data distribution, or variability in the data, toward the upper quartile in the non-IMRT group than in the IMRT group the second year after RT compared to the first year.

Tooth Loss Comparison Between Group up to Two Years After RT Using Repeated Measures

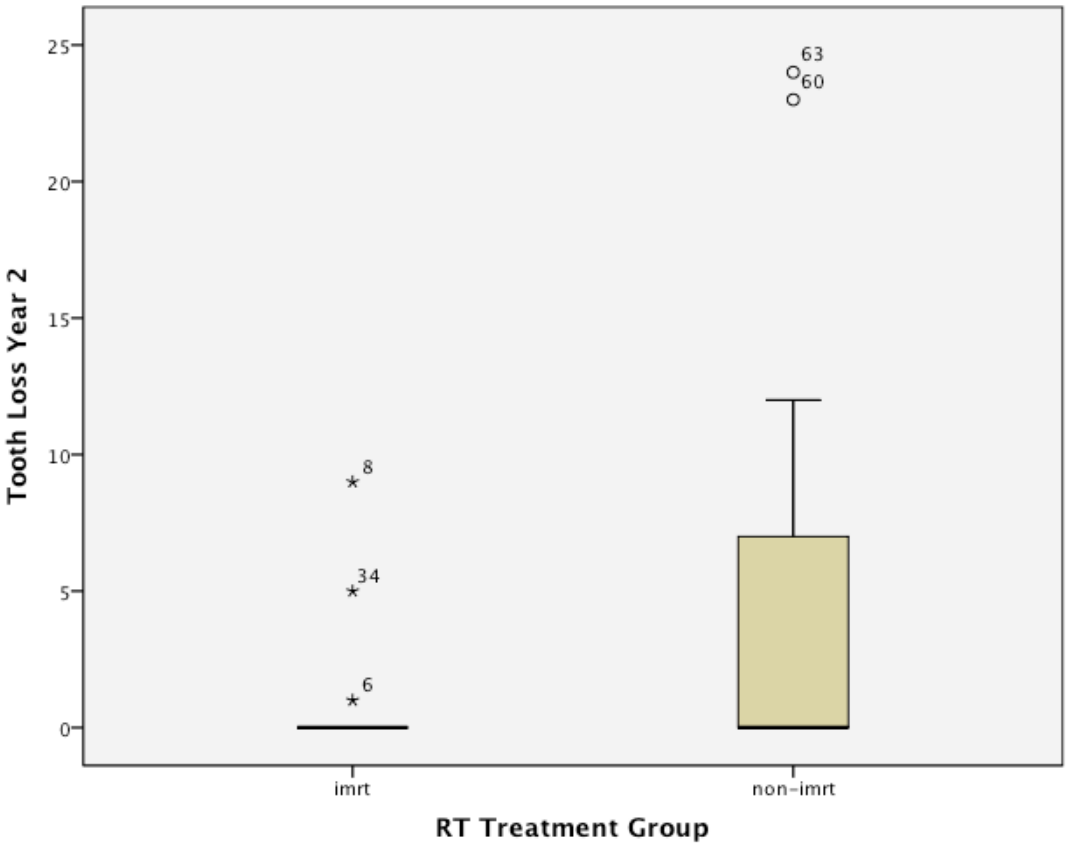

Figure 8: Box plots depicting tooth loss at year two between RT treatment groups. The bold black line within the box represents the median, the gray box represents the interquartile range, and the whiskers extend to extreme values. The outliers are illustrated by the asterisks

and the extreme values are represented by open circles. The numbers represent subject data points.

Tooth Loss After RT

This section pertains to research question 2: Will there be an increased incidence in tooth loss in patients treated with IMRT compared to patients treated with nonintensity modulated radiotherapy?

The difference between the baseline number of teeth between the two groups (IMRT = 20.57, non-IMRT = 21.40) was not significant (t(84) = -.560, p = 0.786). Furthermore, there were no significant differences between groups in the number of teeth lost at year one (mean: IMRT = 0.14, non-IMRT = 1.82; SD: IMRT 0.535, non-IMRT = 3.92) and at year two (mean: IMRT = 1.07, non-IMRT = 5.55; SD: IMRT 2.65, non-IMRT = 9.56) after radiotherapy. After adjusting for the baseline number of teeth, there were no significant between group differences ($F_{(1,22)}$ = 3.20, p = 0.079; 0.127 eta) on the observed power 0.402.

Incidence of tooth loss—including contiguous subject data (used in RM-ANCOVA). In the subjects used in the RM-ANCOVA, the incidence of subjects losing teeth and tooth loss rates were reported in the two groups up to two years after RT. From the 86 subjects with available data at baseline, only 25 subjects (14 IMRT, 11 non-IMRT) had contiguous data points two years after RT. Out of the 25 subjects in both groups, 5 (20%) subjects lost 1 or more teeth one year after RT from baseline. The same 5 subjects, plus another 2 subjects (n=7, or 28%) lost teeth two years after RT. In the IMRT group, 1 subject lost teeth the first and second year after RT (Figure 9). In addition to this subject, 2 other subjects (n=3, or 21%) lost teeth beyond the first

year after RT. Of the 3 subjects who lost teeth, 1 subject lost 1 tooth and the other 2 subjects lost 2 or more teeth. In the non-IMRT group, 4 subjects lost teeth during the first year and second year after RT. Of the 4 subjects who lost teeth, all 4 subjects lost 2 or more teeth.

The incidence of tooth loss in the dentate IMRT subjects was 2 teeth lost (mean tooth loss per subject: 0.14) for year one and 15 teeth lost (mean tooth loss per subject: 1.07) for year two. The mean annual tooth loss rate (mean tooth loss per subject, per year) for the IMRT group was 0.54 up to two years after RT. For the non-IMRT group, the incidence of tooth loss in the dentate subjects was 15 teeth lost (mean tooth loss per subject: 1.82) for the first year after RT and 61 teeth lost (mean tooth loss per subject: 5.55) for the second year after RT. The mean annual tooth loss rate (mean tooth loss per subject, per year) for the non-IMRT group was 2.77 up to two years after RT.

As a result of tooth loss, 3 (12%) of the 25 subjects became completely edentulous due to total tooth loss within the two year follow up period after the initiation of RT (Figure 10). Of the 3 subjects who became edentulous, 1 (7%) subject was from the IMRT group and 2 (18%) subjects were from the non-IMRT group. In terms of proportion of teeth lost, the non-IMRT group lost over five times as many teeth compared to the IMRT group the second year after RT. In addition, the IMRT group lost three times as many teeth the second year after RT compared to the first year and the non-IMRT groups lost over seven times as many teeth in the second year compared to the first year (Tables 10 and 11).

