STROKE AFTER RADIOTHERAPY TO TREAT HEAD AND NECK CANCER - WHAT IS THE RISK?

by

Erin Arthurs

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Abstract

***Background*:** Head and Neck cancers (H&NCa) are typically associated with risk factors such as smoking and alcohol use. The human papilloma virus (HPV) has begun to play a role in the pathogenesis of these cancers, decreasing the age of diagnosis and increasing survival. Curative H&NCa treatments can include surgery (SX) and radiotherapy (RT) and one of the suggested late effects of RT is damage to blood vessels. The current literature identifies vascular injury and stroke as possible outcomes following RT among patients with H&NCa.

***Objectives*:** 1) To determine the risk of ischemic stroke among patients that received any curative RT compared to patients that were treated with SX alone, and quantify this risk with respect to time following treatment, 2) to determine how modifications of RT regimens affect the risk of ischemic stroke, specifically the addition of chemotherapy, preceding the RT with surgical neck dissection and different doses of radiation, and 3) to determine the risk of stroke-related events, including transient ischemic attacks and carotid endarterectomies/stents, among patients that were treated curatively with any RT compared to patients treated with SX alone.

***Methods*:** A retrospective cohort design using incident cases of H&NCa identified through the Ontario Cancer Registry was used to address these objectives. The risk of stroke following RT was assessed using databases from the Institute of Clinical Evaluative Sciences. The risk of – and time to stroke was be examined using a survival analytic approach, accounting for the competing risk of death. Cause-specific Cox proportional hazards models adjusted for stroke risk factors and cumulative incidence functions were estimated for each objective.

***Results*:** The study cohort included 14,069 patients with H&NCa. RT was found to contribute considerably to the risk of stroke compared to SX - both alone (HR=1.70, 95%CI: 1.41,2.05) and after combining all treatment modalities that included any radiation exposure (HR=1.46, 95%CI: 1.23,1.73).

***Conclusion*:** This study's results show that RT contributes a risk of stroke in terms of a late effect of treatment. These findings were consistent with biological hypothesis and contribute a significant and important addition to the body of literature.

Co-Authorship

This thesis is the work of Erin Arthurs in collaboration with co-supervisors, Dr. Stephen F. Hall and Dr. Yingwei Peng and her thesis committee, Dr. Tim Hanna and Dr. Khaled Zaza. The study was designed by Erin Arthurs, Dr. Hall and Dr. Peng. Data linkages and preparation were performed by Ms. Rebecca Griffiths at the Institute for Clinical Evaluative Sciences (ICES). Data preparation and statistical analysis were performed by Erin Arthurs with input and guidance by Dr. Hall and Dr. Peng. This thesis was written by Erin Arthurs with feedback and revisions with respect to wording and content provided by Dr. Hall, Dr. Peng, Dr. Hanna and Dr. Zaza.

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List of Acronyms

AF	Atrial Fibrillation
AMI	Acute Myocardial Infarction
CCE	Cancer Care and Epidemiology
CEA/CAS	Carotid Endarterectomy/Carotid Stent
CIF	Cumulative Incidence Function
CIHI/DAD	Canadian Institute for Health Information Discharge Abstract Database
CT	Chemotherapy
H&NCa	Head and Neck Cancer
HPV	Human Papilloma Virus
ICES	Institute for Clinical Evaluative Sciences
IHD	Ischemic Heart Disease
IMRT	Intensity-modulated radiotherapy
MI	Myocardial Infarction
OCR	Ontario Cancer Registry
OHIP	Ontario health Insurance Plan
OPIS	Ontario Patient Information System
ORGD	Ontario Registrar General Death Database
PVD	Peripheral Vascular Disease
RT	Radiotherapy
SX	Surgery
TIA	Transient Ischemic Attack

Chapter 1: Introduction

1.1 Background

Head and Neck cancers (H&NCa) represent approximately 5% of all cancers in Canada, and 85% are squamous cell carcinomas (1). The most recent 5-year relative age-adjusted survival rate for squamous cell carcinomas of the head and neck has been shown to be as high as 67% (2). H&NCas have typically been associated with risk factors such as smoking and alcohol use, however, with a changing pathogenesis of these diseases due to the human papilloma virus (HPV), a decrease in the age of diagnosis and an increase in survival have been observed (3). Treatments for H&NCas can include surgery (SX), radiotherapy (RT), chemotherapy (CT), or a combination of treatments, however guidelines recommend SX, RT or chemoradiation (concurrent radiotherapy with chemotherapy) when the treatment intent is curative as opposed to palliative (4). For early-stage cancers where either SX or RT are indicated as primary intervention, both treatments show similar cure rates, however acute and late side effects of each treatment can determine the regimen most appropriate for the patient (5).

1.2 Rationale

The acute and late effect of RT are related to damaging healthy, normal cells surrounding the tumour, when targeting cancer cells (1,6). As such, one of the suggested late effects of RT is damage to blood vessels, especially major vessels such as carotid artery (7). The current literature identifies vascular injury and stroke as possible outcomes following radiotherapy among patients with H&NCa, due to thickening and hardening of the carotid arteries (8). Stroke is a debilitating event, potentially causing permanent disability to an individual while costing the health care system millions of dollars (9). With evidence that this is a possible long term outcome for patients who survive their H&NCa following RT, it is of importance to understand the degree to which RT puts patients with H&NCa at risk of stroke and at what point following treatment. The current literature aimed at quantifying this risk is methodologically

flawed and does not represent a Canadian population, the current study aimed to: quantify the risk of stroke and stroke related events after receiving curative radiotherapy compared to surgery, model the time to stroke, and look at variations in radiotherapy treatment that could also affect this risk. A better understanding of the risk of stroke for patients with H&NCa would contribute to the clinical body of knowledge used to assign oncological treatment.

1.3 Objectives

The purpose of the study was to investigate and quantify the risk of stroke following curative treatment for H&NCas. The specific objectives included:

1. Determine the risk of ischemic stroke among patients that received any curative RT compared to patients that were treated with SX alone, and quantify this risk with respect to time following treatment.
2. Determine how modifications of RT regimens affect the risk of ischemic stroke, specifically the addition of chemotherapy, preceding RT with surgical neck dissection and different doses of radiation.
3. Determine the risk of stroke-related events, including transient ischemic attacks and carotid endarterectomies/stents, among patients that were treated curatively with any RT compared to patients treated with SX alone.

Objective 1 was the primary focus of this research, and in addition to obtaining risk estimates, involved descriptive statistics across groups of treatment regimens to provide a contextual background for the alternate grouping of the regimens involving RT. Objectives 2 and 3 were meant to address outcomes following different treatment approaches and to acknowledge the possible risk of stroke-related events following RT, independent from the risk of stroke.

1.4 Thesis Organization

This thesis is organized into five chapters. Chapter 2 provides a review of the literature that is relevant for this study, including: the epidemiology and etiology of H&NCa, curative treatments options

for H&NCa, the definition, etiology and epidemiology of strokes and stroke related events, including symptoms, risk factors and prevention of stroke, the relationship between RT and atherosclerosis, and the evidence of stroke following RT among patients with H&NCa. Chapter 3 outlines the methods used for this study, including more detailed objectives, study design, data sources, study population, study variables, including exposure, outcome, and covariate definitions, and strategies for statistical analysis. Chapter 4 presents the results from the statistical analyses for each objective as well as a description of the study population. A discussion of the findings are described in Chapter 5, including interpretation of the results, contextualizing the findings with respect to the current literature, strengths and limitations of the study and implications of this research.

Chapter 2: Literature Review

2.1 Head and Neck Cancer Epidemiology and Etiology

H&NCas include primary malignancies of the oral cavity, larynx, pharynx, nasal cavity, sinuses, and salivary glands (10). Nearly 85% of H&NCas are squamous cell carcinomas that arise from the lining (mucosa) of the upper aerodigestive tract (1,10). Cancers of other histologies are much less common, and are most often found in the nasal cavity, sinuses and salivary glands (1). Although representing the 10th most common cancer worldwide (10), it is an uncommon disease in Canada, as the overall prevalence of H&NCa represents approximately 5% of all cancers (11). The most recent report from the Canadian Cancer Statistics does not provide the number of incident H&NCa cases per year, however, the two most frequently diagnosed H&NCas are cancer of the oral cavity with 4000 new cases, and laryngeal cancer with 1050 new cases in 2012 (11).

Treatment approaches and prognosis of this disease are histology, site and sub-site and stage dependant (10,12).Overall survival for H&NCas is site dependent, however rates have steadily been increasing (2). Pulte et al. reported on a cohort of patients with H&NCa whose data were collected through the Surveillance, Epidemiology, and End Results (SEER) Program in the U.S., and from 2002-2006 they found that survival among patients with cancer of the oral cavity was 63%, Nasopharynx was 62% Oropharynx was 42%, Hypopharynx was 34%, and Larynx was 67%, while for all H&NCas, survival was 66% (2).

Within the last 15 years, patient characteristics of individuals with H&NCa have changed due to two etiological streams for the disease. Previously, the most commonly cited risk factors for H&NCa were tobacco and alcohol use, as they were associated with approximately 75% of cases (10). The most common subsites have traditionally been the larynx and oral cavity. It has become recognized within the last 10 years that the human papillomarvirus (HPV) now plays a role in the pathogenesis of head and neck squamous cell carcinomas. HPV is a sexually transmitted infection that can affect the genitals as well as

the mouth and throat, and the HPV-16 genotype has been linked to squamous cell carcinoma of oropharynx (13). It is hypothesized that there is a generational wave of HPV-related oropharyngeal cancers due to changes in sexual behaviours that began in the 1960s, and recent increases in the incidence of these cancers could be due to increased exposure to the virus 40 years ago (14). Sturgis et al. reports on the rising trend of oropharyngeal cancers, and comments on the fact that this growing incidence of cancers of the oropharynx does not parallel the reduction in tobacco intake and exposures, and this is likely due to HPV exposures (15). This development has decreased the age at which patients are being diagnosed, changed the risk factor profile and increased overall survival as HPV positive cancer has been shown to be more sensitive to treatment (3,16). A recent meta-analysis reported lower risks of dying from the disease (hazard ratio: 0.85, 95% CI: 0.7-1.0) in HPV-positive H&NCas and better prognosis overall (17,18).

2.2 Head and Neck Cancer Treatment

Treatment modalities for H&NCa can include radiotherapy (RT), chemotherapy (CT), surgery (SX), or a combination of these treatments, although the heterogeneous nature of the disease from patient to patient leads to difficulty in generalizing treatment regimens. The stage and site of the tumour are important details that dictate the course of the treatment. Patient preference must also be considered due to side effects and physiological impacts on the individual that can affect the patient's quality of life (19). It has been commonly cited that in early-stage lesions where either RT or surgical excision of the lesion are indicated as primary intervention, both treatments show similar cure rates (5,12,19). RT may be indicated for patients where organ and cosmetic preservation is a priority and alternatively, in patients where SX alone could potentially cure their cancer, avoiding severe side effects due to RT may be more important (1,5,12). Due to the varying complications and long-term effects, treatment decisions require balancing survival with patient need.

As such, the National Comprehensive Cancer Network (NCCN) clinical guidelines for head and neck cancers provide recommendations of curative treatment for different sites and stages of disease.

Although each individual patient has the potential to follow an unconventional treatment path, the following table is a crude summary of the NCCN guidelines (4).

Table 1: Recommended Curative Treatments by Cancer Site and Clinical Stage

Site	Stage	Curative Treatment
Oral Cavity, Larynx, Hypopharynx	Early (localized) disease (stage I-II)	Surgery, radiation
	Locally advanced disease (stage III-IVb)	Surgery, radiation, concurrent chemoradiation, neoadjuvant chemotherapy, adjuvant radiation
	Metastatic or recurrent disease (stage IVc)	Single-agent or combination chemotherapy
Oropharynx, Nasopharynx	Early (localized) disease (stage I-II)	Radiation (no surgery)
	Locally advanced disease (stage III-IVb)	Concurrent chemoradiation, followed by adjuvant chemotherapy
	Metastatic or recurrent disease (stage IVc)	Platinum-based chemotherapy

2.2.1 Radiotherapy

RT has been a routine part of H&NCa treatment since the 1960s, however while targeting and killing cancer cells, RT can damage surrounding normal cells in the process. As such, radiation-induced changes in head and neck mucosa have been the source of thorough investigation for patients with H&NCa (1,6). Acute and late side effects of RT are common in patients with H&NCa, including mucositis, xerostomia, and hypothyroidism as well as soft tissue necrosis, and carcinogenesis (6). Some studies have suggested an association between RT and carotid vascular disease including stroke (6). RT is often used as a treatment in conjunction with SX, either prior to or following surgical intervention, as adjuvant treatment, however preoperative RT is becoming increasingly uncommon due to slower healing that can occur in an irradiated area (1). Advancements in radiation treatment within the last two decades have included three-dimensional (3D) planning, where axial anatomy and complex tissue contours could be taken into account, and intensity-modulated radiotherapy (IMRT) which allows the intensity of each radiation beam to be modulated and thus enables greater control over the dose distribution within the targeted region (20). In H&NCas, IMRT has become a common favorable treatment as the complexity of H&NCa sites are ideal for this treatment, and there is evidence that it can reduce the amount of radiation-

induced toxicities. As well, since radiation-induced toxicity is of particular concern in the head and neck because there may be very little distance between targeted tumours or disease and critical structures that have the potential to suffer damage, IMRT can decrease the amount of RT (absorbed dose) in normal surrounding tissue and spare toxicities (20). The current evidence on IMRT in H&NCas is such that although organ preservation (e.g.: salivary glands) and reduced xerosotmia can be accomplished (20), IMRT's ability to avoid possible late effects is unknown.

2.2.2 Chemotherapy

CT is a common therapeutic modality for many cancers aimed at halting their rapid reproductive capacity and sensitizing cancerous tissues to radiation (1). CT, however, is not considered a curative treatment when used alone in H&NCa (1). CT can be used prior to surgery or RT with the aim of shrinking the tumour or as adjuvant therapy in order to kill any remaining cancer cells. Within the last 15 years, studies have identified a survival benefit when CT is used synchronously with RT (1,21). In a large meta-analysis of randomized trials evaluating the effect on survival of the addition of CT to RT, Pignon et al. found that concomitant CT (with RT) was associated with a 6.5% increase in survival at 5 years follow-up (22). The caveat to concurrent CT treatment is the added toxicity; there is evidence of more advanced side effects in patients treated with CT concomitant to RT, as compared to patients treated with RT alone(23). Acute and late side effects can include pharyngeal dysfunction, mucositis, soft tissue necrosis and systemic toxicities, however carotid diseases and stroke have not been well investigated to date (21,24).

2.3 Definition, Epidemiology and Etiology of Strokes

The World Health Organization (WHO) defines stroke as a "clinical syndrome consisting of rapidly developing clinical signs of focal (at times global) disturbance of cerebral function, lasting more than 24 hours or leading to death with no apparent cause other than that of vascular origin" (25). Each year, over 14,000 Canadians die from stroke (26), and a 1998 study reported an estimated 50,000 strokes

occur each year in Canada, with an estimated 300,000 that are living with the effects of stroke (27). There are two broad categories of stroke: hemorrhagic, and ischemic. Hemorrhagic strokes occur when a weakened blood vessel ruptures and bleeding develops within necrotizing cerebral tissue (28). An ischemic stroke occurs when there is an interruption of blood flow to the brain due to a blood clot, causing brain tissue damage (7). It is estimated that 80 to 87% of all strokes are ischemic (7,28). There are two types of ischemic stroke – thrombotic and embolic. Plaque accumulation contributes to most ischemic strokes through the process of atherosclerosis where narrowing and hardening of the arteries occurs (internal/external carotid or vertebral). Prolonged atherosclerosis can cause an eventual reduction in blood flow through the arteries, resulting in the formation of a thrombus (blood clot) that occludes blood flow to the brain and causes a thrombotic stroke (7,28). Embolic strokes, on the other hand are caused by blood clot formation in another part of the body that breaks off (becoming an embolus) and travels through the blood stream into the smaller vessels of the brain, similarly blocking the flow of blood and causing an embolic stroke (7,28). Embolic strokes can be caused by carotid disease causing an intra-arterial embolism, or they can originate in the heart due to irregular heart rhythms (cardiac embolisms, such as atrial fibrillation). Cardiac embolisms have been reported to represent approximately 30% of ischemic strokes in the US, and among all ischemic stroke subtypes, they have the lowest survival (55%; 95% CI 0.47–0.63) (29).

2.3.1 Transient Ischemic Attacks

A transient ischemic attack (TIA) is a temporary episode of neurological dysfunction caused by ischemia, or a temporary interruption of blood flow to the brain. TIA symptoms can be equivalent to those of an ischemic stroke, however according to conventional clinical definitions, symptoms tend to last no more than 24 hours. Brain injury can nevertheless occur, and according to the American Heart Association, the 90-day risk of stroke after a TIA is as high as 17% (7). Preventive approaches are similar in both stroke and TIA, as they share pathophysiologic mechanisms (7).

2.3.2 Symptoms and Impact

Symptoms of a stroke can vary in duration, but can include numbness, weakness, paralysis, loss or slurring of speech, loss or blurring of vision, a sensation of motion (vertigo), confusion or a sudden, unusual or severe headache(30).

Ischemic strokes can cause permanent damage to one or more parts of the brain, and contribute a substantial burden to the lives of patients who have suffered a stroke. In the United States strokes are one of the leading causes of functional impairments: 20% of survivors require institutional care and between 15-30% are permanently disabled (31). Disability-adjusted life-years (DALYs) lost for these patients represent approximately 44 million, worldwide (32). Canadians who have suffered a stroke spend more than 639,000 days in acute care and 4.5 million days in residential care facilities every year, as reported by the Canadian Stroke Network (33). In Ontario alone, stroke is the source of close to 1 billion dollars annually in direct and indirect costs (9). Adverse effects following a stroke can range from urinary incontinence and dysphagia to deep-vein thrombosis and cardiac failure (34). Primary prevention is the most effective approach in reducing the burden of stroke, since an estimated 77% of strokes are first presentations of a cerebrovascular event (31).

2.3.3 Stroke Risk Factors

Factors that are most commonly cited for increasing the risk of ischemic stroke or TIA are: smoking, hypertension, diabetes, atrial fibrillation, cardiovascular or atherosclerotic diseases, sex and advanced age (26,28,31,33-35).

2.3.3.1 Smoking

In a 2013 stroke statistics report by the American Heart Association, smoking was reported to increase the risk of stroke by 2 to 4 times (35). Furthermore, smoking has been shown to have a dose response with the risk of stroke, whereby heavy smokers are at a higher risk of stroke than light smokers

(36). In administrative data, smoking status is not available and conditions such as chronic obstructive pulmonary disease (COPD) or asthma are often used as proxies for this measure (37,38).

2.3.3.2 Hypertension

Most studies assessing modifiable risk factors of stroke report that patients with hypertension can be up to 8 times more likely to suffer a stroke than the general population (31). Over time, individuals with high blood pressure can develop atherosclerosis and hardening of the arteries (31). There is a dose response between hypertension and stroke in that the higher an individual's blood pressure, the higher their risk of stroke (35).

2.3.3.3 Diabetes

Type II diabetes mellitus is a commonly cited risk factor for strokes or TIAs (35) however evidence has shown that type I diabetes, or insulin-dependent diabetes, also increases the risk of stroke as well as other cardiovascular events (39-41). The Atherosclerosis Risk in Communities Study reported that the risk of stroke attributable to diabetes was approximately 21%, and results from the Framingham Study showed diabetes to be a significant risk factor for strokes (39,40). Type I and type II diabetes have been associated with risks of stroke of 3.7 and 3.3 to 5.8, respectively and are thus both important risk factors (39-41).

2.3.3.4 Atrial Fibrillation

Embolic strokes are more often the result of cardiac sources, specifically, atrial fibrillation (AF). AF is a cardiac arrhythmia that puts an individual at a 3 to 5 greater risk of blood clot formation, which can result in an emboli travelling to the brain (42). AF is the most common cardiac arrhythmia, holds a 5-fold risk of stroke, and one in five of all strokes is attributed to this arrhythmia (42).

2.3.3.5 Cardiovascular/atherosclerotic Diseases

Particular cardiovascular or atherosclerotic diseases are associated with ischemic strokes, or are linked to the pathophysiology of strokes such as myocardial infarctions, ischemic heart disease and peripheral vascular disease. Myocardial infarctions (MIs) are important sources of cardioemboli, and can thus increase the risk of stroke following this event (43). As well, ischemic heart disease (IHD) and ischemic stroke are often coexisting conditions, where both are most often caused by atherosclerosis (44), and where ischemic strokes that are non-cardioembolic commonly involve coronary arteries. In the Multiple Atherosclerosis Site in Stroke study, autopsies were performed on patients who suffered fatal strokes, and 70% of patients who had no history of coronary diseases were found to have advanced coronary plaque, indicating a cardiac disease involvement in the ischemic strokes for these patients (44). Finally, peripheral vascular disease (PVD), which is a circulatory disease that causes narrowing of major blood vessels and can reduce blood flow to the limbs, has been shown to be associated with ischemic strokes(45). PVD and stroke are associated in that one increases the risk of the other; both are the result of narrowed arteries, and there is thus a high risk of ischemic stroke among patients that have PVD and PVD among patients who suffered a stroke (45).

2.3.3.6 Sex

According to the American Heart Association, stroke is more prevalent among men than among women, and age-specific incidence rates are higher among men. However, women under the age of 45 and older than 85 have higher incidence rates of stroke than men. The increase risk of stroke among younger women can be attributable to factors such as oral contraceptive use and pregnancy (31).

2.3.3.7 Age

Age is considered to be a significant risk factor for strokes and cerebrovascular diseases. According to the American Heart/Stroke Association’s guidelines on primary stroke prevention, the “cumulative effects of aging on the cardiovascular system” can substantially increase the risk of ischemic

stroke; this risk doubles with each decade after the age of 55, and the incidence of stroke at 65 years old is 7 times higher than among patients between 45-55 (31).

2.3.4 Stroke Prevention

Preventive strategies to identify patients at higher risks of stroke are common in clinical practice; methods of detecting certain stages of stroke progression are thus employed in patients with an increased risk (46,47). Guidelines for stroke prevention generally categorize patients as 'symptomatic' or 'asymptomatic', whereby 'symptomatic' individuals would have experienced either a TIA, or a nondisabling stroke, defined by symptoms lasting more than 24 hours but that resolve and leave the patient with no permanent disability (30,48). Clinical guidelines recommend secondary stroke preventive measures for individuals that become symptomatic (7). Such measures can include evaluating the degree of carotid arterial stenosis, of atherosclerosis in the cerebral vasculature or investigating whether there is an occlusion or visible blood clot forming in arterial vessels (49). The US Preventative Task Force (USPTF) recommends against screening for asymptomatic carotid artery stenosis in the general population (50,51), however in practice, stenosis in asymptomatic patients may be found inadvertently from other tests for an unrelated reason or a diagnostic test that could have been ordered by their physician due to symptoms suspected to be a TIA. Additionally, asymptomatic patients with a series of stroke risk factors are at an increased risk of carotid stenosis or atherosclerosis, and some physicians may screen for stenosis as a precautionary measure (31).

Depending on the degree of stenosis that is detected, a patient may undergo surgical procedures to correct the vascular damage, and to prevent further stroke or cerebrovascular events. Clinical characteristics are paramount to the decision to receive surgical intervention for carotid stenosis or atherosclerosis. Within the past 20 years, there have been several randomized controlled trials (RCTs) evaluating the efficacy of different surgical interventions to prevent stroke across symptomatic and asymptomatic patients, as well as across varying levels of detected stenosis (52-54). Carotid endarterectomy (CAE), a surgical procedure introduced in the 1950s that reduces stenosis by removing

the occluding material from inside of the artery (48), has become the standard of care in terms of re-vascularization therapy (55). Carotid artery stenting (CAS), whereby a mesh tube is inserted into the carotid artery to prevent or reduce stenosis, was introduced in 1994 (56). Based on studies that reported complications due to surgery, the American Heart Association (AHA) recommends CAE for symptomatic patients with stenosis of >70% and for asymptomatic patients with stenosis >70% where the risks of perioperative stroke, MI and death are low (57). CAS is recommended as an alternative to CAE if the neck anatomy of the patient is not favorable for arterial surgery, in some cases if the patient has undergone previous surgeries to the neck, or if they suffered radiation injury (57). Additionally, if the patient is at an increased risk of perioperative stroke, CAS is a recommended substitute (57).

2.3.5 Stroke Identification – Administrative Data

Identifying strokes and stroke-related events in administrative databases requires knowledge of possible clinical paths of patients who suffer from these events. Most patients who suffer from a stroke or transient ischemic attack will present to the emergency room where they will either be hospitalized and treated for the event (58). However, the prevalence of 'silent, covert strokes' is estimated to be 5 times higher than overt strokes where the symptoms are very apparent to the patient. Consequently, there is a large subset of patients with transient or mild symptoms that may not seek medical attention during the episode, but only present themselves to their family physician several days following the event, or that may be seen in an emergent care setting but treated acutely without being admitted (59). As such, in order to avoid grossly underestimating the prevalence of strokes or transient ischemic attacks, both inpatient and outpatient information should be consulted when attempting to identify these events (59).

2.4 Radiation and Atherosclerosis

Radiation-induced damage to blood vessels is a well-documented sequelae to irradiation to various parts of the body, and there is increasing evidence that arterial injury can be a late effect of RT (8,60,61). This phenomena was first described in 1959 for a patient that received radiotherapy for

malignant lymphoma and suffered damage to their aorta (62). In 1979, Louis et al. hypothesized three mechanisms through which radiation-induced carotid artery disease can develop: (1) ischemic necrosis resulting in loss of elastic tissue and muscle fibers in the blood vessel (2) fibrosis of the outermost layer of the blood vessel (adventitia) causing compression and narrowing of the vessel and (3) accelerated atherosclerosis (63). The latter is a hypothesized result of RT due to the effect on the arterial wall; the vessel wall can thicken and harden causing plaque to form, resulting in atherosclerosis, and all mechanisms result in morphological features that mimic spontaneous, non-radiation induced atherosclerosis (61,64,65). In studies that looked at the effects of RT to the thoracic region, RT was found to double the risk of death due to coronary artery disease (64). Similarly, women with breast cancer that were irradiated for a cancer in their left breast, were at an increased risk of myocardial infarction of 2.2 compared to women irradiated for a cancer in their right breast (65).

2.5 Evidence of Stroke from Radiation to the Head and Neck in non-Head and Neck Cancer Patients

When RT is targeting sites within the head and neck, the carotid artery can suffer damage and result in stroke, or stroke related diseases (8). After treating children with radiation for leukemia, brain tumors as well as Hodgkin's lymphoma, researchers have shown relative risks of stroke of 6.4, 29 and 4.3, respectively among survivors (66,67). Ischemic events are also documented in adult populations with Hodgkin's lymphoma as well as early-stage breast cancer (68,69). De Bruin et al. found a twofold increase in the risk of stroke and threefold increase in the risk of TIA in Hodgkin lymphoma survivors (69). Compared to the general population, Jagsi et al. found a significantly higher overall risk of primary ischemic or thromboembolic events in patients with early-staged breast cancer that were treated with RT. This was hypothesized to be due to often targeting the supraclavicular fossa, and the proximal carotid artery in breast cancer patients for indications such as node-positive (68).

Currently, there is evidence that vascular injury can be a late effect of RT, and that large vessel injury, particularly damage to the carotid arteries, should be considered a possible delayed outcome to neck

irradiation (8,61,70-73). The hypothesized pathway of accelerated atherosclerosis from radiation induced damage to blood vessels is of particular concern when concentrated around the large vessels of the head and neck, or the cerebral vasculature, as the carotid arteries are the vessels that supply blood to the brain (61). RT can thus cause injury to major arteries resulting in stenosis, TIA or ischemic stroke (7,34). Medical or surgical intervention may be appropriate to prevent such events if carotid stenosis can be detected early (7,34).

