The Fabrication of an Acrylic Repositioning Stent for Use During Intensity Modulated Radiation Therapy (IMRT) and Head and Neck Cancer: a Feasibility Study

by

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Abstract

Objectives: Radiation therapy is one of the main treatment modalities for malignant head and neck cancers. To minimize the damage to normal tissues during radiation therapy, various methods of stabilization have been utilized, including thermoplastic facemasks and bite blocks. Our goal is to assess the feasibility of a customized oral repositioning stent and its potential benefits.

Methods: Ethics Approval: Approval for this project was obtained through the BC Cancer Agency Research Ethics Board. Participants: 10 consecutive patients scheduled to undergo Intensity Modulated Radiation Therapy (IMRT) for cancers of the maxillary sinus, nasal cavity or oral cavity were recruited and consented to participate in the study. Radiation stent fabrication: Hard baseplate wax was used to create a customized wax pattern of the proposed acrylic stent at chair side and the customized wax pattern was processed in heat-cured clear hard acrylic overnight. Measuring the Stability of the Patient Position: Utilizing data from the daily KeV images, the relative stability of the patient setup was assessed. Monitoring of side effects: Participants completed a questionnaire to evaluate side effects. Assessments were performed at four time points at: baseline; 3 weeks (mid-treatment); last day of radiation (6-weeks); and 3-months post-IMRT.

Results: A new workflow protocol has been developed and implemented at the BCCA. Patient stability data demonstrated mean vertical, longitudinal and lateral variations that were not statistically different when compared to two retrospective cohorts. Descriptive analysis of the questionnaire data seems to indicate a similar trend for self-reported oral symptoms as described in the literature.
**Conclusion:** It is possible to fabricate customized repositioning stents for HN cancer patients without affecting their IMRT treatment timeline. In addition, while utilizing the customized repositioning stent we were also able to maintain patient stability comparable to prior protocols and within a range of clinical guidelines as no patients’ treatments were aborted.

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Preface

The research question and study design were initially identified by Dr. Caroline Nguyen and subsequently modified with contributions from Drs. Vincent Lee, Jonn Wu and Catherine Poh. Initial examination and obtaining consent of prospective study participants and were performed by Dr. Vincent Lee. Quality of life questionnaires were administered by Dr. Vincent Lee with the assistance of the certified dental assistants (CDAs) at the Oral Oncology Department (OOD) in the Vancouver Centre of the British Columbia Cancer Agency (BCCA). Wax patterns of the study stents were fabricated chairside by Dr. Vincent Lee. Follow up assessments (quality of life questionnaires) were administered by the CDAs with assistance of Dr. Vincent Lee. Jenny Seow and Christine Rodgerson, radiation therapists at the BCCA Vancouver Centre, extracted positional stability data for the study and retrospective cohorts from Varian’s ARIA treatment software. Dr. Vincent Lee performed data analysis with assistance from Dr. Hsing-Chi von Bergmann.

Ethics approval was required and granted by the University of British Columbia – British Columbia Cancer Agency Research Ethics Board (UBC BCCA REB) [REB certificate number H14-01507].
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List of Abbreviations

BCCA – British Columbia Cancer Agency
CDA – Certified Dental Assistant
COE – Conventional Oral Examination
CT –Computed Tomography
CTV – Clinical Tumour Volume
FDG – Fluorodeoxyglucose
GTV – Gross Tumour Volume
HN – Head and Neck
HNSCC – Head and Neck Squamous Cell Carcinoma
HPV – Human Papilloma virus
IMRT – Intensity Modulated Radiation Therapy
IV - Intravenous
KeV – Kiloelectron volt
LAT – Lateral group
LNG – Longitudinal group
MRI – Magnetic Resonance Imaging
NB – No Bite Block group
OB – Old Bite Block group
OOD – Oral Oncology Department
PET – Positron Emission Tomography
PTV – Planning Target Volume
QOL – Quality of Life
RCT – Randomized Clinical Trial
REB – Research Ethics Board
RND – Radical Neck Dissection
RSR – Relative Survival Rate
RT – Radiation Therapy
SCC – Squamous Cell Carcinoma
ST – Study group
SUV – Setup Volume
TB – Toluidine Blue
TNM – Tumour-Node-Metastasis
VMAT – Volumetric Arc Therapy
VRT – Vertical group
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Dedication

To my dearest wife Divine. You are my rock. Through all my mental ups and downs you were there to guide me to safety. You are always there when I need a hug and a smile. You always look out and take care of me. Without you I could not have accomplished this journey. Thank you from the bottom of my heart.
Chapter 1: Introduction

1.1 Epidemiology of Head and Neck (HN) Cancers

HN cancer is among the ten most common cancers and makes up approximately 3-5% of all cancers reported.\(^1\) Worldwide, each year there are approximately 650,000 new cases and 350,000 deaths from HN cancer.\(^2,3\) Furthermore in 2015, it was estimated that 4400 Canadians were diagnosed with oral cancer\(^4\) and based on the British Columbia Cancer Agency (BCCA) cancer surveillance data, there were 496 new diagnoses of oral cancer and 161 deaths from oral cancer in 2012 province-wide\(^5\). These numbers represent an incidence rate of 10.73 per 100,000 and a mortality rate of 3.48 per 100,000.\(^5\) While these rates appear low, it is estimated that in Canada the five-year relative survival rate (RSR) of patients newly diagnosed with oral cancer is still only 63%.\(^4\)

HN cancers can originate from a wide variety of cells and exhibit a variety of responses. HN cancers can include cancers of the oral cavity, larynx, oropharynx, nasal and paranasal cavities.\(^3\)\(^,\)\(^6\) Despite the wide variety of tissues from which HN cancers can arise, it has been established that the predominant form of cancer in the HN is squamous cell carcinoma (SCC), which represents more than 90% of all HN cancers.

1.1.1 Risk Factors for Head and Neck Squamous Cell Carcinomas (HNSCC)

The main risk factors for developing HNSCC are regular tobacco use and alcohol consumption.\(^7,9\) It has been well documented in the literature that tobacco use and HNSCC has such a strong association that it has been universally accepted as a causative agent\(^3\) with users having a 5-7 times greater risk of developing HNSCC\(^8\). The use of smokeless tobacco has also demonstrated a strong association with HNSCC but tends to present a lower risk than conventional tobacco
smoking\textsuperscript{8,9} with malignant transformation more localized to the site of tobacco placement\textsuperscript{8}.

Similarly in Southeast Asian populations, the chewing of betel quid and reverse smoking results in high incidences of oral squamous cell carcinomas.\textsuperscript{8} The highly carcinogenic betel quid consists of a mixture of areca nuts, slaked lime and often tobacco wrapped in a betel leaf. Chronic use of betel quid has been linked to submucosal fibrosis and as a result a high rate of malignant transformation of the tissues.\textsuperscript{8}

Frequent alcohol consumption has also been demonstrated to be highly associated with developing HNSCC and is considered an independent risk factor.\textsuperscript{3,9} It has also been shown that in addition to being independent risk factors, the combination of alcohol and tobacco synergistically increases mucosal permeability to carcinogenic nitrosamines\textsuperscript{8} thus dramatically increasing the risk of developing HNSCC\textsuperscript{3,9}.

Historically the majority of cases were attributed to older men who regularly partook in the use of tobacco and consumption of alcohol. In recent times, there has been a shift in the demographics of people presenting with HNSCC. There has been an increase in incidence in patients younger than 60 years of age and women who do not present with traditional risk factors.\textsuperscript{8} Previously, men were at a 10:1 risk of developing HNSCC but the ratio has decreased significantly in that the male to female ratio of HNSCC is now only approximately 2:1 or 3:1.\textsuperscript{8}

More recently, it has been established that viruses may have a role in the development of HNSCC. The major viridae associated with HNSCC is the Human Papilloma virus (HPV), specifically HPV-16 and 18, which have been found in 22% and 14% of oropharyngeal tumours,
respectively, and results in a 3-5 fold increase risk of developing HNSCC. As compared to non-HPV associated HNSCC, it has been documented that the incidence rate of HPV associated HNSCC is increasing and tends to been seen more often in people less than 60 years of age, therefore the management and prevention of long-term side effects in this population can have significant lifelong quality of life considerations. Hence despite being histologically similar to tobacco and alcohol related HNSCC, HPV associated HNSCC differs at a molecular level as they cause less frequent mutations of the tumour suppressor genes and the viral genome encode for proteins that can inactivate tumour suppressor genes. HPV associated HNSCC tend to respond much more favourably to treatment resulting in a more favourable long-term prognosis.

While tobacco, alcohol, betel quid and HPV remain the major risk factors for HNSCC, additional risk factors have been identified including: gastroesophageal reflux disease, marijuana use, and occupational risks such as nickel refining, woodworking and textile manufacturing.

### 1.2 Overview of the Molecular Biology of Cancer

Cancer is a group of diseases in which there is abnormal replication and growth of host cells. In normal healthy individuals, there is continual cellular turnover throughout most tissues within the body. A complex network of molecular pathways encoded in the cellular DNA regulates the normal turnover of cells. These encoded messages can signal cells to divide to form new cells as well as signal older or damaged cells to undergo programmed cell death or apoptosis. As damaged cells are being removed and new cells are being replicated there is always the potential for errors or changes to occur within the cell. Theoretically any change within a cell, especially
to the genetic material, can have the potential to illicit a cancerous change. However, damage to the DNA by itself is not adequate to be considered a mutation as there exists additional regulatory systems able to prevent the damaged cells from replicating. Therefore, a major characteristic any alteration must possess to be considered mutagenic is its ability to be replicated and passed on as a heritable change to its clonal progeny.

With regards to cancer, the initiation of carcinogenesis is often associated with mutations to the genes involved in the regulation of cell replication. These cellular mutations can be grouped as either genetic or epigenetic. Genetic mutations are alterations to the genomic sequence of the host cell and can occur as simple point mutations, transversions, transitional changes and/or small deletions of the DNA sequence. Genomic alterations can result from a variety of causes including exposure to chemical mutagens, spontaneous DNA damage and exposure to ionizing radiation. Conversely, epigenetic alterations are defined as heritable changes in gene expression not resulting from a change to the genomic sequencing of the cell. Examples of epigenetic alterations include DNA hypermethylation, DNA hypomethylation, loss of imprinting, histone deacetylation, histone acetylation, histone methylation, mRNA amplification or deletion and viral proto-oncogenes. Successful cancer cells have been selected due to the presences of mutations that: 1) increase the activity of the genes they encode and/or 2) inactivate function or expression of tumour suppressor genes. When these mutations successfully present, the cell no longer responds to the regulatory feedback mechanisms and is able to undergo cancerous transformation. The transformed cell will exhibit uncontrolled replication resulting in a neoplasm or tumour that will continue to grow and expand into adjacent structures.
During the initial phase, abnormal cells can replicate sub-clinically producing similar but not necessarily genetically identical clones as compared to the healthy cell of origin or the primary cancer cell. Clinically detectable tumours can consist of upwards of a billion of clonal progeny cells. A majority of cancers can be linked to a single abnormal cell due to their similar genetic composition; hence, neoplastic lesions are often named based on the tissue of origin. However, recent genetic analysis studies of HNSCC have determined that despite similar histological appearance a large portion of HNSCC contain differences in their DNA profiles suggestive of molecular heterogeneity.\textsuperscript{10}

1.2.1 Benign versus Malignant Neoplasms

Neoplastic growths are also categorized based on their invasiveness and are described as being either benign or malignant. As with all neoplasms, they all have the ability to replicate unregulated and to invade adjacent tissues; however, most benign tumours tend to be less aggressive as they grow and remain in the region of the tissue of origin and only exhibit invasion of local tissues. Due to this behaviour, benign neoplasms can generally be controlled by surgical excision with minimal risk of recurrence. Unlike benign tumours, malignant neoplasms tend to pose a more significant risk to the patient. While benign neoplasms tend to replicate and remain in the primary region of origin; whereas, malignant neoplasms have a more invasive characteristic. Similar to benign lesions, malignant form primary lesions in the tissue of origin; however, malignant neoplasms also possess the potential for clusters of cells to become dislodged from the primary tumour.
As previously mentioned, it has also been suggested that some neoplasms are heterogeneous and behave like multicellular organisms containing subpopulations of cells within the neoplasm.\textsuperscript{14} This characteristic has been observed in malignant neoplasms which typically contain cells similar to the cells of origin but may also contain subpopulations of cells with different metastatic potential. It has been suggested that within the tumour certain cells may possess the characteristics that allow them to become dislodged from the primary tumour.\textsuperscript{14,15} Once dislodged from the primary tumour these clusters of cells can gain access to the circulatory and/or lymphatic networks initiating the metastatic process allowing them to be disseminated to distance tissues throughout the body. However, not all disseminated neoplastic cells survive that process as some are selectively eliminated due to size constraints or incompatibility with their new environment.\textsuperscript{14} Successful secondary neoplasms would need to consist of cells that are able to survive the metastatic transport and adapt to the new tissue environment in which it has established. A major adaptation that is thought to be required for establishment of the secondary neoplasm is the ability to stimulate local angiogenesis to support the growth of the secondary neoplasm.\textsuperscript{2} These observations support the hypothesis that a malignant metastatic neoplasm may behave like an autonomous multicellular organism. The more invasive the neoplasm the more likely the management of the neoplasm will be more complicated and require more aggressive treatment.