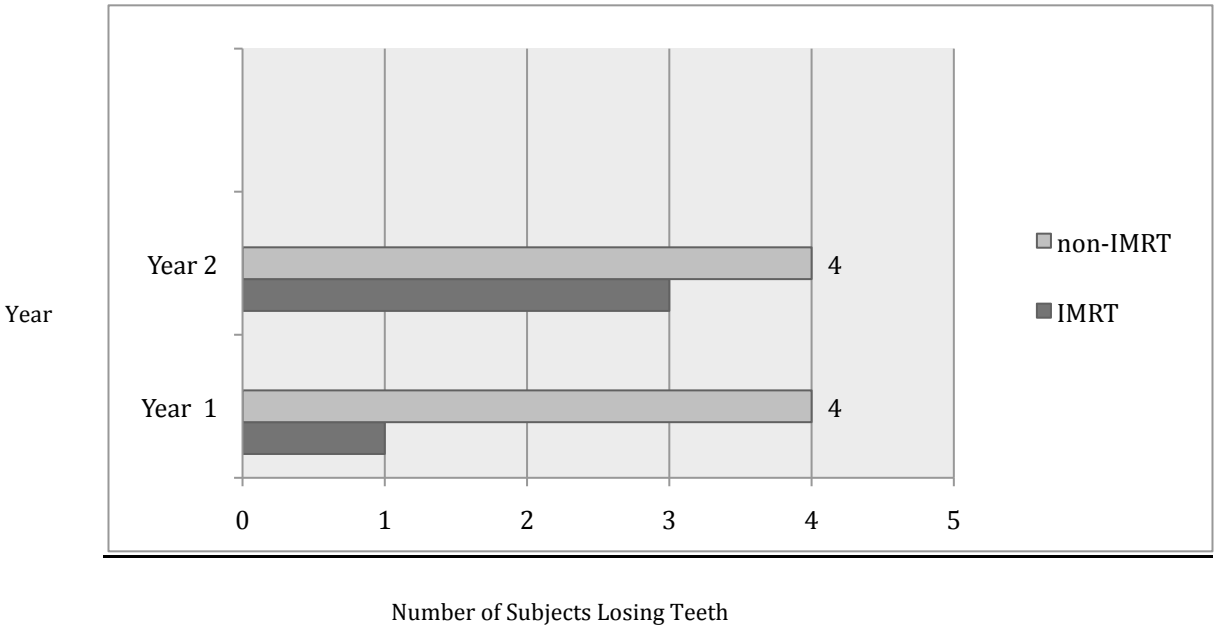

Figure 9. Number of Subjects Losing Teeth up to Two Years after Radiotherapy, compared between Treatment Groups .

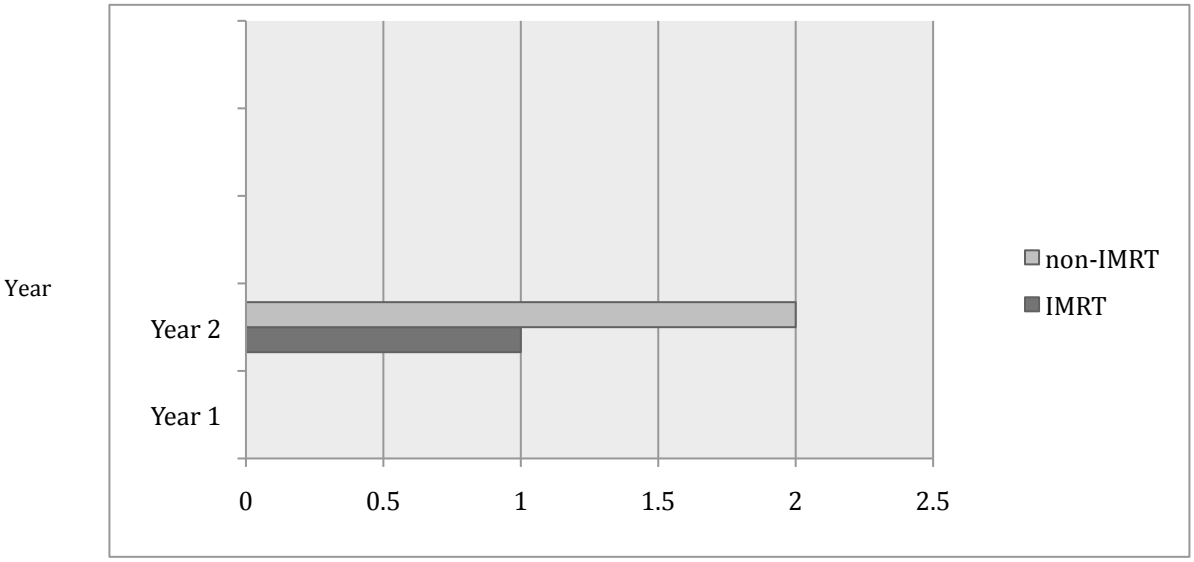

Figure 10. Incidence of subjects becoming Edentulous up to Two Years after Radiotherapy, compared between Treatment Groups

Chapter 5: Discussion

Discussion

The present retrospective study investigated the effects of radiotherapy on tooth loss over time in adult head and neck cancer patients. Research questions were posed regarding differences in dental health and tooth loss between subjects treated with advanced and conventional RT. The primary goal of this study was to understand the status of dentition after advanced and conventional radiotherapy for head and neck cancer.

For this exploratory study, tooth loss was chosen as the objective outcome measure since it could be determined from clinical photographs available in data collected from functional assessments. Assessments of changes to the dentition such as colour changes (black or brown areas of demineralization), tooth fractures, tooth decay, and bone loss were not chosen as outcome measures due to limited available data and the subjective nature of measuring dental changes from clinical photographs. In the present study, the hypothesis of interest involved tooth loss compared among oral cavity (O), oropharyngeal (OP), and nasopharyngeal (NP) cancer patients treated with intensity modulated radiotherapy +/- chemotherapy, +/- surgery and nonintensity modulated radiotherapy +/- chemotherapy, +/- surgery. Results indicated that there were no statistically significant differences in tooth loss between advanced and conventional RT treatment groups. Both RT treatment groups consistently lost teeth over time, with the conventional RT group losing more teeth than the IMRT group, however, the mean difference was not significant. Both treatment groups used in the RM-ANCOVA were comparable regarding the number of subjects losing teeth as well as number of subjects who became edentulous as a result of tooth loss up to two years after RT (Figures 9 and 10). Although the mean difference in tooth loss between the non-IMRT and IMRT

groups was not significant, the non-IMRT mean tooth loss values were higher compared to the IMRT group. In the present study, both treatment groups yielded higher mean tooth loss values (number of teeth lost per subject) as well as annual tooth loss values (number of teeth lost per subject, per year) the second year after RT compared to the first year as described in Tables 10 and 11.