2.6 Evidence of Risk of Stroke in Head and Neck Cancer

2.6.1 Radiotherapy

The risk of stroke and stroke related events following RT in patients with head and neck cancer exists and has been investigated in at least 9 clinical studies, with varying designs (8,70-77). RT has been reported to increase the risk of carotid stenosis, TIA and general carotid injury among patients with H&NCa (8,70-73). In a prospective study by Muzaffar et al., the authors compared ultrasound scans of the carotid artery before and after RT in patients with H&NCa, and found that the carotid wall experienced statistically significant thickening following RT in all of the 36 participating patients within one year ($p<0.01$) (8). Chang et al. calculated a bilateral plaque score from carotid artery stenosis as seen with a carotid duplex sonography in patients that had previously undergone RT for their H&NCa, and compared them to scores from individuals prior to commencement of their cancer treatment. The authors found significantly higher plaque scores in the irradiated group ($p<0.05$) (70). A team from the Duke Cancer Institute conducted a pilot screening study of asymptomatic survivors of H&NCa treated with RT. After biennial screening duplex ultrasounds, they found an actuarial rate of carotid artery stenosis of 14% at 4 years (78). Finally, a group from the University of Hong Kong conducted two cross-sectional studies investigating the prevalence of radiation induced carotid disease, and in examining all patients with H&NCa after RT, both studies found that over 20% of the patients showed 70% carotid artery stenosis (71,72).

One systematic review attempted to synthesize data from 5 studies examining the risk of cerebrovascular events (CVE) following neck and supraclavicular RT (73), and although studies lacked homogeneity, they found that the risk was almost 9 times higher than for non-irradiated patients (risk ratio=8.8) (73).

The risk of stroke in patients with H&NCa treated with RT has been examined in a few retrospective observational studies (75-77,79). Dorresteijn et al. examined 367 patients through chart review, that were younger than 60 years old with H&NCa, and found that the risk of ischemic stroke after 10 years of follow up was 10.1 (RR=10.1; 95% CI: 4.4-20.0) for those that were treated with RT as compared to a community sample from the UK. This study did not employ a clinically relevant study population; a community sample as the comparison group, in this case is not likely to reflect similar risk factor profiles as one would see in a H&NCa population(10). Additionally, restricting their sample to individuals under the age of 60 excludes at least half of the H&NCa population that would also be presumably affected by an increased risk of stroke. Although including patients of all ages, Haynes et al. found a risk of stroke of 2.1 (RR=2.09; 95% CI: 1.28-3.22) among a H&NCa sample of 413 patients treated with RT, with the expected incidence based on population data from a 1981 study, raising similar issues regarding the appropriateness of their comparison group(80). Hong et al. looked specifically at patients over the age of 66, diagnosed with early-stage glottic laryngeal cancer, in a retrospective cohort identified through SEER, and found no significant difference between surgical treatment and radiotherapy in terms of the risk of cardiovascular diseases (HR=1.11 95%CI:0.91-1.37, p=0.31) (79). This study included only a small proportion of patients with H&NCa (over the age of 66, with glottis laryngeal cancer), and by including all cerebrovascular diseases they may have diluted their potential for finding an effect. Chu et al. examined the risk of ischemic stroke among young (20-60+ years) nasopharyngeal cancer patients that were treated with RT and CT, and using a frequency-matched sample of patients obtained through healthcare reimbursement claims data as a comparator, they found a hazard ratio of 1.91 (95%CI: 1.42,2.58) (81). Compared to other estimates that used the general population as a basis for estimating risks, this effect was significantly lower, likely indicating the lower risk of stroke among the

nasopharyngeal cancer population, or a sample of patients that were significantly younger than typical patients with H&NCa. Although methodologically flawed, Chu et al. analyzed the largest patient sample of the current literature.

Finally, Smith et al. contributed the most clinically relevant evidence within the context of our study objectives (76). They identified patients with non-metastatic H&NCa through the Surveillance, Epidemiology and End Results (SEER) – Medicare cohort, and in comparing risk of stroke, carotid revascularization, death from stroke and hospitalization due to TIA, after RT alone treatment to SX alone, they found an increased risk of 1.5 (HR=1.5; 95% CI:1.18-1.9). Although they calculated their risk using patients who underwent SX as the comparison group, which presumably have similar risk factors, the SEER sample included only patients over the age of 65, thus excluding over half of the potential participants. They also excluded patients with a primary cancer site in the larynx; one of the more commonly recorded cancers of the head and neck. An additional shortcoming to this study was that they did not evaluate the individual risks of stroke, carotid revascularization, and hospitalization due to TIA which could have led to muddled effect estimates, and would have been helpful in contextualizing the risk of stroke progression following RT.

2.6.2 Chemotherapy

In a H&NCa population, the literature suggests that there are independent side effects for RT and CT, and although it is hypothesized that CT provides added toxicities when used in conjunction with RT, it is of interest to know the added risk of stroke with this course of treatment (1). Currently, there is little evidence that quantifies this risk, although the connection between CT (independent of RT) and thromboembolic events in other cancers has been addressed in many studies over the last 20 years (82). This relationship has been cited to be of particular concern among platinum-based drugs, suggesting that they may be particularly cytotoxic thus having an impact on coagulation pathways - although to date, the mechanism remains uncertain (83,84).

With respect to H&NCa, there are a small number of studies that included CT in their analysis with stroke or stenosis as their outcome. Huang et al. conducted a stratified analysis based on age (<55, ≥ 55), and found that patients with H&NCa who were younger than 55 and treated with RT or CT or both had an increased risk of stroke of 1.8 (RR=1.8; 95% CI: 1.22-2.56) as compared to the SX alone group. The authors did not find an increased risk in the older population (≥ 55), however their outcome did not include TIAs or death due to stroke, and presumably individuals that died from any cause were censored. Additionally, this study amalgamates risks of potentially three different treatment modalities, and fails to address the different contributions of RT and CT toxicities. In screening asymptomatic H&NCa survivors, Dorth et al. found that CT alone did not contribute an individual risk of carotid stenosis in a univariate analysis (HR=0.8; 95% CI: 0.4-1.6) (78). CT was hypothesized to increase the risk of stenosis in this sample, and was therefore adjusted for in the multivariate analysis, but results of these estimates were not shown (78). Chu et al. looked at the overall risk of stroke in a H&NCa sample compared to the general population, and found risks of stroke of 1.31 (95% CI: 1.00-1.35) and 1.46 (95% CI: 1.22-1.74) among patients treated with CT alone and RT with concurrent CT, respectively (85). In an updated population-based retrospective cohort study by Chu et al., they found that among patients with Nasopharyngeal cancer, the risk of ischemic stroke from combination treatment of chemotherapy and radiotherapy was higher than the risk for patients that were treated with radiotherapy alone, where both risks were calculated using matched hospital based controls (HR= 1.91, 95% CI:1.42,2.58 vs. HR=2.99, 95% CI:2.46,3.64) (81). The caveat to this analysis is that their comparison group was a non-H&NCa population, and due to the slight overlap in the confidence intervals of the estimated hazard ratios implying that the difference between the groups may not be statistically significant, the combination chemoradiation group should have been directly compared to the radiation group (81). As well, this represents a population with H&NCa with different risk factors than in North America; in China, the Epstein Barr virus and other environmental exposures contribute to the H&NCa incidence (as opposed to smoking and/or drinking).

2.7 Rationale for Current Study

The changing etiology of H&NCa with a younger patient population and with more treatment sensitive cancers has led to patients living longer after diagnosis and treatment for the disease. RT to the head and neck can have severe late side effects, especially in patients with long survival times. Previously, the need to examine late side effects of RT in patients with H&NCa was less of a priority because individuals were likely to die of their disease, or other reasons due to the multitude of risk factors. It is now of interest to examine the risks of late effects of this younger patient population, and how further damage can be avoided (86). Current literature identifies vascular injury and subsequent stroke as possible outcomes following RT in various populations. Time to stroke or events related to stroke in previous studies of patients receiving RT to the head and neck to treat Hodgkin's lymphoma has varied anywhere from 5 to 30 years. In H&NCa patients, time intervals between irradiation and first symptoms have been reported to vary between 6 months and 20 years (60,77,87). As stroke and stroke related events often result in devastation to the patient as well as substantial burden to the healthcare system, knowing the degree to which RT puts individuals at risk of stroke, and when, are relevant questions, especially in the H&NCa population, where irradiation to the cerebral vasculature is a common result of treatment. There is existing literature on the topic, however the relevant studies were flawed in their designs. Two studies failed to quantify the risk as compared to patients receiving SX alone, and thus a comparable population, and the other three studies restricted their patient sample to include either only the older or younger patients, or very specific cancer subsites. Additionally, none of these studies incorporated a Canadian population.

Chapter 3: Methods

3.1 Study Objectives

The aim of this project was to quantify the risk of ischemic stroke among head and neck cancer patients following radiotherapy. The study objectives were as follows:

3.1.1 Objective 1

To determine the risk of ischemic stroke among patients that received curative radiotherapy compared to patients that underwent surgery alone as their curative treatment. In order to meet this objective we aimed to:

1.1 To describe the clinical characteristics among the entire cohort of patients with head and neck cancer and to compare characteristics across different treatment regimens.

1.2 Determine a survival estimate and model time to stroke across all treatment regimens compared to surgery alone.

1.3 Determine a survival estimate and model time to stroke for *any* curative radiotherapy, compared to surgery alone.

1.4 Quantify the risk of stroke at varying follow-up time periods of 3, 5, 10 and 15 years following treatment.

3.1.2 Objective 2

To determine how modifications of radiotherapy regimens may affect the risk of ischemic stroke. We therefore aimed to:

2.1 Determine whether the addition of chemotherapy to a radiotherapy regimen increases the risk of stroke, compared to radiotherapy alone.

2.2 Determine whether undergoing a neck dissection prior to being irradiated increases the risk of stroke compared to radiotherapy alone.

2.3 Determine whether varying doses of radiotherapy will affect the risk of stroke (dose response).

3.1.3 Objective 3

To determine the risk of stroke-related events among patients who were treated curatively with any radiotherapy compared to patients treated with surgery alone. This objective included:

3.1 Determining the risk of transient ischemic attack following radiotherapy compared to surgery alone.

3.2 Determining the risk of carotid endarterectomy or carotid stent following radiotherapy compared to surgery alone.

3.2 Study Design

The current study linked clinical, and administrative data from the Institute of Clinical Evaluative Sciences (ICES) data holdings and the Cancer Care and Epidemiology (CCE) database. All objectives were addressed using a retrospective cohort study design with a H&NCa patient population, where relevant variables were identified through these linked data. The primary exposures of interest for this study were curative treatment modalities for H&NCa, specifically radiotherapy, surgery and chemotherapy. The outcome of interest was the occurrence of and time to stroke or stroke related events following oncological treatment.

3.2.1 Timeframe of Study

Figure 1 depicts the study period and the timeline during which variables were defined. Described further in Section 3.4, the H&NCa cohort consisted of patients diagnosed between January 1st, 1990 and January 31st, 2010, and during this period patients were accrued. The date of the diagnosis of head and neck cancer is the time at which patients become eligible for entry into the study. The date of treatment is defined, for the purposes of this study, as the date of the end of the primary, curative treatment (described further in Section 3.5.1). Outcome assessment was done following the date of treatment, to ensure the exposure (treatment) preceded the outcome (stroke) in question, and was carried out until December 31st,

2011 (contributing an additional year of outcome assessment). There was an additional lookback period dating back to 1964, to identify any previous cancers, and back to 1988 to identify previous stroke (or stroke related events), and for variable assessment (described in Section 3.5.3, patients are deemed to have covariates if the diagnosis date occurred prior to their H&NCa diagnosis).

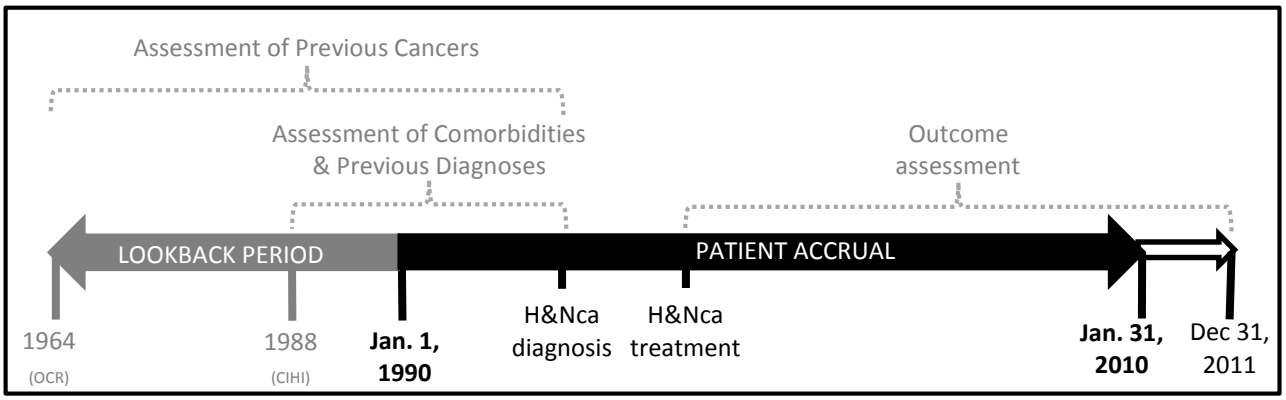

Figure 1: Study Period and Variable Assessment Timeline

3.3 Data Sources and Linkage

Data were obtained from the following data sources: (1) the Ontario Cancer Registry, (2) the Oncology Patient Information System, (3) the Ontario Health Insurance Plan claims database, (4) the Canadian Institute for Health Information Discharge Abstract Database (5) the Ontario Registrar General Death database and (6) five ICES-derived cohorts (Ontario Myocardial Infarction Database, Ontario Diabetes Database, Ontario Hypertension Database, Ontario Chronic Obstructive Pulmonary Disease database and Ontario Asthma Database) . The Ontario Cancer Registry (OCR) and the Oncology Patient Information System (OPIS) are part of the CCE database that was created in 1995 and consisted of linked longitudinal data on all patients diagnosed with cancer across Ontario from 1982. The Ontario Health Insurance Plan Claims Database (OHIP), the Canadian Institute for Health Information Discharge Abstract Database (CIHI/DAD), the Ontario Registrar General Death (ORGD) database and the ICES derived cohorts are part of the ICES data holdings. ICES is an independent, non-profit organization whose infrastructure funding and access to Ontario's large administrative databases is provided by the

Ontario Ministry of Health and Long Term Care. ICES links de-identified population-based health information at the patient level in a way that ensures privacy and confidentiality of patients. All of these databases contributed to the study dataset and are described further in detail.

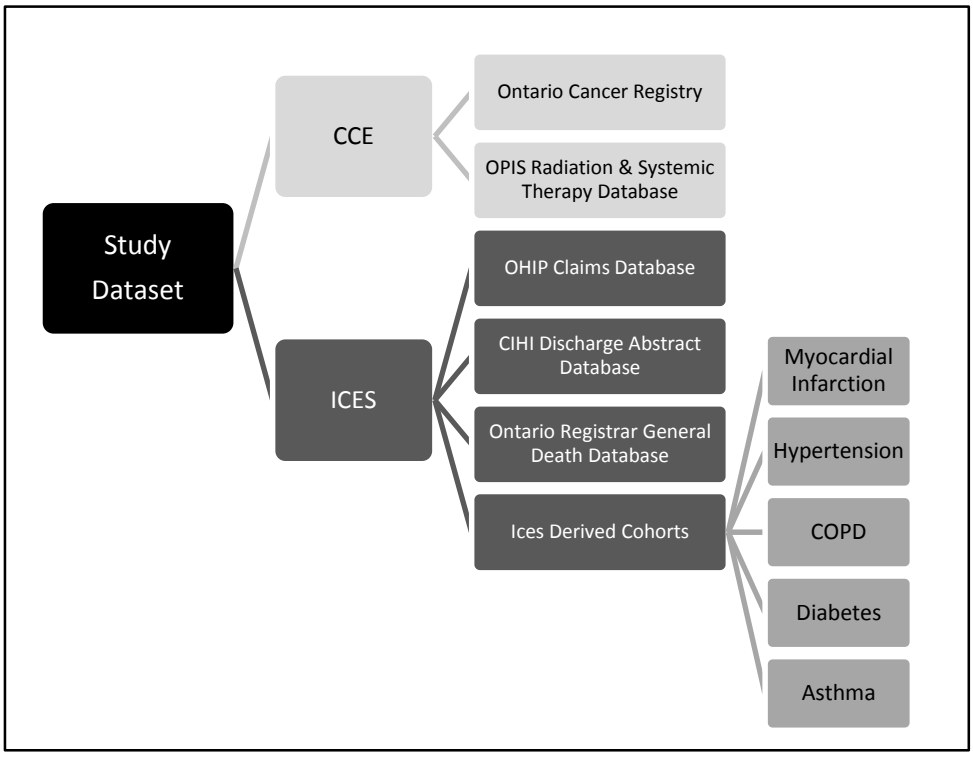

Figure 2: Data Sources

3.3.1 Ontario Cancer Registry

The Ontario Cancer Registry (OCR) is a passive, population based cancer registry that captures information on all incident cases of cancer in Ontario, with the exception of nonmelanoma skin cancers. It is maintained by Cancer Care Ontario, an Ontario government agency that collects data from cancer service providers across Ontario, in order to drive research in the areas of cancer surveillance, quality of health services and treatment guidelines (88-91). The registry is based on cancer-related pathology reports, electronic records from the nine Regional Cancer Centers (plus the Princess Margaret Hospital), hospital discharge records with a cancer diagnosis from CIHI, and reports of cancer-related deaths from the Registrar General of Ontario (92). Probabilistic linkage is used to reconcile information from all

sources, in order to create records of incident cancer cases (92), and depending on the site, the OCR has been shown to capture from 91% to 97% of all new cancer cases (90). Information stored in the OCR database that was used for this study included: patient demographics such as age and sex, date of diagnosis, vital status, and primary cancer site based on the International Classification of Disease, 9th and 10th editions (ICD-9, ICD-10) (91,92). Hall et al. investigated the accuracy of the OCR's assigned tumour sites and date of diagnosis among head and neck cancer patients, and found that the cancer site was correct in 91% of cases that were captured by the registry and the vital status was accurate in all but one patient (92). The OCR began data collection in 1964, and this information will be used to collect data on previous cancers among our patient sample.

3.3.2 Oncology Patient Information System

The Oncology Patient Information System (also referred to as: Activity Level Reporting (ALR) database) is a common electronic database used among the Cancer Care Ontario Regional Cancer Centers that was developed in 1985 in order to collect further demographic information as well as treatment summaries for all radiotherapy treatments. This database currently contains data from the Radiation Planning/Treatment Activity database and the Systemic Drug Delivery Event database, that holds information on all activity related to RT and systemic therapy services for cancer treatment as well as outpatient oncology visits (93). This data is obtained from the Integrated Cancer Programs (ICPs) in Ontario. ALR is one of CCO's data holdings and was an analytical data repository for the Oncology Patient Information System (OPIS) application. OPIS is a computerized prescriber order entry system that is customized to the cancer setting and was developed by CCO. Since 2005, all ICPs were instructed what data to submit to CCO, and the ALR is currently populated from these submissions. ALR contains RT information, systemic therapy (CT) details, patient disease information, and additional codes that are stored in order to capture the duration of treatment, dose and type of treatment. The Princess Margaret Hospital has a similar but independent system that was integrated into the OPIS database (89,94).

The OPIS database is effective in terms of capturing most patients that received radiotherapy or chemotherapy, however the overall quality of content is unknown. Despite its previous high accuracy (95%), reporting of chemotherapy and radiotherapy data is more recently, non-uniform throughout the Regional Cancer Centers and as such, RT and CT data from some centers are not complete (95).

3.3.3 Ontario Health Insurance Plan Claims Database

The Ontario Health Insurance Plan (OHIP) claims database contains data on fee-for-service claims made by Ontario physicians that are covered and paid for by the OHIP, from 1991 onward. Approximately 5% of physicians in Ontario are remunerated under an alternate plan to the fee-for-service approach. These physicians nevertheless submit 'shadow billing' whereby they submit claims to mimic billing services to OHIP, ensuring adequate data collection (96). Shadow billings do not capture 100% of the services provided by these physicians as those who work for Community Health Centres or Health Service Organizations are not paid by fee-for-service, nor are they required to shadow bill (96). With a higher frequency in the South East, North East, Waterloo Wellington and Hamilton Niagara Haldimand Norfolk Local Health Integration Networks (LHINs), there may be underrepresentation of physician services from these regions in the OHIP claims database. Each record in the database represents a single service and a diagnosis associated with that service. Certain services provided by physicians are excluded from this database, including certain services in laboratories and psychiatric hospitals, inpatient diagnostic procedures and laboratory services that occur in hospital. Once linked at ICES, items listed in the OHIP claims dataset included: the fee code for the service provided, the OHIP diagnostic code associated with the service provided, the date of service, and the physician specialty (96,97).

The OHIP claims database has been reported to contain accurate information for procedural and diagnosis data (98,99); Pinfold et al. reported 95-98% agreement between OHIP and chart reviews for breast cancer surgical procedures (100) and To et al. reported an agreement of 84% between expert chart review and OHIP diagnosis codes for asthma-related diagnoses in children (101).

3.3.4 Canadian Institute for Health Information Discharge Abstract Database

The Canadian Institute for Health Information Discharge Abstract Database (CIHI/DAD) is a database that contains information dating back to 1988, regarding the hospitalization of patients throughout Canada, including patient demographics, diagnosis and procedure information, and administrative data on the hospital stay itself (102). Patient charts are used to compile information regarding a hospital stay to be able to compose a discharge abstract. Each entry corresponds to one hospital stay, and once held at ICES, the CIHI/DAD database contains variables including: date of admission, discharge date, diagnoses related to the hospitalization, diagnoses related to conditions existing prior to the hospitalization, procedures performed during the hospital stay (surgeries, diagnostic imaging, etc.).

Juurlink et al. conducted a re-abstraction study whereby over a two year period (2002-2004) chart abstractions were conducted for a sample of approximately 14,500 admission records from varying hospitals across Ontario in an attempt to test the validity of this database (102). For diagnosis codes, an overall 85% exact match was found across both years, over 98% agreement was found for demographic data, and 77% agreement for intervention data (102). In a similar reabstraction study by CIHI, carried out on 2005-2006 hospitalization data, a sensitivity of 76% and 72% reliability were found for diagnosis information in Ontario (103). There may as well be an underreporting of diagnoses in the CIHI/DAD database, despite the relatively high agreement. Fortunately there have been various algorithms validated that use a combination of hospitalization and physician billing data to generate diagnoses in order to maximize agreement, sensitivity and specificity (59,101,104-107). These algorithms were used to compile some of the ICES derived cohorts described in Section 3.3.6, to extract some of the clinical covariates, and for outcome assessment as described in Section 3.5.2 and Appendix A.

3.3.5 Ontario Registrar General Death Database

The Ontario Registrar General Death Database (ORGD) is “cumulative dataset containing information on all deaths registered in Ontario starting on January 1, 1990. Information on cause of death

is included and the data is obtained from the office of the Registrar General of Ontario. The main purpose of this database is to identify the cause of death for the cohort of patients.

3.3.6 ICES Derived Cohorts

ICES Derived Cohorts are databases created from a combination of hospitalization, physician billing and registered persons data, that were developed in order to easily access diagnostic information regarding a set of common conditions, where individual diagnoses from administrative data alone may not be adequate in accurately identifying these diseases. All of the cohorts are updated annually whenever updated administrative databases become available (usually at the end of each calendar year). The derived cohorts used for this study are further described below.

3.3.6.1 Ontario Myocardial Infarction Database

The Ontario Myocardial Infarction Database (OMID) was developed to study the longitudinal trends of outcomes following acute myocardial infarction (AMI) hospitalizations in patients between the ages of 20-105. It therefore captures new AMIs associated with hospitalizations through ICD-9 and ICD-10 diagnostic codes from CIHI (410 & I21 respectively) – patients are excluded from this database if they were found to have an AMI related hospitalization within the previous year. Among other variables, this dataset contains information on the date of the AMI, and the unique identifier for the patient that enable linking the dataset to the rest of the ICES and CCE databases.

Although not a validation study of the ICES derived cohort, Tu et al. evaluated using similar diagnostic codes to identify AMIs from administrative data. In comparing an AMI diagnosis from CIHI to a chart abstracted AMI diagnosis with electrocardiogram confirmation, they found 60% sensitivity, 99% specificity, 89% positive predictive value and 98% negative predictive value (108). This database may suffer from an underrepresentation of the number of AMIs that occur.

3.3.6.2 Ontario Diabetes Database

The Ontario Diabetes Database (ODD) contains all Ontario diabetic patients identified since 1991, and is a cumulative dataset that is updated yearly. The ODD is updated using a compilation of information from the CIHI discharge abstract database, from the OHIP claims database and demographics from the Registered Persons Database (RPDB) (the latter contains information on all persons eligible for health care coverage in Ontario). The algorithm used to derive diabetes diagnoses among adults involves any of the following: two OHIP diabetes diagnosis codes (250.x) within 2 years or 1 OHIP procedure code categorized under 'diabetic care' (Q040-"diabetes management", K029-"intensive insulin support", K030-"diabetes monthly management") or 1 CIHI admission with a diabetes diagnosis code (250.x). Hux et al. validated this algorithm in 2002, and found 86-90% sensitivity, 92-97% specificity and 61-80% positive predictive value (109).

This dataset contains the patient identifier, the date of diabetes diagnosis, the age at diagnosis and the data source of the diagnosis. Patients diagnosed with gestational diabetes, or who are diagnosed during a birth episode are excluded from the dataset. It should be noted that the ODD does not differentiate between type 1 and type 2 diabetes, however this difference is not important for the purposes of this study as both diagnoses are cited as significantly increasing the risk of stroke (see Section 2.3.3.3).

3.3.6.3 Ontario Hypertension Database

The Ontario Hypertension Database (HYPER) contains all Ontario hypertension patients identified since 1988. Populating this database was done through an algorithm developed by Tu et al. using both hospitalization data (CIHI) and physician billing data (OHIP claims). Any patient in Ontario is said to have hypertension if they had (a) one hospital admission with a hypertension diagnosis, or (b) two OHIP claims with a hypertension diagnosis within 2 years, or (c) one OHIP claim and one hospital admission with hypertension diagnoses within 2 years (105,110). Validation of this algorithm against primary care physician offices' chart reviews was found to have a sensitivity of 73%, specificity of 95%, a positive predictive value of 87% and negative predictive value of 88%, and was selected against

alternative case-definitions (105). The hypertension diagnoses from the administrative datasets were based on the following ICD-9 and ICD-10 codes: 401.x, 402.x, 403.x, 404.x, or 405.x (ICD-9) or I10.x, I11.x, I12.x, I13.x, or I15.x (ICD-10). Items in this dataset included the patient identifiers and dates of diagnosis (the date of the first CIHI or OHIP diagnosis found that was used in the algorithm).

3.3.6.4 Ontario Chronic Obstructive Pulmonary Disease Database

The Ontario Chronic Obstructive Pulmonary Disease database (COPD) contains all Ontario COPD patients identified since 1991, and is a cumulative database that is updated yearly. The database was created using hospitalization data from CIHI and physician billing information from OHIP claims data, and similar to the ODD, demographics from the RPDB. Incident cases of COPD were identified using a case definition developed by Gershon et al.: one OHIP claim with a COPD diagnosis or one hospitalization with a COPD diagnosis (106). In a chart validation study, Gershon et al. validated this case definition they found it to yield 85% sensitivity, 78% specificity, 58% positive predictive value and 94% negative predictive value. Although high sensitivity, a low positive predictive value reflects the fact that this definition could be capturing patients that do not in fact have COPD, however Gershon et al. admit to the potential for bias due to their sample weighted heavily towards COPD conditions, which could cause an underestimation of the test characteristics (106). The OHIP diagnostic codes used to identify COPD included: 491, 492, 496 and ICD codes used to identify COPD diagnosis in the CIHI databases included: (ICD-9) 491, 492, 496, (ICD-10) J41, J43, J44. Dates of diagnosis, as well as patient identifiers were the items of interest from this database.

3.3.6.5 Ontario Asthma Database

The Ontario Asthma Database (ASHTMA) contains all Ontario asthma patients identified since 1991, based on the case definition developed by To et al.: one hospital admission (CIHI) or two OHIP claims with asthma diagnoses within two years (101). The database is updated yearly, and uses CIHI, OHIP and RPDB data.