1.3 Diagnosis and Assessment of HNSCC

1.3.1 Physical Examination

Due to the varied nature of HNSCC, signs and symptoms can vary depending on origin of the lesion as well as the stage of the cancer.\textsuperscript{9} Cancers originating in certain regions within the head
and neck present more readily for early detection. In its early stages, oral cancers can present as pain, non-healing ulcerations, red and/or white lesions, and patients may notice loosening of teeth, and alterations in the fit of their dental prostheses.\textsuperscript{6,9} Common sites for presentation in the oral cavity include the tongue, floor of mouth, buccal mucosa, gingival tissues and alveolar ridge.\textsuperscript{6} In the nasal cavity and paranasal sinuses, early symptoms can include sinusitis and unilateral obstruction of the nasal airway.\textsuperscript{9} Conversely, some HN cancers do not present early symptoms and are often detected at much later stages of development. It is possible that due to the air-filled nature of the paranasal and nasal cavities, a tumour can grow undetected until it reaches a more advanced stage. Late symptoms of paranasal and nasal cancers are presence of a mass, epistaxis, cranial neuropathy, pain, blindness and facial edema.\textsuperscript{10,16} Cancers of the oropharynx and hypopharynx can present as a persistent sore throat and otalgia.\textsuperscript{9} If a lesion is suspected to be pre-malignant or malignant further assessment is warranted to assess the cancerous potential of the lesion. Definitive diagnosis of any suspected lesion is determined by obtaining a tissue biopsy from which the histopathology of the tissue can be determined and a diagnosis provided. In order to assess the need for an invasive tissue biopsy, a thorough examination and workup of the lesion is required. The following sub-sections will describe the examination process and adjunct screening tools that may aid in the early detection of pre-malignant or malignant lesions within the oral cavity.

\subsection*{1.3.2 Conventional Oral Examination (COE)}

For many suspected lesions the initial screening method involves having an intraoral COE performed by their health professional. Lesions are identified by visual or palpable differences in the presentation of the suspected tissues from the normal presentation. In the oral cavity,
normal tissues usually present as firm, pink, non-bleeding and non-ulcerated; whereas, the initial clinical presentation of a pre-cancerous lesion may be of a leukoplakia, an erythroplakia or a non-healing ulceration. It is important to distinguish that a leukoplakia is a white patch that cannot be removed and an erythroplakia is an area of redness that cannot be attributed to any other cause. The ability to identify and distinguish healthy from abnormal is critical to the detection of oral cancers. While the effectiveness of the COE has not been definitively described, it has been reported in a large study of oral cancer screening programs that COE has an overall sensitivity of 0.74 and specificity of 0.99. Furthermore, a randomized clinical trial (RCT) of the efficacy of oral cancer screening concluded that COE did not result in a significant reduction on the mortality of oral cancer or improvement of the survival rate for the overall population; however, there was an increase in survival rate among males with high risk habits such as smoking. These observations seem to indicate that the routine COE may be useful as it provides a regular convenient opportunity to perform an oral cancer screening on our patients, especially for high-risk habit individuals.

1.3.3 Adjunct Oral Cancer Screening Tools

In an attempt to further improve the detection of oral cancers, several adjunctive tools have been developed for use during oral cancer screening including oral cytology, toluidine blue and light based detection systems. Commonly utilized cancer screening techniques include: 1) standard screening test – COE; 2) Established diagnostic adjuncts – Oral cytology and toluidine blue (tolonium chloride); or 3) Light based detections systems – Vizilite Plus (Zila Pharmaceuticals), MicroLux DL (AdDent, Inc.) or VELscope (LED Dental).
1.3.3.1 Oral Cytology

Oral cytology involves the microscopic assessment of sample cells from suspected lesions. Superficial cells are removed by brush or swab and deeper cells are acquired via fine needle aspiration for assessment. Several studies have attempted to assess the efficacy of oral cytology as a screening tool but the main limitation of many of the studies is the lack of a histopathologic control to compare the samples. The sensitivity and specificity of oral cytology have been reported to range from 70-100% and 27-94% respectively, and it has been noted to have potential to be considered a useful screening tool. Lingen et al.\textsuperscript{17} suggests that despite the limitations in the literature, oral cytology can be of benefit as this technique would be a less invasive means of assessment for patients with multiple lesions who would be reluctant to consent for multiple biopsies and for non-compliant patients who are unlikely to attend an additional appointment to obtain a tissue biopsy.

1.3.3.2 Toluidine Blue (TB)

Toluidine blue (tolonium chloride) is a vital dye applied to suspected lesions. TB may preferentially bind to increased nucleic acids and defective intercellular barriers in SCC, thereby producing a visible blue stain on potentially affected tissues.\textsuperscript{19} From a review of the literature by Lingen et al.\textsuperscript{17}, TB sensitivity ranged from 0.78 to 1.00 and specificity ranged from 0.31 to 1.00. Similarly Patton et al.\textsuperscript{18} reported more wide-ranging results for TB sensitivity and specificity of 38-98% and 9-93% respectively. These results are not necessarily surprising as the toluidine blue will not only bind to tissues with pre-malignant potential but will also bind to benign lesions such as non-specific ulcers. Despite only being able to identify dysplasia approximately 50% of the time, with repeated testing two weeks apart the sensitivity and specificity of TB improve and
appears to be good at identifying carcinomas\textsuperscript{17}. In addition, TB has been shown to be useful in predicting risk of malignant transformation even in lesions that displayed no clinical or microscopic dysplasia\textsuperscript{18}.

1.3.3.3 Tissue Fluorescence

Light-based systems such as the ViziLite Plus (DenMat Holdings LLC), MicroLux DL (AdDent Inc.) and VELscope (LED Dental) are marketed as screening tools for oral cancers. The ViziLite Plus and MicroLux DL are marketed as tissue reflectance fluorescence tools where the application of a blue-white light on previously acetic acid rinsed tissues produces a bluish-white tissue colour if the epithelium is normal or distinctly white appearance if the tissue is abnormal.\textsuperscript{17, 18} However, the lack of well controlled clinical trials and the poor sensitivity and specificity of these techniques may not provide any clinical diagnostic benefit over a conventional oral examination done under standard room lighting.

The VELscope utilizes normal tissues ability to produce autofluorescence to aid in the detection of potentially pre-malignant and malignant lesions. The VELscope device emits light in the 400-460nm wavelengths onto the region of concern. When viewed through the built in filter, normal tissues will appear to have a fluorescent green appearance; whereas, tissues that have undergone tissue and cellular alterations will display lower levels of autofluorescence and appear dark when viewed through the device.\textsuperscript{17} Several studies have looked at the efficacy of the VELscope device as a screening tool for detecting oral cancers. For lesions that were readily identified via COE, there was a reported 98\% sensitivity and 100\% specificity for detecting dysplasias and carcinomas when compared to histologic results.\textsuperscript{20} It was also demonstrated in a small sample
case report, the VELscope device was able to identify three lesions that were not visible during a COE. Furthermore, the VELscope device was able to identify the extent of the field cancerization of the lesion, which in one study extended as much as 25mm beyond the margins of the clinically identifiable lesion. This observation may be beneficial in aiding the delineation of the extent of the surgical resection possibly reducing the risk of recurrence of the tumour due to field cancerization.

1.3.3.4 Tissue Biopsy and Histology

As previously mentioned, the gold standard for diagnosis of HNSCC is the tissue biopsy. Tissue biopsies are obtained by means of incisional or excisional techniques for more easily accessible lesions or by ultrasound guided fine needle aspiration. The samples are fixed and prepared for histologic assessment by a pathologist from whom a histologic diagnosis is obtained. As mentioned earlier, initial presentation of oral lesions can include leukoplakia and erythroplakia and while these terms are often mistaken as diagnoses it is important to note that these descriptive terms can present histologically in a variety of ways.

Hyperplasia refers to thickening of the tissue due to an increase in number of cells within the epithelial layer. This can be in response to a specific stimulus and if the lesion consists of generally normal cells, the lesion will often cease to progress or even recede. However, if the cells do not respond to the removal of the original stimulus this can result in a potentially pathologic hyperplasia that continue to progress in its transformation.
Oral epithelial dysplasia (OED) is the diagnostic term used to describe the progressive changes of the oral mucosa associated with premalignant lesions\textsuperscript{23} and according to the 2005 World Health Organization Classification of Tumours the following criteria are used to diagnose dysplasia\textsuperscript{24} (Table 1):

**Table 1 Diagnostic criteria for tissue dysplasia**

<table>
<thead>
<tr>
<th>Architecture</th>
<th>Cytology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Irregular epithelial stratification</td>
<td>Abnormal variation in nuclear size</td>
</tr>
<tr>
<td>Basal cell hyperplasia</td>
<td>Abnormal variation in nuclear shape</td>
</tr>
<tr>
<td>Drop-shaped rete pegs</td>
<td>Abnormal variation in cell shape</td>
</tr>
<tr>
<td>Increased number of mitotic figures</td>
<td>Increased nuclear-cytoplasmic ratio</td>
</tr>
<tr>
<td>Abnormally superficial mitoses</td>
<td>Increased nuclear size</td>
</tr>
<tr>
<td>Pre-mature keratinization in single cells</td>
<td>Atypical mitotic figures</td>
</tr>
<tr>
<td>Keratin pearls with rete pegs</td>
<td>Increased number and size of nucleoli</td>
</tr>
<tr>
<td>Loss of polarity of basal cells</td>
<td>Hyperchromasia</td>
</tr>
</tbody>
</table>

Dysplastic changes are graded according to the severity of the microscopic changes and a common grading system was described in the 2005 WHO classification paper.\textsuperscript{24} Mild dysplasia refers to architectural changes limited to the lower third of the epithelium with minimal cytological atypia and this represents the minimum epithelial changes to obtain a diagnosis of dysplasia.

Moderate dysplasia is the next progression from a mild dysplasia and is a result of architectural changes extending into the middle third of the epithelium. The grading of moderate dysplasia can be modified depending on the observed concurrent cytological atypia, with minimal atypia and marked atypia representing mild and severe dysplasia, respectively.
In addition to the situation described above, severe dysplasia starts when greater than two-thirds of the epithelium exhibits marked architectural alterations and associated cytological atypia. If left unmanaged epithelial hyperplasia or mild dysplasia can progress along the spectrum to becoming severe dysplasia or carcinoma in situ and further progressing by transformation into an invasive carcinoma.²

1.3.4 Imaging

Advanced imaging of the lesions is usually performed to supplement the results of the physical exam and histologic assessment to determine the extent and severity of the disease. The use of imaging techniques is critical in the detection, diagnosis and treatment planning of cancer.