In the present study, the second year after RT revealed higher mean tooth loss values compared to other studies concerning the general North American population (Table 1).[92-94] The data from the second year after RT (especially in the nonIMRT group) were more comparable with the tooth loss values reported by Bruins[103] as well as studies relating to subjects without periodontal therapy (Table 2).[88,96-101] Although the results from the present study were comparable to the study by Bruins, it is difficult to generalize the results as it is unknown if the Netherland population received funded dental care similar to the iRSM subjects, which could potentially bias the outcome being measured due to the difference in the access to dental care. In the present study, it is likely that tooth loss was influenced by factors related to radiotherapy due to the higher tooth loss values the second year after RT when compared to the general North American population.

In the present study, there were no significant differences using the outcome tooth loss before and after RT between groups using RM-ANCOVA. The observed power as well as the effect size for the interaction between RT group and time was very low. Since the RM-ANCOVA only includes contiguous data points at each time interval and excludes subjects with missing data points it is difficult to achieve significance in the results or obtain a moderate effect from the treatment due to the small samples. Due to the loss of data and short follow up period after

the initiation of RT, the results from the study only reveal trends of tooth loss within a short period of time after treatment.

Limitations of the Present Study

Several limitations encountered in the present study are discussed in this section. These include limitations such as the use of archival data, interpreting clinical photographs, small samples, loss of power, threats to internal and external validity, and generalizability.

The study design relied on archival data; this was a disadvantage as records may have been incomplete or missing. The researcher had no control over the reliability with which data were recorded in the subject's charts. For the majority of the subjects' charts, a limitation of using archival data was the absence of detailed dental records that provided the subject's dental examination and diagnosis (i.e., radiation caries) and the rationale for why interventions such as tooth extractions or dental restorations were performed.

For the present study, it was not feasible to have a radiation oncologist retrospectively interpret each subject's planning and RT treatment records to determine the teeth and glands involved in the RT treatment volumes. This information would be extremely important for future research to analyze dental health outcomes (i.e., tooth loss patterns) in relation to specific radiation-related factors. Information regarding organ sparing techniques were infrequently reported in the RT treatment summaries and therefore could not be included as a covariate in the final analysis. Similarly, chemotherapy and pilocarpine records were underreported in patient charts with respect to treatment regimens such as drug name, dosage, and length of drug treatment.

There were challenges with the quality and consistency of the clinical photographs that were used to determine the outcome measure. For example, some of the posterior teeth were not captured in the clinical photographs and could not be included in the final analysis. Another limitation of using clinical photographs is the possibility that a restored tooth such as an implant or bridge could have been counted as an existing tooth. In order to reduce this error, the sole researcher, a dental hygienist, used supplemental information to cross-reference the clinical photographs if the data were available.

Other limitations were threats to internal and external validity. Threats to internal validity such as history (events outside the study), maturation (subjects change over the study), mortality, and interaction of factors may have confounded the outcome measure since it was difficult to account for a variety of factors that could have had a significant effect on the validity of the data collected. In other words, the archival data may not have provided the researcher with valuable information that might have accounted for the treatment effect. For example, teeth may have been lost for many reasons unrelated to RT treatment, such as age, trauma, oral or system diseases, barriers to care (geographic, financial, logistical), or a combination of these factors.

Some features that limited the external validity or the ability to generalize the results of this study also should be noted. Threats to external validity such as subject selection, and multiple-treatment interference may have limited the extent to which the results can be generalized to other people, settings, measurements, and treatment.[111] In this study, external validity was threatened by subject selection. Subjects participated in a HNC treatment follow up program at iRSM and only the subjects who had problems related to oral function or their teeth

returned beyond the first year after treatment. The other concern is that iRSM is a government-funded program where patients are provided with oral and dental rehabilitation that is provincially funded. The results of this study can be generalized only to patients in similar treatment facilities and settings. Results of a multiple-treatment (or multimodality) study can be generalized only to people who would receive the same sequence and number of treatments. In this study, multiple-treatment interaction was a potential confounding factor since there were only two groups being compared and within those groups each of the subjects would have had individual treatment planning and interventions to treat their specific stage, location, and type of disease. The findings from this study can be generalized only to populations that are similar to the population in this study. Furthermore, the sample was predominately Albertan, Caucasian, adult male, and 42 (49%) had a salivary gland transfer, an intervention not performed routinely around the world. As regional differences may mitigate the findings from this study, the results could not be generalized to head and neck cancer patients in other functional programs or settings.

Other limitations of using archival data in this study included bias. Subjects from the HNSFAL who were included in the study would have been seen for follow-up up to one year after surgery, a form of selection bias that is inherent in all follow-up studies. Since the study analyzed subjects who attended follow-up appointments, a potential bias exists in the patient population. For example, subjects with excellent outcomes may have decided not to return for follow-up appointments, which could bias the outcome being analyzed. Conversely, subjects with poorer outcomes (e.g., speech, mastication) were potentially more likely to drop out of a longitudinal study or return for follow-up appointments which could have resulted in the large

attrition rate in the study.[37] Subjects not returning for follow up appointments resulted in small samples and loss of postintervention data; these factors potentially bias and limit the conclusions that may be drawn from the data. Due to the paucity of the data after the first year time point as well as the small population samples from one treatment institute, the largest threat to external validity was the small sample size available for the study; this decreased the statistical power of the results. Out of the three subsets of HNC, nasopharyngeal cancer had the smallest inclusion of subjects (n=7) in the study compared to oropharyngeal having the largest number of subjects in both groups (65 of the total 86 subjects).

In the present study, the largest reasons for the loss of pre- or postintervention data can be attributed to 1) HNC recurrence, 2) second treatment intervention, and 3) subjects reported as palliative or deceased. Other less common reasons for patient attrition after one year were comments in the subject's chart related to geographical, financial, logistical, or other barriers to care.