To et al. validated this case definition against chart reviews with a patient population of children, and found 91% sensitivity, 83% specificity, a false positive rate of 13% and a false negative rate of 2% (101). Upon conducting further analysis on the false positives, they found that only 4% was likely to have been caused by inappropriate coding in the administrative data (where the rest were due to uncertain diagnoses for asthma-like conditions). In a second validation study, Gershon et al. investigated how this diagnostic algorithm performed among adult patients, and they found 84% sensitivity, 76% specificity, 62% positive predictive value and 91% negative predictive value (107). Gershon et al. also looked further into their low positive predictive value (which is indicative of the number of false positives), and they attributed nearly 75% of the cases identified through administrative data as having asthma, but not through chart review, to the fact that their respiratory information was missing from their primary care physician chart since they saw more than one doctor. Under the assumption that single primary care physician chart abstraction is not itself a perfect measure, the rate of false positives is likely to be much lower than the validity statistics may show.

Similar to the other cohorts, the ASTHMA dataset contains patient identifiers (of those found to have asthma) and the dates of diagnosis. Codes used to identify patients with asthma were as follows: OHIP: 493, CIHI: (ICD-9) 493, (ICD-10) J45.

3.3.7 Data Linkage

The patient population for this study included all individuals newly diagnosed with H&NCa between 1990 and 2010, as identified through the OCR held at CCE. Once the patient sample was identified, the CCE dataset was assembled and migrated to the ICES. Using an ICES patient identifier known as the ICES Key Number (IKN) to ensure privacy, the CCE dataset was linked to several ICES databases from which additional clinical, demographic and treatment related variables were drawn.

3.4 Study Population

The study population included patients diagnosed with H&NCa across Ontario and the cohort was identified through the OCR. All H&NCa patients in Ontario between the ages of 35 and 75 who were diagnosed with single, primary squamous cell carcinoma of the oral cavity, oropharynx, larynx, hypopharynx and nasopharynx, between January 1 1990 and January 31st, 2010, were eligible for inclusion. Cancer sites were determined from the 'site' variable in the OCR database and were based on the International Classification of Disease, 9th edition (ICD-9) codes indicated in Table 2. If more than one H&NCa site was indicated for a patient, the site with the earlier date of diagnosis was recorded.

Table 2: ICD-9 Codes by Cancer Site for Study Inclusion

Cancer site	ICD-9 codes
Oral Cavity	140; 140.0; 140.1 ;140.3-6; 140.8-9; 141; 141.1-6; 141.8-9; 143; 143.0-1; 143.8-9; 145.0-1; 145.5-6; 145.8-9
Nasopharynx	147; 147.0-3; 147.8-9
Oropharynx	146; 145.3-4; 141.0; 146.0-8; 146
Hypopharynx	148; 148.0-3; 148.8-9
Larynx	161; 161.0-3; 161.8-9
Misc	149; 149.0; 149.8-9; 195

3.4.1 Exclusion Criteria

Patients were excluded from the final H&NCa cohort used for analysis based on five criteria outlined as follows:

3.4.1.1 Non-Squamous Cell Carcinomas

Patients with diagnoses of the following cancer sites were excluded from the initial cohort: cancers of the nasal cavity, sinuses and salivary glands. These sites were excluded due to their histologies (lymphomas, adenomas or adenocarcinomas). They tend to be rare, have different risk profiles and would therefore contribute heterogeneity to the patient sample (19,111).

3.4.1.2 Palliative Intent

Patients were also excluded if they did not receive treatment with a curative intent for their cancer, or received palliative treatment. This was to exclude patients that were likely to die of their disease soon after treatment, and not likely to survive long enough to suffer from a stroke. Palliative treatment for H&NCas often include either radiotherapy or chemotherapy with the aims of either shrinking the tumour, reducing the pain, relieving other symptoms or even prolonging the patient's life (112).

This criteria was implemented using data from the OPIS, OHIP and CIHI databases, and in 3 ways: (1) a clinical standard for curative therapy for most H&NCas is to have treatment initiated within 4 months of a diagnosis; if a patient's treatment was initiated longer than 4 months following the date of their diagnosis, the patient was considered to have been treated palliatively and was excluded. (2) A clinical standard for palliative radiotherapy is a dose of less than 50 gray (Gy), or a number of fractions less than 20; patients who were treated with radiotherapy with a dose less than 50 Gy or a number of fractions less than 20 were therefore excluded from the sample (based on information obtained from the OPIS database) (19). This exclusion included patients that were in the OPIS database with a RT record, but where the dose of the radiation was missing. (3) Since chemotherapy is not used as a curative treatment for this patient sample, all patients who were treated with chemotherapy alone were excluded.

3.4.1.3 Radiotherapy for Second Cancers

Patients were excluded if they were found to have a second H&NCa diagnosis (from OCR) and were treated with radiotherapy more than 4 months after the end of their primary treatment. This exclusion was intended to avoid treatment misclassification (as patients were categorized based on a treatment within 4 months of diagnosis – see Section 3.5.1).

3.4.1.4 Previous Cancers

Patients found to have record from the OCR of a previous diagnosis of salivary gland cancer or lymphoma were also excluded from the study, because these patients could have had previous RT to the head and/or neck regions.

3.4.1.5 Previous Stroke or Stroke-Related Events

Lastly, since the focus of this study was to capture ischemic strokes that represented incident events caused by radiotherapy, patients were excluded if they had experienced either an ischemic or hemorrhagic stroke, a transient ischemic attack or underwent a carotid endarterectomy/stent prior to their H&NCa diagnosis. Diagnoses and procedures for this exclusion were extracted from the OHIP and CIHI. An algorithm (59) using both hospitalization and physician billing data to estimate the number of prevalent cases of strokes in Ontario, was used to identify ischemic strokes, hemorrhagic strokes and transient ischemic attacks that occurred prior to patients' cancer diagnosis (see Appendix A for additional details). As well, previous carotid endarterectomies or carotid stents were identified using physician billing codes in OHIP and ICD-9 and 10 codes in CIHI (see Appendix B) – where any difference was reconciled by using the first dated procedure.

3.5 Variables

3.5.1 Exposure Variable

The exposure of interest throughout this study, or independent variable, was the curative treatment regimen for the cohort of patients with H&NCa. This variable was captured using a combination of the OPIS, OHIP and CIHI/DAD databases. The OPIS database provided information on patients' radiotherapy and chemotherapy treatments, including: radiation dose, radiation fractionation schedule, treatment start date, treatment end date, body region targeted by treatment, systemic therapy name and dose. This database only contains patients that received these treatments, so if a patient was present in the OPIS database they were categorized as having had radiotherapy or systemic treatment. For

radiotherapy to be included as treatment for the patient's H&NCa, the irradiated field had to be part of the head and/or neck as specified by the body region variable, captured in OPIS.

Although uncommon, in some circumstances where chemotherapy may have been delivered by medical oncologists who are not associated with the Regional Cancer Centers or Princess Margaret Hospital (where OPIS data originates from), chemotherapy physician billing codes were used to identify chemotherapy treatment through the OHIP database (89). Information obtained from OHIP, however, included only the date of the systemic therapy.

As patients that were only treated palliatively were to be excluded from the study population, the radiation dose, and the date marking the start of the radiotherapy obtained from OPIS were used to categorize patients into curative or palliative RT.

Patients who received surgical treatment for their cancer were identified through both OHIP and CIHI/DAD. Since both databases contain procedural codes, all surgical excisions to the head and neck region were extracted and compared based on date and associated diagnostic codes in order to reconcile any differences between the two. If a patient had duplicate codes in both databases, the earliest surgery was recorded for that patient. See Appendix C for a list of the procedure codes from both databases that were used to extract head and neck surgical status.

According to a US cancer database report on H&NCa, because regimens can vary greatly between patients, most individuals tend to fall into one of the following five curative treatment categories (113):

Table 3: Curative treatment categories

Treatment Regimen
1. Surgery only
2. Surgery & Radiotherapy
3. Surgery & Radiotherapy & Chemotherapy
4. Radiotherapy only
5. Radiotherapy & Chemotherapy

We therefore categorized patients into one of the above regimen categories, however in order to do so, combinations of treatments needed to be evaluated in terms of whether they were part of the same initial curative regimen, as opposed to treatment for a recurrent disease. Multiple treatments were deemed to be part of the same initial curative regimen if the end of one treatment and the start of another treatment were less than 4 months apart. If treatments were separated by more than 4 months, the first treatment was recorded as the primary curative treatment. Figure 3 shows the treatment timeline for three example patients. Patient 1 indicates a situation where the patient received all three treatments and they were all within 4 months of each other, and thus all considered to be part of the initial primary treatment (categorized as 'surgery & radiotherapy & chemotherapy). Patient 2, on the other hand, is an example of when the second treatment (CT) falls beyond 4 months from the first treatment (RT), and is thus omitted from the initial curative treatment regimen. Lastly patients 3 and 4 depict two circumstances where the patients were excluded from the sample: Patient 3 because their initial treatment was more than 4 months away from their date of diagnosis; and Patient 4 because they received a second treatment (that fell beyond 4 months of their first treatment) that was radiotherapy (as seen in Section 3.4.2). Excluding patients that received radiotherapy as a later treatment for a second cancer (not considered primary curative treatment) is an important exclusion to avoid misclassification; since the main objective of this study is to determine the effect of radiotherapy on the risk of stroke, even if the radiation was not included as the primary curative treatment, later exposure to radiation may also contribute to the possible risk, and these patients should thus not be categorized as having only had the first treatment alone (eg: surgery alone). As well, this reduces the risk of including patients that were treated palliatively.

The primary objective of this study was to examine the effect of radiotherapy on the risk of stroke, and as such, Objective 1 was designed to examine the effect of radiotherapy alone and to evaluate the effect any radiation exposure (from their curative treatment) on the risk of stroke. Patients that fell into treatment groups 2 to 5 were combined into one *Any Radiotherapy* treatment group for the purposes

of generating effect estimates and modelling the time to stroke, as well as time to TIA and CAE for Objective 3.

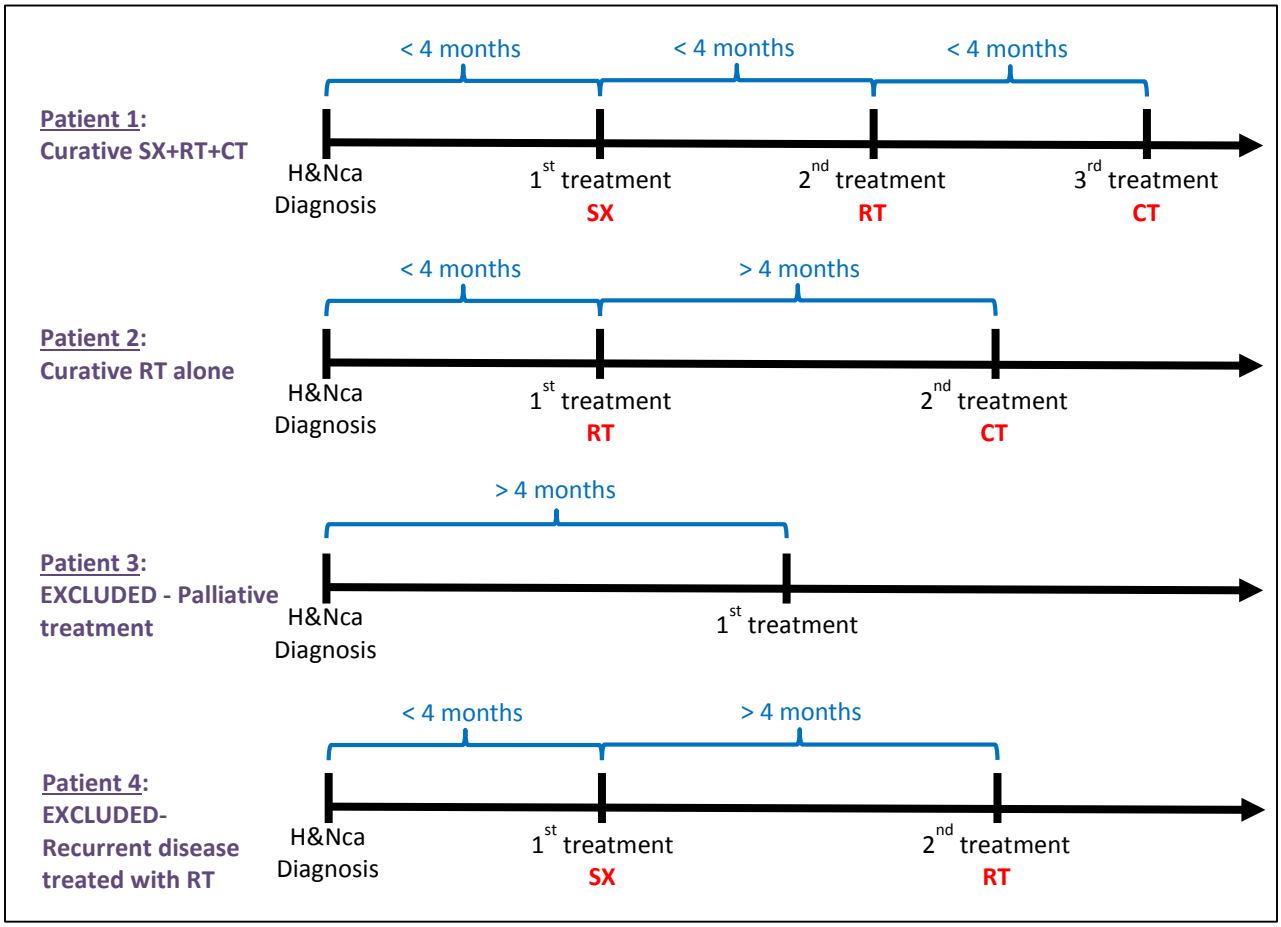

Figure 3: Treatment timelines for four example patients

In Objective 2.2, the aim was to examine the added effect of having a neck dissection prior to RT on the risk of stroke. Patients with neck dissections followed by RT were taken from treatment groups 2 or 3 from Table 3 (*Surgery & Radiotherapy* or *Surgery & Radiotherapy & Chemotherapy*). If the surgical code used to define the patient's surgical treatment was any of the neck dissection codes as specified in Appendix C, and the surgery preceded the RT, the patient was categorized as having had a neck dissection followed by RT for the Objective 2.2 analyses (this categorization was solely for this Objective).

3.5.2 Outcome Variable

The primary objective of this study is to quantify the risk of, and time to ischemic stroke and stroke death and time to these events were our primary outcomes, or dependent variables. However, due to the survival approach of the main analysis of this study, non-stroke related death and stroke-free survival was evaluated for the purposes of censoring. As well, it was of interest to capture stroke-related events, such as transient ischemic attacks and carotid endarterectomies/stents, in order to assess the risk of the events that could reflect disease progression leading to a stroke.

Figure 2 below depicts outcomes of particular interest to this study. Items in red: stroke death, stroke, TIA, CAE/CAS reflect events that are considered outcomes for various objectives for this study, and items in white/grey: death from the cancer or death from other causes are other events that patients may experience following treatment. The final white box refers to patients that did not experience an event, and were considered lost to follow-up, or have experienced stroke-free survival. The larger boxes are mutually exclusive events, where patients are not categorized into more than one of the five outcomes. The smaller boxes, linked with dashed lines, considered stroke-related outcomes, are not mutually exclusive from stroke and stroke death. These variables were defined such that any given patient could be coded as having experienced a stroke/stroke death, TIA and CAE, and would be included in all three analyses using these events as outcomes. The results in Section 4.4 provide detail of the overlap of these patients within outcome groups.

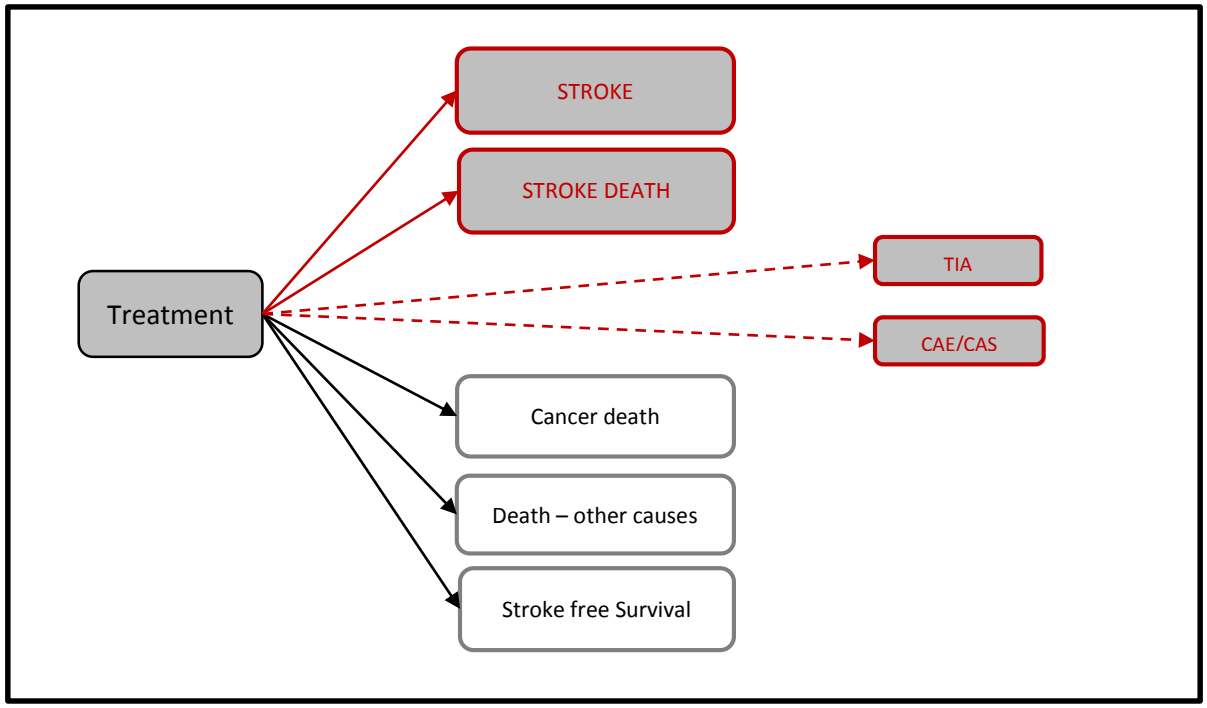

Figure 4: Diagram of possible outcomes following curative treatment for Head and Neck Cancer

3.5.2.1 Stroke Death

Stroke death refers to a recorded death where the cause of death was ischemic stroke, and this information was obtained from the Registrar General database. If the *cause of death* variable indicated any of the ICD-9 codes for *ischemic stroke* (Appendix A), their date of death would be recorded and their outcome would be coded as stroke death.

3.5.2.2 Ischemic Stroke & Transient Ischemic Attack

Ischemic strokes and transient ischemic attacks were identified using a modified version of the algorithm developed by Tu et al (59). For the dependent variable of this study, this algorithm was used with ischemic stroke and TIA diagnosis codes from CIHI and procedures associated with ischemic stroke and TIA diagnosis codes from OHIP to generate a most reliable identification of incident cases of stroke or TIA (see Appendix A for the algorithm and a discussion on the relevance to this project). This process

reflects using both inpatient and outpatient data, where a diagnosis would be provided as reason for a hospital stay or a cause for an outpatient visit or physician consultation. In implementing this algorithm, it is being assumed that it will provide high validity statistics for this project (sensitivity, specificity, positive predicate value, negative predictive value) due to: (1) higher stroke prevalence among head and neck cancer patients, (2) the modification to the algorithm involved using physician billing information from specialists that are hypothesized to provide precise diagnoses with respect to cerebrovascular events (neurosurgery, internal medicine, vascular surgery, neurology, physical medicine, cardiology and emergency medicine), and (3) the objective was to identify incident cases of stroke (as opposed to lifetime prevalent cases). The algorithm was coded such that the date for the event that caused the identification of stroke for a particular patient was recorded as the date of stroke (similarly for TIA).

For two of the three objectives, the outcome of interest was a composite outcome of either stroke or stroke death. If a stroke was identified from the algorithm and the same patient was found to have died from a stroke no more than 30 days after the stroke, both events were considered to be the same stroke and the patient was coded as 'stroke death'. If it was a greater than 30 day difference, the patient was considered to have suffered more than one stroke, and thus the first (nonfatal) stroke was recorded as the outcome, with the associated date.

Although stroke death and stroke were captured separately such that they are mutually exclusive outcomes, all patients who died of a stroke or suffered a stroke were considered to have the 'stroke' outcome, and throughout the analyses these categories were grouped together to form the dependent variable.

3.5.2.3 Carotid Endarterectomy/Carotid Stent

Carotid endarterectomies/carotid stents (CEA/CAS) were captured as a way to establish atherosclerotic disease progression, since stroke guidelines report that individuals who become symptomatic or who are at a high risk of a cerebrovascular event should undergo corrective or preventive intervention (7). Similarly, if an asymptomatic individual has stenosis detected through a diagnostic test

for an unrelated problem, or has a high number of risk factors that would concern their physician, the recommendations are that preventive intervention be indicated. It was not possible to capture pharmacological interventions through our available databases, and since CEA and CAS have been cited as the most commonly used surgical techniques to correct the damage done by arterial stenosis, either intervention indicates that a patient suffered arterial damage, and is at a high risk of stroke. CEA/CAS were identified through the OHIP and CIHI databases. Surgical billing codes were used to extract these surgical procedures from OHIP, and CIHI procedure codes were used to identify these procedures among the hospitalization data. To reconcile any differences between the databases, the first dated procedure was retained as the outcome.

3.5.2.4 Time to Events

As indicated in Section 3.2.1 the index date for the outcome was the date of the end of curative treatment. The time variable was therefore calculated for each patient from the time of curative treatment to their outcome. For objectives 1 and 2, with the outcome: stroke or stroke death, time was calculated as the number of years between the date of curative H&NCa treatment and the date of the stroke or stroke death. Patients who died of other causes would have a time variable that would reflect the number of years between their treatment and the date of their death, and finally patients who survived, stroke-free until the end of the follow-up period had a time variable that reflected the number of years between their date of treatment and the last date of follow-up (December 31st, 2011).

For objective 3, new time variables were created for the outcomes of TIA and CEA/CAS. For those who experienced either event, time was defined as the number of years between the date of curative treatment and date of TIA or CEA/CAS, where patients who died of any cause would have a time variable indicating the number of years between their treatment and their date of death. TIA or CEA/CAS free survivors were assigned a time variable reflecting the difference in years between their date of treatment and the end of the follow-up period (December 31st, 2011).

3.5.3 Covariates

A number of covariates were included in this study, conceptualized as: stroke risk factor variables or other variables hypothesized to act as confounders or effect modifiers. There has been very little evidence that enabled the creation of a conceptual model regarding possible confounders or effect modifiers in the relationship between curative cancer treatment (RT) and stroke. The approach to identifying confounding factors, or variables that would modify the effect between exposure and outcome was mostly exploratory, as the literature to date has provided very little insight into forming a priori assumptions on confounding or modifying effects. Other studies that have investigated similar relationships fail to mention the possibility of confounding, and only control for covariates in their multivariate models that are deemed to be stroke risk factors, or treatment characteristics. As such, stroke risk factors, as well as other variables that *could* be related to both treatment decisions and stroke that were available through the databases held at ICES or CCE were included in the analyses in order to test for possible confounding and effect modification.

Stroke risk factors, as outlined in Section 2.3.3 include: age, sex, atrial fibrillation, diabetes, hypertension, chronic obstructive pulmonary disease, asthma, myocardial infarctions, ischemic heart disease and peripheral vascular disease. The other covariates include: date of diagnosis, cancer site, HPV 'likely' and comorbidities. All variables that were not related to the cancer diagnosis were based on definitions of disease that occurred prior to the date of H&NCa diagnosis. See Appendix D for a complete list of included covariates and associated codes used to extract these variables.

3.5.3.1 Stroke Risk Factors

Age at H&NCa diagnosis and **sex** were obtained from the OCR database. Both age and sex are common covariates in most studies that have looked at the risk of stroke or cerebrovascular events following radiotherapy. Although their confounding effects have not been tested in this context, in a study that examined the risk of stroke following radiation exposure from the Hiroshima and Nagasaki atomic bombs, age and sex were both reported to modify the relationship between RT and stroke (risk was higher

for younger individuals, and for men) (114). The confounding effects of these variables have not been determined a priori, however H&NCa sites have a strong impact on the choice of treatment regimen and the literature suggests that the emergence of oropharyngeal cancer is associated with a younger patient sample. Both sex and age were hypothesized to be independently related to both exposure and outcome. It was important that the effect of age be clear and interpretable with respect to this patient demographic. As such the age variable was transformed into a categorical variable based on clinically meaningful cutpoints that relate to the disease and outcome in question. H&NCa is more prevalent among older individuals and 55 years of age marks the point under which patients are considered to be "young" to have this disease under these standards, or more likely to have HPV positive tumours (74,115). As well, as seen in Section 2.3.3.7 the risk of stroke increases with age, but becomes significantly higher after the age of 65 in the general population (35). In order to incorporate these clinically meaningful ages into the categorization, age was grouped into the following categories: less than 55, 55 to 65 and 65 to 75. Atherosclerotic and cardiac conditions reported as stroke risk factors have not been shown to each be independently related to cancer treatment decisions. It was hypothesized that there may have been particular conditions that could influence certain clinicians to tend towards radiotherapy versus surgery due to a high risk of surgical death, however this was based on clinical expertise and the extent of these associations had to be examined further. Patients from the H&NCa cohort with **atrial fibrillation** and **peripheral vascular disease** were identified from the CIHI database using ICD-9,10 codes. The **Ischemic heart disease** variable was created using an algorithm developed by Tu et al. discussed further in Appendix E (104). The remaining variables, **diabetes, hypertension, chronic obstructive pulmonary disease, asthma,** and **myocardial infarctions** were all obtained from their ICES derived cohorts described in Section 3.3.6, whereby if the patients were present in the derived cohorts with a date of diagnosis that preceded their cancer diagnosis, they were considered to have the disease in question. These variables were coded as separate dichotomous variables, with values of 1 if the patients were found to have the disease in question, and 0 if not.

3.5.3.2 Other Covariates

As described in Section 2.2, among other characteristics, **cancer site** plays a role in determining appropriate curative treatment regimens for H&NCa. Although it was not expected to find that cancer site had an independent relationship with the risk of stroke, it merited investigation as to whether or not the risk of stroke following radiotherapy was higher for certain cancer sites. The H&NCa sites were obtained for the purposes of identifying the cancer cohort through the primary site of diagnosis in the OCR. Advancements in oncological treatments occur over time, particularly changes to radiotherapy techniques (20). Due to the long follow-up period of this cohort (21 years), it's possible that slight changes in treatments could have occurred during this time. It was therefore of interest to examine whether the risk of stroke due to radiotherapy differs between time periods. Cited as having organ preserving properties (20), IMRT was introduced in the 2000s, and the regular integration of this technique into H&NCa treatment regimens was estimated to have occurred around 2004-2005 in Ontario. A change in risk was therefore hypothesized around this time period, if at all. **Date of diagnosis** was obtained from the OCR at the time of cohort selection, dichotomized as <2005 or ≥2005, and tested for modifying effects. There is no reason to believe that the date of diagnosis would be independently related to the risk of stroke, and was therefore not hypothesized to have confounding effects on the relationship between radiotherapy and stroke.

The **Human Papilloma Virus** (HPV) indicates a different etiology of H&NCa, where HPV positive tumours of the head and neck are associated with better overall survival, younger patients, and are usually treated with radiotherapy and chemotherapy, as opposed to surgery. HPV status of the tumours were not available, however through evidence of the patient characteristics of HPV positive H&NCas, HPV *likely* and *unlikely* categories were formed (116). Patients were identified as HPV *likely* if they were 55 years of age or under, if they were diagnosed with a primary cancer site of the oropharynx, and if they were diagnosed after 2000. The hypothesis for this variable was that if confounding or modifying effects are found in variables such as age, cancer site or date of diagnosis, perhaps these effects

can be explained by their association with HPV status. HPV *likely* therefore used a compilation of the age, cancer site and diagnosis date variables as described previously.