1.3.4.1 Computed Tomography (CT) and Magnetic Resonance Imaging (MRI)

Computed tomography is an advanced radiographic technique where the region of interest is scanned in numerous slices or sections after which the adjacent slice data is stitched together to create a 3-dimensional recreation of the region of interest. The high-energy output of the x-ray tubes produces a wide dynamic range allowing for the discrimination of hard and soft tissues. Modern computed tomography machines acquire the image data through the use of a rotating anode that generates the x-rays, whose energy is attenuated as it passes through the body. The exiting x-rays are captured on one or more circular array of sensors where the remaining energy levels of the x-rays are digitized and into 3-dimensional volumes of data, called voxels. The voxels allow for the computerized reconstruction of the image based on the remaining energy as it strikes the sensors.²⁵ For use with HNSCC, an IV administered iodinated contrast medium is often used to enhance the tissue image, as tumours tend to be more highly vascularized than
normal tissues. The contrast medium will tend to accumulate in the lesions and produce a more defined margin around the lesion.\textsuperscript{25, 26}

MRI is another potential imaging technique utilized with head and neck cancers. The procedure involves placing the patient within a large electromagnet, which aligns the hydrogen atom dipoles within the body creating a high-energy state. Concurrently, a radiofrequency is pulsed into the field creating a high energy state, which following the removal of the radiofrequency the excess energy will be released and captured by receiver coils and its information is utilized to recreate the image.\textsuperscript{25, 26} A common MRI protocol for use with HN cancers would involve the administration of a contrast agent, such as gadolinium, that would accumulate in neoplastic tissues and a fat-suppressed image to further enhance the contrast between the tumour and normal tissues.

1.3.4.2 Nuclear Imaging – Positron Emission Tomography (PET)

PET involves the use of a positron-emitting radioisotope to create the radiographic image. The procedure involves the intravenous injection of a radioisotope into the circulatory system where it is disturbed throughout the body. The most common radioisotope utilized in a PET scan is \textsuperscript{18}fluorodeoxyglucose (\textsuperscript{18}FDG), which is a D-glucose molecule with an \textsuperscript{18}F isotope replacing one of the hydroxyl groups on the glucose molecule.\textsuperscript{26} Patients are subsequently positioned on the treatment table, which is encircled by photon detectors arranged in a ring around the table. As positrons are released from the radioisotope they interact with available electrons and result in an annihilation reaction that releases photons of energy simultaneously in opposite directions. The image is created as the resultant photons strike the detector array.
The rationale for PET in cancer imaging is the differential appearance of a tumour in a PET. Cancer cells exhibit a much higher metabolic activity than non-malignant cells therefore resulting in an increased glucose demand. In order to satisfy the increased demand cancer cells upregulates the production of glucose transporter proteins. When the $^{18}$FDG molecule is injected, it will be recognized by cells as glucose and be transported into the cells as a result of the increased metabolic activity. The $^{18}$FDG molecules will begin to accumulate within the cancer cells due to the upregulated phosphorylation of the $^{18}$FDG molecule, which prevents it from being metabolized by the cancer cells resulting in the increased signal from the cancer cells.

1.3.4.3 PET-CT Combined Imaging\textsuperscript{36}

The individual imaging modalities were discussed in the previous sections. Both are invaluable tools in the pre-treatment detection and assessment of malignant lesions and planning of treatment for the identified lesion. However, both imaging methods have shortcomings and the combination of the two methods attempt to overcome each of the individual deficiencies. Contrast enhanced CT produces images that result from larger structural changes; as a result may not be able to provide enough sensitivity to detect smaller lesions, viable lesions within residual masses, or characterizing secondarily enlarged lymph nodes. In addition, due to the effects of radiation therapy there can be significant changes to the structural anatomy, which render the images impossible to compare.

PET has the advantage of being able to identify distant metastases or smaller lesions in the surrounding tissues. Images are produced based on the metabolic activity of the cells and while it is very good at detecting metabolically active tumours, PET does not have the specificity to allow for easy discrimination of tumours from tissues of higher physiologic activity.
The combination of PET-CT has improved the ability to discriminate between physiologic and pathologic FDG resulting in more accurate tumor localization.

1.3.5 Staging of HNSCC*

Staging is used to describe the extent and severity of a cancer and can involve information gathered from the clinical examination and results from CT, MRI or PET-CT imaging. For HNSCC the most common staging system was established by the American Joint Commission on Cancer and is based on the Tumour-Node-Metastasis (TNM) system. Clinical staging is based on the combination of T, N and M ratings. As described in Table 2 for oral cavity tumours, with increases in tumour size the T rating increases. Similarly, with increasing lymph node involvement the N rating increases and presence of distant metastases increases the M rating.

### Table 2 TNM assessment for head and neck cancers*

<table>
<thead>
<tr>
<th>Symbol</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>TX</td>
<td>Primary tumour cannot be assessed</td>
</tr>
<tr>
<td>T0</td>
<td>No evidence of primary tumour</td>
</tr>
<tr>
<td>Tis</td>
<td>Carcinoma in situ</td>
</tr>
<tr>
<td>T1</td>
<td>Tumour ≤ 2cm in greatest dimension</td>
</tr>
<tr>
<td>T2</td>
<td>Tumour &gt; 2cm, but ≤ 4cm</td>
</tr>
<tr>
<td>T3</td>
<td>Tumour &gt;4cm</td>
</tr>
<tr>
<td>T4</td>
<td>Tumour invades adjacent structures</td>
</tr>
<tr>
<td>NX</td>
<td>Regional lymph nodes cannot be assessed</td>
</tr>
<tr>
<td>N0</td>
<td>No regional lymph node metastasis</td>
</tr>
<tr>
<td>N1a</td>
<td>Metastasis to a single ipsilateral lymph node (≤ 3cm)</td>
</tr>
<tr>
<td>N2a</td>
<td>Metastasis to a single ipsilateral lymph node (&gt;3cm, but ≤6cm)</td>
</tr>
<tr>
<td>N2b</td>
<td>Metastasis to multiple ipsilateral lymph nodes (none &gt;6cm)</td>
</tr>
<tr>
<td>N2c</td>
<td>Metastasis to bilateral or contralateral lymph nodes (none &gt;6cm)</td>
</tr>
<tr>
<td>N3</td>
<td>Metastasis to a lymph node (&gt;6cm)</td>
</tr>
<tr>
<td>MX</td>
<td>Presence of distant metastasis cannot be assessed</td>
</tr>
<tr>
<td>M0</td>
<td>No evidence of distant metastasis</td>
</tr>
<tr>
<td>M1</td>
<td>Distant metastasis</td>
</tr>
</tbody>
</table>

*Oral cavity tumours were used as the example*
Using the T, N, M ratings, clinical staging can be determined and assigned by combining the factors as shown in Table 3. The clinical staging of the head and neck cancer is important as it aids in determining the treatment modality best suited to treat the patient. Stage I and II tumours are earlier lesions and can be managed more conservatively. Stage III, IVa and IVb tumours relate to more invasive lesions that have more extensive regional metastases that may require more extensive treatment potentially including surgical neck dissections or resections. When widespread metastasis has been detected and a designation of M1 has been provided the stage of cancer is assigned as Stage IVc.

<table>
<thead>
<tr>
<th>Table 3 Clinical staging for head and neck cancers</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1</td>
</tr>
<tr>
<td>----</td>
</tr>
<tr>
<td>N0</td>
</tr>
<tr>
<td>N1</td>
</tr>
<tr>
<td>N2</td>
</tr>
<tr>
<td>N3</td>
</tr>
</tbody>
</table>

*Stage IVc – evidence of widespread metastasis (M1)*

1.4 Treatment Modalities

HNSCC is treated with a variety of different modalities including surgical resection, radiation therapy, chemotherapeutics, or a combination of these modalities. The decision regarding the modality of treatment can relate to the stage of the lesion, the potential for patient disfigurement and functional impairment following surgery, and patient and/or physician preference. Primary tumours of HNSCC with early staging (Stage I or II) can be treated be either surgical or radiation therapy. Late stage tumours (III or IV) are generally treated by a combination of surgical with post-operative radiation or post-operative chemoradiation. In addition, if there is a potential for significant functional morbidity following surgical resection consideration is placed
into the use of combination chemoradiation therapy for treatment of the tumour in an attempt to avoid foreseeable functional or esthetic issues resulting from surgical resection. 

1.4.1 Surgical Management

Surgical intervention has been and continues to be a widely accepted treatment modality for some HNSCC. It is still considered one of the main treatment modalities for HNSCC and is considered for early to late stage tumours. Conventional surgical removal of tumours may result in significant morbidity issues due to the size of surgical defects required for access and adequate management. However, modern microsurgical techniques may maintain treatment outcomes while improving functional outcomes by reducing the extent of surgical defects. 

1.4.1.1 Neck Dissections

As part of the surgical management of head and neck cancers, consideration must be given to the possibility of regional metastasis to the neck, which may entail surgical resection of lymphatic, circulatory, neural, lymphoid and muscular tissues affected by the metastasis. The earliest reports of such a neck dissection involved removal of the lymph nodes in levels I-V, sternocleidomastoid muscle, internal jugular vein and cranial nerve XI (spinal accessory); as a result of the extensive nature of the dissection this technique was called the radical neck dissection. Subsequently, a slightly more conservative approach was described ie. the modified radical neck dissection (MRND); the MRND involved the removal of lymph nodes in cervical neck levels I-V and the preservation of uninvolved non-lymphoid structures, thus improving appearance and decreasing functional morbidity. As the pattern of metastasis became better understood, it became possible to be even more conservative and perform a selective neck
dissection of the cervical lymph nodes at most risk for developing a metastatic lesion based on the location of the primary tumour.

1.4.2 Radiation Therapy

Radiation therapy (RT) has been one of the main treatment modalities of primary malignant HN cancers.\textsuperscript{2,28} RT has been shown to be effective as a single modality treatment; one study reported a cumulative 5-year survival rate of 81\% while another study observed an overall survival rate of 97\% and a 5-year recurrence free rate of 89\% for early glottis cancers\textsuperscript{3}. With respect to radiation therapy of cancer cells, the aim is to deliver the radiation to an accurately localized lesion to ensure control of the tumour while minimizing the effect on the surrounding tissues.\textsuperscript{29}

Common to most modern external beam modalities, the therapeutic radiation dose is generally applied by means of fractionation. Fractionation involves the delivery of sub-lethal doses of radiation to the tumour site 5 days per week over a 5 to 7 week treatment period. A typical regimen of definitive head and neck radiation therapy can consist of daily fractions of 2.0 grays, 5 days per week for up to a 7 week course of treatment.\textsuperscript{2}

Due to fractionation, it is imperative to ensure the consistent reproduction of the initial patient position, as captured during the planning CT, throughout the entire course of treatment. Difficulties in patient positioning relate to gradual weight loss and physiologic changes due to oncologic treatment, as well as the anatomy of the maxilla-mandibular complex. Gross positioning errors can be managed through the use of patient stabilizing devices such as thermoplastic facemasks. However, facemasks are not entirely accurate and continue to allow
movement of the tongue and mandible.\textsuperscript{29} It has been documented that the mandible can move up to 11mm from a fully retruded position to fully protruded position\textsuperscript{30}, up to 20mm from full left and right laterotrusion\textsuperscript{30} and up to 4mm inferiorly from full maximum intercuspation (interdigitation of upper and lower tooth surfaces) while in a supine position\textsuperscript{31}. As a result, it has been suggested in the literature to utilize intraoral stents during radiation therapy to stabilize the mandible and minimize these effects.\textsuperscript{32-35}

1.4.2.1 Radiation Biology and Oral Complications

Radiation therapy utilizes the ability of ionizing radiation to cause biologic effects on cells. Ionizing radiation can cause defects or changes in the chromosomes of the affected cells and can lead to different effects.\textsuperscript{36} The effects of ionizing radiation are related to numerous factors including the type of radiation and the characteristics of the tissue. Different types of radiation possess differing levels of energy and can cause different damages based on the type of tissues.\textsuperscript{36} The amount of energy absorbed by the tissues is described as the “absorbed dose”. The absorbed dose of radiation will have differing effects within the body dependent on the type radiation.\textsuperscript{36} Factors that modulate the effects of the radiation on tissue such as high cell replication rates and higher oxygen concentration are related to increased radiosensitivity.