Limitations regarding follow up time occurred because subjects had variable one year post surgery functional outcome appointments (approximately 11 months post-RT). For example, if the delivery of RT after surgery was delayed and delivered a few months after surgery the subjects would have a shorter interval from the date of the functional assessment appointment to the initiation of RT. Subjects were included if RT had been delivered greater than 6 months from the initiation of radiotherapy.

Conclusion

Although there were some interesting trends in the data such as increased tooth loss the second year after RT and higher tooth loss values in the non-IMRT group compared to the

IMRT group, it is difficult to make conclusions or compare results with other studies with larger samples with long-term data over 3 - 5 years as was summarized in Tables 1 and 2. In the present study, mean rates for tooth loss were higher the first and second year after RT compared to the baseline data, the preliminary results of this study have significant practical implications in the clinical setting as well as theoretical implications concerning the status of dental health years after RT. Tooth loss is a complex outcome with multiple disparate factors contributing to the partial or complete loss of dentition. Preventive dental care before, during and after RT is strongly encouraged to promote better oral-dental outcomes for the HNC survivor. To fully understand the status of the dentition years after RT, and to aid in proper preventive dental treatment planning and collaborative care, continued research is needed to build upon the present study.

Chapter 6: Future Direction

Future Direction

The search for knowledge about the status of dental health years after radiotherapy in head and neck cancer patients has many relevant clinical implications. With people keeping their teeth longer, and an increase in younger subjects being diagnosed with HNC, there is potential for more teeth to be at risk of radiation-related changes years after HNC RT. Significant advances in dental outcomes in the general population have been made as a result of previous research opportunities. There has been a significant improvement in dental health and tooth retention in the general North American population as a result of the incorporation of fluoride programs and better access to dental care over the past decades.[90] In order to maximize these advances and benefits of dental outcomes research and to apply these findings to HNC patients, ongoing commitment to the advancement of new knowledge and its translation is needed. Collaboration with other countries increases the potential to advance research and improve oral health outcomes for Canadians and around the world. A better understanding of dental status after HNC radiotherapy is still needed if the condition is to be minimized. Research of head and neck cancer patients is challenged by small patient numbers at any one centre. Through international collaboration, an analysis of a larger data set could provide valuable insights that could not be obtained any other way. Several unexplored questions about this topic could be answered by using a larger patient sample. For future study, potential research questions could include:

1) Is there a difference between the level of dental breakdown (or tooth loss) between patients treated with primary RT or treated with surgery and RT (+/- chemotherapy)?

2) Is there a relationship between the RT treatment volumes and the level of dental changes to teeth exposed in the RT field?
3) Is there a difference in the number of teeth in patients treated with organ sparing RT compared to patients with no sparing techniques?
4) What percentage of teeth are present less than 3 years after RT and greater than 5 years after RT compared to pre-RT (baseline data) and compared between RT groups?

For this reason, a prospective multination, multisite project is recommended to study the long-term effects on the dentition resulting from radiotherapy. Appendix D is an initial draft proposal for such a collaborative multisite project.

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A: Validated Quality of Life Questionnaires

Validated Quality of Life Questionnaires
1) University of Washington Quality of Life Scale[81] 2) European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC-HN35)[47] 3) Functional Assessment of Cancer Therapy Head and Neck Module (FACT-HN)[124] 4) Performance Status Scale for Head and Neck Cancer Patients[125]

Appendix B: Example demographic collection sheet

Subject	RT treatment	Treatment Modality	included/excluded
1	1	a	
2	1	a	y
3	1	b	a
4	1	b	c
5	1	c	a
6	1	c	a
7	2	c	d
8	2	c	y
9	2	c	y
10	2	c	y
11	2	c	c
12	2	c	a
13	2	c	y
	Legend	Legend	Legend
	1 - IMRT	a - + surgery	y - yes
	2 - nonIMRT	b - + chemotherapy	a - missing pre
		c - + surgery + chemotherapy	b - missing post
			c - no RT
			d - secondary Ca

Appendix B continued: Example demographic collection sheet

	Gender	DOB (mm/dd/yy)	Age (years)	N Stage
oral	1	07/30/60	50	1
op	2	02/09/53	57	1
op	1	02/24/46	64	2
op	1	06/23/57	53	2
op	1	01/20/55	55	1
op	1	03/31/42	68	1
op	2	04/01/42	49	1
op	1	04/02/42	64	1
oral	1	12/08/54	56	1
oral	2	03/25/56	56	1
oral	1	04/27/41	69	1
op	1	04/28/41	55	1
Legend	Legend	Legend	Legend	Legend
oral - oral cavity	1 - Male	NA	NA	1 - N1
op - oropharyngeal	2 - Female			2 - N2
np - nasopharyngeal				3 - N3
				4 - N4

Appendix B continued: Example demographic collection sheet

T Stage	Surgery date	RT start date	RT end date	total dose cGy	fraction
1	1/9/09	04-Apr-07	5-Jun-07	6000	30
2	12/13/06	09-Feb-07	26-Mar-07	6000	30
1	12/9/07	12-Feb-08	26-Mar-08	6000	30
2	7/7/07	08-Nov-07	21-Dec-07	6000	30
1	7/7/08	18-Sep-08	30-Oct-08	6000	30
2	12/4/08	11-Feb-09	26-Mar-09	6200	30
1	10/8/09	22-Dec-09	21-Jan-10	3600	20
1	8/8/08	26-Oct-09	4-Dec-09	6000	28
2	10/19/08	15-Sep-03	23-Oct-03	5919	30
2	7/8/08	08-Oct-08	21-Nov-08	6000	30
2	10/16/08	04-Oct-08	21-Jan-09	5600	28
1	7/16/08	31-Aug-09	9-Oct-09	5600	28
Legend	Legend	Legend	Legend	Legend	Legend
1 - T1	NA	NA	NA	NA	NA
2 - T2					
3 - T3					
4 - T4					