Comorbidities are considered diseases that are in coexistence with the disease of interest (117), and among cancer populations ranking the level of comorbidities in a patient is a proxy for overall health. Evidence suggests that the number of comorbidities can influence decisions for care and treatment for many cancer sites, including head and neck (118). The Elixhauser comorbidity index (119) is a validated measure of comorbid illness. Creation of this index was published in 1998, and was designed for use with administrative databases. It is a prognostic scale including diagnoses in 31 domains ranging from hypertension to depression (see Appendix C for a complete list), but excludes the primary condition that is the basis of the hospitalization (120). The algorithm for calculating a comorbidity score for each patient involves summing the number of comorbidities, and categorizing them into 0,1,2,3+. Based on previous use of this index in a cancer setting, conditions relating to the presence of H&NCa were omitted by excluding all patients with previous cancers of the head and neck (121). The Elixhauser scale has shown benefits over the Charlson comorbidity index across many settings, including cancer and cerebrovascular disease (122,123), and most importantly, for stroke risk assessment in hypertensive patients (124). The evidence therefore suggests an independent association with both H&NCa treatment decisions, and stroke resulting in the hypothesized confounding effects of level of comorbidity. ICD-9 and 10 codes were used to ascertain the status for all of the conditions included in this index (extracted from the CIHI database). A SAS macro from a previous study was used to compile the diagnostic information and calculate a score for each patient (where the scores were categorized as indicated above). Similar to the other risk factor statuses, diagnoses included in the algorithm had to have occurred prior to the date of cancer diagnosis.

3.6 Statistical Analyses

All statistical analyses were performed using SAS® (Version 9.2, SAS Institute Inc., Cary, North Carolina) at the ICES@Queen's Health Services Research Facility.

3.6.1 Descriptive Analyses

Descriptive analyses were performed for the clinical and demographic patient characteristics for the entire patient sample as well as across treatment groups in order to evaluate differences in baseline characteristics. These characteristics included age, sex, cancer site, comorbidity status, year of cancer diagnosis, HPV 'likely' status and stroke risk factors. All variables were considered categorical variables (including age, which was transformed as described in Section 3.5.3.1), and were reported with frequency distributions and proportions. Characteristics were compared across treatment groups using chi-square tests, which were two-tailed and performed at a significance level of 5%.

3.6.2 Survival Analysis – Time to Stroke/Stroke-related Events

When performing survival analysis to investigate the association between treatment regimens and time to stroke/stroke-related events, the competing risks or semi-competing risks in the data should be taken into account (125). Competing risks occur when there is more than one cause of an endpoint in question, but only an event of one cause can occur for each patient, which precludes the occurrence of the other events (126). A semi-competing risk refers to two events where one prevents the other from happening, but not vice versa (125). The outcome of interest of this study was stroke or stroke death, and as described in Section 3.5.2, following treatment, along with stroke-free survival, was non-stroke related death. In this case, non-stroke death would prevent a stroke from occurring, however a stroke would not stop the patient from dying from other causes. On the other hand, the composite nature of the endpoint (stroke or stroke death) implies partial reciprocity when referring to a competing risk since a stroke death would preclude the occurrence of other cause death.

A standard approach for competing risks involves modelling the cause-specific hazard function (which is the instantaneous risk of experiencing an event due a specific cause – stroke or stroke-related events- given that the subject did not experience any events at time *t*) via Cox's proportional hazards model (127). However, if the aim is to estimate the cumulative incidences of stroke or stroke-related

events by different treatment groups, the cause-specific hazard is no longer useful. Gray (1988) and Fine and Gray (1999) proposed methods to directly model the cumulative incidence (127,128).

In the context of this study, to plot the cumulative incidences of stroke over time by treatment groups, and to estimate the time-specific risk ratios of developing stroke/stroke death in the presence of deaths of other causes, cumulative incidence functions (CIFs) were estimated based on the nonparametric approach (128). A SAS macro published by Lin et al., %CIF, was used to estimate the CIFs stratified by the treatment groups under question (129). The index point for these analyses was the date of curative treatment, and time was measured from treatment date to date of event (as described in Section 3.5.2.4). For Objectives 1 and 2, the cumulative incidence of stroke and stroke death were of interest and patients were considered to experience events of competing risks if they died of non-stroke related causes (at their date of death) and were censored if they were alive and stroke-free at the end of the follow-up period (December 31st, 2011). The focus for Objective 3 (3.1 and 3.2) was the cumulative incidence of TIAs and CAE/CAS, and as such, patients were considered to have a competing risk if they died of any cause (at their date of death) and were censored if they were alive TIA or CAE/CAS free at the end of the follow-up period, December 31st, 2011. Differences between treatment groups were tested using Gray's Test for Equality of CIFs that is based on comparing weighted averages of the hazards of the distributions of each competing risk (129).

Cox's proportional hazards (PH) models were used to model effects of treatment and other covariates on the cause-specific hazard function for stroke/stroke death by treating patients competing risk events as censored. The following statistics from the Cox PH model were generated: Hazard Ratios (HR - measure of effect), 95% confidence intervals, type III p-values to test for overall differences between levels of categorical variables and p-values of statistical significance for each level (compared to the reference category) of categorical variables. Breslow's method was used to handle ties (130). For all three study objectives, unadjusted Cox PH regression analyses were conducted to provide univariate risk estimates for each covariate. Model selection was performed separately for each objective, using a

backwards elimination approach (131). While keeping the exposure of interest in the model (treatment), covariates were retained if they were associated with the outcome in question (stroke, stroke-related events) at a liberal significance level of 10% using the Wald test. Given that the primary aim of this study was to determine the relationship between curative treatment, particularly radiotherapy, and stroke, and since confounders were not defined a priori with the intention of assessing confounding in an exploratory way, the Change-in-estimate criteria was used to test each covariate for confounding effects. Variables were thus considered for inclusion in the model if either they were significant at a 0.10 level or if they changed the treatment coefficient (primary exposure) by 10% or more (132). Goodness-of-fit likelihood ratio tests were performed to test the significance of the remaining covariates (133,134).

The effect estimates that are generated from the Cox's PH models are cause-specific hazard ratios defined by the ratio of the hazards (between two groups of interest), of experiencing a particular event (or cause) at time *t*, conditional on the fact that the patient survived, event-free, up until that point *t*. These estimates can therefore be interpreted as the conditional risks of the event in question.

3.6.3 Regression Diagnostics

To establish whether the specified model is an appropriate fit for the data, certain regression diagnostics were examined: the assumptions of the Cox PH model (proportional hazards assumption), the existence of outlying observations, and whether there were some observations that were driving the model.

The proportional hazard assumptions are the underlying properties of the Cox PH models that must be met to be able to use this semi-parametric approach (the semi-parametric refers to the fact that there are no assumptions on the baseline hazard). The first assumption is: the censoring that occurs in modelling the time to event is random, or non-informative. This refers to the idea that the event that is causing the censoring is statistically independent of the time to event, or the probability of the event occurring (134). An example of a situation that would violate this assumption could be in a prospective study where patients end up lost to follow-up, and therefore censored, due to their poor medical condition.

In the context of this study, patients are censored when lost to follow-up (stroke-free survival), and this censoring is arguably non-informative as the retrospective nature of this study ensures the uniformity of the follow-up window for all patients that did not experience the other events, precluding any medical condition from causing this censoring. The second assumption of the PH model is that the effects of covariates on the hazard are multiplicative (additive on the log scale), in that hazard functions for two strata, or between two groups (e.g.: men vs. women) are proportional over time (135). This means that for a single binary covariate, with values of 0 and 1, and where the hazard functions should theoretically be proportional, the ratio of the hazard functions, or the HR, would necessarily be constant with respect to time (this is the non-linear component of the model that should be constant over time) (134,135).

The latter PH assumption must therefore be tested with the addition of new variables in the Cox PH model. With the final models adjusting for significant covariates for each objective, the PH assumption was tested by using the observed standardized score process with the associated p-value from the Kolmogorov-type supremum test for proportional hazards assumption (134).

Testing for outliers was done by plotting the deviance residuals against the linear component of the fitted Cox PH model (also referred to as the risk score or prognostic factor) (134). Deviance residuals are standardized residuals about the mean, and any clustering that occurs either above or below the mean with extreme points would indicate that the model may not be the best fit for the data (134).

3.6.4 Time-Dependent Estimates

Objective 1.4 was to determine the risk of developing stroke by varying time points (t = 3, 5, 10, 15 years). The cumulative incidence of stroke generated from the CIFs at different time points reflect the probability of developing a stroke or dying from stroke at time t. Taking the ratio of the probabilities between groups can generate risk ratios for stroke or stroke death by year t. It is of interest to estimate the risk of stroke or stroke death following radiotherapy, compared to surgery, therefore risk ratios were generated by taking the ratio of the probability of stroke or stroke death between: (1) patients that received any radiotherapy and patients that underwent surgery alone and (2) patients that received

radiotherapy alone and patients that underwent surgery alone. The %CIF macro automatically produces a table of cumulative incidences for each strata being compared, and risk ratios were therefore calculated at t =3, 5, 10, 15 years by calculating the quotient of stroke or stroke death incidence among RT patients and stroke or stroke death incidence among SX patients.

3.6.5 Additional Analyses – Excluded, No Documented Treatment Group

Additional analyses were run for the subgroup of patients that were excluded from the final H&NCa cohort due to no documented treatment (NDT). Patients who did not have record of being treated curatively for their cancer were excluded, and it was of interest to know whether this group of patients differed significantly across clinical characteristics compared to the patients included in the analysis, if there were potential misclassification of this group that was differential between treatment groups. Descriptive analyses were therefore run for the NDT group, and characteristics were compared between the NDT group and all other treatment groups using chi-square tests, which were two-tailed and performed at a significance level of 5%. Using the date of diagnosis as the index date (since no treatment date could be identified) a CIF curve was generated for this group, with stroke or stroke death as the endpoint, while censoring individuals that died from other causes, or lost to follow-up. This curve was plotted alongside stroke CIF curves among the SX alone treatment group and the RT alone treatment group to further examine the possibility of misclassification. Overall survival for these patients was also of interest due to the hypothesis that patients receiving palliative or no treatment are likely to have advanced stage H&NCa, and thus more likely to die of their disease quickly, therefore the CIF of non-stroke death curve was plotted with stroke death as a competing risk. RT alone and SX alone non-stroke death CIF curves were plotted to compare the death rate among this NDT group and the curative treatments.

3.6.6 Effect Modification

Based on factors hypothesized a priori, modifying effects were tested for certain covariates. Covariates were deemed effect modifiers if an interaction between the covariate and the exposure of

interest (treatment) was significantly associated with the stroke outcome, in the presence of the main effects in the Cox PH model. Stratified analyses were also conducted for each level of the variables in question, while controlling for other confounding factors.

3.7 Ethical Considerations

Research ethics board (REB) approval has been obtained for this study (#OTOL-045-11) from Queen's University Health Sciences and Affiliated Teaching Hospitals Research Ethics Board, and student contribution has been amended to the original application. Due to the nature of this project, retrospective design using de-identified data, the study meets the requirements of the TCPS2 and has received a waiver of the requirement for consent from the Queen's University Health Sciences and Affiliated Teaching Hospitals Research Ethics Board. This project has the ICES Cancer Program approval and confidentiality agreements were signed.

Chapter 4: Results

4.1 Identification of Study Population

The creation of the final study population is outline in Figure 5, based on the exclusion criteria listed in Section 3.4.1. After linking OCR data with the administrative databases listed in Section 3.3, 22,863 patients were identified as having been diagnosed with incident squamous cell carcinoma of the head and neck between January 1st, 1990 and January 31st, 2010 (other histologies and patients with previous cancers of varying histologies were excluded as described in Section 3.4.1.1). Patients who were identified as having record of a previous stroke, transient ischemic attack (TIA) or carotid endarterectory/carotid stent (CEA/CAS) were excluded (n=1361). For the purposes of analyses for the three objectives, 6633 patients were excluded because either they did not receive curative treatment for their cancer (no documented treatment or palliative treatment, NDT) or there was not sufficient information to be able to categorize them into a curative treatment regimen (this group of patients will be examined further in Section 4.6). An additional 794 patients were excluded from the dataset because they received radiotherapy (RT) for a second cancer. Removing 6 patients due to unresolvable errors in their treatment date (patients' date of death came before their treatment date), left 14,069 patients in the final H&NCa study cohort.

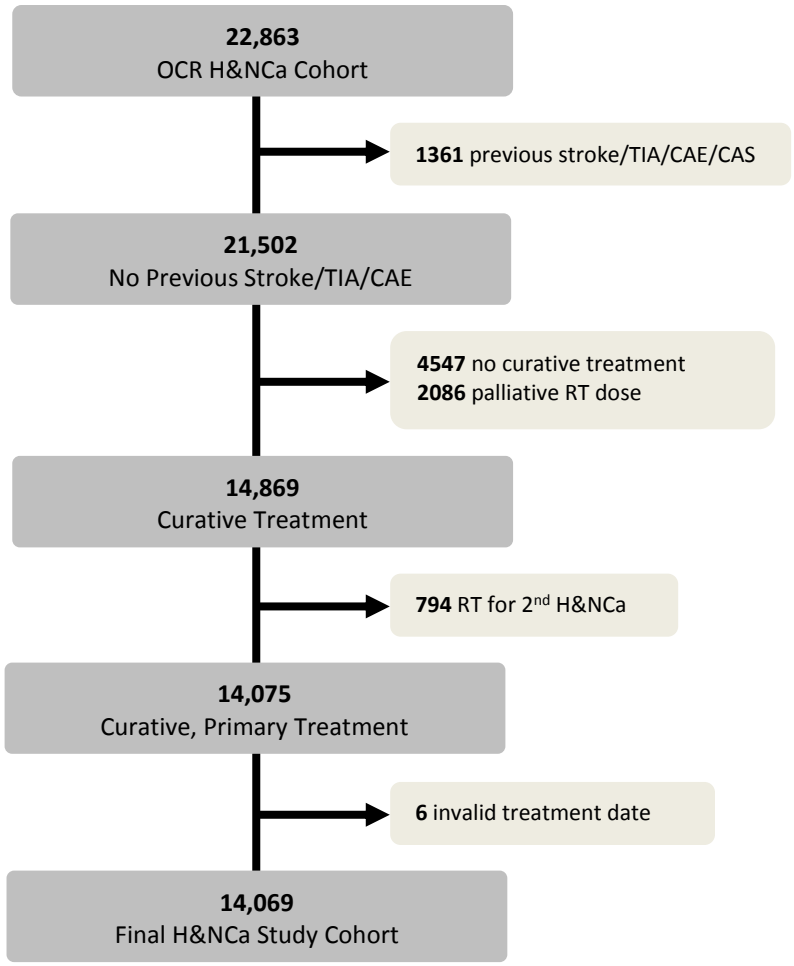

Figure 5: Study Population Flow Chart

4.2 Objective 1 – Risk of Stroke Following Radiotherapy

4.2.1 Descriptive Statistics

Characteristics of the study population are listed in Table 4. Patients were evenly distributed across age groups, with the most patients categorized as 55 to 65 years of age (n=5024, 36%). The majority of patients included in this study were male (n=10596, 75%). Less than 10% of patients were diagnosed with each of the stroke risk factors, with the exception of chronic obstructive pulmonary disease (COPD) and hypertension, with 14% and 21%, respectively (remaining risk factors: ischemic heart disease (IHD), myocardial infarction (MI), peripheral vascular disease (PVD), asthma, atrial

fibrillation, diabetes). Approximately 9% of the patients included in this study were categorized as being *likely* to have an HPV-positive tumour (n=987), and the majority of the patients were diagnosed with their H&NCa prior to 2005, reflective of the overall declining incidence of H&NCas in more recent years. The most common cancer sites among the study population were: oral cavity (n=2950, 27%), oropharynx (n=2770, 25%) and larynx (n=2452, 32%). 77% of patients were found to have no comorbidities based on the Elixhauser index, described in Section 3.5.3.2. The largest proportion of patients were treated with *Radiotherapy alone* (n=4475, 32%) followed by *Surgery & Radiotherapy* (n=4045, 29%) and *Surgery alone* (n=3120, 22%).

Table 4: Head and Neck Cancer Study Cohort Characteristics, N=14069

Characteristic	N (%)
Age	
<55	4650 (33.1)
55-65	5024 (35.7)
65-75	4395 (31.2)
Sex, M	10596 (75.3)
Ischemic Heart Disease	438 (4.5)
Myocardial Infarction	144 (1.4)
Peripheral Vascular Disease	42 (0.4)
Asthma	399 (4.0)
Atrial Fibrillation	62 (0.6)
Chronic Obstructive Pulmonary Disease	1380 (14.0)
Hypertension	2161 (21.4)
Diabetes	722 (7.1)
HPV 'likely'	987 (8.7)
Cancer Site	
Oral Cavity	2950 (27.1)
Nasopharynx	872 (6.7)
Oropharynx	2770 (25.1)
Hypopharynx	593 (5.9)
Larynx	2452 (31.6)
Unspecified neoplasm of head and neck	387 (3.5)
Cancer diagnosis year	
<2005	7030 (73.2)
≥2005	2994 (26.8)
Elixhauser Comorbidity Score	
0	7692 (76.6)
1	1103 (11.1)
2	575 (5.9)
3+	654 (6.4)
Treatment Regimen	
Surgery alone	3120 (22.2)
Surgery & Radiotherapy	4045 (28.8)
Surgery & Radiotherapy & Chemotherapy	835 (5.9)
Radiotherapy alone	4475 (31.8)
Radiotherapy & Chemotherapy	1594 (11.3)

Table 5 lists the outcomes for each treatment regimen as were defined in Section 3.5.2. The largest number (and proportion) of strokes or stroke deaths were found among the *Radiotherapy alone* group, followed by *Surgery & Radiotherapy* and *Surgery alone* (8.0%, 5.9%, 5.2%, respectively). Less than 100 strokes or stroke deaths (<3%) occurred among the remaining groups. The treatment group with the largest proportion of patients that died during the study period due to non-stroke causes (cancer or other) was the *Radiotherapy alone* group, and the *Surgery alone* group had the smallest proportion (61.7%, 36.0%, respectively). The *Radiotherapy alone* group had the smallest percentage of patients that were lost to follow-up (or that survived to the end of the study period, stroke-free) (30.3%), with *Surgery alone* having the highest (58.5%).

Table 5: Head and Neck Cancer Cohort Outcome distribution by Treatment Regimen

Treatment Regimen	Stroke / stroke death	Other Cause Death	Lost to Follow-up (Stroke-free survival)
Surgery alone (%)	162 (5.2)	1133 (36.0)	1825 (58.5)
Surgery & Radiotherapy (%)	240 (5.9)	2230 (55.1)	1575 (38.9)
Surgery & Radiotherapy & Chemotherapy (%)	20 (2.4)	343 (41.0)	472 (56.5)
Radiotherapy alone (%)	357 (8.0)	2763 (61.7)	1355 (30.3)
Radiotherapy & Chemotherapy (%)	43 (2.7)	689 (43.0)	862 (54.1)
Total	822	7158	6089

In Figure 6, the Kaplan-Meier survival curves are plotted by treatment group. These curves are meant to reflect the overall, other cause survival of the study population across treatment groups, when stroke/stroke death is ignored. The *Surgery alone* treatment group has a survival that is considerably better than the rest of the treatment regimens; at 5 or so years the plot indicates that patients treated with *Surgery alone* were at just under 80% survival, whereas the remaining treatments fall closer to a 60% survival. The *Radiotherapy alone* group has a survival that decreases the most rapidly, although *Surgery & Radiotherapy* only falls slightly above.

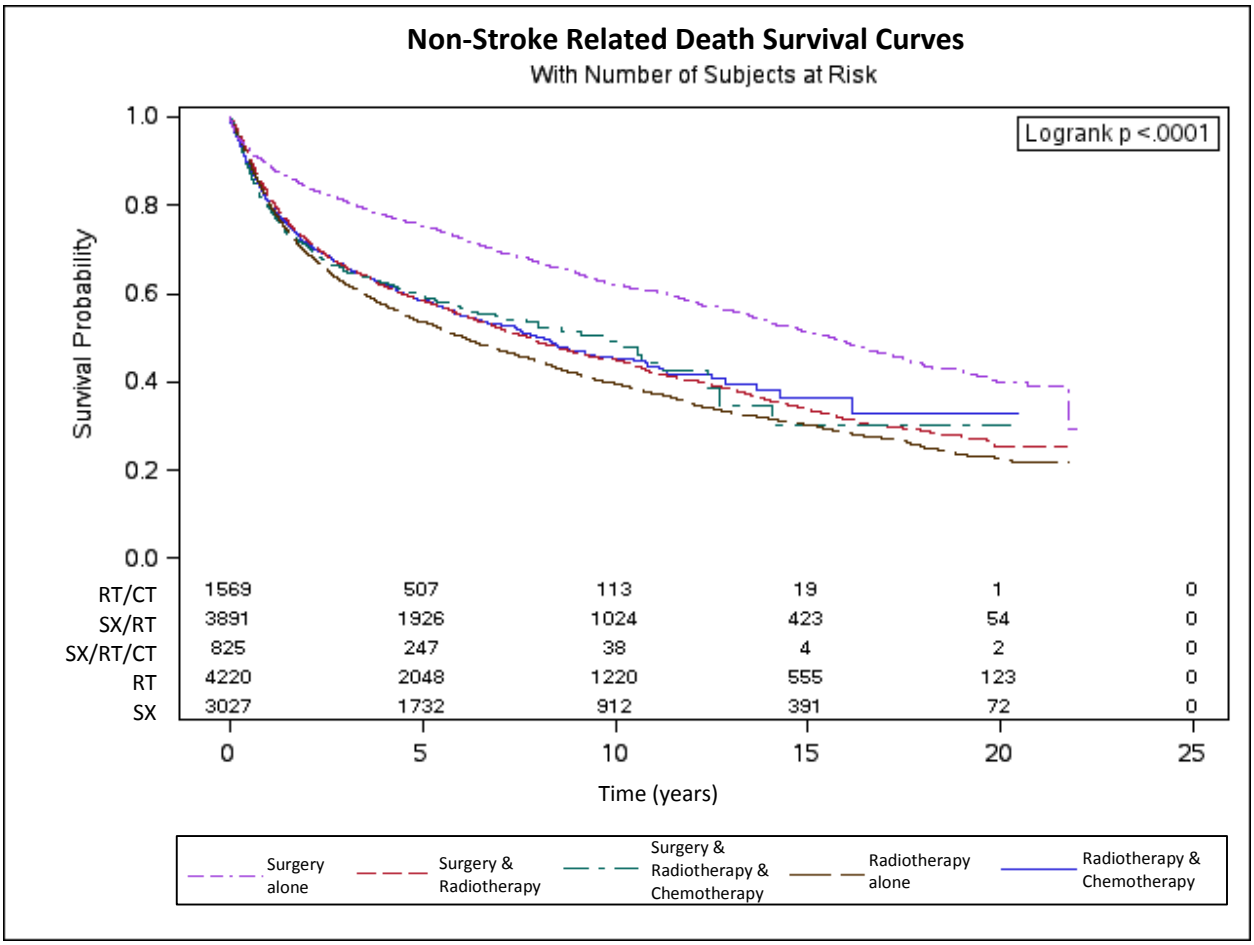

Figure 6: Overall Survival by Treatment Group

Table 6 describes the clinical characteristics across each curative treatment regimen. Using chi-square tests at a 5% significance level, statistically significant differences were found for age, sex, peripheral vascular disease, chronic obstructive pulmonary disease, hypertension, diabetes, HPV status, cancer site, year of cancer diagnosis and comorbidity status.

The regimen with all three treatments (*Surgery & Radiotherapy & Chemotherapy*) had the largest proportion of younger patients (<55), followed by the *Radiotherapy & Chemotherapy* regimen (49%, 46% respectively). The treatment with the lowest proportion of men was the *Surgery alone* group, with 65% (compared to 77-79%). Peripheral vascular disease and chronic obstructive pulmonary disease were most prevalent among the *Radiotherapy alone* group (0.6 and 15%, respectively), whereas hypertension

(26%), diabetes (9%) and HPV *likely* status (31%) were most common among the group of patients that were treated with *Surgery & Radiotherapy & Chemotherapy*. Among patients that were treated with *Surgery alone*, the largest proportion were diagnosed with a primary cancer site of the oral cavity (71%). Patients diagnosed with laryngeal cancer were the largest proportion of patients treated with both surgery and radiotherapy, and radiotherapy alone (49% and 38%, respectively). A combination of all three treatments and *Radiotherapy & Chemotherapy* were curative regimens that were most common among patients diagnosed with cancer of the oropharynx (45% and 48%, respectively).

Treatment regimens that involved either all three treatments (*Surgery & Radiotherapy & Chemotherapy*) or a combination of *Radiotherapy & Chemotherapy* were more prevalent in cancers diagnosed in or after 2005. Contrarily, *Surgery alone*, *Surgery & Radiotherapy* and *Radiotherapy alone* were regimens used most often for patients diagnosed prior to 2005. Although seemingly evenly distributed across treatment regimens, the highest percentage of patients with no comorbidities (based on the Elixhauser Index) were in the treatment group involving all three treatments.

Table 6: Clinical Characteristics across Curative Treatment Regimens

Characteristic	SX alone (%)	SX + RT (%)	SX + RT + CT (%)	RT alone (%)	RT + CT (%)	p-value*
n	3120	4045	835	4475	1594	
Age						<0.001
<55	1040 (33.3)	1212 (30.0)	411 (49.2)	1249 (27.9)	738 (46.3)	
55-65	1030 (33.0)	1507 (37.3)	295 (35.3)	1630 (36.4)	562 (35.3)	
65-75	1050 (33.6)	1326 (32.8)	129 (15.5)	1596 (35.7)	294 (18.4)	
Sex, M	2058 (65.0)	3196 (79.0)	659 (78.9)	3443 (76.9)	1240 (77.8)	<0.001
Ischemic Heart Disease	152 (4.9)	193 (4.8)	36 (4.3)	188 (4.2)	62 (3.9)	0.395
Myocardial Infarction	42 (1.3)	50 (1.2)	17 (2.0)	53 (1.2)	32 (2.0)	0.057
Peripheral Vascular Disease	12 (0.4)	9 (0.2)	<5 (<0.6)	26 (0.6)	<5 (<0.3)	0.027
Asthma	128 (4.1)	161 (4.0)	39 (4.7)	159 (3.6)	73 (4.6)	0.309
Atrial Fibrillation	15 (0.5)	29 (0.7)	<5 (<0.6)	36 (0.8)	8 (0.5)	0.290
Chronic Obstructive Pulmonary Disease	386 (12.4)	595 (14.7)	110 (13.2)	673 (15.0)	211 (13.2)	0.008
Hypertension	720 (23.1)	844 (20.9)	217 (26.0)	835 (18.7)	389 (24.4)	<0.001
Diabetes	254 (8.1)	272 (6.7)	76 (9.1)	263 (5.9)	129 (8.1)	<0.001
HPV 'likely'	83 (2.7)	230 (5.7)	260 (31.1)	195 (4.4)	449 (28.2)	<0.001
Cancer Site						<0.001
Oral Cavity	2227 (71.4)	864 (21.4)	165 (19.8)	452 (10.1)	106 (6.6)	
Nasopharynx	16 (0.5)	74 (1.8)	63 (7.5)	415 (9.3)	378 (23.7)	
Oropharynx	268 (8.6)	761 (18.8)	376 (45.0)	1359 (30.4)	767 (48.1)	
Hypopharynx	47 (1.5)	241 (6.0)	62 (7.4)	375 (8.4)	109 (6.8)	
Larynx	443 (14.2)	1995 (49.3)	129 (15.4)	1704 (38.1)	176 (11.0)	
Unspecified neoplasm of head and neck	119 (3.8)	110 (2.7)	40 (4.8)	170 (3.8)	58 (3.6)	
Cancer diagnosis year						<0.001
<2005	2073 (66.4)	3274 (80.9)	310 (37.1)	3927 (87.8)	720 (45.2)	
≥2005	1047 (33.6)	771 (19.1)	525 (62.9)	548 (12.2)	874 (54.8)	
Elixhauser Comorbidity Score						<0.001
0	2339 (75.0)	3084 (76.2)	679 (81.3)	3392 (75.8)	1282 (80.4)	
1	369 (11.8)	463 (11.4)	75 (9.0)	513 (11.5)	146 (9.2)	
2	181 (5.8)	256 (6.3)	42 (5.0)	271 (6.1)	81 (5.1)	
3+	231 (7.4)	242 (6.0)	39 (4.7)	299 (6.7)	85 (5.3)	

* All variables are categorical and tests were carried out using the χ^2 statistic.