For adequate tumour control, it would be necessary to apply an adequate radiation dose high enough to kill all tumour cells, including the cancer stem cells. However, as one can deduce, high radiation doses will also affect normal healthy tissues. Therefore, as previously mentioned the concept of fractionation has been developed. Fractionation of the radiation dose has several benefits: 1) it allows for re-oxygenation of the tumour, which is now considered to be important
as inadequate oxygenation of the tumour may result in a more radioresistant tumour; 2) it will affect more tumour cells during the radiosensitive phases of the cell cycle and; 3) allowing a period between fractions where normal cells seem to recover from the sublethal radiation better than the tumour cells.\textsuperscript{37}

The effects of ionizing radiation can be direct or indirect. When the ionizing radiation causes damage/alterations to the cellular DNA it is considered a direct effect. If the DNA damage is extensive enough where normal DNA repair mechanisms are insufficient, the cell would be signaled to undergo apoptosis.\textsuperscript{36} The indirect effects of ionizing radiation causes hydrolysis of water molecules creating DNA altering free radicals and/or creating a highly oxidized environment which will eventually lead to cell death.\textsuperscript{36} With respect to HNSCC, the effects of ionizing radiation can manifest as some common oral complications/toxicities including xerostomia, mucositis, dysphagia, trismus, dysgeusia and osteoradionecrosis.\textsuperscript{38} The most common acute complication is mucositis, which results from a decrease in the squamous epithelial layer due to an increased rate of cell death compared to cell regeneration.\textsuperscript{39} Mucosal recovery generally occurs following cessation of radiation therapy. Xerostomia is a common complication, which can result from the destruction or fibrosis of the major salivary glands. While the decrease in the quantity of saliva is often detectable early on during radiation therapy there may also be an alteration in the quality of the saliva, which can affect the buffering capacity of the saliva.\textsuperscript{39} The alterations in the quality of the saliva can affect the ability to wear a dental prosthesis, as well as affect the health of the remaining teeth. An additional early complication is altered taste perception. It has been shown that altered taste can occur as early as the first two weeks of treatment\textsuperscript{37} and can progress to complete loss of taste throughout the
Some have shown that taste perception can recover 3-6 months following the end of treatment; however, taste acuity may never return potentially due to diminished salivary flow.\textsuperscript{37, 39}

The other complications noted tend to occur as late complications resulting from accumulation of tissues damage and can present months to years following radiation therapy. Linked to xerostomia, dental caries is common among radiation therapy patients related to pain associated with oral hygiene and the decrease in pH of the saliva that can increase the susceptibility to caries. Another group of late complications results from radiation induced fibrosis of soft tissue structures and can result in trismus - fibrosis of the muscles of mastication causing a decreased mouth opening; dysphagia – fibrosis of the tongue and muscles involved in swallowing causing difficulty swallowing; and velopharyngeal incompetence – neuromuscular impairment of the structures involved in partitioning the nasal and oral cavities.\textsuperscript{37} In addition to soft tissue complications, post-radiation bone can exhibit decreased vascularity, decreased cellularity and significant fibrosis. These changes decrease the capacity for the bone to handle trauma; as a result, they can lead to a persistent non-healing exposure of bone called osteoradionecrosis that can result in significant defect of the head and neck region.

\textbf{1.4.2.2 Conventional Radiation Therapy (RT)}

Standard/Conventional external beam radiation therapy involves the application of parallel opposing beams of radiation focused on the identified tumour along a single plane. Patients are placed in a supine position and the head is stabilized with a thermoplastic facemask where identifiers are placed to aid in patient repositioning. Planning of the treatment site involves a
lateral radiograph onto which the shape of the tumour is delineated and transferred to the patient. The lateral tracing can then be utilized to fabricate beam-shaping devices to exclude tissues outside the region of interest or attenuate the radiation dose to more radiosensitive tissues. Despite the use of beam-shaping devices, the main disadvantage of the conventional parallel-opposed beam technique is that all tissues, including healthy non-involved tissues, along the beam path will constantly be exposed to the radiation dose potentially eliciting additional complications.

1.4.2.3 Intensity Modulated Radiation Therapy (IMRT)

More recently, the development of 3-dimensional imaging has allowed for better localization of cancerous tumour lesions. Better localization and visualization of the tumour has resulted in the development of 3D conformal radiotherapy in which the external beams can be more focused to the tumour location and approximate shape. As described earlier, imaging in the form of either a CT, PET-CT or MRI is utilized to determine the location of the target lesion. Based on the imaging data, the radiation oncologist can proceed with planning the radiation therapy.

As illustrated in Figure 1, in order to establish the final volume to be irradiated the radiation oncologist begins by identifying the boundaries of the gross tumour. This is accomplished by careful examination of the imaging slices and delineating the outer boundary of the gross tumour on the individual slices. Following the determination of the gross tumour volume, an additional volume of tissue is added to account for potential subclinical tumour extension (possible field cancerization) resulting in the establishment of the clinical tumour volume. The final volume
added to the CTV, named the Setup Volume, relates to the aforementioned difficulty with patient positioning reproducibility and maxilla-mandibular relationships.

Taking advantage of the development of advanced imaging techniques and treatment is the highly developed form of 3D-conformal radiation therapy called Intensity Modulated Radiation Therapy (IMRT). IMRT is designed to provide a highly customized dose volume of radiation to the target lesion via a programmable and moveable metal leaf aperture that alters its shape to closely match the pre-determined tumour dimensions depending on the position of the rotating gantry in relation to the patient. IMRT allows for the application of radiation in a circular fashion due to the rotating gantry minimizing the exposure of healthy tissues adjacent to the tumour. In addition IMRT has the benefit of allowing for different radiation isodoses to be applied to different volumes simultaneously.\textsuperscript{41}
1.4.2.4 Potential Benefit of IMRT on Toxicities

In order to treat HNSCC, radiation doses tend to be relatively high and can result in a significant amount of damage to tissues within the region to be irradiated. As discussed in section 1.4.2.1, potential oral complications/toxicities from therapeutic irradiation include xerostomia, mucositis, dysphagia, trismus, dysgeusia and osteoradionecrosis. Significant research has been conducted to assess the relationship between radiation therapy and their observed complications. A retrospective study of consecutively treated head and neck cancer patients demonstrated that oral mucositis occurs in virtually all patients (91%), was more common in patients with oral or oropharyngeal primary carcinomas (OR 44.5) and was associated with severe pain, significant weight loss and increase cost of care.

It has also been reported that xerostomia is the most common complaint following conventional RT with a prevalence ranging from 70.9 to 90.9% often with no improvement even 2 years post-RT. It has been suggested to be a result of the cumulative absorbed dose of radiation within the salivary glands resulting in permanent damage decreasing salivary production. However, the extent and severity of xerostomia varied dependent on the salivary glands affected by the RT. Patients treated for laryngeal/epilaryngeal cancers reporting the least dryness and patients treated for nasopharyngeal cancers reporting the most severe symptoms.

The goal of IMRT and dose fractionation is to concentrate the majority of the dose on the identified tumour while minimizing tissue toxicities by exposing the surrounding tissues to lower fraction doses thus sparing healthy tissues and minimizing complications/toxicities. As a result, research has been conducted to assess potential validity and benefits of IMRT in treating
advanced HNSCC especially in its ability to help minimize complications. A retrospective comparison of conventional RT and IMRT for oral cancer was conducted to assess failure rates and observed toxicities between these two modalities.\textsuperscript{44} Seventy-six patients were assigned to either group and appropriate radiation planning for each patient was devised and the patients were followed for up to 5.5 years. There was no significant difference in 3-year patient survival of 77\% vs. 66\% for conventional RT and IMRT, respectively. In addition, there were significantly lower late toxicities, including xerostomia and dysphagia, in patients who received IMRT.

Furthermore, Eisbruch \textit{et al.}\textsuperscript{45} set out to assess the relationship between 3D dose distributions in the parotid glands to salivary production. They monitored the salivary flow of 88 patients (with 152 involved parotid glands) undergoing IMRT for HN cancers. The authors reported that there was a significant decrease in parotid salivary function following IMRT and that doses of 24 Gy for unstimulated and 26 Gy for stimulated salivary flow were the threshold below which the parotid glands demonstrated functional recovery. For the parotids that received less than the threshold dose there was an observed improvement in salivary flow over the 12 month follow up period. However, the authors noted in order to properly assess the long term effects of IMRT on parotid function, future studies should consider expanding their follow-up period beyond 12 months as there may be continued improvement beyond that point.

These findings were confirmed by a multicenter randomized controlled trial in which 94 patients were evenly and randomly assigned to receive either conventional RT or IMRT for HNSCC. For patients undergoing IMRT, the mean dose to contralateral parotids were planned to be
constrained to below 24 Gy, which was significantly less than for their cohorts receiving conventional RT. As a result at all follow-up time-points a smaller proportion of IMRT patients reported a grade 2 or worse xerostomia.\textsuperscript{46}

Furthering these findings, researchers have attempted to assess the impact of RT on patient’s quality of life (QOL). Jabbari \textit{et al.}\textsuperscript{47} conducted a prospective longitudinal matched case control study in which they aimed at comparing the QOL and xerostomia of patients receiving either standard RT or IMRT. They observed no statistical difference between groups in reported xerostomia symptoms at any post-therapy point despite a twice as high (worse) score for standard RT at 12 months. With respect to QOL, both groups exhibited significant worsening following treatment, but at 6 months post treatment the IMRT group started to show improvements and at 12 months there was a four-fold difference in QOL score between IMRT and standard RT.

In an attempt to quantify salivary function and correlate it to a patient’s QOL, scintographic assessments were performed and their results were correlated to the results of the QOL questionnaires. The results showed that for parotids exposed to less than the median dose (44.69 Gy), there was a statistically significant difference in recovery of up to 83\% of baseline function compared to 41\% recovery in those exposed to higher than the median dose. It was also interpreted that preservation of parotid gland function with IMRT was shown to exhibit higher QOL than those receiving conventional RT.\textsuperscript{48}
IMRT has also been investigated as a means to potentially help reduce the possibility of developing dysphagia. A preliminary investigation has identified the structures that are related to dysphagia and aspiration following chemoradiotherapy and researchers were able to suggest based on simulated radiation planning that IMRT could potentially limit the absorbed dose to these structures thus decreasing the probability of developing dysphagia.  

1.5 Use of Intraoral Stents

As previously mentioned, the application of external beam radiation is one of the main modalities for treating HN cancers; however, it does come at an increased risk of potential damage to adjacent healthy tissues. As discussed in the previous section, IMRT has been proposed as advanced treatment modality that may have the advantage of focusing the dose to the area of interest while minimizing the dose exposure to adjacent tissues. As an adjunct, intraoral stents have been proposed in the literature as a means of repositioning, stabilizing, separating or shielding the unaffected tissues from high radiation doses in order to help reduce potential radiation toxicities. Many of the identified articles are simple case reports outlining the design and clinical protocol to fabricate their respective stents. All of the identified literature pertaining to intraoral stents for RT only present the particular authors clinical steps for producing an indirectly fabricated and customized repositioning stent. It has also been demonstrated in the literature that the use of an acrylic repositioning stent during IMRT can produce the desired effect of reducing radiation dose exposure to unaffected tissues by creation of separation from the intended target volume. Furthermore, a small clinical trial assessing the effect of a repositioning stent on radiation complications seemed to indicate a decrease in incidence and severity of mucositis and xerostomia through their short study length.
Despite these potential reported advantages, there has been very little research conducted to assess the influence of an intraoral repositioning stent on the reproducibility; hence stability, of patient positioning throughout their course of RT. Only two articles were identified as attempting to assess the influence of intraoral stabilization on patient positioning.\textsuperscript{51, 52} Both articles utilized bite registrations attached to an extraoral support or framework as their method of stabilization during their studies. Lopatta \textit{et al.} reported mean deviations of $<1.5$mm of deviation for all measured axes when an intraoral mouthpiece was utilized. Baumert \textit{et al.} conducted a study on three population of patients: 1) bite registration attached to the upper jaw support; 2) upper jaw support from the extraoral stereotactic framework and 3) no additional support (stabilization only provided by a thermoplastic facemask). The researchers reported improvement in patient repositioning accuracy with the use of their customized bite block as compared to the other two groups.
Chapter 2: Rationale and Specific Aims of the Project

Based on the literature review presented above, one of the main goals of RT is to deliver the therapeutic radiation dose to an accurately localized lesion while attempting to preserve as much healthy tissue as possible. It has also been noted that the use of RT can induce significant early and late toxicities to the affected tissues; hence, the attempt to minimize both these complications through the use of IMRT. Furthermore, patient stabilizing devices such as the intraoral repositioning stent have been recommended as an adjunct tool, which, if effective, could help minimize variations in position that can affect the setup volume. As a result, the following specific aims were created to assess the feasibility of the new stent design for use during head and neck IMRT.