Appendix B continued: Example demographic collection sheet

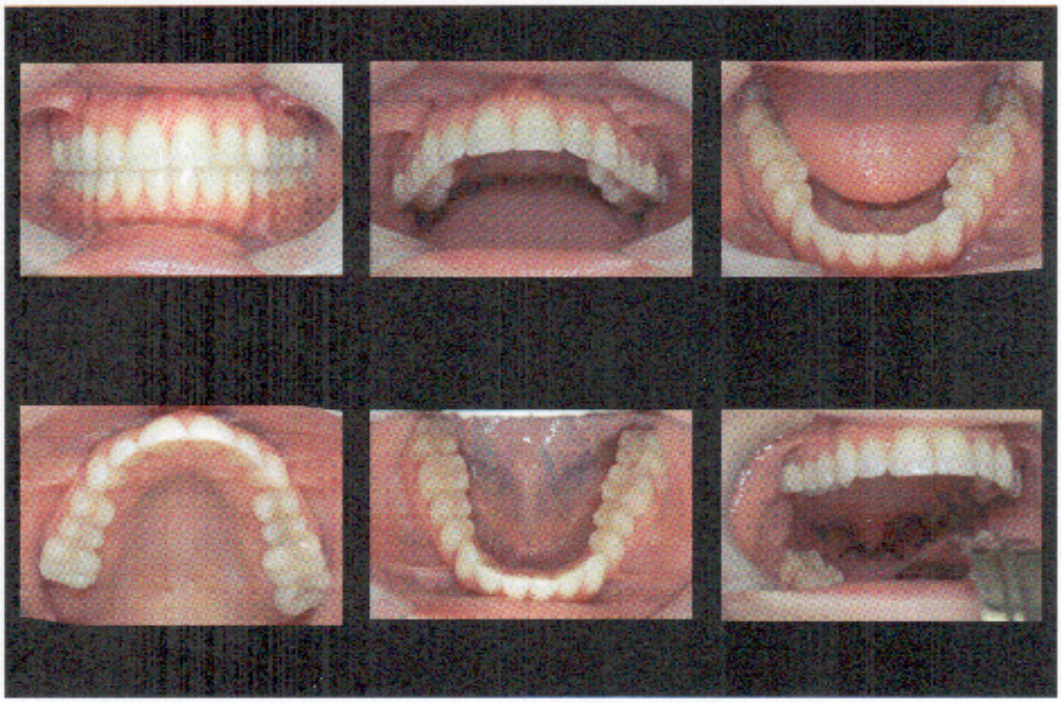
smoking status	Diabetes Hx	method collection	baseline date	pre # teeth	date yr 1
2	4	fx	29-Mar-07	13	11-Oct-07
2	4	fx	20-Aug-08	25	
2	2	fx	22-Jan-08	20	
2	4	fx, correspond	21-Nov-07	11	14-Oct-08
2	4	fx	12-Aug-08	27	07-Jul-09
2	4	fx	13-Jan-09	8	28-Jan-10
2	4	fx	24-Nov-09	24	19-Oct-10
2	4	fx	15-Sep-09	9	26-Jul-10
2	4	fx, pan	09/16/03	15	27-Jul-04
2	4	fx	17-Sep-08	16	01-Sep-09
2	2	fx	25-Nov-08	23	15-Oct-09
		fx	18-Aug-09	26	29-Jun-10
Legend	Legend	Legend	Legend	Legend	Legend
1 - never	1 - Type I	Fx - image fx	NA	NA	NA
2 - past	2 - Type II	correspondence			
3 - current	3 - Not diabetic				

Appendix B continued: Example demographic collection sheet

# teeth yr 1	Difference yr 1	# teeth yr 2	date yr 2	difference yr 2	SGT/Salagen
8	5				
		22	20-Aug-08	3	1
20	0	20	26-Feb-09	0	1
11	0	/			2
26	1				1
8	0	7	04-Oct-10	1	2
24	0				1
7	2	0	27-Jan-11	7	1
15	0	15	07-Sep-05	0	2
16	0				1
	0	22	20-Sep-10	1	1
26	0				2
Legend	Legend	Legend	Legend	Legend	Legend
whole #	baseline - yr 1				1 - SGT
					2 - Salagen

Appendix C: Work instruction for intraoral clinical photographs

9.4. INTRA ORAL



Appendix D: Introduction and outline of a prospective multisite assessment

The search for knowledge about the status of dental health years after radiotherapy in head and neck cancer patients has many relevant clinical implications. With more people keeping their teeth longer, and an increase in younger subjects being diagnosed with HNC, there is potential for more teeth to be at risk of radiation-related changes years after HNC RT. Research in this area is a natural extension of the desire to understand and improve oral-dental outcomes in this unique patient population. Significant advances in dental outcomes have been made as a result of previous research opportunities. For example, there has been a significant improvement in dental health and tooth retention in the general North American population as a result of the incorporation of fluoride programs and better access to dental care over the past decades.[90] In order to maximize these advances and benefits of dental outcomes research, ongoing commitment to the advancement of new knowledge and its translation is needed. Collaboration with other countries and institutions increases the potential to advance research and improve oral health outcomes in Canadians and globally. A better understanding of the relationship between dental status such as tooth loss and edentulism after HNC radiotherapy is still needed if the condition is to be minimized. Several unexplored questions about this topic could be answered by using a larger sample. Research of head and neck cancer patients is challenged by the small patient numbers at any one centre and analysis of a larger data set can provide valuable insights that could not be obtained any other way. For this reason, recommendations for a prospective multination, multisite project to study the long-term dental effects from radiotherapy are discussed.

Study design. Due to the limitations of relying on archival data with a one year follow up, a prospective longitudinal study is recommended. This design involves repeated observations of the same variable(s) and subjects over long periods of time. The advantages of an observational study (i.e., cohort study) include studying the same subjects over time which makes the observation of the changes more accurate compared to other studies that analyze different subjects. The primary goal of observational analytic studies is to test the hypotheses about the relationship between exposure (i.e., radiotherapy) and dental health (tooth retention). The advantage of the prospective design is the ability to control and monitor data collection and measure variables completely and accurately; such control cannot be guaranteed when using archival data.[111] Since tooth loss is reported to occur years after RT, a prospective longitudinal design is necessary to understand dental changes years after RT treatment. Disadvantages of the prospective approach are that it is expensive and time consuming compared to the retrospective design. In addition, because of the longitudinal nature of prospective cohort studies, this design is especially prone to attrition from the subjects lost to follow up. One method to address the issue of subject attrition is to include multiple research sites that provide access to large data sets, increasing sample size and thus make up for subjects lost to follow up.