4.2.2 Stroke Incidence and Cause-Specific Hazard across All Curative Treatment Groups

Figure 7 is a graphical depiction of how the five treatment groups differ with respect to the stroke outcome over time. The cumulative incidence functions of stroke or stroke death for each group are plotted, as described in Section 3.6.2. Gray's test of cumulative incidence functions equivalence performed to the equality of time to event over the strata indicated, showed a statistically significant difference in the stroke cumulative incidences between treatments ($\chi^2 = 16.87$, p=0.002). This figure emphasizes the difference between the *Radiotherapy alone* group compared to the rest of the treatments, with the cumulative incidence function of stroke and stroke death seemingly higher than the other treatments, particularly both *Surgery alone* and *Surgery & Radiotherapy* (whose curves cross just after 15 years). The incidence curve for the *Radiotherapy & Chemotherapy* treatment group illustrates the more recent use of this treatment modality, as the straight line that begins at around 12 years indicates that there were no longer any events, and that these patients were only able to be followed for 10 or so years (due the introduction into standard practice in the early 2000s). The curve indicating the incidence of stroke or stroke death among the *Surgery & Radiotherapy & Chemotherapy* group emphasizes the small number of patients that remained alive (after either suffering a stroke or dying of other causes) between 5 and 10 years following treatment, and that this combination of treatments is a more recently employed regimen. The majority of the patients in this group experienced their outcome early on during the follow-up period, and there were few patients that were available to follow in the later years of the follow-up period.

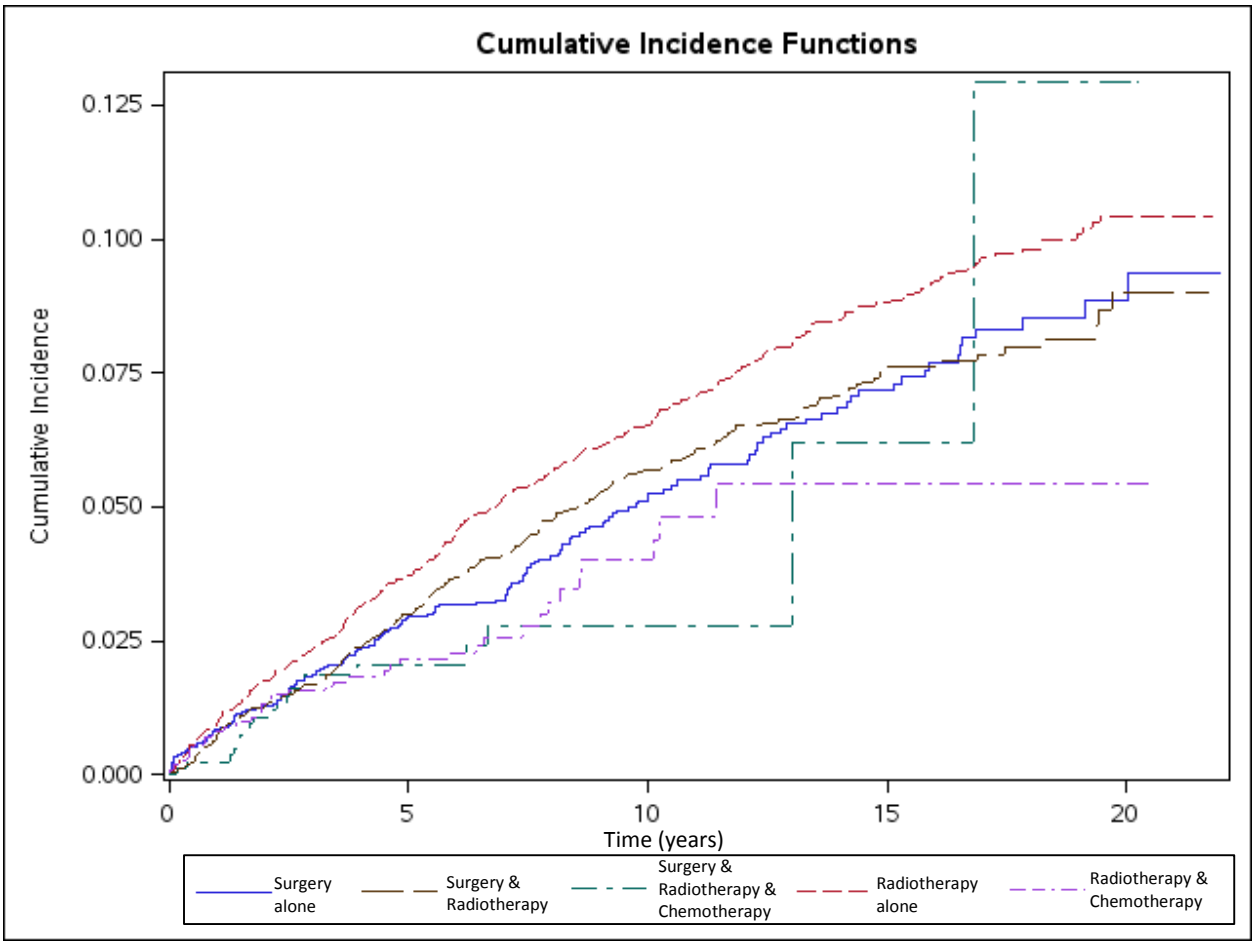

Figure 7: Stroke/Stroke Death Cumulative Incidence Functions by Treatment Groups

To assess the effects of the treatment groups and other covariates on the time to stroke/stroke related death, we consider the Cox proportional hazards model for the cause-specific hazard of the time to stroke/stroke related death. Results from univariate and multivariate analyses are presented in Table 7. Univariate analyses were performed for all covariates and multivariate analyses estimated hazard ratios for the exposure of interest, treatment, while controlling for other factors that were retained during the model selection process. Variables that were crudely associated with the outcome of stroke, based on the Type III p-values were: age, PVD, IHD, hypertension, diabetes, COPD, HPV status, cancer diagnosis year, and comorbidity status. There was a significant crude relationship between treatment and stroke (Type III p-value<0.001), and this association varied by each treatment regimen using the *Surgery alone*

group as the reference category. The *Surgery & Radiotherapy* group was found to have a conditional risk of stroke that was 30% higher than the risk among patients who were treated with surgery alone (HR = 1.31, 95% CI: 1.07,1.60, p=0.008) and patients treated with *Radiotherapy alone* had a conditional risk of stroke of 1.70 compared to *Surgery alone* (HR = 1.70, 95% CI: 1.41,2.05, p<0.001). The remaining groups (*Surgery & Radiotherapy & Chemotherapy* and *Radiotherapy & Chemotherapy*) were not significantly different than *Surgery alone* with respect to their crude association with stroke.

Age and comorbidity status were controlled for in the multivariate analysis after a backwards selection process using a significance level of 10%, while no variables were found to be significant confounders using a change-in-estimate approach for the remaining covariates. Adjusted estimates of effect between treatment groups and stroke did not differ from the crude estimates: *Surgery & Radiotherapy* (HR = 1.27, 95% CI:1.04,1.56, p=0.020) and *Radiotherapy alone* (HR = 1.70, 95% CI:1.41,2.04, p<0.001) remained the only treatment groups that were significantly different from *Surgery alone* in terms of the risk of stroke after controlling for age and comorbidities.

Patients that were between the ages of 55 and 65 had a conditional risk of stroke that was 75% higher than patients that were under the age of 55 at diagnosis (HR = 1.75, 95% CI:1.45,2.10, p<0.001) . As well, the conditional risk of stroke among patients that were over 65 was 2.65 times the risk for patients under the age of 55 (HR = 2.65, 95% CI:2.21,3.20, p<0.001). In terms of comorbidity status, each level of comorbidity was significantly different from no comorbid diseases; having 3 or more comorbid diseases increased the risk of stroke by 82% (HR = 1.82, 95% CI:1.37,2.41, p<0.001), and 2 and 1 comorbidity(ies) yielded an increase in risk of 64 % (HR = 1.64, 95% CI:1.25,2.15, p<0.001) and 25% (HR = 1.25, 95% CI:1.01,1.55, p=0.038), respectively.

Table 7: Univariate and Multivariate Cox Proportional Hazards Analyses - All Treatment Groups N=14,069

Variable	Univariate					Multivariate				
	HR	p-value	95% CIs		Type III p-value*	HR	p-value	95% CIs		Type III p-value*
Treatment					<0.001					<0.001
Surgery alone	1.00	---	---	---		1.00	---	---	---	
Surgery & Radiotherapy	1.31	0.008	1.07	1.60		1.27	0.020	1.04	1.56	
Surgery & Radiotherapy & Chemotherapy	0.93	0.775	0.59	1.49		1.15	0.550	0.72	1.84	
Radiotherapy alone	1.70	<0.001	1.41	2.05		1.70	<0.001	1.41	2.04	
Radiotherapy & Chemotherapy	0.97	0.849	0.69	1.36		1.16	0.386	0.83	1.63	
Age					<0.001					<0.001
<55 years	1.00	---	---	---		1.00	---	---	---	
55 – 65	1.83	<0.001	1.53	2.21		1.75	<0.001	1.45	2.10	
65 – 75	2.85	<0.001	2.38	3.42		2.65	<0.001	2.21	3.20	
Sex										
Female	1.00	---	---	---						
Male	1.04	0.596	0.89	1.22						
Myocardial Infarction	1.27	0.506	0.63	2.54						
Peripheral Vascular Disease	5.48	<0.001	3.02	9.93						
Ischemic Heart Disease	1.46	0.015	1.08	1.99						
Hypertension	1.26	0.013	1.05	1.51						
Asthma	1.08	0.714	0.71	1.64						
Diabetes	1.38	0.034	1.03	1.86						
Atrial Fibrillation	1.66	0.215	0.74	3.71						
Chronic Obstructive Pulmonary Disease	1.33	0.015	1.06	1.66						
HPV – 'likely'	0.44	<0.001	0.29	0.67						
Cancer Site					0.002					
Oral Cavity	1.00	---	---	---						
Nasopharynx	1.00	0.977	0.74	1.36						
Oropharynx	1.15	0.176	0.94	1.42						
Hypopharynx	1.66	0.005	1.17	2.37						
Larynx	1.39	<0.001	1.16	1.65						
Unspecified neoplasm of head and neck	1.11	0.621	0.74	1.66						
Cancer diagnosis year										
<2005	1.00	---	---	---						
≥2005	0.64	<0.001	0.49	0.82						
Elixhauser Comorbidity Score					<0.001					<0.001
0	1.00	---	---	---		1.00	---	---	---	
1	1.43	<0.001	1.16	1.77		1.25	0.038	1.01	1.55	
2	1.86	<0.001	1.42	2.43		1.64	<0.001	1.25	2.15	
3+	2.03	<0.001	1.54	2.69		1.82	<0.001	1.37	2.41	

* Type III p-values are presented for categorical variables with multiple degrees of freedom

Focusing specifically on the effect of *Radiation alone* on the risk of stroke compared to *Surgery alone*, the cumulative incidence curves of these two groups were extracted from Figure 7 for a more thorough exploration. The cumulative incidences of stroke for *Radiotherapy alone* and *Surgery alone* are depicted graphically in Figure 8. These curves were generated from the CIF estimator, adjusting for the competing risk of death, and show that the incidence of stroke among the *Radiotherapy alone* group begin to increase more rapidly than the *Surgery alone* group at approximately 5 years following treatment. The curves continue to slowly grow apart until the end of the follow-up period. The Gray test of equivalence indicated that these incidence curves were significantly different at 5% significance level ($\chi^2 = 5.37$, p=0.021). This significant difference is consistent with the significant difference in the cause-specific hazard (stroke) between the *Radiotherapy alone* group and the *Surgery alone* group (Table 7, HR=1.70).

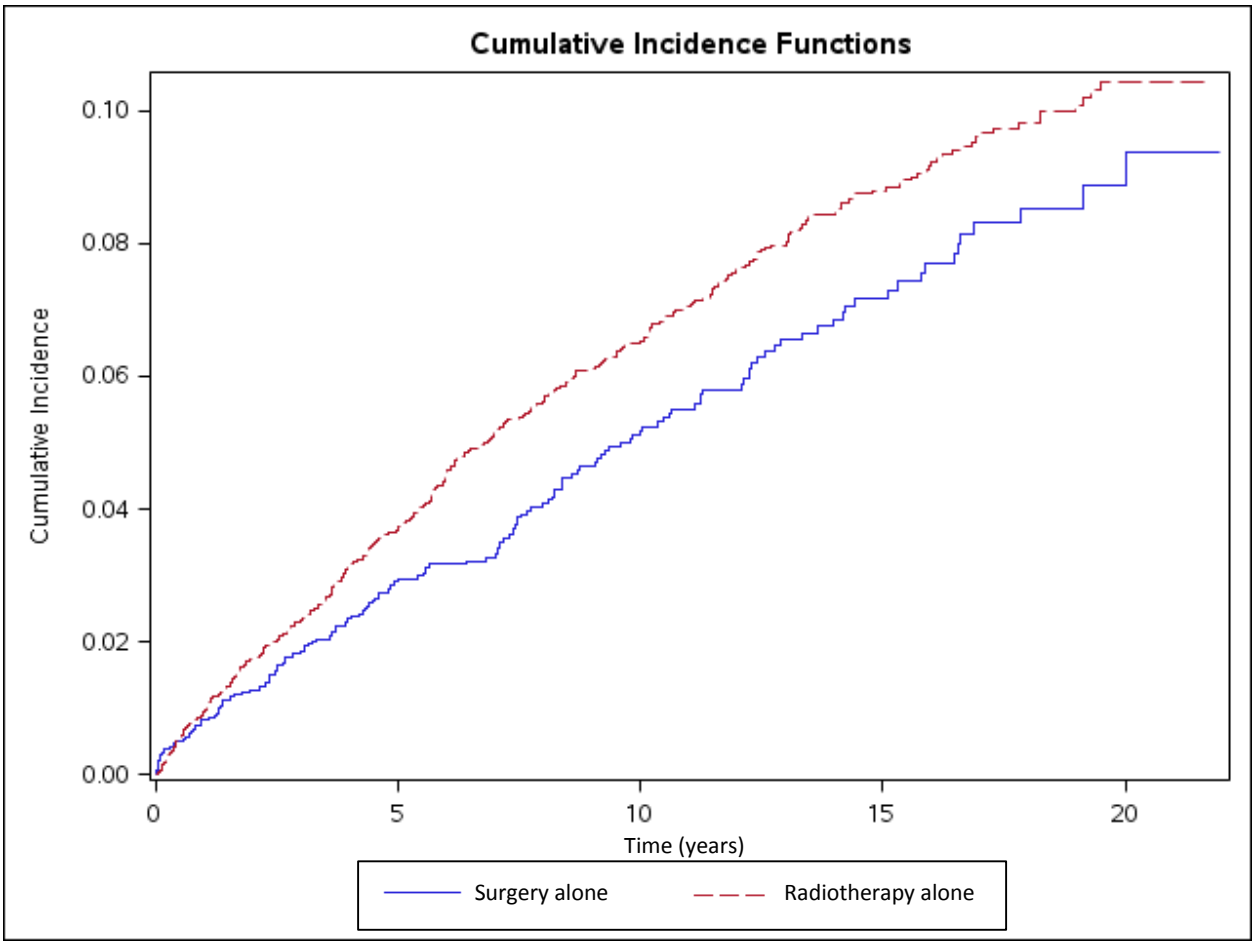

Figure 8: Stroke/Stroke Death Cumulative Incidence Functions by Radiotherapy alone and Surgery alone

4.2.3 Any Radiotherapy versus Surgery Alone

Results from Table 7 indicated that two of the treatment groups involving radiotherapy (*Radiotherapy alone* and *Surgery & Radiotherapy*) were found to have larger conditional risks of stroke compared to *Surgery alone*, and the remaining treatment groups were not found to be significantly different from *Surgery alone*, univariate and multivariate analyses were completed after collapsing 4 of the 5 treatment groups, as described in Section 3.5.1, and the exposure of interest became a dichotomous variable: *Any Radiotherapy* or *Surgery alone*. This approach was to evaluate the effect of any exposure to radiation to the head and neck on the risk of stroke.

4.2.3.1 Clinical Characteristics

Table 8 presents the results of descriptive analyses once collapsing the treatment groups that involved any combination of radiotherapy with other treatments. Covariates that differed significantly between *Surgery alone* and *Any Radiotherapy* included age, sex, COPD, hypertension, diabetes, HPV status, cancer site, year of cancer diagnosis and comorbidity status.

The proportion of male patients was higher in the radiotherapy group compared to the surgery group (78% vs. 65%). As well, COPD (14.5% vs. 12.4%) and HPV *likely* (10.4% vs. 2.7%) were covariates that had higher percentages among the radiotherapy group. The other diseases that were significantly different between treatment groups where a larger proportion were represented in the *Surgery alone* group, were hypertension (23% vs. 21%) and diabetes (8% vs. 7%). The primary site of cancer was significantly different between treatments because the majority of the patients in the *Surgery alone* group were diagnosed with cancer of the oral cavity (71%), whereas patients who were treated with *Any Radiotherapy* were mostly diagnosed with cancers of the larynx (37%), oropharynx (30%), and oral cavity (15%). A larger percentage of patients treated with *Any Radiotherapy* were diagnosed with their cancer prior to, or in 2005 compared to surgery (75% vs. 66%). In terms of comorbidities, there was a larger proportion of patients with no comorbid conditions in the *Any Radiotherapy* group (77% vs. 75), and a larger proportion with 3 or more comorbid conditions in the *Surgery alone* group (7% vs. 6%).

Table 8: Clinical Characteristics – Any Radiotherapy versus Surgery

Characteristic	SX alone (%)	Any Radiotherapy (%)	p-value*
n	3120	10949	
Age			<0.001
<55	1040 (33.3)	3610 (33.0)	
55-65	1030 (33.0)	3994 (36.5)	
65-75	1050 (33.6)	3345 (30.6)	
Sex, M	2058 (65.0)	8538 (78.0)	<0.001
Ischemic Heart Disease	152 (4.9)	479 (4.4)	0.237
Myocardial Infarction	42 (1.3)	152 (1.4)	0.859
Peripheral Vascular Disease	12 (0.4)	39 (0.4)	0.816
Asthma	128 (4.1)	432 (3.9)	0.692
Atrial Fibrillation	15 (0.5)	76 (0.7)	0.190
Chronic Obstructive Pulmonary Disease	386 (12.4)	1589 (14.5)	0.002
Hypertension	720 (23.1)	2285 (20.9)	0.008
Diabetes	254 (8.1)	740 (6.8)	0.008
HPV 'likely'	83 (2.7)	1134 (10.4)	<0.001
Cancer Site			<0.001
Oral Cavity	2227 (71.4)	1587 (14.5)	
Nasopharynx	16 (0.5)	930 (8.5)	
Oropharynx	268 (8.6)	3263 (29.8)	
Hypopharynx	47 (1.5)	787 (7.2)	
Larynx	443 (14.2)	4004 (36.6)	
Unspecified neoplasm of head and neck	119 (3.8)	378 (3.5)	
Cancer diagnosis year			<0.001
<2005	2073 (66.4)	8231 (75.2)	
≥2005	1047 (33.6)	2718 (24.8)	
Elixhauser Comorbidity Score			0.019
0	2339 (75.0)	8437 (77.1)	
1	369 (11.8)	1197 (10.9)	
2	181 (5.8)	650 (5.9)	
3+	231 (7.4)	665 (6.1)	

* All variables are categorical and tests were carried out using the χ^2 statistic.

4.2.3.2 Stroke Incidence and Cause-Specific Hazard

Figure 9 represents the cumulative incidence of stroke or stroke death curves generated from the CIF estimator, adjusting for the competing risk of non-stroke death. The red curve, indicating the incidence of stroke over time among patients that were treated with any radiotherapy diverges only slightly from the blue curve (surgery) after approximately 5 years. Thereafter, the curves are seemingly parallel until the end of the follow-up period where the curves seems to taper towards each other. The Gray test of equivalence over the strata indicated, does not show a statistically significant difference between the cumulative incidences for each treatment ($\chi^2 = 1.16$, p=0.281).

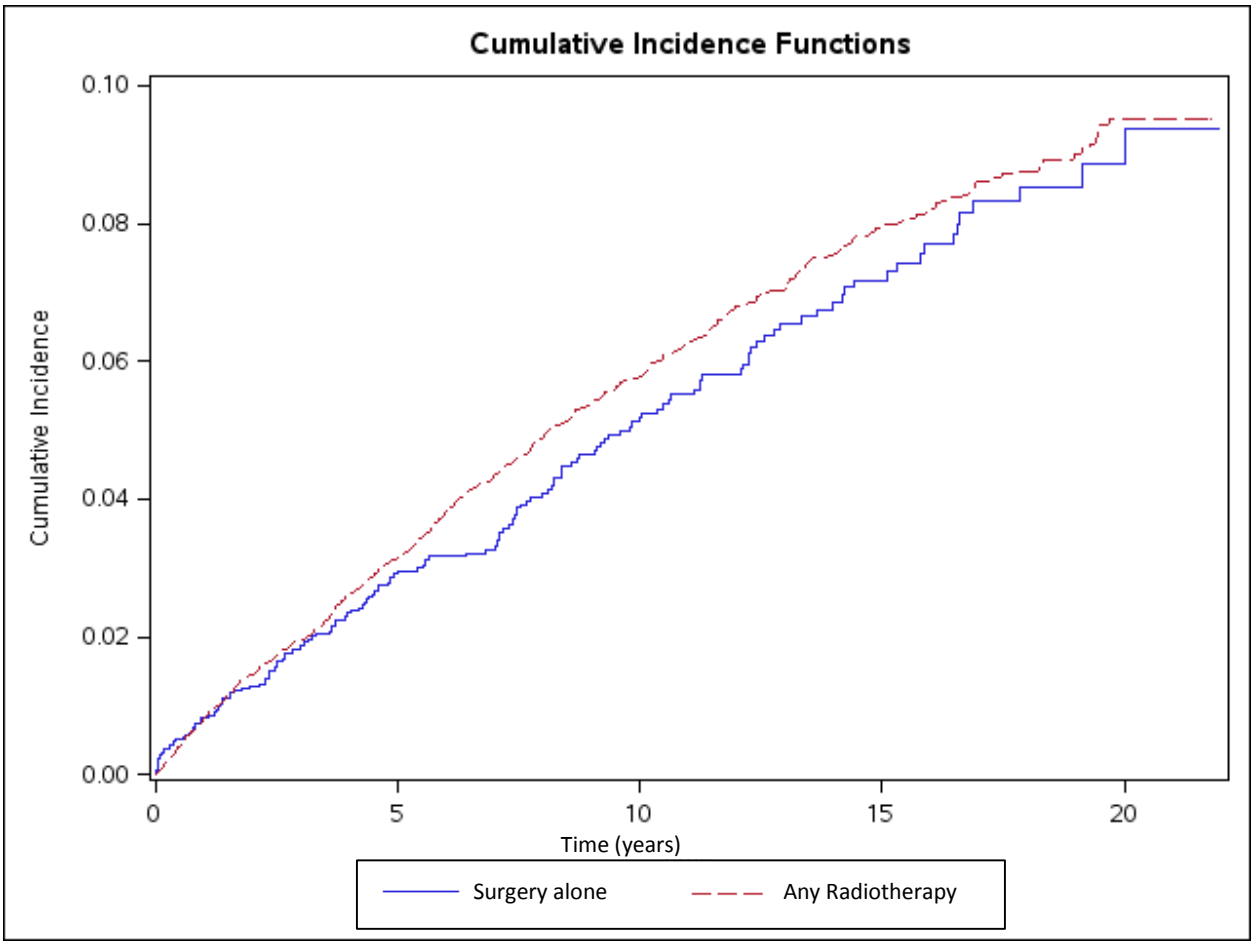

Figure 9: Stroke/Stroke Death Cumulative Incidence Functions by Any Radiotherapy and Surgery alone

Table 9 presents the crude (univariate) and adjusted (multivariate) cause-specific hazard ratio estimates for *Any Radiotherapy* compared to S*urgery alone*, based on Cox PH models. Estimates for the covariates from the univariate analyses remained the same as presented in Table 7, since the analysis was based on the same patient sample. Additionally, the same covariates were retained following backwards model selection, and age and comorbidity status were adjusted for in the multivariate analysis. As indicated with a hazard ratio of 1.46, patients that had a curative treatment regimen which included *Any Radiotherapy* (with or without other treatments) had a 46% higher conditional risk of suffering a stroke than patients treated with *Surgery alone* (HR = 1.46, 95% CI:1.23,1.73, p<0.001). This estimate is similar

to that of the univariate analysis, where prior to adjusting for age and comorbidities, the conditional risk of suffering a stroke among patients that were treated with any radiotherapy was 44% higher than patients who were treated with surgery alone. The above results show that the cause-specific hazards of stroke are significantly different between *Any Radiotherapy* and *Surgery alone* while the cumulative incidences of stroke between the two treatment groups are not statistically different; these differences will be reconciled in Chapter 5.

Table 9: Univariate and Multivariate Cox Proportional Hazards Analyses - Any Radiotherapy N=14,069

Variable	Univariate*					Multivariate**				
	HR	p-value	95% CIs		Type III p-value	HR	p-value	95% CIs		Type III p-value
Treatment					<0.001					<0.001
Surgery alone	1.00	---	---	---		1.00	---	---	---	
Any Radiotherapy	1.44	<0.001	1.21	1.71		1.46	<0.001	1.23	1.73	

* Covariate univariate analyses were identical to Table 7 - the patient sample remained the same
** Multivariate analysis was adjusted for: age & comorbidity score

When amalgamating treatment modalities that entailed any exposure to radiation, the stroke risk estimate became diluted, possibly due to the heterogeneity of the radiation exposure within curative treatment groups; this is clear when examining *Radiotherapy alone* effect estimates since the hazard ratio was nearly 30% higher among this group. The combined exposure was nevertheless deemed appropriate to use to evaluate the time-dependent risk estimates of stroke, as well as when examining the outcomes of TIA and CAE (for objective 4).

4.2.4 Relative Risk Estimation of Stroke Incidence

Time-dependent estimates of risk were calculated based on the cumulative incidences, which were obtained as described in Section 3.6.2.2. Probability of suffering a stroke at time *t* was obtained, and risk ratios were calculated at *t*=3 years, 5 years, 10 years and 15 years for both RT scenarios (comparing *Any Radiotherapy* to *Surgery alone* and comparing *Radiotherapy alone* to *Surgery alone*. Table 10 shows the results from these calculations and the estimated risk ratios at each time point. These estimates reflect the trends that were seen in the graphical depictions of the stroke CIF curves (see Figure 8 and Figure 9), therefore the risk ratios comparing the risk of stroke between *Any Radiotherapy* and *Surgery alone* reflect a slightly higher risk, but there is no indication of a substantial trend (increase of 0.01 at each time until 15 years). The risk ratios for the *Radiotherapy alone* versus *Surgery alone* comparison indicates a consistently higher risk of stroke even at 3 years following treatment, with a 1% increase between 3 and 10 years.

Table 10: Cumulative Incidence Function based Stroke Risk Estimates at 3, 5, 10, 15 Years Following Treatment

	Cumulative Incidence			Risk Ratio $\frac{P(T < t)\|RT}{P(T < t)\|SX}$	
	Any Radiotherapy	Radiotherapy alone	Surgery alone	Any Radiotherapy	Radiotherapy alone
3 YEARS	0.019	0.023	0.019	1.08	1.25
5 YEARS	0.031	0.037	0.029	1.06	1.26
10 YEARS	0.058	0.065	0.051	1.13	1.27
15 YEARS	0.079	0.088	0.060	1.10	1.22

4.3 Objective 2 - Modifications to Radiotherapy Regimen

4.3.1 Addition of Chemotherapy

To further investigate the potential added effect of CT on the risk of stroke when used in conjunction with RT, the cumulative incidence function curves for these treatment groups were isolated from Figure 7 in Objective 1. Figure 10 depicts the stroke cumulative incidence curves adjusting for competing risk of death for the *Radiotherapy & Chemotherapy* treatment group, and the *Radiotherapy alone* group. The *Radiotherapy alone* curve seems to indicate a more rapidly increasing rate of stroke than the *Radiotherapy & Chemotherapy* curve. The Gray test of equivalence, indicates a statistically signficant difference between these curves ($\chi^2 = 10.25$, p=0.0014).