2.1 Specific Aims

- To establish protocols for fabricating the proposed acrylic stent.
- To determine the feasibility of the proposed stent design in treating 2 populations of head and neck cancer patients (oral cavity or maxillary sinus and nasal cavity).
- To assess the stability of patient positioning via comparisons of daily reconstructed kiloelectron volt (KeV) images to the images reconstructed from the planning CT scan.
- To document the side effects of IMRT while stabilizing jaw movements throughout IMRT treatment and up to the 3-month post-IMRT follow-up time point.
Chapter 3: Materials and Methods

3.1 Patient Recruitment

As this prospective longitudinal feasibility study involved patients at the BCCA Vancouver Centre, ethics approval was sought and received through the University of British Columbia – British Columbia Cancer Agency Research Ethics Board (UBC BCCA REB) [REB certificate number H14-01507].

Patient recruitment involved the initial referral from our radiation oncologist colleagues based on the inclusion criteria of: 1) primary oral or oral tongue cancer or 2) primary maxillary sinus or nasal cavity cancers, which were determined to need an oral stent by the radiation oncologists. Patients were excluded if they presented with: 1) recurrent cancerous lesions or 2) have metastasis of cancerous lesions. In order to determine suitability for inclusion, a comprehensive oral examination was performed and if deemed suitable the study details were discussed with the patient and the informed consent information sheets were provided to the patient to review (see Appendix A). Upon receiving informed consent from the patient, initial dental examination and baseline side effects of IMRT questionnaire were completed. The side effects questionnaire was adapted and compiled from previously validated questionnaires utilized at the BCCA (Appendix A).

3.2 Fabrication of the Customized Acrylic Repositioning Stent

Some factors that were considered during the design of the stent included the ease of fabrication, accuracy of registration of cuspal anatomy, durability of the material, ease of use for the patient,
and comfort of wear during patient treatment appointments. The general final design of the wax pattern of the customized stent can be seen in Figure 3-1.

The chairside process of creating the wax pattern involved the use of two sheets of pink Extra Hard Baseplate wax (Dentsply). The initial step involved softening and folding one sheet of the extra hard baseplate wax width-wise to create the flat plate of the mandibular occluding surface. Placing the plate into the mouth, aligning the posterior border over the most posterior teeth and lightly registering the cusps of the maxillary arch in the softened wax it is possible to initially verify the size and shape of the plate. Utilizing the indentations in the wax as a guide the flat plate is trimmed with a heated Fahnstock wax knife to remove the excess material and create a handle. Alternatively, a full arch registration can be made using a polyvinylsiloxane bite registration material to create a template that can be used extraorally to initially shape the flat plate and handle (Figure 2).

![Initial shaping of flat plate](image)

**Figure 2**: Initial shaping of flat plate
A second sheet of extra hard baseplate wax is softened with a butane torch then folded and rolled width-wise eight times to create a wax block that is cut in half to create two equal length blocks. The blocks are then placed on the maxillary surface of the flat plate over top of the indentations of the posterior teeth bilaterally (Figure 3).

![Figure 3 Wax pattern fabrication](image)

The position of the blocks are fixed by means of melting and fusing the wax of the flat plate and the wax blocks. At this stage, the basic shape of the wax pattern has been developed. Once the basic shape of the stent is developed, the top surface of the wax blocks are softened and the wax pattern is brought to the mouth and the blocks are aligned with the maxillary posterior teeth. Once aligned, bimanual pressure is applied to the flat plate to create indentations of the maxillary cusps on the superior surface of the wax blocks. Minimal indentation depth is required
if an adequate number of teeth are present. The maxillary indentations are cooled in an ice water bath to aid in cooling and setting the softened wax in order to minimize distortions or changes to the indentations as the remaining steps are performed. In order to capture the cusp tips or incisal edges of the mandibular teeth, the mandibular surface of the wax plate is gently softened in a hot water bath or with a butane torch. The wax pattern is then placed and aligned on the maxillary teeth based on the previous registration indentations; then the patient is asked to slowly close and bite into the softened wax to register the mandibular teeth. Once mandibular teeth are registered, the wax pattern is smoothed producing the finished wax pattern. The average time required to fabricate the wax pattern was 30 minutes. In addition, we were able to utilize a similar protocol as described above to fabricate stents for the two edentulous study participants. The protocol required minimal modification utilizing green thermoplastic modeling compound. Once the basic shape of the wax pattern is fabricated, green compound is softened with a butane torch and then applied to the top of the pillars. Temper the softened compound in a 140°F hot water bath prior to inserting into the patient’s mouth utilizing the softened compound to capture the details of the maxillary residual alveolar ridges. Following the completion of the maxillary registration, the mandibular registration is completed in a similar manner. Following the completion of the wax pattern, the patient is placed in the supine position in the dental chair as close to the treatment position as possible to ensure the device does not result in any discomfort or gagging reflex and adjustments can be performed at this point prior to processing.
Dependent on the urgency of scheduling the patient’s planning CT, it was possible to utilize the wax pattern while the thermoplastic facemask is formed and the planning CT is taken. However, prior to initiation of RT the wax stents are processed in heat cured clear acrylic (Figure 5) by a commercial dental laboratory to ensure uniformity of processing for standardization. The commercial laboratory will take the developed wax pattern and mount the pattern in an investment rings. To the wax pattern a sprue former is attached and then the pattern is mounted in stone within one half of the investment apparatus. Following the setting of the initial investment, it is coated to ensure easy separation from the second half of investment. The remaining half of the investment is completed by applying additional stone to the exposed half of the wax pattern. The stone is allowed to harden and set creating an investment. Following which the wax pattern is eliminated from the stone investment creating a negative of the stent into which clear heat cured acrylic is injected thus creating the final repositioning stent.

Figure 4 Finished wax pattern. (left) maxillary surface. (right) mandibular surface.
The finished stent is provided to the participants for insertion prior to every day’s treatment (Figure 6).

3.3 Follow-up Examinations

Follow-up appointments were scheduled at mid-treatment (3 weeks), end of treatment (5 or 6 weeks) and 3 months post-final day of RT. At these appointments, the participants were asked to complete a Quality of life/Side-effects of IMRT questionnaire provided by one of the CDAs in
the OOD or Dr. Vincent Lee at BCCA Vancouver Centre (Appendix A). OOD staff dentists or Dr. Vincent Lee performed examinations as required at these follow-up appointments.

3.4 Assessment of Patient Stability

In order to assess patient stability for the study, at the start of each treatment appointment the radiation therapist will utilize the on board imaging module on the linear accelerator to capture a daily KeV image of the patient. From the daily KeV images, frontal and lateral images are reconstructed and these daily KeV images are manually matched to the reconstructed images from the planning CT image by the radiation therapist using the on board imaging software match tool. Utilizing the surrogate bony landmarks, distances from the planned radiation isocentre to the bony landmark are measured on both the reconstructed planning CT image and the daily KeV images. These measurements are stored in Varian’s ARIA treatment software. The stability measurements represent the difference of the measurements from the daily KeV images to the initial planning CT image. Due to the ability of the treatment table to adjust and accommodate for some variation in patient positioning, daily measurements were recorded following any automatic adjustments of the treatment table. Deviations in position are calculated as differences in the measurements from the initial position from the planning CT and the adjusted daily position (Figure 7 and Figure 8). Differences in the two positions were calculated in 3 axes: 1) Vertical, 2) Longitudinal and 3) Lateral. This data was extracted from the ARIA software by several radiation therapists and provided for review and assessment. The study group was compared to two retrospective cohorts, one who utilized the previous stent design and the other who utilized no bite block and was stabilized through interdigititation of the teeth alone. The two retrospective cohorts were obtained through an extensive search through the historical
treatment records of the BCCA. Cohort matching was attempted by tumour site utilizing an extensive search through the BCCA records by several radiation therapists at BCCA. Due to the low incidence rates of the included tumours, a very limited number of tumour-matched cohorts were identified and it was impossible to further match the cohorts based on any other demographic parameters. Similar criteria as used for the study group was utilized to extract positional stability data for each of the identified matched cohorts.

Figure 7 Frontal imaging. (l) planning CT image. (m) daily KeV image. (r) matching tool on daily KeV image. As seen in the image on the right, the matching tool superimposes the corresponding image reconstructed from the planning CT image (within the box) over the daily KeV image to produce the matching image.
3.5 Analysis of the Data

The initial portion of the project was to develop and assess the potential workflow related to incorporating a chairside-customized acrylic repositioning stent. As such, this initial portion of the project will be descriptive. Similarly, due to some of the questionnaires being lost to follow-up, the small sample size and the short follow-up period the results from the Side Effects questionnaires will be assessed in a descriptive manner.

Although, it is expected that there is low power to any statistical analyses of the stability and repositioning data it will be analyzed statistically in SPSS statistical software for comparison of the results between the three groups: 1) ST – study group, 2) OB – old bite block and 3) NB – no bite block.
Chapter 4: Results

4.1 Proposed Treatment Workflow Developed During the Study

Based on the present experience, we were able to modify and adapt the patient’s radiation workflow to accommodate the fabrication of the customized acrylic repositioning stent without significantly affecting the radiation workflow. Table 4 describes the overall workflow observed for a patient in which the radiation oncologists have not indicated that there is any immediate urgency to starting the patient’s radiation workflow. This workflow is essentially the same as what has been carried out historically at the BCCA and does not include any additional appointments. This workflow allows for at least one day between wax pattern fabrication appointment and the appointment for facemask fabrication and planning CT image capture with the radiation therapists.

Table 4 Developed treatment workflow – non-urgent treatment

<table>
<thead>
<tr>
<th>Appointment</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Intake from radiation oncologist &amp; referral to dentistry</td>
</tr>
<tr>
<td>2.</td>
<td>Pre-radiation (baseline) dental examination Consistent fabrication of acrylic repositioning stent wax pattern</td>
</tr>
<tr>
<td>3.</td>
<td><strong>IF NON-URGENT</strong>* – the wax pattern is processed in clear acrylic and facemask fabrication and Planning CT is carried out by radiation therapists with the processed acrylic stent</td>
</tr>
<tr>
<td>4.</td>
<td>Patient undergoes IMRT as planned by Radiation Oncologist utilizing the customized acrylic repositioning stent</td>
</tr>
<tr>
<td>5.</td>
<td>Assessment at 3 weeks post initiation of IMRT</td>
</tr>
<tr>
<td>6.</td>
<td>Assessment at 6 weeks – end of IMRT</td>
</tr>
<tr>
<td>7.</td>
<td>Follow up assessment for up to 3 months post-IMRT</td>
</tr>
</tbody>
</table>

*In non-urgent cases, time between appointment 2 and 3 allows for the processing of the stent in acrylic prior to appointment 3
However, one major advantage observed with our proposed sent design was the ability to adapt the workflow to situations in which the radiation oncologists have identified that there is a need to initiate RT as quickly as possible. Table 5 describes the adapted treatment workflow for time sensitive treatment needs when indicated by the radiation oncologists. The adapted workflow can be utilized in situations where the initiation of RT has been recommended to occur as soon as possible or for patients travelling long distances. This protocol allows for the scheduling of the initial dental exam/wax pattern fabrication on the same day as the facemask/planning CT appointment thus eliminating one appointment. The stent can be processed while the RT is being planning by the radiation oncologist.