Sample size and power. There are many advantages to multisite research that cannot be achieved using one institution. One of the largest limitations of the present study was the loss of data beyond the first year after radiotherapy. Small samples due to attrition is one of the challenges when researching head and neck cancer patients at one institution. To increase the sample size in the prospective study, other international centres would be included to allow

access to large numbers of subjects. Sample size has a substantial influence on the power of a test; the larger the sample size, the greater the statistical power.[111] In addition, larger samples are better representations of population characteristics, thereby making true differences between groups more likely to be recognized.[111]

Power analysis and sample size calculations as well as previous communications and research were used when deciding how many centres would be included in the future study. Power analysis was used to estimate the sample size required to achieve the desired level of statistical power before data were collected and to estimate the appropriate sample size. If the proposed study used a MANOVA design with approximately 3 variables (for example, control group or non RT group, primary radiotherapy, combined modality HNC therapy which included RT) the sample size requirement for a three-group MANOVA design with an alpha at 0.05, beta = 0.20 and moderate effect size = 0.75 would require 52 subjects for each group.[113]

For the prospective study, five international centres were chosen as a manageable number of centres to access a large group of head and neck cancer subjects. A large group of subjects and data sets will increase the samples of smaller subsets of HNC, such as nasopharyngeal cancer that is prevalent in other parts of the world compared to Canada. While some international centres similar to iRSM might enrol approximately 200 subjects per year, other larger centres located in the United States, Europe, China, and India have the potential to enrol larger populations. Since the five year survival rate for head and neck cancer patients is around 50%, multisite participation in a longitudinal follow up study will increase samples beyond the first few years after treatment; this could not be achieved using one centre. The disadvantage of adding nondeveloped or low income centres that have large populations is the

potential for subjects to have poorer dental status or higher periodontal disease risk that can bias the outcome measure being analyzed.

Outcome measure and measurement tool. From the literature, it was evident that there is limited research in the area of objective oral-dental outcomes after HNC radiotherapy. The proposed initiative is expected to identify and improve outcome measures as well as improve patient oral health and quality of life in individuals treated with HNC RT. The creation of standardized endpoints that are realistic, effective outcome measures has the potential to improve compliance of participants and researchers involved in the study and to compare endpoints that are especially important in the context of meta-analyses.[115]

A variety of dental outcomes have been used to assess the status of dental health,[65,91,93,102] but the indices may not always be a valid, reliable, and feasible health outcome measures.[115,116] The future study proposes to collaborate with international research partners to identify and define clinical outcome measures for dental health after radiotherapy; outcome measures will be based on the OMERACT (outcome measures in rheumatoid arthritis clinical trials) process.[115,117,118]

OMERACT is an international network aimed at improving outcome measurement in rheumatology. The OMERACT approach strives to develop and improve endpoint outcome domains and endorses valid, responsive, feasible health outcome measures.[115] A measure is applicable or endorsed when it passes the OMERACT Filter in its intended setting. The OMERACT Filter has three criteria: truth, discrimination, and feasibility;[115] applications of these criteria are described below.

1. Truth: Is the measure truthful? Does it measure what it intends to measure? Is the result unbiased and relevant? Truth captures issues of internal validity such as face, content, construct, and criterion validity.
2. Discrimination: Does the measure discriminate between situations of interest? The situations can be states measured at one time (for classification or prognosis) or states measured at different times (to measure change).Discrimination captures issues of reliability and sensitivity to change.
3. Feasibility: Can the measure be applied easily, given the constraints of time, money, and interpretability? This criterion may be decisive in determining a measure's success.

The OMERACT process has had wide international impact on clinical outcomes in rheumatology research and works under the auspices of the World Health Organization (WHO).[115,116] The OMERACT system is now linked to the Cochrane Collaboration Musculoskeletal Review Group, where the outcomes endorsed by OMERACT are recommended for use in Cochrane Systematic Reviews.[115]

For the future study, international researchers would collaborate to apply a rigorous and accepted methodology based on the OMERACT process. The endpoint of this collaboration would be to develop consensus on clinical outcome measures that can be applied to broad populations to measure dental health after HNC RT. Standardized endpoints in prospective studies are extremely important to facilitate comparisons of outcomes across studies and provide the best evidence of therapeutic interventions across different patient populations.[115,116]

Threats to validity. When using a longitudinal study, data collection of factors or confounding variables is useful to reduce threats to internal validity such as history and maturation. To increase the validity of the collected data, a standardized data collection sheet would be developed for use at all centres involved in the study. All centres will collect and submit in the same manner demographic information such as medical history, dental history, head and neck cancer treatment, nutritional information, economic information, and dental outcome measures. Since each of the centres enrolled in the study will have preexisting functional outcomes and/or dental programs, the majority of the data collection requirements will be a part of the centre's current program.

In the present study subject selection was biased, as data were obtained from subjects returning past the one year interval due to problems related to function or their teeth. To reduce the threats to external validity, subjects who are presently in a follow up program such as iRSM will be recalled to participate in a two year follow up study; this will capture data beyond the first year after treatment. In addition, the present and prospective subjects will be recruited to participate in a two year follow study. The advantage of enrolling subjects in a follow up study is that the same subjects will be seen annually to collect outcome data that will span beyond the first year after RT. Thus, subject selection bias will be reduced since dental outcome data will be collected beyond the first year after treatment of the recalled and recruited subjects.

Since the present study had limited data past the first year after RT, it was difficult to determine trends in the data or make generalizations about changes to the dentition years after RT. Since teeth are known to breakdown years after RT, long-term research data are

needed on HNC subjects to determine the factors that influence this breakdown. In order to capture data beyond the first year after RT, subjects can be recalled into a prospective longitudinal cohort study. Since some centres (such as those who belong to the Head and Neck Research Network) would already be collecting functional outcome data up to one year after HNC treatment, the groups (cohorts) described in Table 10 can be used to capture long term data.

Cohort Description of group
• Cohort 1 – recruit present and prospective subjects to participate in a two year follow up program (data approximately 1 - 3 years after RT) • Cohort 2 – recall subjects beyond the second year but less than four years after RT to participate in a two year follow up program (data approximately 3 - 5 years after RT) • Cohort 3 – recall subjects beyond the fourth year after RT to participate in a two year follow up program (data approximately 5 years after RT)

Table 12: Recalled and Recruited Subjects in a Prospective Longitudinal Cohort Study

To improve the generalizability of the study, data will be collected using the standardized data sheet for two years from the commencement of the study using the following assessment protocol:

1) Preintervention dental examination to collect dental outcome data

2) Preintervention panoramic image - adhering to the ALARA principle (As Low As Reasonable Achievable) for x-ray exposure.
3) Preintervention clinical photographs
4) Postintervention panoramic image
5) Annual recall to collect subject demographic and dental outcome data

Potential research questions include:

- Is there a relationship between the level of dental breakdown and the number of years after RT?
- Is there a difference in tooth loss between primary RT versus surgery and RT (+/- chemotherapy)?
- Is there a relationship between the RT treatment volumes and the level of dental changes to teeth exposed in the RT field?
- Is there a difference in the number of teeth in patients treated with organ sparing RT compared to patients with no sparing techniques?
- What percentage of teeth are present less than 3 years after RT and greater than 5 years after RT compared to pre-RT (baseline data) and compared between RT groups?