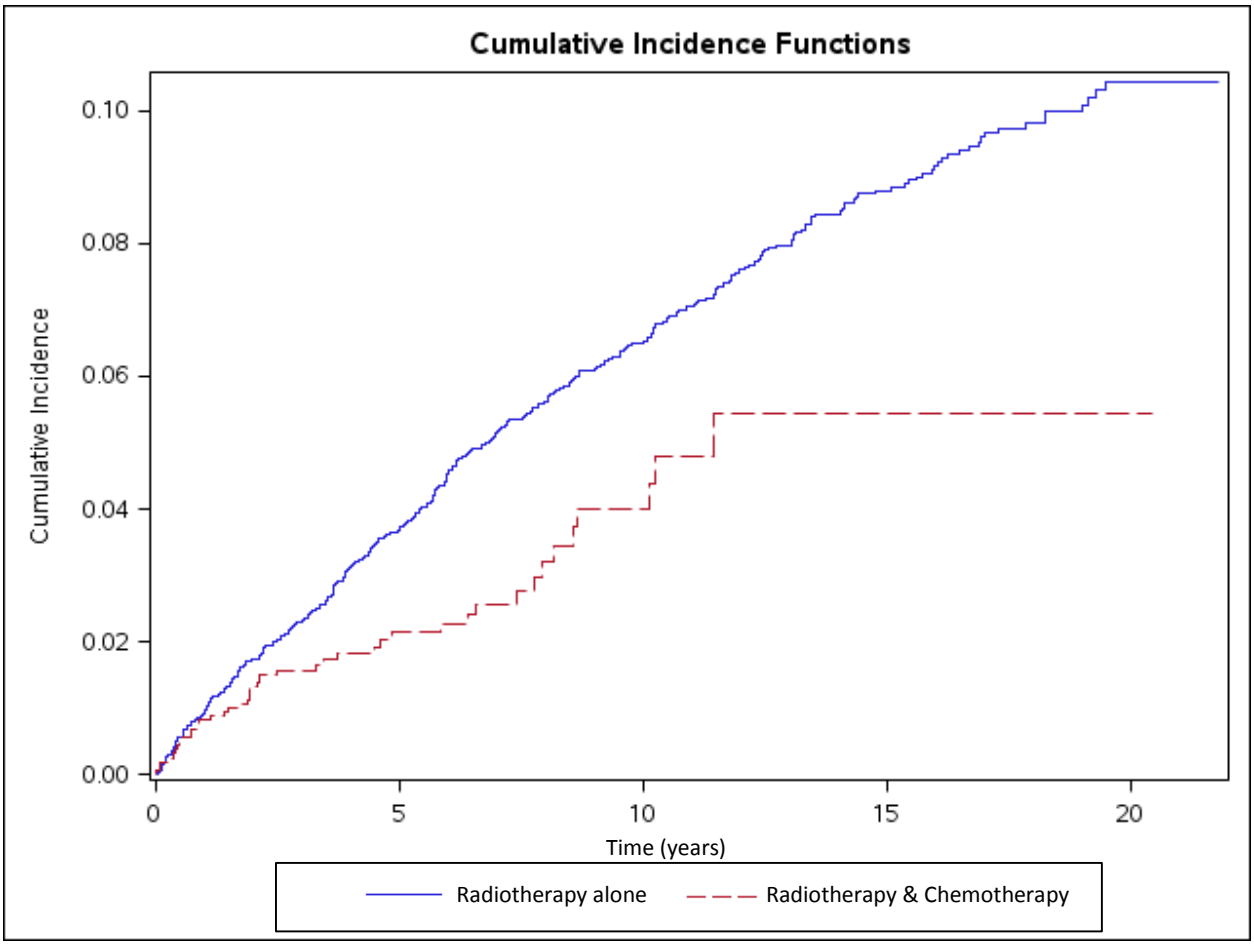

Figure 10: Cumulative Incidence Functions by Chemotherapy & Radiotherapy and Radiotherapy alone

The addition of chemotherapy to a radiotherapy regimen was examined through modelling the cause-specific hazards and directly comparing *Radiotherapy & Chemotherapy* to *Radiotherapy alone*; this was done by changing the reference group in the analysis from Section 4.2.2 to be *Radiotherapy alone* instead of *Surgery alone* and estimating a cause-specific hazard ratio for this comparison. The same model was used since only the reference category changed for this analysis, and both age and comorbidities were adjusted for, yielding the same effect estimates as in Table 7. Results of the univariate and multivariate analyses are presented in Table 11. With the *Radiotherapy alone* group as the reference category, the unadjusted cause-specific hazard ratio associated with the *Radiotherapy & Chemotherapy*

treatment regimen was 0.57 (95% CI:0.41,0.78, p<0.001), indicating a reduction in conditional risk of stroke of 43% among patients treated with both radiotherapy and chemotherapy compared to patients that were treated with radiotherapy alone. After adjusting for age and comorbidities, the conditional risk of stroke became 0.69 among the *Radiotherapy & Chemotherapy* group, indicating a 31% reduction in conditional risk of stroke compared to the *Radiotherapy alone* group (95% CI:0.50,0.94, p=0.021). The adjusted estimates for the remaining treatment categories, incidentally, show that patients treated with each treatment modality are at a statistically significant lower risk of stroke than patients treated with *Radiotherapy alone*, with the exception of the treatment regimen that included all three treatments (as it does not meet the 5% significance standard). Among patients treated with *Surgery & Radiotherapy*, there was a 25% reduction in risk of stroke compared to *Radiotherapy alone*, a result that is consistent with the CIF curves from Section 4.2.2.

Table 11: Univariate and Multivariate Cox Proportional Hazards Analyses – All Treatment Groups (Radiotherapy alone as the Reference) N=14,069

Variable	Univariate*				Multivariate**			
	HR	p-value	95% CIs	Type III p-value	HR	p-value	95% CIs	Type III p-value
Treatment				<0.001				<0.001
Radiotherapy alone	1.00	---	---	---	1.00	---	---	---
Radiotherapy & Chemotherapy	0.57	<0.001	0.41 0.78		0.69	0.021	0.50 0.94	
Surgery & Radiotherapy	0.77	0.002	0.65 0.91		0.75	<0.001	0.63 0.88	
Surgery & Radiotherapy & Chemotherapy	0.55	0.009	0.35 0.86		0.68	0.096	0.43 1.07	
Surgery alone	0.59	<0.001	0.49 0.71		0.59	<0.001	0.49 0.71	

* Covariate univariate analyses were identical to Table 7- the patient sample remained the same
** Multivariate analysis was adjusted for: age & comorbidity score

4.3.2 Neck Dissection

Neck dissection prior to radiotherapy is hypothesized by clinicians to increase the risk of stroke as the tissue surrounding the carotid artery following neck dissection could be compromised and provide little barrier between the irradiation and the blood vessel. A patient sample including only patients that were either treated with radiotherapy alone or with neck dissection followed by radiotherapy were identified as described in section 3.5.1. (n=5,995). Due to the restricted sample of patients that were included for this objective, descriptive statistics were generated, and are presented in Table 12. Differences between these two treatment groups were statistically significant for age, sex, hypertension, HPV status, cancer site and year of diagnosis ($p<0.001$, for each variable). Compared to a regimen that included *Radiotherapy alone*, *t*he group of patients that were treated with a neck dissection followed by radiotherapy were younger (40.8% were <55years), had slightly fewer males (72.6% vs. 76.9%), had more cases of hypertension (22.8% vs. 18.7%), had a larger proportion of patients that were categorized as HPV *likely* (10.5% vs. 4.4%), the majority of the patients were diagnosed with cancer of the oral cavity (51.1% vs. 10.1%) while there were far fewer patients with laryngeal cancer (14.4% vs. 38.1%), and fewer cancer diagnoses occurred prior to 2005 than among the *Radiotherapy alone* group (66.6% vs. 87.8%).

Table 12: Clinical Characteristics – Neck Dissection & Radiotherapy versus Radiotherapy alone (N=5,995)

Characteristic	RT alone (%)	Neck Dissection & RT (%)	p-value*
n	4475	1520	
Age			<0.001
<55	1249 (27.9)	620 (40.8)	
55-65	1630 (36.4)	542 (35.7)	
65-75	1595 (35.7)	358 (23.6)	
Sex, M	3443 (76.9)	1104 (72.6)	<0.001
Ischemic Heart Disease	188 (4.2)	61 (4.0)	0.751
Myocardial Infarction	53 (1.2)	21 (1.4)	0.547
Peripheral Vascular Disease	26 (0.6)	<5 (<0.3)	0.026
Asthma	159 (3.6)	65 (4.3)	0.199
Atrial Fibrillation	36 (0.8)	10 (0.7)	0.572
Chronic Obstructive Pulmonary Disease	673 (15.0)	211 (13.9)	0.271
Hypertension	835 (18.7)	346 (22.8)	<0.001
Diabetes	263 (5.9)	114 (7.5)	0.024
HPV 'likely'	195 (4.4)	159 (10.5)	<0.001
Cancer Site			<0.001
Oral Cavity	452 (10.1)	777 (51.1)	
Nasopharynx	415 (9.3)	63 (4.1)	
Oropharynx	1359 (30.4)	308 (20.3)	
Hypopharynx	375 (8.4)	90 (5.9)	
Larynx	1704 (38.1)	219 (14.4)	
Unspecified neoplasm of head and neck	170 (3.8)	63 (4.1)	
Cancer diagnosis year			<0.001
<2005	3927 (87.8)	1013 (66.6)	
≥2005	548 (12.3)	507 (33.4)	
Elixhauser Comorbidity Score			0.150
0	3392 (75.8)	1187 (78.1)	
1	513 (11.5)	146 (9.6)	
2	271 (6.1)	96 (6.3)	
3+	299 (6.7)	91 (6.0)	

* All variables are categorical and tests were carried out using the χ^2 statistic.

Figure 11 shows the plotted stroke CIF curves for each treatment group. The incidence of stroke seems to grow over time more rapidly among the *Radiotherapy alone* group, compared to the patients that were treated with *Neck dissection & Radiotherapy*. The Gray tests of equivalence associated with the CIFs showed a statistically significant difference between these two curves ($\chi^2 = 10.43$, p=0.0012).

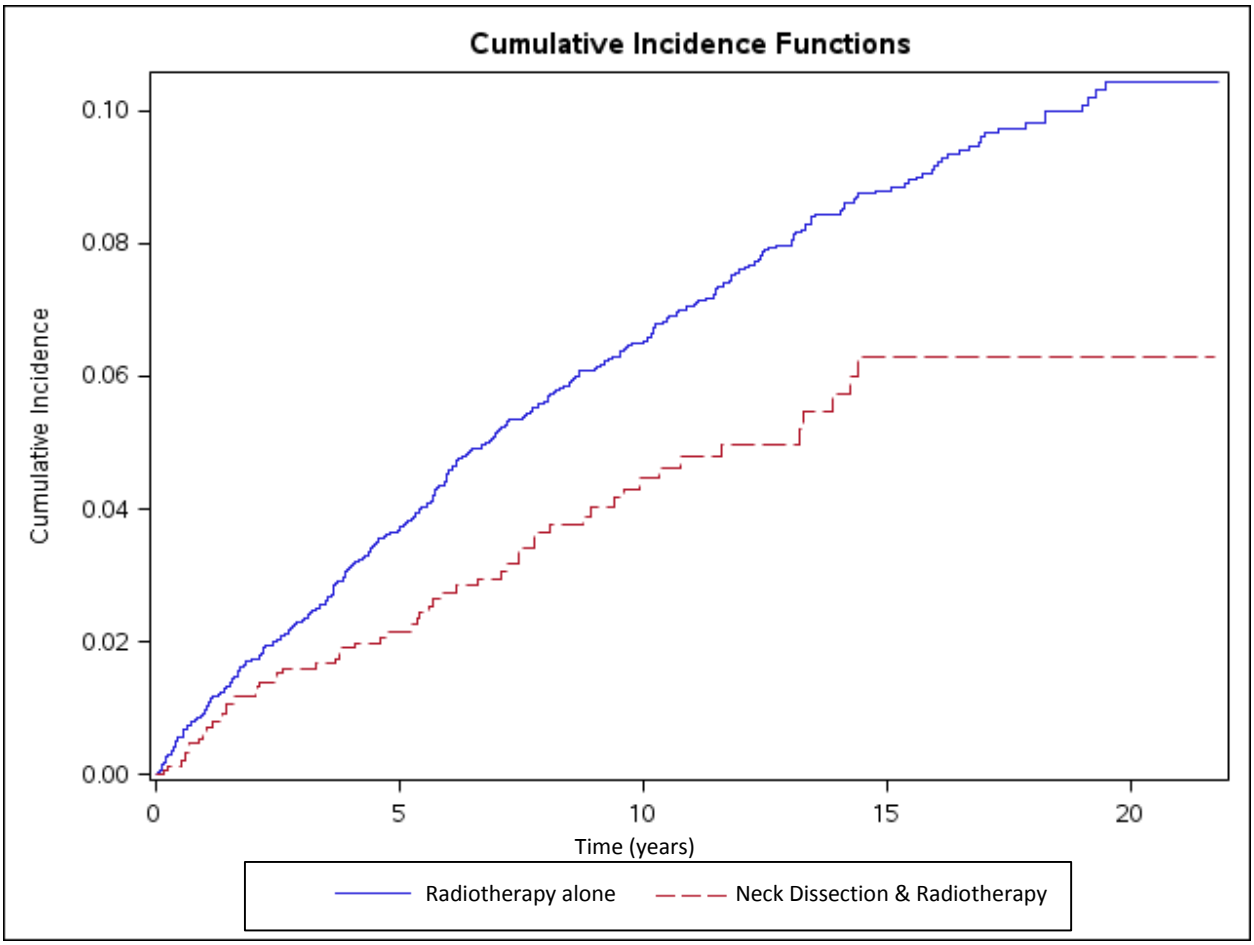

Figure 11: Cumulative Incidence Functions by Neck Dissection & Radiotherapy and Radiotherapy alone

Results from univariate and multivariate analyses are presented in Table 13. Among this patient sample similar covariates were crudely associated with stroke as in previous analyses at a 5% significance level (treatment, age, PVD, hypertension, diabetes, atrial fibrillation, HPV, diagnosis year and comorbidity status). After controlling for age and comorbidities, as identified through model selection, N*eck dissection & Radiotherapy* remained (although only slightly) to have a significantly smaller risk of stroke compared to *Radiotherapy alone* (HR=0.75 95% CI:0.57,0.99, p=0.043). Differences between univariate and multivariate risk estimates are likely due to confounding by age, since comorbid conditions were not found to differ significantly between treatment groups.

Table 13: Univariate and Multivariate Cox Proportional Hazards Analyses – Neck Dissection & Radiotherapy versus Radiotherapy alone, N=5,995

Variable	Univariate HR	Univariate p-value	Univariate 95% CIs		Univariate Type III p-value*	Multivariate HR	Multivariate p-value	Multivariate 95% CIs		Multivariate Type III p-value*
Treatment					0.005					0.043
Radiotherapy alone	1.00	---	---	---		1.00	---	---	---	
Neck Dissection	0.67	0.005	0.51	0.88		0.75	0.043	0.57	0.99	
Age					<0.001					<0.001
<55 years	1.00	---	---	---		1.00	---	---	---	
55 – 65	1.99	<0.001	1.54	2.58		1.88	<0.001	1.45	2.44	
65 – 75	3.07	<0.001	2.37	3.97		2.80	<0.001	2.15	3.63	
Sex										
Female	1.00	---	---	---						
Male	0.87	0.200	0.70	1.08						
Myocardial Infarction	1.37	0.535	0.52	3.66						
Peripheral Vascular Disease	5.39	<0.001	2.68	10.86						
Ischemic Heart Disease	1.27	0.315	0.79	2.04						
Hypertension	1.27	0.078	0.97	1.65						
Asthma	1.28	0.389	0.73	2.22						
Diabetes	1.63	0.023	1.07	2.50						
Atrial Fibrillation	2.46	0.046	1.02	5.95						
Chronic Obstructive Pulmonary Disease	1.20	0.156	0.92	1.72						
HPV – 'likely'	0.49	0.027	0.26	0.92						
Cancer Site					0.186					
Oral Cavity	1.00	---	---	---						
Nasopharynx	0.73	0.153	0.48	1.12						
Oropharynx	1.10	0.564	0.80	1.50						
Hypopharynx	1.04	0.887	0.62	1.74						
Larynx	1.28	0.099	0.96	1.71						
Unspecified neoplasm of head and neck	0.83	0.528	0.45	1.50						
Cancer diagnosis year										
<2005	1.00	---	---	---						
≥2005	0.54	0.013	0.33	0.88						
Elixhauser Comorbidity Score					<0.001					<0.001
0	1.00	---	---	---		1.00	---	---	---	
1	1.61	0.002	1.19	2.17		1.39	0.030	1.03	1.88	
2	2.31	<0.001	1.64	3.27		2.09	<0.001	1.47	2.96	
3+	2.15	<0.001	1.45	3.20		1.96	<0.001	1.31	2.92	

* Type III p-values are presented for categorical variables with multiple degrees of freedom

4.3.3 Dose Response

Whether a dose response exists with respect to the time to stroke (ie: if risks of stroke increase with increasing radiation dose) was of interest for Objective 2. The data quality of the dose information was questionable, and patients were only retained for this analysis if they were treated with radiotherapy and had a recorded dose between 50 and 70 Gy (the standard range in curative radiotherapy doses). 4327 patients who appeared to have accurate and complete dose information were included for analysis and the effects of dose were examined both as a continuous variable and as a dichotomous exposure (50-60 vs. 60-70) in the Cox PH model for the cause-specific hazard of stroke. In both cases, dose was not statistically significantly associated with the risk of stroke, even in the adjusted model. When comparing 60-70 Gy to 50-60 Gy, the hazard ratio was 1.12 (95%CI:0.88,1.42, p=0.356) after adjusting for age and comorbidities, and with dose as a continuous variable, the estimate of effect was essentially null (HR=1.0 95% CI:1.00,1.00, p=0.090).

4.4 Objective 3 - Risk of Stroke-related Events

Stroke-related events were defined as either transient ischemic attacks (TIAs) or carotid endarterectomies/carotid stents (CAE/CAS), and as indicated in Section 3.5.2, these events in addition to stroke or stroke death, are not mutually exclusive. As such, an individual patient could be considered to have the outcome of interest in all three circumstances (stroke, TIA or CAE/CAS). Figure 12 is a Venn diagram indicating the amount of overlap between these three outcomes in order to facilitate interpretation of the proceeding analyses.

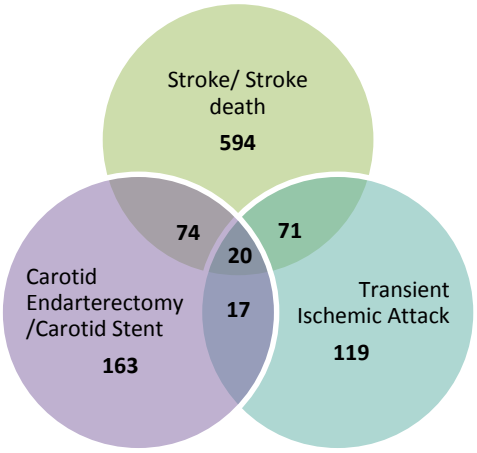

Figure 12: Venn Diagram of Stroke and Stroke-Related Event Outcomes

4.4.1 Transient Ischemic Attack

Survival analyses were performed with the endpoint of transient ischemic attack (TIA). Exposure groups were maintained from Objective 1.3 – *Any Radiotherapy* versus *Surgery alone* (Section 4.2.3), in order to retain the entire cohort due to the small number of events. This patient sample included the entire cohort of eligible patients (n=14,069), and the number of events that occurred (TIAs) was 227. Figure 13 shows the TIA CIF curves of the two treatment groups, adjusted for the competing risks of death (any-cause death, including stroke death). These curves are overlapping throughout the entire follow-up period, and the Gray test of equivalence associated with the CIF estimator yielded a difference that was not statistically significant ($\chi^2 = 0.01$, p=0.916). To verify that this non-significance was not due to a dilution of effect as seen in Section 4.2.3, Gray's test was also performed for the CIF curves between *Radiotherapy alone* and *Surgery alone*, and the cumulative incidence of TIA did not differ significantly between these treatment groups either.

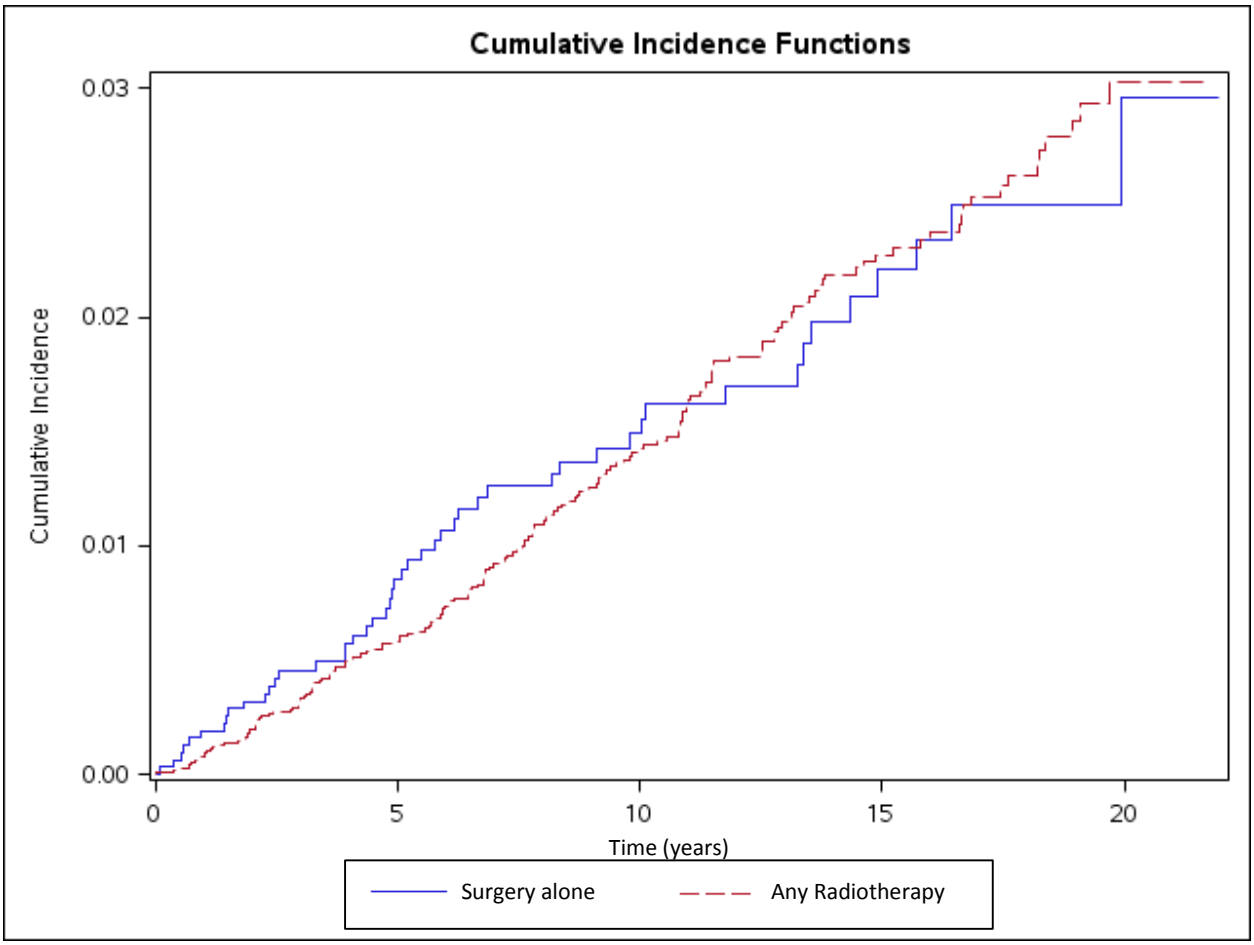

Figure 13: TIA Cumulative Incidence Functions by Any Radiotherapy and Surgery alone

Univariate and multivariate Cox's PH regression analyses were performed with the cause-specific hazard of the TIA endpoint, and the model selection process followed similar suit to previous analyses. Cause-specific hazard ratios are presented in Table 14, and show that after controlling for age, ischemic heart disease and comorbidities, the conditional risk of TIA was only marginally significant (HR=1.37, 95% CI:0.99,1.88, p=0.054). The crude estimates show increased age, ischemic heart disease, hypertension, diabetes, cancer diagnosis year, and 1 or 3+ comorbidities being associated with an elevated conditional risk of TIA. Adjusted estimates indicated that advanced age, ischemic heart disease and comorbidities remained significant.

Table 14: Univariate and Multivariate Cox Proportional Hazards of Transient Ischemic Attack – Any Radiotherpy versus Surgery alone, N=14,069

Variable	Univariate HR	p-value	95% CIs		Type III p-value*	Multivariate HR	p-value	95% CIs		Type III p-value*
Treatment										
Surgery alone	1.00	---	---	---		1.00	---	---	---	
Any Radiotherapy	1.35	0.067	0.98	1.85		1.37	0.054	0.99	1.88	
Age					<0.001					<0.001
<55 years	1.00	---	---	---		1.00	---	---	---	
55 – 65	1.51	0.021	1.07	2.14		1.42	0.050	1.00	2.02	
65 – 75	2.87	<0.001	2.06	4.00		2.63	<0.001	1.88	3.68	
Sex										
Female	1.00	---	---	---						
Male	1.28	0.127	0.93	1.75						
Myocardial Infarction	2.07	0.211	0.66	6.49						
Peripheral Vascular Disease	0**	---	---	---						
Ischemic Heart Disease	2.45	<0.001	1.51	3.98		1.74	0.032	1.05	2.90	
Hypertension	1.37	0.080	0.96	1.94						
Asthma	0.95	0.914	0.39	2.31						
Diabetes	1.62	0.092	0.92	2.86						
Atrial Fibrillation	2.20	0.268	0.55	8.82						
Chronic Obstructive Pulmonary Disease	1.01	0.961	0.61	1.69						
HPV – 'likely'	0.72	0.346	0.37	1.42						
Cancer Site					0.026					
Oral Cavity	1.00	---	---	---						
Nasopharynx	0.56	0.123	0.27	1.17						
Oropharynx	1.36	0.123	0.92	2.00						
Hypopharynx	0.75	0.580	0.27	2.08						
Larynx	1.49	0.019	1.07	2.09						
Unspecified neoplasm of head and neck	1.53	0.219	0.78	3.01						
Cancer diagnosis year										
<2005	1.00	---	---	---						
≥2005	1.54	0.054	0.99	2.38						
Elixhauser Comorbidity Score					<0.001					0.035
0	1.00	---	---	---		1.00	---	---	---	
1	1.90	<0.001	1.31	2.75		1.57	0.021	1.07	2.24	
2	1.50	0.180	0.83	2.70		1.20	0.544	0.66	2.19	
3+	2.30	0.002	1.35	3.91		1.84	0.030	1.60	3.18	

* Type III p-values are presented for categorical variables with multiple degrees of freedom

** There were no patients with PVD who suffered a TIA

4.4.2 Carotid Endarterectomy/Carotid Stent

The second stroke-related event of interest was carotid endarterectomy or carotid stent (CAE/CAS), as these procedures reflect preventive treatments aimed at halting stroke progression. This combined outcome was examined through the same process of CIF curves to examine the crude difference in incidence of CAE/CAS between exposure groups, followed by univariate and multivariate analyses on the cause-specific hazard. Figure 14 shows the CAE/CAS CIF curves between *Any Radiotherapy* and *Surgery alone*. Differences between these treatment groups in the incidence of CAE/CAS are clear within the first year of follow-up. The rate of CAE/CAS also seems to be growing faster among patients treated with *Any Radiotherapy*. The Gray test of equivalence to examine the homogeneity of these curves indicates that the cumulative incidence of CAE/CAS among patients treated with *Any Radiotherapy* is statistically different from patients treated with *Surgery alone* ($\chi^2 = 8.45$, p=0.004).