Table 5 Adapted workflow - urgent treatment

<table>
<thead>
<tr>
<th>Appointment</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Intake from radiation oncologist &amp; referral to dentistry</td>
</tr>
<tr>
<td>2.</td>
<td>Pre-radiation (baseline) dental examination Fabrication of acrylic repositioning stent wax pattern • <strong>IF TREATMENT IS URGENT</strong> - Patient sent for facemask fabrication and Planning CT with wax pattern prior to processing in stent in clear acrylic <strong>IF NOT TIME SENSITIVE</strong> – the wax pattern is processed in clear acrylic and Face mask fabrication and Planning CT is carried out by radiation therapists with the processed acrylic stent</td>
</tr>
<tr>
<td>3.</td>
<td>Patient undergoes IMRT as planned by Radiation Oncologist utilizing the customized acrylic repositioning stent</td>
</tr>
<tr>
<td>4.</td>
<td>Assessment at 3 weeks post initiation of IMRT</td>
</tr>
<tr>
<td>5.</td>
<td>Assessment at 6 weeks – end of IMRT</td>
</tr>
<tr>
<td>6.</td>
<td>Follow up assessment for up to 3 months post-IMRT</td>
</tr>
</tbody>
</table>

*Situations where facemask & planning CT appointments are scheduled on the same day as the initial dental examination due to urgency of treatment or patient logistic issues.*
4.2 Patient Positioning and Stability Data

4.2.1 Patient Demographics

Ten patients consented to participate in the study and had chairside-customized acrylic stents fabricated. Of the initial ten patients, 9 completed treatment and one was lost due to death. The demographics of the recruited patients are summarized in Table 6.

<table>
<thead>
<tr>
<th>Participant</th>
<th>Age</th>
<th>Sex</th>
<th>Tumour Site</th>
<th>Prescribed Radiation Dose (Gy)</th>
<th>Fractions</th>
<th>Radiation Modality</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>High-risk Area</td>
<td>Low-risk Area</td>
<td></td>
</tr>
<tr>
<td>ST1</td>
<td>52</td>
<td>male</td>
<td>Nasal cavity</td>
<td>45</td>
<td></td>
<td>25 VMAT IMRT</td>
</tr>
<tr>
<td>ST2</td>
<td>69</td>
<td>female</td>
<td>Anterior mandible and FOM</td>
<td>66</td>
<td>56</td>
<td>33 VMAT IMRT</td>
</tr>
<tr>
<td>ST3</td>
<td>66</td>
<td>male</td>
<td>Nasal Cavity</td>
<td>70</td>
<td>70</td>
<td>35 VMAT IMRT</td>
</tr>
<tr>
<td>ST4</td>
<td>65</td>
<td>male</td>
<td>Nasal cavity</td>
<td>60</td>
<td>50</td>
<td>25 VMAT IMRT</td>
</tr>
<tr>
<td>ST5</td>
<td>59</td>
<td>female</td>
<td>Anterior FOM</td>
<td>60</td>
<td>54</td>
<td>30 VMAT IMRT</td>
</tr>
<tr>
<td>ST6</td>
<td>82</td>
<td>male</td>
<td>Anterior mandible</td>
<td>60</td>
<td>60</td>
<td>25 VMAT IMRT</td>
</tr>
<tr>
<td>ST7</td>
<td></td>
<td>male</td>
<td>Anterior FOM</td>
<td></td>
<td></td>
<td>Deceased</td>
</tr>
<tr>
<td>ST8</td>
<td>87</td>
<td>male</td>
<td>Maxillary posterior alveolus</td>
<td>60</td>
<td>60</td>
<td>25 IMRT</td>
</tr>
<tr>
<td>ST9</td>
<td>69</td>
<td>male</td>
<td>Oral tongue</td>
<td>66</td>
<td></td>
<td>33 VMAT IMRT</td>
</tr>
<tr>
<td>ST10</td>
<td>80</td>
<td>male</td>
<td>Oral tongue</td>
<td>70</td>
<td></td>
<td>35 VMAT IMRT</td>
</tr>
</tbody>
</table>

*FOM – floor of mouth; VMAT – volumetric arc therapy; IMRT – intensity modulated radiation therapy

High-risk area – region receiving definitive radiation dose or regions at higher post-operative risk of recurrence

As previously mentioned, attempts to match the cohorts to the study group based on available demographic information of the study group. However, due to the low number of cases identified based on the inclusion criteria, case matching was only accomplished by tumour site. The two retrospective cohorts were identified and grouped according to the method of stabilization: 1) OB – old bite block or 2) NB – no bite block. The demographic information for the groups is shown in

Table 7.
Table 7 Tumours anatomical sites among different groups

<table>
<thead>
<tr>
<th>Tumour site</th>
<th>Study group (ST)</th>
<th>Old Bite Block group (OB)</th>
<th>No Bite Block group (NB)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n=)</td>
<td>(n=)</td>
<td>(n=)</td>
</tr>
<tr>
<td>Superior Nasal Cavity</td>
<td>3</td>
<td>4</td>
<td>7</td>
</tr>
<tr>
<td>Gingivoalveolar</td>
<td>1</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>Inferior Oral Cavity</td>
<td>3</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Oral Tongue</td>
<td>2</td>
<td>3</td>
<td>5</td>
</tr>
<tr>
<td>TOTALS</td>
<td>9</td>
<td>9</td>
<td>18</td>
</tr>
</tbody>
</table>

4.2.2 Positioning Measurements

Deviations were presented in for each participant in 3 axes: 1) Vertical (VRT), 2) Longitudinal (LNG), and 3) Lateral (LAT). Deviations were calculated relative to the determined isocentre ranging from negative to positive values depending on which side of the isocentre the patient is positioned on that day. Absolute values for each measurement were generated as this represents the deviation irrespective of the directionality and avoids nullifying the magnitude of the variations due to directional reporting. Absolute averages were generated for each participant for each axis. Subsequently, due to variations in the days of treatment absolute weighted means were calculated and presented in Table 8.

Table 8 Absolute weighted mean and standard deviation of positioning measurement among groups

<table>
<thead>
<tr>
<th></th>
<th>Vertical (cm ± SD)</th>
<th>Longitudinal (cm ± SD)</th>
<th>Lateral (cm ± SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study group (ST)</td>
<td>0.14 ± 0.12</td>
<td>0.20 ± 0.13</td>
<td>0.16 ± 0.12</td>
</tr>
<tr>
<td>Old Bite Block group (OB)</td>
<td>0.19 ± 0.13</td>
<td>0.17 ± 0.13</td>
<td>0.15 ± 0.18</td>
</tr>
<tr>
<td>No Bite Block group (NB)</td>
<td>0.18 ± 0.14</td>
<td>0.16 ± 0.14</td>
<td>0.12 ± 0.11</td>
</tr>
</tbody>
</table>

Statistical comparisons of the data were completed using the SPSS statistical software. The initial analysis was to determine the distribution for each set of data for each patient for every
group. Due to small sample size a Shapiro-Wilk test for normality was selected. The results of the normality tests are presented in Table 9.

Table 9 Shapiro-Wilk test for normality of positioning stability among groups in vertical and lateral axes.

<table>
<thead>
<tr>
<th>Group</th>
<th>Statistic</th>
<th>df</th>
<th>Sig.</th>
</tr>
</thead>
<tbody>
<tr>
<td>VRT</td>
<td>NB</td>
<td>0.926</td>
<td>17</td>
</tr>
<tr>
<td></td>
<td>OB</td>
<td>0.780</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td>ST</td>
<td>0.810</td>
<td>8</td>
</tr>
<tr>
<td>LNG</td>
<td>NB</td>
<td>0.951</td>
<td>17</td>
</tr>
<tr>
<td></td>
<td>OB</td>
<td>0.850</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td>ST</td>
<td>0.863</td>
<td>8</td>
</tr>
<tr>
<td>LAT</td>
<td>NB</td>
<td>0.961</td>
<td>17</td>
</tr>
<tr>
<td></td>
<td>OB</td>
<td>0.858</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td>ST</td>
<td>0.907</td>
<td>8</td>
</tr>
</tbody>
</table>

*VRT—vertical axis; LNG—longitudinal axis; LAT—lateral axis  
NB—no bite block group; OB—old bite block group; ST—study group

It should be noted that the results from the VRT OB and ST groups were significant (P<0.5), therefore these data sets are not normally distributed and as a result were be analyzed with a non-parametric independent sample Kruskal-Wallis test. It is possible to see from the whisker and box plots that the data for the OB and ST groups appeared to be skewed confirming the results of the Shapiro-Wilk test. In addition, outliers exist within both the OB and ST groups that may skew the data. However, based on the results of the Kruskal-Wallis test no statistically significant differences were detected between the ST, NB and OB cohorts within the VRT group. These results are displayed in Figure 9 below.
For comparisons of the data within the LNG and LAT groups, the cohort data within each group was compared by means of a one-way ANOVA analysis. The overall results of the ANOVA demonstrate no statistically significant difference between any of the cohorts within each respective group, LAT and LNG with p>0.05. Post-hoc Tukey test was also run to determine if there were any specific comparisons that may have presented with a significant difference; however, no combination of comparisons presented with any significant difference (p>0.05). The summary of the ANOVA and post-hoc Tukey test are presented in Table 10 and Table 11. However, as previously mentioned factors such as differences in tumour site, small sample sizes,
differences in treatment technique between cohorts, differences in data acquired, and difficulty in finding adequately matched cohorts may limit the power of the statistical analyses and as a result make it difficult to identify any true variations.

Table 10 Analysis of variance comparing LAT and LNG axes between and among groups

<table>
<thead>
<tr>
<th></th>
<th>Sum of Squares</th>
<th>df</th>
<th>Mean Square</th>
<th>F</th>
<th>Sig.</th>
</tr>
</thead>
<tbody>
<tr>
<td>LAT</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Between Groups</td>
<td>0.009</td>
<td>2</td>
<td>0.005</td>
<td>0.590</td>
<td>0.560</td>
</tr>
<tr>
<td>Within Groups</td>
<td>0.254</td>
<td>32</td>
<td>0.008</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>0.263</td>
<td>34</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LNG</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Between Groups</td>
<td>0.008</td>
<td>2</td>
<td>0.004</td>
<td>0.439</td>
<td>0.649</td>
</tr>
<tr>
<td>Within Groups</td>
<td>0.289</td>
<td>32</td>
<td>0.009</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>0.297</td>
<td>34</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*LAT – lateral axis; LNG – longitudinal axis; df – degrees of freedom; F – ANOVA F-value; Sig. – significance level

Table 11 Post-hoc Tukey comparisons for LAT and LNG axes between and among groups

<table>
<thead>
<tr>
<th>Dependent Variable</th>
<th>Mean Difference</th>
<th>Std. Error</th>
<th>Sig.</th>
<th>95% Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Lower Bound</td>
</tr>
<tr>
<td>LAT</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NB</td>
<td>-.03765</td>
<td>.03672</td>
<td>.567</td>
<td>-.1279</td>
</tr>
<tr>
<td>ST</td>
<td>-.02542</td>
<td>.03672</td>
<td>.770</td>
<td>-.1157</td>
</tr>
<tr>
<td>OB</td>
<td>.03765</td>
<td>.03672</td>
<td>.567</td>
<td>-.0526</td>
</tr>
<tr>
<td>ST</td>
<td>.01222</td>
<td>.04199</td>
<td>.954</td>
<td>-.0910</td>
</tr>
<tr>
<td>ST</td>
<td>.02542</td>
<td>.03672</td>
<td>.770</td>
<td>-.0648</td>
</tr>
<tr>
<td>OB</td>
<td>-.01222</td>
<td>.04199</td>
<td>.954</td>
<td>-.1154</td>
</tr>
<tr>
<td>LNG</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NB</td>
<td>-.00163</td>
<td>.03919</td>
<td>.999</td>
<td>-.0979</td>
</tr>
<tr>
<td>ST</td>
<td>-.03497</td>
<td>.03919</td>
<td>.649</td>
<td>-.1313</td>
</tr>
<tr>
<td>OB</td>
<td>.00163</td>
<td>.03919</td>
<td>.999</td>
<td>-.0947</td>
</tr>
<tr>
<td>ST</td>
<td>.03497</td>
<td>.04482</td>
<td>.740</td>
<td>-.1435</td>
</tr>
</tbody>
</table>

*LAT – lateral axis; LNG – longitudinal axis; NB – no bite block group; OB – old bite block group; ST – study group; Sig – significance level

4.3 Reporting of Side Effects from IMRT

From the initial ten participants, two participants were excluded from the assessment of the results. One patient was lost due to death and the other participant was lost due to insufficient data resulting from failure to return for follow-up appointments. A graphical assessment for each of the self-reported side-effect/quality of life questionnaires was performed. From these assessments, a trend was observed in some patient responses in which from baseline through to
the end of active IMRT there was an increase in symptoms of oral side effects. Subsequently, following the post-IMRT follow-up period there was generally a decrease in the subjective severity of the side effects. Furthermore, no trends could be established for self-reported symptoms between the participants whose tumours were in the superior oral cavity/maxillary sinus/nasal cavity when compared to those in the lower/mandibular region. In an attempt to present a succinct summary of the questionnaire results the questions were combined for assessment into three major themes: 1) mouth and throat soreness, 2) taste alterations, and 3) dryness of mouth. One representative question for each of the identified themes will be presented.