When performing collaborative studies, the study must be conducted in an identical way at each centre to ensure that the results will be valid. To ensure the validity of multi-centre research, any change in the protocol should be made at every collaborating institution. Study

protocol modifications made at one institution but not all will defeat the purpose of multi-centre research.

International collaborations. Effective oral health research requires the collective efforts of individuals and organizations with complementary research interests and commitment to improving outcomes. The Canadian Institutes of Health Research (CIHR)[119] encourage Canadian researchers to engage in international research collaborations and recognize the benefits of these collaborative partnerships. The benefits of collaborative partnerships may be applied to oral health research to provide:

- Access to unique patient populations or resources;
- Knowledge transfer and learning opportunities from foreign researcher expertise;
- Contributions to global oral health research and knowledge, and application of the resulting information in policy and practice;
- Solutions to global health system challenges;
- Creation of new knowledge and its translation into improved oral health outcomes;
- Improved health services or oral health care systems;
- Interdisciplinary collaborative care; and
- Larger sample sizes.

International data pooling. The future study would not be registered as a clinical trial since there is no implementation of an intervention as part of the prospective observational study. The study would not be considered an organized registry since it is a separate research study that would involve data collection of five international centers over a designated period of time. The future study could be considered a consortium, or group, since it would involve the

participation of five international centres to assess and measure dental status after HNC radiotherapy. Each centre would collect subject and clinical outcome data in accordance with the research protocol with the intention of amalgamating the data later to be analyzed at the principle research site. Each site would be responsible for handling, collecting, and submitting the collected data electronically to the primary researcher every six months until completion of the two-year study. The prospective multination collaboration would include developed and developing countries to encompass global oral outcome research. The international collaboration will include institutions that manage head and neck cancer using primary and/or combined modality radiotherapy. With the advances in technology and the desire to improve outcomes after treatment, the use of advanced radiation systems has gained popularity over the years. Leading research institutions in developed countries such as Canada and the United States may primarily use IMRT, making comparisons between conventional and advanced RT difficult due to the limited research sites using conventional RT. To address the relationship to dental health of conventional radiotherapy exposure, underdeveloped countries such as India and Asia—where conventional RT is expected to be more prevalent than advanced RT—will be included in the international collaborations. Another advantage of including the aforementioned countries is the large head and neck cancer population—and thus an increase in subjects afflicted with less common cancers such as NP—compared to centres located in Canada and the United States.

Funding. Support for this international project will be requested by submitting grants from industry and academia to obtain government support. Since the nominated principal applicant is located in Canada, prospective funding would likely include the Canadian Institutes

of Health Research. This agency recognizes the importance of fundamental collaborative research to improve the health of Canadians and to contribute to the global advancement of health.[102] Since the study would originate from iRSM (Covenant Health), the principle applicant would apply to CIHR to request funding to support the research to be carried out in direct collaboration with researchers based in other countries. According to CIHR, nominated principal applicants may transfer funds to project participants based in other countries through a transfer of funds from the primary institution to the secondary institution. For more information on transferring funds internationally consult Schedule 9: Transfer of Funds From a Primary Institution to a Secondary Institution of the Tri-Agency (TCPS),[120] or the Memorandum of Understanding (MOU) on the Roles and Responsibilities in the Management of Federal Grants and Awards.[120]

For the future study, the primary funding would cover the costs for a research coordinator and resources deemed necessary to conduct the study at each centre. Each research coordinator would be trained on the research protocol and will work with the studies' research investigator at iRSM and the participating centres researcher to set up and recruit the subjects for the study. The majority of the research protocol and data collection procedures that is proposed for the future study would potentially already be established and conducted at the research centres. For example, countries that are already participating in the Head and Neck Research Network would already be seeing patients before and after RT treatment and may be performing clinical photographs at each appointment.

Safeguarding confidentiality. The Health Information Act (HIA)[121] regulations establish rules about the collection, use, and disclosure of health information, and aim to make the process transparent to those involved in the health sector. The HIA Guidelines and Practices Manual provide guidelines to protect the privacy of individuals and the confidentiality of health information. HIA rules are designed to ensure that health information is shared appropriately and that health records are managed and protected properly. The HIA provides custodians (i.e., health care professionals) with a framework within which they must conduct the collection, use, and disclosure of health information. The Office of the Information and Privacy Commissioner (OIPC)[122] was created to assist the Commissioner to fulfill his mandate under the Freedom of Information and Protection of Privacy Act , the Health Information Act, and the Personal Information Protection Act.

For the future study, to ensure respect for the security and privacy of subjects and their health information, data will be anonymized at each centre. Anonymized data are protected and unidentifiable when stored and transferred to a second or third party. Each centre will have a standardized coded form that will be known only by the primary researcher at each centre. The identifiers will be kept separate from the data collection and will be protected under a network security appliance (fire wall) that is accessible only to the primary researcher designated at each research facility and the network administrators (if required). Further investigation of additional concerns regarding confidentially will be researched such as the incorporation of encryption software for each centre to protect the data file.

Ethical considerations. Proposals to conduct research involving human subjects must be submitted for review of their scientific merit and ethical acceptability to one or more scientific

review and ethical review committees. The review committees must be independent of the research team, and any direct financial or other material benefit they may derive from the research should not be contingent on the outcome of their review. The investigator must obtain their approval or clearance before undertaking the research. The ethical review committee should conduct further reviews as necessary in the course of the research, including monitoring the progress of the study. Scientific and ethical review of multicentre studies may be facilitated by agreement among centres to accept the conclusions of a single review committee. Members could include a representative of the ethical review committee at each of the centres where the research is being conducted. Alternatively, a centralized review committee could be complemented by local review committees consisting of local participating investigators and institutions. The central committee could review the study from scientific and ethical standpoints, and the local committees could verify the practicability of the study in their communities, including the infrastructures, the state of training, and ethical considerations of local significance.

Ethics approval would be required from an ethics review board (ERB) prior to conducting an international research collaboration involving the collection and transfer of data. Since the principle investigator and researcher of the prospective, multination, multisite study would be at the iRSM (Covenant Health), ERB documentation approving the study would be sent from the iRSM to other institutions with an invitation to participate in the international research collaboration project. Ethics approval would be considered a local obligation at each centre, that is, independent ethics approval would be required at each facility prior to being accepted in the research study.