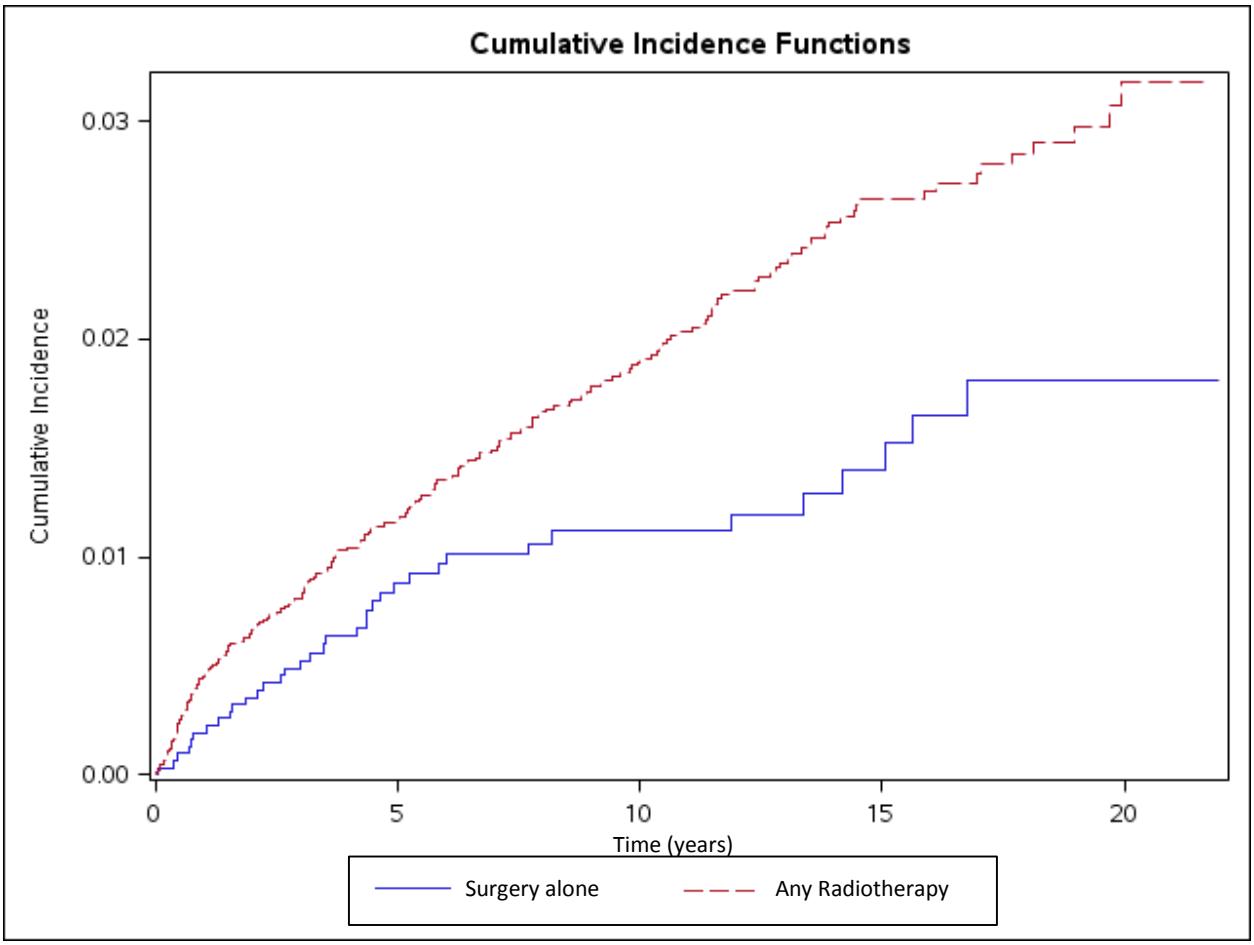

Figure 14: CAE/CAS Cumulative Incidnce Functions by Any Radiotherapy and Surgery alone

Results from the Cox PH analyses are presented in Table 15. Among a patient sample of 14,069, there were 274 CAE/CAS. Univariate analyses indicated that individual characteristics that were associated with the conditional risk of CAE/CAS (with a 5% significance level) were treatment, age, MI, IHD, HPV *likely* status, and comorbidity status. After model selection and adjusting for relevant covariates, the conditional risk of CAE/CAS associated with patients that were treated with *Any Radiotherapy* was 2.13 times higher than that of patients treated with *Surgery alone* (HR=2.13, 95%CI: 1.50,3.03 p<0.001). Covariates that were adjusted for included age and comorbidity status, and their results indicated an increased risk of CAE/CAS for both age groups over 55 (compared to <55 years), and only patients with 3 or more comorbid conditions (compared to none) were associated with an increased risk of CAE/CAS.

Table 15: Univariate and Multivariate Cox Proportional Hazards of Carotid Endarterectomy/Carotid Stent – Any Radiotherapy versus Surgery alone, N=14,069

Variable	Univariate HR	Univariate p-value	Univariate 95% CIs		Univariate Type III p-value*	Multivariate HR	Multivariate p-value	Multivariate 95% CIs		Multivariate Type III p-value*
Treatment										
Surgery alone	1.00	---	---	---		1.00	---	---	---	
Any Radiotherapy	2.14	<0.001	1.50	3.04		2.13	<0.001	1.50	3.03	
Age					<0.001					0.001
<55 years	1.00	---	---	---		1.00	---	---	---	
55 – 65	1.90	<0.001	1.39	2.52		1.77	<0.001	1.31	2.38	
65 – 75	1.54	0.010	1.11	2.14		1.44	0.033	1.03	2.01	
Sex										
Female	1.00	---	---	---						
Male	1.20	0.227	0.90	1.60						
Myocardial Infarction	2.89	0.011	1.28	6.50						
Peripheral Vascular Disease	1.41	0.732	0.20	10.02						
Ischemic Heart Disease	1.94	0.007	1.20	3.14						
Hypertension	1.05	0.776	0.75	1.47						
Asthma	1.27	0.480	0.65	2.47						
Diabetes	1.23	0.457	0.72	2.11						
Atrial Fibrillation	1.65	0.481	0.41	6.64						
Chronic Obstructive Pulmonary Disease	1.03	0.902	0.67	1.58						
HPV – 'likely'	0.33	0.008	0.15	0.75						
Cancer Site					0.004					
Oral Cavity	1.00	---	---	---						
Nasopharynx	0.64	0.209	0.31	1.29						
Oropharynx	1.64	0.008	1.14	2.36						
Hypopharynx	1.25	0.552	0.60	2.67						
Larynx	1.69	0.002	1.22	2.35						
Unspecified neoplasm of head and neck	1.67	0.124	0.87	3.19						
Cancer diagnosis year										
<2005	1.00	---	---	---						
≥2005	0.77	0.188	0.52	1.14						
Elixhauser Comorbidity Score					<0.001					<0.001
0	1.00	---	---	---		1.00	---	---	---	
1	1.40	0.081	0.96	2.06		1.36	0.120	0.92	1.99	
2	1.55	0.095	0.93	2.58		1.47	0.139	0.88	2.46	
3+	2.56	<0.01	1.66	3.96		2.43	<0.001	1.57	3.77	

* Type III p-values are presented for categorical variables with multiple degrees of freedom

4.5 Effect Modification

Variables that were hypothesized to act as effect modifiers in the relationship between treatment and stroke, as specified *a priori*, were tested for modifying effects while controlling for age and comorbidity status (based on the final model of Objective 1, using *any radiotherapy* versus *surgery alone* as the exposure). Variables that were tested for modifying effects included: age, sex, cancer site, HPV *likely* status and date of diagnosis. Interaction terms between each variable and the treatment variable were inserted into the final adjusted model. Results from these investigations are displayed in Table 16.

Table 16: Multivariate Interaction Significance by Hypothesized Effect Modifiers

Variable Tested for Interaction (Effect Modification)	p-value*
Age **	
<55 years	---
55 – 65	0.363
65 – 75	0.402
Sex	
Female	---
Male	0.063
HPV – 'likely'	0.447
Cancer Site	
Oral Cavity	---
Nasopharynx	0.620
Oropharynx	0.541
Hypopharynx	0.557
Larynx	0.472
Unspecified neoplasm of head and neck	0.070
Cancer diagnosis year	
<2005	---
≥2005	0.213

* p-values are associated with interaction terms between the specified variable and the exposure (treatment) after adjusting for age and comorbidity status.
** Age interaction term was evaluated based on adjustment for comorbidity status alone.

At the 5% level, none of the interaction terms were found to be significant in the final model after adjusting for age and comorbidity status. This indicates the effect modification of the variables tested is not statistically significant.

A more traditional epidemiological approach was also conducted to examine possible modifying effects, through running stratified analyses and examining whether the effect of radiotherapy on stroke differs between strata of a variable. Hazard ratios indicating the conditional risk of stroke for *any*

radiotherapy versus *surgery alone*, controlling for age and comorbidities are indicated in Table 17, for each strata.

Table 17: Effect Estimates for Stratified Analyses, by Hypothesized Effect Modifiers

Variable Tested for Interaction (Effect Modification)	HR*	95% CI	
Age			
<55 years	1.74	1.19	2.53
55 – 65	1.37	1.03	1.83
65 – 75	1.40	1.08	1.82
Sex			
Female	1.82	1.33	2.50
Male	1.30	1.06	1.60
HPV			
'likely'	0.89	0.21	3.86
'unlikely'	1.49	1.25	1.77
Cancer Site			
Oral Cavity	1.39	1.04	1.86
Nasopharynx	0.83	0.11	6.06
Oropharynx	1.85	0.97	3.51
Hypopharynx	0.98	0.23	4.07
Larynx	1.78	1.12	2.84
Unspecified neoplasm of head and neck	0.71	0.33	1.56
Cancer diagnosis year			
<2005	1.49	1.24	1.79
≥2005	1.03	0.63	1.71

* HRs are estimates of the effect of exposure (any RT versus SX alone) on stroke, adjusted for age and comorbidities, stratifying by each level of the hypothesized effect modifiers

The conditional risk of stroke remained significant after stratifying across age groups, with a slightly larger effect estimate for patients that were diagnosed with their cancer under the age of 55 (HR=1.74, 95%CI: 1.19,2.53), and although the age categories were not found to be statistically significantly different in terms of an interaction with treatment, each strata differed slightly with respect to risk. Among females, the risk of stroke was 50% higher than among males, although the interaction of treatment and sex did not meet the 5% significance criteria (HR=1.82, 95%CI: 1.33,2.50). From the stratified results, there does not seem to be an association between treatment and stroke among patients that are categorized as being HPV *likely* (HR=0.89, 95%CI: 0.21,3.86), contrarily, among HPV *unlikely* group, the effect of *any radiotherapy* on stroke seems to reflect the overall estimate from the multivariate model (HR=1.49, 95%CI: 1.25,1.77). Stratified analyses by cancer site yielded no association (non-significant estimates) between treatment and stroke for cancers of the nasopharynx, oropharynx,

hypopharynx and unspecified neoplasms. The effect between treatment and stroke remained significant among patients with cancers of the oral cavity and of the larynx, with the larynx site yielding an effect nearly 40% higher than that of the oral cavity site (HR=1.78, 95%CI:1.12,2.84; HR=1.39, 95%CI: 1.04,1.86, respectively). Among patients that were diagnosed with their cancer in or after 2005, the effect of radiotherapy on the risk of stroke was not significant (HR=1.03, 95%CI: 0.63,1.71), whereas prior to 2005, the conditional risk of stroke remained constant with the overall estimate for the entire population (HR=1.49, 95%CI:1.24,1.79).

4.6 Additional Analyses – Excluded, No Documented Treatment

Additional analyses were performed to describe the characteristics of the patients that were excluded from analyses due to no documented treatment (NDT). Clinical characteristics were compared between the H&NCa cohort used for analyses (that had curative treatment) and the NDT group. Significance was evaluated at the 5% level using chi-squared statistics. Depicted in Table 18, significant differences were found for age, diabetes, HPV status, cancer site, year of cancer diagnosis and comorbidity status. There are slightly more patients in the 65-75 age group in the NDT group, compared to the rest of the sample (36.5% vs. 31.2%, $p<0.001$). There is a slightly larger proportion of patients with diabetes in the NDT group (7.8 vs. 7.1, $p=0.046$), and there 2% more patients with HPV *likely* status in the curative treatment group compared to the NDT group (8.7% vs. 6.6%, $p<0.001$). Cancer of the oral cavity is the most common site among the NDT group (45.5% vs. 27.1%, $p<0.001$), where there are far fewer patients with laryngeal cancer (31.6 vs. 17.1, $p<0.001$). The percentage of patients that were diagnosed prior to 2005 was only slightly larger for the curative treatment group (73.2% vs. 71.6%, $p=0.014$), and the category of comorbid conditions that differed the most between groups was 3 or more comorbidities, where 8.2% of the NDT group compared to 6.4% of the curative treatment group were found to have 3 or more comorbid conditions ($p<0.001$).

Table 18: Clinical Characteristics across Patients with Curative Treatment versus No Treatment

Characteristic	Curative Treatment (%)	No Treatment (%)	p-value*
N	14069	6633	
Age			<0.001
<55	4650 (33.1)	2116 (31.9)	
55-65	5024 (35.7)	2098 (31.5)	
65-75	4395 (31.2)	2419 (36.5)	
Sex, M	10596 (75.3)	4942 (74.5)	0.210
Ischemic Heart Disease	438 (4.5)	314 (4.7)	0.423
Myocardial Infarction	144 (1.4)	92 (1.4)	0.963
Peripheral Vascular Disease	42 (0.4)	31 (0.5)	0.262
Asthma	399 (4.0)	296 (4.4)	0.104
Atrial Fibrillation	62 (0.6)	52 (0.8)	0.266
Chronic Obstructive Pulmonary Disease	1380 (14.0)	899 (13.6)	0.347
Hypertension	2161 (21.4)	1424 (21.5)	0.858
Diabetes	722 (7.1)	520 (7.8)	0.046
HPV 'likely'	987 (8.7)	439 (6.6)	<0.001
Cancer Site			<0.001
Oral Cavity	2950 (27.1)	3019 (45.5)	
Nasopharynx	872 (6.7)	462 (7.0)	
Oropharynx	2770 (25.1)	1263 (19.0)	
Hypopharynx	593 (5.9)	343 (5.2)	
Larynx	2452 (31.6)	1132 (17.1)	
Unspecified neoplasm of head and neck	387 (3.5)	414 (6.2)	
Cancer diagnosis year			0.014
<2005	7030 (73.2)	4750 (71.6)	
≥2005	2994 (26.8)	1883 (28.4)	
Elixhauser Comorbidity Score			<0.001
0	7692 (76.6)	4898 (73.8)	
1	1103 (11.1)	745 (11.2)	
2	575 (5.9)	443 (6.7)	
3+	654 (6.4)	547 (8.2)	

* All variables are categorical and tests were carried out using the χ^2 statistic.

Stroke and stroke death incidences was also examined for the group of patients that were excluded from the patient cohort due to no curative treatment, where the stroke CIF curve is depicted graphically alongside the stroke CIFs for two curative treatment groups, *Surgery alone* and *Radiotherapy alone* in Figure 15. These curves show that the incidence of stroke among the no treatment group seems to fall in between the radiotherapy and surgey incidence curves, until around 12 or so years. At that point, with the curve falling below that of the *Surgery alone* group, the cumulative incidence of stroke increases less rapidly. The Gray test of equivalence was performed, and with a 5% level of significance, these groups were found to be statistically significantly different in terms of stroke or stroke death incidence (χ^2= 11.15, p=0.004).

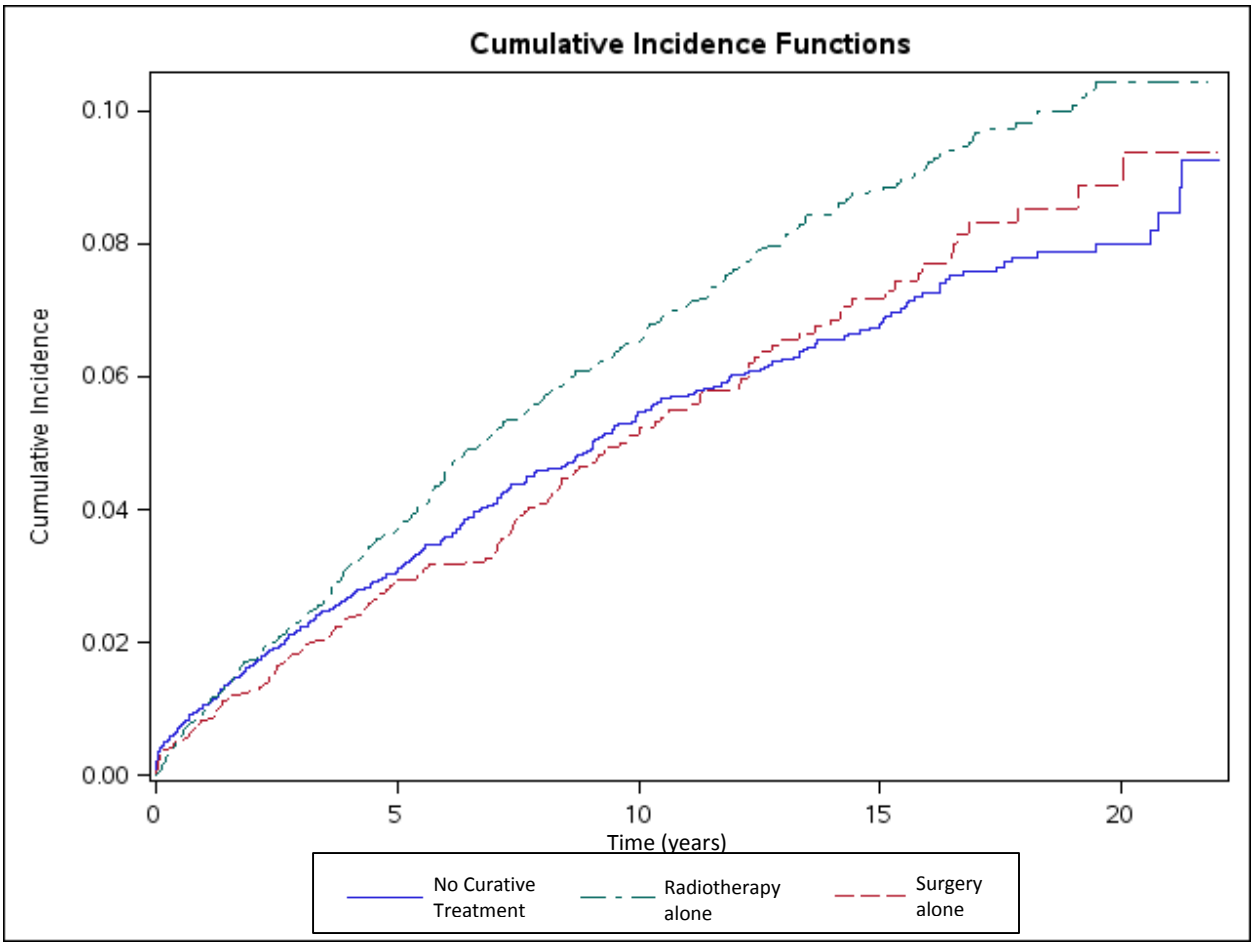

Figure 15: Stroke/Stroke Death Cumulative Incidence Functions by Curative (Radiotherapy, Surgery) & No Documented Treatment

Finally, non-stroke related deaths were of interest to evaluate whether this group was, in fact, more likely to die of their cancer faster than the rest of the cohort. As such, non-stroke related death CIF curves were compared between the two curative and no treatment groups, with non-stroke related deaths as the endpoints, stroke deaths as competing events, and patients lost to follow-up censored. Figure 16 shows the CIF curves, indicating a steeper increase in the number of deaths among the no treatment group within the first three years following treatment (or diagnosis for the no treatment group). After three years, the no treatment mortality rate remained approximately half way between the non-stroke death CIF curves for *Radiotherapy alone* and *Surgery alone* groups. The Gray test associated with these CIFs indicated a statistically significant difference between the three curves ($\chi^2 = 341.91$, $p<0.0001$).

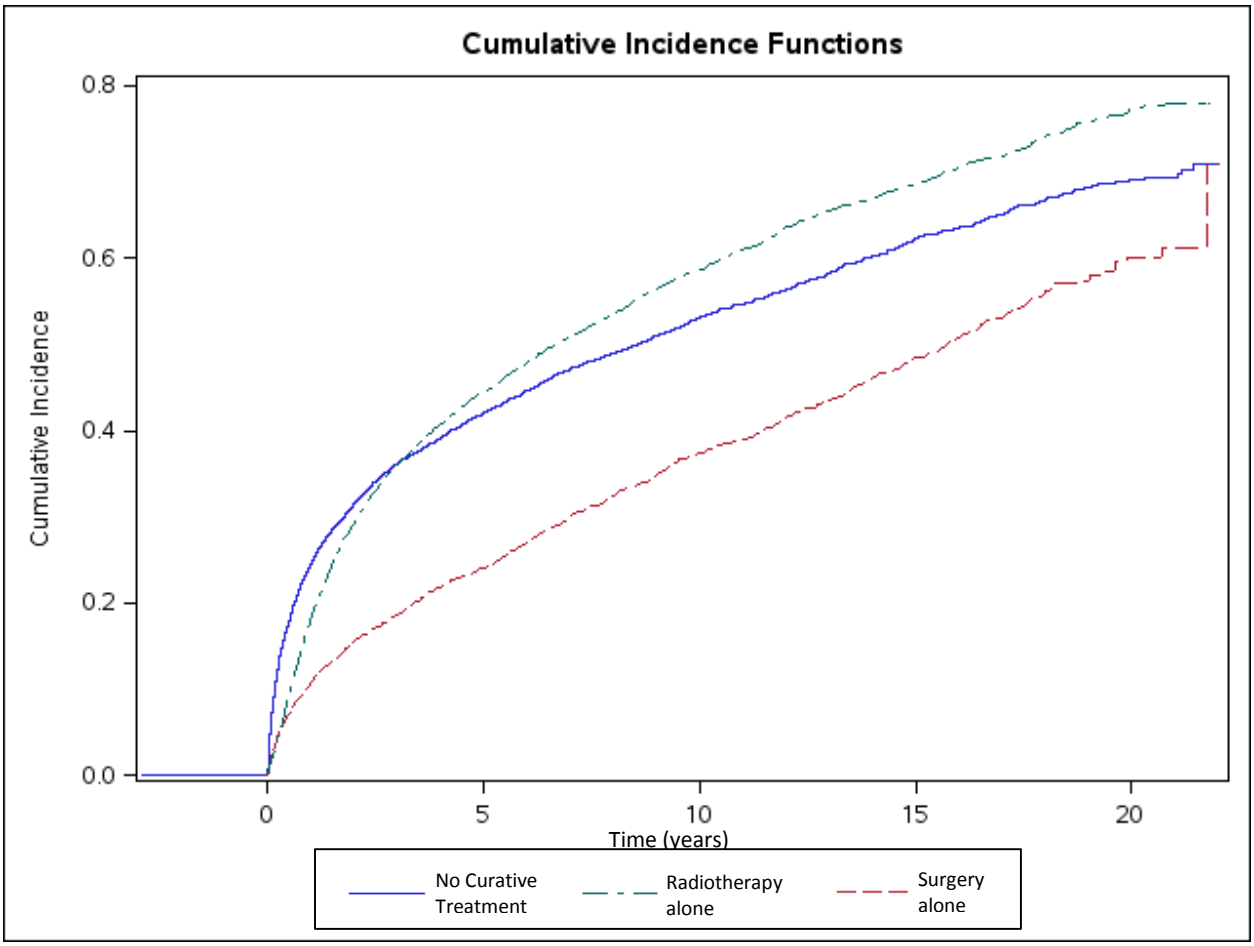

Figure 16: Non-Stroke Death Cumulative Incidence Functions by Curative (Radiotherapy, Surgery) & No Documented Treatment

The trends for both of these figures indicated the accurate detection of some of the patients that were treated palliatively or not at all due to their advanced disease, however there are a certain number of radiotherapy patients that were grouped into this exclusions category as well as surgical patients due to incidence curves lying in between these two groups at some point in both cases (stroke incidence and non-stroke death incidence).

4.7 Regression Diagnostics

To test that the proportional hazards (PH) assumption held for the multivariate model (with age and comorbidity status covariates), the observed standardized score process was used. The final model from Objective 1.3 was used to test this assumption, and p-values from the Kolmogorov-type supremum test were examined (where a significant p-value would indicate a PH-assumption violation). This test yielded no covariate that violated the PH assumption, with no p-values falling below 30%. Appendix H, Figure 17 is a graphical depiction of the score process plotting by the time variable for each non-reference category level of the covariates adjusted for in the model from Objective 1.3. The p-values for the supremum tests are indicated in the bottom right corners of each plot. Results from our main objective are therefore valid because there is no significant evidence that the PH assumption was violated in the model. As well, plotting deviance residuals, as seen in Figure 18 of Appendix H gave no indication that there were any outlying observations for this analysis.

Chapter 5: Discussion

5.1 Study Summary

The purpose of this study was to determine the effect of RT on the risk of stroke among patients with H&NCa. Using a retrospective cohort design including patients diagnosed with squamous cell carcinoma of the head and neck within an 11 year period, this aim was addressed through three objectives. Linked administrative databases from Cancer Care and Epidemiology (CCE) at Queen's Cancer Research Institute and the Institute of Clinical Evaluative Sciences (ICES), enabled the identification of the study cohort, the characterization of different cancer treatment regimens, the definition of stroke and stroke-related events as well as the collection of relevant patient clinical characteristics. A survival analysis approach accounting for competing risks was used throughout the objectives of this study.

This chapter will outline and interpret the key findings of this study, put the results in the context of the current literature, while outlining methodological shortcomings and strengths and future directions and implications of this research.

5.2 Key Findings

The description of the study population as outlined in Section 4.2.1 portrayed a cohort of patients with H&NCa that were mostly men, were late to middle aged, where only a small proportion had each of the stroke risk factors or more than 1 comorbid condition. The cancer sites were reflective of general estimates of prevalence of H&NCa, with the largest proportion of patients having a diagnosis of either cancer of the oral cavity, of the larynx or the oropharynx (11). Among treatment regimens, those that were treated with surgery had less strokes, and had a better overall survival compared to the other modalities.

The key findings of this project are outlined as follows. Radiotherapy (RT) was found to contribute considerably to the risk of stroke compared to surgery (SX) - both alone and after combining

all treatment modalities that included any radiation exposure. RT alone led to an added conditional risk of stroke of 70% compared to surgery alone (HR=1.70, 95%CI: 1.41,2.05, p<0.001), and while the any RT combination treatment category yielded results that appeared to be diluted to show no difference in the cumulative incidence curves and a lower conditional risk estimate, any radiation exposure was nevertheless found to increase the risk of stroke by 46% compared to surgery alone, after controlling for age and comorbid conditions (HR=1.46, 95%CI: 1.23,1.73, p<0.001). These results are consistent with the biological evidence on the topic as well as the literature on RT-induced vessel damage among other cancer sites. Investigating the harm of both chemotherapy (CT) and neck dissection when used in conjunction with RT reveals results that were counter-intuitive (HR=0.69, 95%CI: 0.50,0.94, p=0.021; HR=0.75, 95%CI:0.57,0.99, p=0.043, respectively). Upon examining the effect of any RT exposure on the risk of suffering stroke-related events, it was found that the conditional risk of transient ischemic attacks (TIA) was not significantly different between any RT and SX alone treatment modalities (HR=1.37, 95%CI: 0.99,1.88, p=0.054), whereas the cause-specific hazard ratio indicated a two-fold increased conditional risk of carotid endarterectomy/carotid stent (CEA/CAS) among the RT group compared to SX group (HR=2.13, 95%CI: 1.50,3.03, p<0.001).