The first question relates to throat soreness: “On a scale of 0 to 10, how would you rate your overall mouth and throat soreness during the past 24 hours? 0 (none) – 10 (extreme)”.

Figure 10 presents the results from this question.
The general trend with respect to overall mouth and throat soreness among the participants was that by the 3-month follow-up most participants reported either no further increase in soreness or a reduction in the overall mouth and throat soreness (Figure 10). Participant ST2 reported having increased discomfort beyond baseline at the three-month post-IMRT time point.

The next question that presented relates to alterations in taste: “During the past 24 hours, was your taste sensitivity reduced? 0 (none) – 4 (extreme)”.

![Figure 11 Taste sensitivity alteration during past 24 hours at each assessment time point](image)

Once again, a trend that was observed was a reduction in self-reported taste sensitivity, especially during the early to mid-treatment phases of their RT (Figure 11). While the subjective reporting seemed to indicate no further taste alterations by the end of the course of treatment, it was noted by several participants that the lack of further alteration in taste sensitivity was mainly due to the “complete” loss of taste at an earlier time point of their treatment.
The final question presented relates to oral dryness: “During the past 24 hours, rate the dryness your mouth feels when eating a meal? 0 (none) – 10 (extreme)”.

![Figure 12 Mouth dryness during past 24 hours at each assessment time point](image)

When assessing this chart, it is possible to see the same general trend with six out of the 8 participants reporting mouth dryness that worsened during treatment but returned to baseline level or better following the 3-month post-IMRT follow-up period. Only one participant (ST4) reported worse mouth dryness at the 3-month post-IMRT follow-up period. In addition, the magnitude of difference from baseline self-reported dryness is relatively small except for the participant ST3 who presented with a tumour in the nasal cavity (Figure 12).
Chapter 5: Discussion

5.1 Stent Design

As been identified previously, much of the available literature regarding the use of intraoral repositioning stents are case reports and as such provide little for comparison other than to compare the potential treatment workflow issues. While the design of the particular stent varies by study, there are several notable similarities of our proposed stent developed in the current study. Firstly, most of the designs were fabricated from durable materials such as processed methylmethacrylate acrylic.\textsuperscript{32, 33, 35, 50} The only exception was the design presented by Hollow et al., which utilized flexible ethylene vinyl and silicone for the pillars. Secondly, as one of the fundamental purposes of this device is to create separation between the maxillary arch and mandibular arch the vast majority of stents utilized vertical pillars/blocks/wedges to accomplish this task.\textsuperscript{29, 32, 33, 35, 50} Thirdly, all designs incorporated some feature that would aid in the stabilization and depression of the tongue, such as tongue blades, vacuformed polyethylene sheets, and processed acrylic plates. As seen in Figure 5, we have incorporated these three design features into our stent. We have also considered the characteristics of an \textit{ideal} stent and designed a stent that is customized chair-side, can be readily converted into hard clear acrylic, maintains its dimensional stability, provides stabilization of the tongue, and separation of the maxillary and mandibular structures.

5.2 Treatment Workflow

In the majority of the case reports, the treatment workflow included additional time between initial dental examination and planning CT imaging due to the indirect nature of their protocols.\textsuperscript{29, 32, 33, 35, 50} In order to fabricate the intraoral prosthesis in such an indirect manner,
dental impressions of the maxillary arch, mandibular arch and a jaw relation record are made. The impressions are then poured in a dental stone and the casts are mounted in a dental articulator utilizing the jaw relation record at which point the fabrication of the stent can commence. In addition to chair time and reliance on dentist’s skills, these extra steps and laboratory procedures would require several days to complete creating a delay in the commencement of planning of the RT and as a result the start of RT.

In contrast, with the workflow developed around the proposed study stent we are able to demonstrate that it is possible to incorporate a direct chair-side customization of the repositioning stent without adversely affecting the RT workflow. In addition, with the adapted protocol it may be also possible to shorten the delay to the initiation of RT, as compared to indirect methods. The chair-side fabrication of the wax pattern of the proposed stent allows for the immediate transfer of the patient for fabrication of the thermoplastic facemask and subsequent capture of the planning CT image right after the completion of the wax pattern at the same appointment. The amalgamation of the wax pattern fabrication and subsequent thermoplastic mask fabrication and planning CT on the same day can eliminate the need for a separate appointment for the thermoplastic facemask and planning CT. Following which, the wax pattern is processed in clear acrylic and patients undergo IMRT as planned by the radiation oncologist utilizing the processed repositioning stent.

The durability of the stents can also affect the treatment workflow. At the BC Cancer Agency, the OOD has been utilizing a chair-side prosthesis customization protocol based on the one proposed by Epstein et al.40 In the original design by Epstein et al., a hollow acrylic tube was
utilized to create the separation and airway for the patient. To which a resin tongue blade was attached with a rubber band and soft baseplate wax was softened in a hot water bath and molded around the acrylic tube. The patient was then asked to bite into the softened wax while the wax was molded to the surrounding tissues. Once completed, the wax pattern of this prosthesis was available for use during the planning CT, after which the wax pattern was flanked and processed in acrylic to be used during RT. More recently, it has been observed that while the design of the prosthesis has endured, none of the prostheses were subsequently processed to replace the wax with acrylic resin. As a result, the durability of the prostheses were significantly compromised and often did not survive the entire course of IMRT. Some of the mid-treatment failures with this design have been due to fracture of the wax registration material, breakage of the rubber bands and inability to wear due to sharp wax edges causing pain and ulcerations, and unfortunately, can result in the need to re-plan and start RT anew.

We were also able to overcome this deficiency and potentially improve treatment workflow with the current study design proposed. Similar to Epstein et al.\textsuperscript{40}, the current study design is customized at chair-side and the wax pattern can be utilized immediately for molding of the thermoplastic facemask and for the planning CT imaging. Furthermore, this current design allows a simpler procedure to convert the wax to acrylic, which can be done by the Certified Dental Assistants. To ensure consistency of the results, we utilized a single commercial laboratory to process the stents into acrylic for the study cases. However, we were also able to adapt the protocol to demonstrate that we were able to easily duplicate the developed wax pattern into clear acrylic resin within two hours simply utilizing a customized duplicating flask, irreversible hydrocolloid impression material, and autopolymerizing clear methylmethacrylate at
an approximate cost of $5-10 per stent. As it is possible to observe, direct chair-side fabrication and customization has the advantage of being more globally time efficient and potentially lower cost than indirect methods that would require more materials and equipment. Anecdotally, all study patients were able to insert the stent on their own and were comfortable with the stent in place during the course of their IMRT. In addition, the radiation therapists involved reported the processed clear acrylic repositioning stents were more durable and easier to handle than the previous design.

5.3 Stability and Repositioning

Many publications have stated that the use of an intraoral stent or prosthesis will ensure the consistent reproducibility of patient position during RT.\textsuperscript{29, 32, 33, 50} However, very few publications have attempted to quantify these statements. Studies by Lopatta \textit{et al.}\textsuperscript{52} and Baumert \textit{et al.}\textsuperscript{51} conducted clinical trials to the measure the effects of intraoral stabilization on the reproducibility of patient positioning throughout the course of RT. Lopatta \textit{et al.} (English language abstract) assessed 29 patients planned for stereotactic RT of the head. Eighteen of these patients were assigned to receive additional intraoral fixation of either the maxilla or mandible through the attachment of a molded thermoplastic intraoral mouthpiece to the external thermoplastic facemask. Positional reproducibility was assessed by comparison serial frontal and lateral radiographs containing calibration rings to the reference radiographs. The authors reported statistically significant improvements in patient repositioning in all axes when the mouthpiece was utilized with mean deviations of $<1.5\text{mm.}$\textsuperscript{52} Baumert \textit{et al.}\textsuperscript{51} conducted a similar study in which 57 participants were divided into 3 groups for comparison. Thirty-five patients were provided upper jaw support attached to the open stereotactic ring, seventeen
patients were provided a customized bite block attached to the ring and five were treated without additional fixation. Instead of serial radiographs, the authors utilized serial check CT images, captured weekly over the 3-6 week course of treatment, for software comparison of daily isocenters to those captured on initial planning CT. Mean deviation for their bite-block group was 2.2 ± 1.1mm, for the upper jaw support was 3.3 ± 1.8mm and for the no additional fixation group was 3.7 ± 2.8mm. No significant difference in positional accuracy was noted in the comparison of upper jaw support and no fixation groups. Nor was there any reported difference in deviation when the no fixation group was compared to the bite block group. The only significant reduction in the deviation was noted in the comparison of the upper jaw support to customized bite block groups. While the authors concluded that the use of additional fixation in their study improved patient repositioning accuracy it is difficult to accept this conclusion due to the two other conflicting comparisons. From our study the mean deviations for the study group was 0.16 ± 0.12 cm, the old bite block group was 0.17 ± 0.15 cm, and the no bite block group was 0.15 ± 0.13 cm. The lack of any statistical difference between our three cohorts is most likely due to the small sample size limiting the statistical power. However, when compared to the results of Baumert et al. it can been seen that all three of our cohorts demonstrated less mean deviation than their upper jaw and no additional fixation groups and is comparable to the bite-block group. Our study groups demonstrated similar deviations to those reported by Lopatta et al.

When comparing the current study to the two previous studies it is quite evident that there are significant differences in the variable being assessed. In the two previous studies, intraoral fixation was provided by means of extensions of extraoral frameworks or facemasks. However
in the present study, the variable that is being assessed is the customized intraoral repositioning stent. Similar to Baumert et al., we compared positioning relative to the planned isocentre from the planning CT. However, unlike the previous study that utilized serial CT images for comparisons, the protocol at the BCCA utilizes the daily KeV images, which are taken as part of the standard of care, for these comparisons. These differences in measurement protocols make comparison of results between the different studies more difficult.

While assessing the results of the current study data some limitations were identified that make drawing inferences or conclusions difficult. Limitations of the study include small sample size, inter-examiner variability, lack of grouping and standardized landmarks based on tumour location, the inability to ensure the tongue is properly restrained, and retrospective data from the matched cohorts. Furthermore, the retrospective nature of matched cohort data creates biases resulting from differences in measurement frequency, measurement protocols, treatment modalities and variations in site of treatment. The small sample size limited the statistical power of our data and the identified confounding factors limited the ability to make any comparisons of patient positioning variability within our study or between our retrospective groups and any other published study. Furthermore, difficulty of the retrospective chart search limited the variables to which the participants could be matched. As a result, additional variability may exist between each cohort thus further limiting our ability to create any significant conclusions from the data.

In addition, one of the main functions of the intraoral stent is to reliably relate the mandible to the maxilla. Our ability to properly assess the efficacy of the independent intraoral repositioning stent may lie in our ability to utilize landmarks specifically related to the maxilla/base of skull
and to the mandible. The identification of stable reproducible maxillary and mandibular bony landmarks that are easily identifiable on the daily KeV images may allow for a more accurate assessment of the role of the intraoral repositioning stent in daily patient and mandibular repositioning. In addition, as daily KeV images are taken at the start of each IMRT session there is a potential for an intra-appointment difference of positioning due to patient fatigue, weight loss or muscular relaxation during treatment. In order to properly investigate this possible factor, additional KeV images would be required at the end of the treatment session; however, this would subject the patient to extra radiation and as a result is not part of the standard protocol.