CIHR Research Ethics Board. The CIHR research ethics board ensures that individual projects involving human participants or identifiable data meet the requirements of the Tri-Council Policy Statement (TCPS): Ethical Conduct of Research Involving Humans 2nd edition, as well as university policy and provincial, federal, and other legislation and regulations.[110] To be eligible to receive research funds from Canada's three federal research agencies, institutions such as the University of Alberta must ensure that research conducted under their auspices adheres to the TCPS.

Considerations of ethical conduct of research involving humans are complex and continually evolving; this section discusses options, procedures, and considerations for the review of ethics (or arrangements) involving collaborative partnerships among researchers from multiple institutions or countries (multijurisdictional research). International collaborations in research may require institutions to adopt policies and procedures by other ERBs (e.g., the TCPS) in addition to relevant policies and applicable laws and regulations that apply to their institutions. Multijurisdictional research should ensure that research involving humans is designed, reviewed, and conducted in a manner that acknowledges the core principles of the TCPS: respect for persons, concern for welfare, and justice.[120] The principle institution may approve alternate review models or implement a mix of models for research involving multiple ERBs and institutions as long as the model is in accordance with the TCPS. Whatever research ethics review model is chosen, roles and responsibilities of all involved in the process should be defined and agreed upon at the commencement of the project. An institution is accountable for research undertaken within its jurisdiction or under its auspices, irrespective of where the research is being conducted.

According to the TCPS, most middle-income countries, and several low-income countries, have laws, policies, or guidelines governing the ethical conduct of research, while in other countries, research ethics infrastructure is evolving or has not been developed. No international ethics review standards have yet been developed. A Canadian ERB must meet the requirements of the TCPS in addition to taking responsibility for the initial and continuing ethics review of research conducted under its auspices. Researchers at each institution in the prospective study shall obtain the required approval of the ethical acceptability of the research before recruiting participants, obtaining access to data, or collecting human biological materials.

Informed consent. The investigator will obtain the voluntary informed consent of prospective subjects of the prospective research study. Participation in the study will be voluntary and subjects may drop out of the study at any time. The risks and benefits of the study will be explained to prospective subjects. The purposes of the study are to obtain generalizable knowledge, and to gain an understanding of the status of dental health after HNC radiotherapy. The potential risks of the proposed study include a minimal risk of radiation exposure from the two panoramic image images taken at baseline (preintervention) and at the end of the two years study. It is this researcher's opinion that the benefits from the information gained from the radiograph outweigh the risks from the minimal radiation exposure, however, participants will be informed about this risk.

Privacy impact assessment (PIA). A PIA is a thorough analysis of potential impacts on privacy and a consideration of actions to mitigate or eliminate any potential impacts on privacy.[123] The privacy impact assessment is a due diligence exercise in which the research

organization identifies and addresses potential privacy risks that may occur in the course of its operations. A PIA is not required for the future prospective research study, as the study will be collecting data for research purposes for a set period of time. The anonymized data will likely be accumulated on hard copy or electronic copy that can be accessed by each centre. The advantages and disadvantages of hard copy and electronic copy have been explored. The advantage of collecting, storing and transferring data electronically is the decrease in the potential for the data to be lost or damaged. Electronic data would also be easier to transfer the data to spreadsheets for statistical analysis. The disadvantage of using electronic data collection systems is the need for the equipment and increased time to open the necessary programs. Completed documents would be submitted to the principle researcher for data analysis every 6 months. Prior to the initiation of this study, consultation with the ERB by relevant bodies will be reviewed in order to meet the HIA's requirements. At this time, the intentions of this study will not be to form a network, registry, or organization that would collect long term subject data. After the completion of the study, if the researcher decides to form a network, registry, or organization, a PIA would need to be completed prior to the study according to the Privacy Impact Assessment document.[123] Alberta's Health Information Act requires that the Information and Privacy Commissioner receive a PIA for review prior to implementing administrative practices or information systems related to the collection, use, or disclosure of individually identifying health information. The researcher may fall under the definition of custodian, or affiliate (a researcher who works with or for a custodian) under the HIA. If the study proposes to implement administrative practices or information systems to collect, use, or disclose health information about identifiable individuals, a PIA must be

submitted to satisfy the requirements of section 64 of the Health Information Act. Examples of situations where a PIA should be considered under section 64 of the HIA include:

- The collection, use, or disclosure of new health information that has not been collected, used, or disclosed previously;
- Implementation of a new service, delivery, or management technology that stores, transmits, or retrieves health information;
- Implementation of a new or different electronic health record system;
- The creation of a new organization that will collect, use, or disclose health information.

Summary of prospective study. Effective oral health research requires the collective efforts of individuals and organizations with complementary research interests and commitment to improving outcomes. There are many advantages for researchers to engage in international collaborative partnerships that could not be obtained any other way. A better understanding of the clinical and social implications of dental health years after radiotherapy is desirable to advance research and improve oral health outcomes in Canadians and globally.

Appendix E: Glossary of Terms

Term	Description of Term
HNC	Head and Neck Cancer
RT	Radiotherapy
Chemoradiation	Chemotherapy in combination with radiotherapy
ORN	Osteoradionecrosis
IMRT	Intensity Modulated Radiotherapy
CBCT	Cone Beam Computed Tomograpy
MR	Magnetic Resonance
PET	Positron Emission Tomography
2D	Two Dimensional
3D	Three Dimensional
CRT	Conformal Radiotherapy
NP	Nasopharynx
O	Oral Cavity
OP	Oropharynx
QOL	Quality of Life
cGy	Centigray
SPT	second primary tumour
HPV	Human Papilloma virus
SCC	Squamous Cell Carcinoma
HBO	Hyperbaric Oxygen
HNSFAL	Head and Neck Surgery Functional Assessment Laboratory
SGT	Salivary Gland Transfer
HT	Helical Tomography
PASW	Predictive Analytical Software
RM-ANCOVA.	Repeated Measures Analysis of Covariance
NCCN	National Comprehensive Cancer Network
TCOS	Tri-Council Policy Statement
CIOMS	Council for International Organizations of Medical Sciences
CIHR	Canadian Institutes of Health Research
MOU	Memorandum of Under- standing
HIA	Health Information Act
RTOG	Radiation Therapy Oncology Therapy Group
AJCC	American Joint Committee on Cancer staging classification
T	Tumour stage
N	Nodal Stage