5.4 Assessment of Side-Effects

As was presented in the results section, there was a reasonably consistent pattern of self-reported side-effect symptomology. In the study by Goel et al., 33 patients were followed and assessed for radiation side effects for 60 days. The authors noted a significant improvement associated with mucositis and xerostomia over time. Reduction of incidence and severity of mucositis and xerostomia was reported in the group provided a positioning stent. The presented pattern in our study group with respect to mouth/throat soreness and dryness appear to be consistent with the results presented by Goel et al. However, it is possible to see that reporting of side effects is subjective. In Figure 10, one can observe that two participants, ST3 and ST6, were experiencing more discomfort prior to the start of RT, which continued to decrease over time. Whereas, ST2 reported higher discomfort at the 3-month post-IMRT time point. Similarly, irrespective of tumour location some participants (ST4 and ST6) experienced an increase in mouth dryness following IMRT; whereas other participants (ST2, ST3 and ST10) experienced decreased issues related to mouth dryness. Also for edentulous participant ST6 the use of the study stent did not
appear to increase his reported mouth soreness throughout the course of IMRT. Whereas, the other edentulous patient ST2 reported an increase in mouth soreness through the end of their treatment; therefore, the role of the repositioning stent on mouth soreness cannot not be excluded. However, due to the design of the study, small number of cases, and incompleteness of the questionnaire data, it is impossible to draw any conclusions from our observations.

Similar, taste alteration appeared to demonstrate a decrease in subjective symptoms; however, this may be due to patients’ adaptation and acceptance to the loss of taste sensitivity earlier during the course of their treatment as noted by some of the study participants. Goel et al.33 reported similar results that within their study participants there was no improvement in the taste alteration criteria.

One of the main limitations regarding documenting participant side effects during this study was the length of the questionnaire and the structure of some of the questions. Reduction in the number of questions and more focus on the key questions should would require less time to complete and result in much more focused responses related to their side effects. In addition, the use of structured interview questions would also provide more insight into personal experiences regarding any side effects. The combination of this information would allow for a more quantitative and qualitative analysis of the patient side effect experience.

5.5 Future Directions

Our current study was designed as a feasibility study to demonstrate the feasibility of utilizing the proposed repositioning stent. As a result, it is reasonable to understand that due to the lack of
sample size we did not observe any significant difference between the new study stent design and other designs including our old protocol. We have identified numerous confounding variables that may have affected the outcome. As very little has been published on the uses of an independent stent, there is still an opportunity to further assess the value of the stent on patient repositioning stability. Future studies should ideally be prospectively designed to help minimize limitations. Potential future studies of positional stability should aim to manage the confounding variables identified such as examiner variability; standardization of anatomic landmarks based on tumour site; patient groupings based on tumour sites, radiation type, radiation dose, and demographic information; and sample size to ensure adequate study power. In addition, it may be important to assess the variability of positioning at specific time points during the IMRT to assess if there is a relationship between the point of IMRT and magnitude of variations.

As previously mentioned, the effect of the intraoral stent on patient reported side effects should also be investigated more thoroughly. Simplifying the questionnaire and utilizing structured interview questions may help gather more information on qualitative patient experiences regarding radiation side effects. It may also be possible to relate side effects to tumour site and the dose distribution resulting from the use of an intraoral stent to the data gathered from questionnaire and structured interviews. Further, as our study was limited in scope, no attempts to relate tumour/radiation site to side effects was carried out. It may be beneficial to attempt to incorporate a standardized COE to record tumour site and clinical presentation to which documented side effects experienced can be associated. In addition, the incorporation of salivary flow measurements as part of the follow-up appointments will allow for the quantification of the salivary gland function to which the qualitative information can be related. It may be of value to
increase the length of follow-up for any future side-effects/QoL studies. Some side-effects have been documented to persist longer than the 3 month post-IRMT time point; therefore, it may be of value to extend the follow-up period to at least 12 months post-IMRT. This will also bring the follow-up period closer to those previously reported in the literature and may allow for more appropriate comparisons. Lastly, it may be important to understand the effects of different thicknesses or separation distances of the acrylic repositioning stent on radiation dose distribution and how these variables may affect potential RT side effects.
Chapter 6: Conclusion

Based on our experience in this study, we were able to develop and incorporate the creation of a chair-side customized and fabricated repositioning stent without altering the RT workflow. The design and protocol have the potential to improve time efficiency of the prosthesis fabrication process without incurring significant financial costs. In addition, based on the experiences reported by the radiation therapists involved, the proposed design has been demonstrated to be durable and observed to be comfortable enough for the patient to be utilized through an entire course of IMRT.

The results from the repositioning/stability assessment seem to agree with the limited publications that have been conducted to assess the role of intraoral fixation on patient repositioning. However, as this is a feasibility study with a small sample size and short 3-month post-IMRT follow-up, it is difficult to extrapolate the results to the general population. Nevertheless, when utilizing the customized study stent, the stent appeared to maintain positional stability as well as the previous design and did not appear to negatively impact on the daily patient repositioning or comfort.
Bibliography


[22] Poh CF, Zhang L, Anderson DW, Durham JS, Williams PM, Priddy RW, Berean KW, Ng S, Tseng OL, MacAulay C, Rosin MP. Fluorescence visualization detection of field alterations in


[52] Lopatta E, Liesenfeld SM, Bank P, Wurm R, Gunther R, Wiezorek T, Wendt TG. [Improved patient repositioning accuracy by integrating an additional jaw fixation into a high
## Appendix

### Appendix A - Side-effects Questionnaire

<table>
<thead>
<tr>
<th>IMRT Stent Study QOL Questionnaire</th>
<th>Unique Study ID</th>
<th>Date of questionnaire:</th>
</tr>
</thead>
<tbody>
<tr>
<td>How many days (months) from the start of radiation therapy?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>How would you rate your OVERALL HEALTH during the PAST 24 HOURS?</td>
<td>0 1 2 3 4 5 6 7 8 9 10</td>
<td>Good</td>
</tr>
<tr>
<td>During the PAST 24 HOURS, how much MOUTH AND THROAT SORENESS did you have?</td>
<td>0 1 2 3 4</td>
<td>None</td>
</tr>
<tr>
<td>During the PAST 24 HOURS, how much did MOUTH AND THROAT SORENESS limit you in swallowing?</td>
<td>0 1 2 3 4</td>
<td>None</td>
</tr>
<tr>
<td>During the PAST 24 HOURS, how much did MOUTH AND THROAT SORENESS limit you in Drinking?</td>
<td>0 1 2 3 4</td>
<td>None</td>
</tr>
<tr>
<td>During the PAST 24 HOURS, how much did MOUTH AND THROAT SORENESS limit you in Eating?</td>
<td>0 1 2 3 4</td>
<td>None</td>
</tr>
<tr>
<td>During the PAST 24 HOURS, how much did MOUTH AND THROAT SORENESS limit you in Talking?</td>
<td>0 1 2 3 4</td>
<td>None</td>
</tr>
<tr>
<td>During the PAST 24 HOURS, how much did MOUTH AND THROAT SORENESS limit you in Sleeping?</td>
<td>0 1 2 3 4</td>
<td>None</td>
</tr>
<tr>
<td>On a scale of 1 to 10, how would you rate your OVERALL MOUTH AND THROAT SORENESS during the PAST 24 HOURS?</td>
<td>0 1 2 3 4 5 6 7 8 9 10</td>
<td>None</td>
</tr>
<tr>
<td>During the past 24 hours, how much did tooth sensitivity distress or bother you?</td>
<td>0 1 2 3 4</td>
<td>None</td>
</tr>
<tr>
<td>During the past 24 hours, how much did the overall feeling of your mouth distress or bother you?</td>
<td>0 1 2 3 4</td>
<td>None</td>
</tr>
<tr>
<td>Question</td>
<td>Score</td>
<td></td>
</tr>
<tr>
<td>------------------------------------------------------------------------</td>
<td>-------</td>
<td></td>
</tr>
<tr>
<td>During the past 24 hours, how much did the overall feeling of your oral cavity affect your well-being?</td>
<td>0-4</td>
<td></td>
</tr>
<tr>
<td>During the past 24 hours, how would you rate your overall quality of life?</td>
<td>0-10</td>
<td></td>
</tr>
<tr>
<td>During the past 24 hours, how would you describe your throat symptoms?</td>
<td>0-8</td>
<td></td>
</tr>
<tr>
<td>During the past 24 hours, what was your worst/most bothersome symptom from your throat?</td>
<td>0-8</td>
<td></td>
</tr>
<tr>
<td>How bothersome is your worst throat symptom now?</td>
<td>0-10</td>
<td></td>
</tr>
<tr>
<td>Have you been able to follow mouth care recommendations that you have received?</td>
<td>0-2</td>
<td></td>
</tr>
<tr>
<td>During the past 24 hours, did you have a change in taste?</td>
<td>0-4</td>
<td></td>
</tr>
<tr>
<td>During the past 24 hours, was your taste sensitivity reduced?</td>
<td>0-4</td>
<td></td>
</tr>
<tr>
<td>During the past 24 hours, how much did taste changes distress or bother you?</td>
<td>0-4</td>
<td></td>
</tr>
<tr>
<td>If you have taste change, what time of the day is it worst?</td>
<td>1-5</td>
<td></td>
</tr>
<tr>
<td>Question</td>
<td>Rating Options</td>
<td></td>
</tr>
<tr>
<td>-------------------------------------------------------------------------</td>
<td>--------------------------------------------------------------------------------</td>
<td></td>
</tr>
<tr>
<td>During the past 24 hours, rate the discomfort of your dentures due to dryness</td>
<td>0 1 2 3 4 5 6 7 8 9 10&lt;br&gt;None&lt;br&gt;Extreme</td>
<td></td>
</tr>
<tr>
<td>During the past 24 hours, rate the difficulty you experience in speaking due to dryness of your mouth and tongue</td>
<td>0 1 2 3 4 5 6 7 8 9 10&lt;br&gt;None&lt;br&gt;Extreme</td>
<td></td>
</tr>
<tr>
<td>During the past 24 hours, rate the difficulty you experience in chewing food due to dryness</td>
<td>0 1 2 3 4 5 6 7 8 9 10&lt;br&gt;None&lt;br&gt;Extreme</td>
<td></td>
</tr>
<tr>
<td>During the past 24 hours, rate the difficulty you experience in swallowing food due to dryness</td>
<td>0 1 2 3 4 5 6 7 8 9 10&lt;br&gt;None&lt;br&gt;Extreme</td>
<td></td>
</tr>
<tr>
<td>During the past 24 hours, rate the dryness your mouth feels when eating a meal</td>
<td>0 1 2 3 4 5 6 7 8 9 10&lt;br&gt;None&lt;br&gt;Extreme</td>
<td></td>
</tr>
<tr>
<td>During the past 24 hours, rate the dryness in your mouth while not eating or chewing</td>
<td>0 1 2 3 4 5 6 7 8 9 10&lt;br&gt;None&lt;br&gt;Extreme</td>
<td></td>
</tr>
<tr>
<td>During the past 24 hours, rate the frequency of sipping liquids to aid in swallowing food</td>
<td>0 1 2 3 4 5 6 7 8 9 10&lt;br&gt;None&lt;br&gt;Extremely Frequent</td>
<td></td>
</tr>
<tr>
<td>During the past 24 hours, rate the frequency of fluid intake required for oral comfort when not eating</td>
<td>0 1 2 3 4 5 6 7 8 9 10&lt;br&gt;None&lt;br&gt;Extremely Frequent</td>
<td></td>
</tr>
<tr>
<td>During the past 24 hours, rate the frequency of sleeping problems due to dryness</td>
<td>0 1 2 3 4 5 6 7 8 9 10&lt;br&gt;None&lt;br&gt;Extremely Frequent</td>
<td></td>
</tr>
<tr>
<td>Salivary Collection Protocol Reviewed with Patient?</td>
<td>Yes / No</td>
<td></td>
</tr>
<tr>
<td>Whole Resting Saliva</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Whole Stimulated Saliva</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Which Appointment is this?</td>
<td>☐ Baseline&lt;br&gt;☐ Intra-IMRT – 3 weeks&lt;br&gt;☐ End of IMRT – 6 weeks&lt;br&gt;☐ 3 months post-IMRT</td>
<td></td>
</tr>
</tbody>
</table>