5.3 Radiotherapy and the Risk of Stroke

5.3.1 Overall Effect

The aim of this study and purpose of Objective 1 was to quantify the effect of RT on the risk of stroke compared to surgery alone among patients with H&NCa. This was done both by looking at RT alone, and by combining treatment groups that had any exposure to radiotherapy. The most compelling result from this approach was that RT alone was associated with a conditional risk of stroke that was 70% higher than the risk of stroke among patients that were only treated with surgery. This finding confirmed the hypothesis that patients that are treated with RT alone are more likely to suffer increased late effects of their treatment including stroke when contrasted with patients that are treated with SX alone. Even

after amalgamating treatment groups that involved any exposure to radiation, an increased risk was found and was significant. Combining treatment categories with any RT exposure was a method that was rationalized in two ways. (1) In a cohort study design, clear definitions should be made for the 'exposed' and the 'non-exposed' to avoid measurement error and biased effect estimates (136). In this study, exposure was defined as head and/or neck exposure to radiation, therefore making it appropriate to estimate an overall risk attributed to this exposure. (2) The second justification is based on the notion that cancers of the H&NCa are so heterogeneous that treatment regimens can vary from patient to patient. As such, restricting the analysis to look only at two treatment regimens (SX alone and RT alone), which most studies to date have done, would not provide generalizable results. However, it was evident that the creation of the *Any Radiotherapy* treatment group led to diluted effects, and results from the adjusted model in Table 7 of Section 4.2.2 explain why that occurred. The SX with RT treatment group was shown to significantly increase the risk of stroke compared to SX alone, however, this cause-specific hazard ratio was smaller than that of the RT alone group (HR=1.27, 95%CI:1.04,1.56, p=0.020). Additionally, both hazard ratios between RT/CT and SX alone and SX/RT/CT and SX were not significant (HR=1.16, 95%CI:0.83,1.63, p=0.386 and HR=1.15, 95%CI:0.72,1.84, p=0.550, respectively). The results from the adjusted model presented in Table 11 of Section 4.3.1 show that the risk of stroke differs significantly between RT alone and RT/CT, contributing to the concern of a dilution of effects. However, combining all treatments with any RT is an approach that remains justified for the purposes of generalizability and generating an estimate of overall risk for radiation exposure since none of the treatment categories were found to have a lower risk of stroke than the SX alone group thus maintaining the same direction of risk estimates.

As the current state of literature on the risk of stroke due to RT among a H&NCa population is minimal and methodologically flawed, these results are most relevant within the context of a similar study by Smith et al. (76). Among patients diagnosed with H&NCa (excluding laryngeal cancer) and treated with RT alone, Smith et al. examined the risk of cerebrovascular events, and found a hazard ratio of 1.50

compared to patients treated with SX alone. As well, the authors examined the relationship between a combination treatment category, defined as the combination of RT alone and SX with RT, and surgery alone, and they found a non-significant hazard ratio of 1.17. It is possible that the higher risk estimates (including a significant estimate for the *Any Radiotherapy* evaluation) is attributable to the fact that Smith et al.'s outcome was composite, including stroke, carotid revascularization and hospitalization for TIA. Although this study found that the risk of carotid revascularization (CEA/CAS) was more than double among patients treated with any RT, the risk of TIA was found to be null, thus implying that combining stroke, TIA and carotid revascularization surgeries could have weakened their effect. In spite of these slight differences, the current study's findings are consonant with the estimates generated by Smith et al., the only methodologically comparable report on the subject. Papers by Haynes et al. and Dorresteijn et al. reported significant stroke risks that were large in magnitude, among RT patients (5.1 to 8.5 and 2.1, respectively), however these were generated by comparing the rate of stroke among patients treated with RT to an incidence of stroke calculated from a sample of patients from the general population (75,77). These seemingly inflated risk estimates are not clinically relevant in the context of treatment outcomes in this patient sample.

5.3.2 Risk of Stroke over Time

Objective 1.4 was to investigate whether the risk of stroke following treatment with any RT varied over time. Section 4.2.4 describes the results from this objective and shows that the risk ratios calculated using the cumulative incidences estimated by the CIFs, at 3, 5, 10 and 15 year points, were found not to change over time substantially. Using surgery alone as the comparator, any RT remained at an approximate 10% increased risk across each time point, while RT alone remained at an approximate 25% increased risk. These patterns are consistent with the CIF curves found in Figures 8 and 9, where although there are slight divergences in the cumulative incidences for both RT alone and any RT, compared to SX, the differences between these curves changed so minimally at each time point that the risk ratios appeared quite similar with the largest difference being 7% for the any RT estimates and 3%

for the RT alone estimates. It is difficult to contextualize these findings within the body of literature, as each study used different methods to assess risk. Haynes et al. reported cumulative incidences of stroke of 7% at 3 years and 12% at 5 years following irradiation, calculated using the number of events per person-years of follow-up (75). The authors reported survivals of 71% and 55% at 3 and 5 year time points, indicating that patients were being lost to follow-up during the study period and that incidence rates without considering loss to follow up or competing risks of death are biased estimates (136). Dorresteijn et al. considered loss to follow up over time using a lifetable method to calculate cumulative incidences, and reported a "cumulative risk" of 12% at 15 years (77). For both studies, risk ratios were calculated in relation to the incidence of stroke among the non-H&NCa comparison groups. Smith et al. was the only study that provided stroke incidence estimates for each treatment group: for RT alone, 19% at 5 years and 34% at 10 years and for SX alone, 14% at 5 years and 26% at 10 years (76). These incidences are much higher than those presented in this study (RT alone: 3.7% at 5 years, 6.5% at 10 years & SX alone: 2.9% at 5 years, 5.1% at 10 years) likely because the latter accounted for competing events through the CIF estimation. Nevertheless, when taking the ratios of the incidences reported by Smith et al., the risk ratios do not reflect a notable change over time (1.36 at 5 years and 1.31 at 10 years), substantiating the validity of the risk estimates presented in Table 10. As well, the hypothesis that the H&NCa population is likely to have a higher underlying risk of stroke than the general population was confirmed with these estimates, since in a study by Johansen et al. a stroke incidence of 0.14% was reported for both men and women in Canada (137), a difference of nearly 3% for the SX group.

It is unclear why the risk does not seem to increase with time, however possible explanations could be that either the patients that were candidates for RT may have had a higher underlying risk of stroke, or perhaps the RT-induced atherosclerotic damage presented itself among the RT group earlier than 3 years following treatment. Nevertheless, these results confirm that the risk of stroke remains considerable even after 15 years following treatment.

5.3.3 Statistical Considerations

When interpreting the findings from the investigation into the effect of RT (for all objectives), it should be noted that while risks of competing events were considered throughout, two different statistical approaches were used: (1) estimation of cumulative incidence functions (CIFs) and (2) modelling the cause-specific hazards (CSH), and they employ different assumptions. According to Latouche et al., the CSH "refer to the instantaneous rate of occurrence of a given event among the patients still event-free" whereas the CIF "is the probability of occurrence of a given event by time, *t* (138). This definition extends to the idea that the CIF can provide the proportion of patients expected to experience the event by specific time points, and thus plotted to show the change over time, and the CSH uses information from the entire duration of the study to produce an estimate that reflects the probability that a certain event will occur (at time *t*), conditional on the fact that the event did not yet occur up until that point. Latouche et al. asserts that both methods should be used concurrently, as when considering competing risks, the CSH cannot be used to estimate cumulative incidence (where in the absence of competing risks, the CIF is simply the complement of the survival function) (138). Analyzing competing risk endpoints by using proportional CSH models is the most common approach that is used in the medical literature, however a more recent method that has a direct relationship to the cumulative incidence, is referred to as proportional subdistribution hazards models by Fine and Gray (127). This technique is not yet common in analyzing medical outcomes, however it has been shown to be slightly more interpretable in the competing risk context when cumulative incidences of occurrence are of interest for a particular event (127,129,138,139). Due to technological restrictions, the proportional subdistribution hazards method could not be used for this data, however, using CSH models remains the standard in the medical literature and is appropriate to account for the risks of competing events (139).

There are usually some differences between the results from models for cause-specific hazards and those based on in the CIF plots. The stroke CIF curves were not found to be statistically different between patients that were treated with any RT and SX alone (Figure 9), however the hazard ratio showed a conditional risk of RT that was 46% higher than that of SX (Table 9). The homogenous curves reflect

the dilution of effect, since the curves in Figure 8 (RT alone vs. SX alone) were significantly different, so a change after combining treatment groups was to be expected, however interpreting these curves and Gray's test such that any RT exposure does not lead to a cumulative incidence of stroke that is different from undergoing SX alone conflicts with our estimates of risk. Because of these differences, it is clear that future studies that aim to model health-related events over time using a survival approach, ignoring competing risks if they are present will lead to grossly inaccurate estimates. As well, careful consideration should be put into the statistical methods used to account for competing risks, since a combination of different approach may lead to conflicting results that are difficult to interpret together.

5.4 Modifications to Radiotherapy Regimen

5.4.1 Chemotherapy

Although the added contribution to the risk of stroke by combining chemotherapy to a radiotherapy regimen has not been conclusively defined, the current evidence suggests that this risk is at least comparable to other treatment modalities and CT alone has been shown to affect the coagulation process causing thromboembolic events among other cancers (82,85,140). The results of this study indicating a potential protective effect of chemotherapy when used in conjunction with RT are not supported in the literature, as well, due to the heterogeneity of the exposure groups in this analysis, the 0.69 cause-specific hazard ratio should be interpreted with caution. Referring to Table 6 that outlined clinical characteristics across all treatment modalities, there were three marked differences between the RT group and the RT/CT group: there were near 20% more patients that were under the age of 55 in the RT/CT group (46% vs. 27%) and while 88% of patients treated with RT were diagnosed prior to 2005, only 45% of RT/CT patients were diagnosed during this time period. Lastly, 28% in the RT/CT group compared to 4% in the RT group of patients were categorized as HPV *likely*. The multivariate Cox PH model adjusted for age, therefore the risk estimate is presumably free of confounding by age, however, the remaining two observations of heterogeneity speak to the issue that concurrent chemoradiation is a more recently adopted treatment modality. Issued as clinical practice guidelines for patients with H&NCa

in Ontario in 2000, the recommendation that concurrent chemoradiation be used to treat all locally advanced H&NCas has only truly become integrated into practice within the last decade (95). As such, the majority of the patients in this study's cohort that ended up being treated with radiotherapy and chemotherapy were diagnosed with their cancers in the last half of the study timeframe, thus decreasing the amount of time for follow-up and stroke assessment. This assumption is further substantiated as a result of the risk estimates generated through stratifying by diagnosis year; looking only at patients diagnosed after 2005, there was no significant effect of RT on the risk of stroke (HR=1.03, 95%CI:0.63,1.71). Additionally, the higher proportion of HPV *likely* patients in this treatment group indicates the possibility that H&NCas due to the HPV etiological stream yielding younger, healthier patients are better represented among patients treated with RT/CT than patients treated with RT. Further investigation indicates that more patients in the RT/CT treatment group were shown to have hypertension and diabetes compared to RT alone, and because these are important stroke risk factors and yet this group was not at a higher risk of stroke, this is indicative of the fact that the recent generation are likely to be receiving better medical care, controlling their comorbidities to a point where they do not progress. There is thus reason to interpret the 31% reduction in stroke risk due to CT with the caveat that it is quite possible that these patients were either not followed for an adequate amount of time to observe the event in question, or the patient characteristics among this cohort could indicate a lower underlying risk of stroke.

5.4.2 Neck Dissection

The clinical hypothesis that undergoing a neck dissection prior to being irradiated is likely to cause more damage than would have occurred with RT alone is not a conclusive assertion supported by the literature. One study in 2005 found that among 22 patients with H&NCa that were treated with a neck dissection, 7 of them suffered carotid artery stenosis compared to 1 of 22 patients that did not undergo a neck dissection, and although marginally significant (p=0.05), findings based on events observed among 7 patients are far from conclusive (141). Much of the conception of added stroke risk from a neck

dissection is based on evidence of an increased rate of late toxicity (ranging from tissue necrosis to wound infection and breakdown (142)) after combined SX and RT in H&NCas (141), as well as perioperative risks of stroke following any neck surgeries (143). The American Heart Association recommends against surgical carotid revascularization procedures for patients that are at a higher risk of stroke because of the exposure and the manipulation of the vascular structures of the neck (57). However, this precaution is to avoid perioperative strokes (30 days following the procedure) as opposed to strokes occurring 5-15 years later (30-day risk of stroke was reported to be 7.7% among symptomatic patients undergoing CEAs (144)). Although exposure and manipulation of the vessels in the neck prior to treating that same physiological region with radiation seems biologically plausible to act additively with the damage due to radiation alone, however no study has suggested evidence contrary to this hypothesis. The findings of this study follow suit, as neck dissections prior to RT were not found to increase the risk of stroke compared to RT alone. The protective effect that neck dissections are posited to have on the risk of stroke, as evidenced from this study, is in fact in line with the relationship between the surgery & radiotherapy and radiotherapy alone treatment groups. Analyses from Objective 1.2 and 2.1 showed that a treatment regimen of surgery and radiotherapy was found to have a higher risk of stroke than surgery alone (HR=1.27, 95%CI:1.04,1.56, p=0.020), and a lower risk of stroke than radiotherapy alone (HR=0.75, 95%CI: 0.63,0.88, p<0.001), both statistically significant. Both of these findings are perhaps due to the effect of RT dose, which will be explained further in Section 5.4.3.

5.4.3 Radiation Dose

The intention of Objective 2.3 was to explore the possibility of a dose response relationship between RT and ischemic strokes or stroke death. Findings from this analysis were not conclusive due to the quality of the data available. Among the 10,949 patients that received any radiotherapy (either neoadjuvant, concomitant or adjuvant) there were only 4,327 patients retained for the dose response analysis due to questionable content in the dose variable from the OPIS database. There was reason to believe that dose per fraction (per day) for some patients may have been duplicated when calculating total

dose administered for each patient at each course of treatment. Patients could only be considered for this analysis if their dose information seemed to reflect the standard range of possible curative RT doses (50-70 Gy). The non-significant cause-specific hazard ratio of 1.12 (95%CI: 0.88,1.42, p=0.356), could be attributed to a sample that was too small to detect an effect, however it could also reflect the fact that even 50 Gy, which was the minimum curative dose, may be above the dose threshold for clinically significant carotid stenosis. No study to date has confirmed the existence of a dose-response relationship between RT and cerebrovascular events in a H&NCa population, although a reasonable approach to addressing this question without adequate dose information is comparing different treatment modalities that are known to vary in RT dose. Fu et al. conducted a clinical trial comparing survival between different approaches to RT fractionation schedules among patients with squamous cell carcinoma of the head and neck, and reported that when administered as the primary curative treatment, RT doses range from 70 to 72 Gy (145). Ang et al., Cooper et al. and Storey et al. each investigated outcomes among patients treated with surgery and RT (postoperative RT), and reported RT doses that ranged from 50-67 Gy (5,146,147). These studies are indicative of a possible dose variation between RT alone and SX with RT treatments, and referring to results from Section 4.2.2 and Table 7 where there was a 30% increase in conditional stroke risk following SX with RT compared to SX alone, and 70% increase in conditional stroke risk following RT alone, a speculated dose-response relationship may be reasonable. Smith et al. had similar findings where the risk of cerebrovascular events was highest when comparing RT alone versus SX alone (HR=1.50, 95%CI: 1.18,1.90, p=0.0009), and was slightly lower between RT alone and SX with RT (HR=1.42, 95%CI:1.14,1.77, p=0.002) (76). Their reasoning for this difference was variations in administered RT dose, and they hypothesized that the clinical threshold to see this effect is likely to be between 60 and 70Gy.

Smith et al. also cited studies among other cancer cohorts to substantiate the dose response claim, which was reiterated by Gujral in a clinical review of features of radiation-induced carotid atherosclerosis (62,76). In both cases, the authors referred to breast cancers and lymphomas where patients consistently

receive lower RT doses for curative treatment than tumours of the head and neck, and cerebrovascular risks among these patient cohorts are lower. The contrast to this rationale, however, is the fact that risk estimates among a H&NCa population have not been properly established, and there are studies on Hodgkin's lymphoma studies that report between 2 to 5 times higher risks of cerebrovascular events among patients that were irradiated, eventhough doses typically range from 30 to 40 Gy for curative treatment of this cancer (67,69).

The question of dose therefore remains unanswered in the context of this study, however the inferences that were made based on theoretical dose variations between treatment regimens supports the idea that there is likely to be a dose response relationship between RT and the risk of stroke, and it merits proper investigation with adequate dose data with a broad enough range to be able to detect the effect.

5.5 Stroke-Related Events

5.5.1 Transient Ischemic Attack

The rationale for using an algorithm to detect strokes and TIAs in administrative data was that patients experiencing events that are transient are much less likely to seek (or be recommended for) hospitalization, and to be able to attempt to capture those that were not hospitalized, physician billing data should be consulted. However, even in using this approach, it is likely that transient events, particularly TIAs are underreported. As well, diagnosing a TIA after the fact is quite difficult since the blood clot is no longer occluding the artery in question, and physicians are working with descriptions of symptoms from the patients. Section 4.4.1 describes how there were 224 TIAs observed among this H&NCa cohort following treatment. This number corresponds to 1.6% of the sample having experienced a TIA. Tu et al. found an identical percentage for an estimate of the prevalence of TIAs among an Ontario population over the span of several months (59). Since the rate of TIAs should in theory be higher in a H&NCa population than among the general public, as are strokes, these similar rates are indicative of the fact that the number of TIAs may not only be underrepresented due to barriers in defining the event among patients and physicians (where patients would simply not present to a physician for a transient episode), but there may

also be significant misclassification of this event by the physician, since a diagnosis of TIA would be speculative at best.

When modelling the cause-specific hazards for TIAs, the relationship between any RT and the occurrence of TIAs was found to be just short of significant, with a hazard ratio of 1.37 (95%CI:0.99,1.88, p=0.054), for Objective 3.1. Interpreting these findings should be done while considering the aforementioned issues with defining these events within the confines of administrative data. Among studies that considered TIA as a possible outcome, only one reported a separate risk of TIA; with a hazard ratio of 1.6, Chu et al. reported an increased risk of TIA among patients treated with RT as compared to their general population comparison group (140). This flawed design and lack of additional evidence makes it difficult to contextualize findings from this study's analysis on the occurrence of TIAs following treatment. Stroke literature confirms that TIAs and strokes share the same pathophysiology and have the same risk factors (7), therefore the assumption is that if RT increases the risk of strokes, it should also increase the risk of TIAs, even if they are less frequent in occurrence. It is therefore likely that the lack of association found in this analysis is due to misclassification of the event in the administrative data because its occurrence cannot be confirmed by the physician.

5.5.2 Carotid Endarterectomy/Carotid Stent

A two-fold increased risk of CEA/CAS was found among patients that were treated with any RT (HR=2.13, 95%CI:1.50,3.03, p<0.001). This outcome was examined because requiring carotid revascularization implies substantial damage to the carotid artery that a physician would want to correct in order to prevent a stroke. As such, it could be indicative of stroke progression due a certain level of atherosclerosis, and if that is the case, this result substantiates the increased risk that was found for strokes following RT. This result reflects the findings from the clinical studies that reported increased carotid stenosis, increased arterial wall thickness and increased plaque accumulation among the patients that were treated with RT (8,70,71,78). However, similar to TIAs, among the studies that aimed at quantifying a

risk of stroke/TIA/CEA/CAS, none of them reported separate risks of carotid revascularization (75,76,140,148).

The possibility of selection bias should be acknowledged as a possible source of the higher risk of CEA/CAS; there may be an inherent higher rate of follow-up imaging that is done for the head and/or neck among patients that are treated with RT compared to SX, leading to more frequent detection of stenosis or atherosclerosis, followed by recommendations for surgical intervention, among the RT group. Although this cannot be confirmed, if this is the case, this would indicate an inflated risk estimate due to selection bias (particularly ascertainment bias) (149).

5.6 Effect Modification

Evidence of effects that modify the relationship between RT and the risk of stroke is limited, and the approach in this study was therefore mostly exploratory, although certain covariates were hypothesized to modify effects and were therefore identified *a priori* to be tested. Testing the significance of interactions between RT and the following variables was done with the final model used for analysis: age, sex, HPV status, cancer site, and year of cancer diagnosis. None of the interaction terms were found to be significant. Similarly, Smith et al. tested age, sex, race, comorbidities, administration of chemotherapy, the presence of positive nodes (indicating advanced stage where the cancer has spread to the lymph nodes) and cancer site for modifying effects by testing the significance of interaction terms in the model. None of their interactions between the suspected modifiers and RT were found to be significant (76). However, three studies presented risk estimates stratified by age, and found differences between age groups (although the difference between the groups were not deemed statistically significant) (74,77,140). Huang et al. stratified their sample by age using 55 years as the cutoff, and found a hazard ratio of 1.76 among patients under the age of 55 that were treated with RT or CT or both compared to SX alone, whereas they found no association among patients that were 55 or older (74). Chu et al. reported hazard ratios comparing RT to a general population comparison group, and found that the stratified analysis by age indicated that although the incidence of stroke was highest among the older group (≥60),

the age category that had the highest association between RT and stroke were patients between the ages of 20-40 at cancer treatment (140). Finally, Dorresteijn et al. compared a H&NCa group treated with RT to a sample of the general population, and upon stratifying by age, found that the risk of stroke due to RT was highest for patients under the age of 50 (RR=9.8) compared to 50 or older (RR=4.5), although the difference was not found to be significant (77). These findings were consistent with the age-stratified analyses in this study, where the cause-specific hazard ratio assessing the conditional risk of stroke due to RT, was highest for patients that were diagnosed before the age of 55 (HR=1.74) compared to the older age groups (55-65: HR=1.37, 65-75: HR=1.40). This is contrasted with the results from all of the multivariate analyses of this study that showed that the risk of stroke increased with increasing age. Huang et al. hypothesizes that atherosclerotic response in the carotid artery is more severe in younger patients, due to an aggressive repair process (74), while neither Chu et al. nor Dorresteijn et al. provided any reasoning for this phenomena (77,140). Indeed, there may be some biological differences that are attributed to age that affect the way the body repairs damage done to the carotid artery, however, the differences that were seen between age categories were not found to be significantly different as seen in the tests for significance among the interaction terms (Table 16).

Paradoxically, stratification based on HPV status (a covariate that has yet to be addressed in the RT-stroke literature) yielded a null effect among the HPV *likely* group, which was defined among other factors by being under the age of 55 (HR=0.89, 95%CI:0.21,3.86), with a hazard ratio of 1.49 among the HPV *unlikely* patients (95%CI:1.25,1.77). Despite the caveat that these differences were not statistically significant, this higher hazard ratio among the HPV *unlikely* group could reflect the existence of two separate H&NCa etiological streams with HPV *unlikely* being the patients that smoked and/or drank most of their lives. This is an interesting concept since the concern with the risk of stroke is particularly high when patients are being diagnosed younger with their disease, and thus may survive longer after cure, although results from the age stratification would contradict that assertion. It is also possible that the null association among the HPV *likely* group is due to the date of diagnosis, since stratified analyses by date of

diagnosis (<2005 & ≥2005), yielded null findings among the patients diagnosed on or after 2005 (HR=1.03, 95%CI:0.63,1.71). This trend is consistent with previous hypotheses (Section 5.4.1) that it is likely that patients diagnosed and treated more recently were not followed long enough to detect events that would establish the association between RT and stroke.

The clinical assumption is that the risk of stroke should vary by cancer site, since the targeted fields in treatment approaches for each site differ, with different carotid exposures. Hong et al. who focused only on patients with glottis laryngeal cancer, found no association and attributed this to the fact that RT targeted at glottis laryngeal tumours likely has a lower impact on the carotid arteries than other H&NCas (148). Contrarily, results from analyses stratified by site show that the significant association between RT and stroke was highest among patients with laryngeal cancer (HR=1.78, 95%CI:1.12,2.84). The only remaining cancer site that yielded a significant relationship between RT and stroke was cancer of the oral cavity (HR=1.39, 95%CI:1.04,1.86). The difference in magnitude of risk between these two sites can be attributed to the targeted field when administering RT, as suggested by Smith et al. when justifying testing for an interaction between RT and cancer site (76), as well as the higher prevalence of smokers among patients with laryngeal cancer (1). However, the non-significance of the interaction term, in this case, indicates that the differences between cancer sites are not significant, and risk estimates for each strata should not be over-interpreted.

5.7 Excluded – No Curative Treatment Group

There were 6633 patients that were excluded from the study due to no documented treatment (NDT), or presumed palliative treatment, corresponding to 29% of the original H&NCa cohort. This surpasses an approximate 16% of patients with H&NCa in Ontario that were not treated curatively, as estimated by Gupta et al. (95). Further analysis was therefore merited among this NDT group, since there was concern of over exclusion, perhaps due to misclassification (e.g.: carcinoma *in situ*). Table 18 presents the results of clinical characteristics comparisons between the curative group that was retained for analysis and the NDT group. The most compelling result was the difference in number of patients that

were diagnosed with cancer of the oral cavity; there were 45% of the NDT patients vs. 27% of the curative patients with cancer of the oral cavity ($p<0.001$). This could be indicative of the treatment for a number of patients being missed in the OHIP and OPIS databases because they could have been treated by an oral surgeon whose procedures would not be captured in a provincial database (150). Groome et al. reported that approximately 24.7% of patients with cancer of the oral cavity in Ontario had their cancer detected by a dentist or oral surgeon (151). It is therefore possible that a proportion of the patients that were excluded were misclassified as having received no treatment, because their surgeries that treated their oral cavity cancers were not captured.

Patients that were treated curatively with RT were also likely missed due to RT data not being submitted after 2004 among certain cancer centers (lead to missing dose information and default categorization as palliative).

Additional investigation was made into the cumulative incidence of stroke, and the cumulative incidence of non-stroke death. Curves for both of these cases were plotted in Figures 15 and 16, and were compared to both the patients treated curatively with SX and with RT. It is possible that the stroke CIF curve for the no treatment patients falling in between the two curative treatment groups, could reflect the fact that there were some patients misclassified as no treatment from both curative regimens (not only surgery). As well, the cumulative incidence of death curve for the no treatment group reflects the fact that there were patients correctly identified as having had no curative treatment, since within the first 3 or so years, the rate of death was higher among this group than the other two curative treatment groups. In theory, patients treated palliatively or not at all, are more likely to die soon after diagnosis, than patients treated for cure (152). The no treatment non-stroke death CIF curve eventually falls between the two curative treatment curves, emphasizing the previous conclusion that there were likely an equal number of patients that were missed when actually treated with RT as the number of patients that were missed when having been treated with surgery. This non-differential misclassification of patients to be excluded, therefore, was not likely to have biased the results, although this cannot be confirmed.

5.8 Strengths and Limitations

This study is filling an important knowledge gap in Canada, as this retrospective, large-scale population based cohort is ideal for evaluating the risk of such a rare event, among a sample of patients with a disease that is not very common in Canada. However, this study is not without its limitations.

5.8.1 Study Population

Identification of this study population was done through the Ontario Cancer Registry, which records cancer diagnoses across Ontario, therefore this sample was indeed a population based cohort. Since the OCR diagnoses are based on a variety of different sources, it is not likely that certain groups of patients are over- or under-represented in this cohort. However, misclassification in terms of cancer site, or treatment modality is possible to have caused incorrect inclusions or exclusions when forming the final H&NCa study cohort, although that is not likely to decrease the generalizability of findings from this study.

5.8.2 Measurement and Misclassification

The availability of Ontario-wide administrative data was a tremendous advantage in attempting to answer this research question, however when using administrative data, and categorizing exposures, outcomes and covariates based on diagnostic and procedural codes, the possibility of misclassification is quite high. Adequate validity has been shown across all of the databases that were used, however, they are far from perfect measures of assessment.

5.8.2.1 Outcome Assessment

Establishing a working definition of stroke, stroke death, TIA, CEA/CAS in the context of administrative data was challenging. However, with the availability of a validated algorithm for ICES data to combine diagnostic and procedural codes from various sources to define strokes and TIAs, the outcome assessment is likely to have been as precise as one could hope. Tu et al.'s algorithm was used for stroke assessment and TIA assessment, and the validity statistics for the stroke outcome were higher than

for TIA (59). As well, the null findings from the TIA analysis led to the conclusion that many TIAs were likely misclassified, either through transcription errors, or diagnostic error by the physician. As well, despite the modifications to the algorithm aimed at improving the validity among this patient sample, it is entirely likely that some events were misclassified. Additionally, if an alternative algorithm to identify strokes and TIAs was used, it is unclear how the results of this study could have changed, due to the inability to validate these algorithms in this context. In terms of stroke death, the cause of death based on death certificates through the Registrar General have been shown to have as high as a 31% error rate (92).

In spite of these likely misclassifications, the errors are non-differential, as there is no reason to assume that misclassification would occur differentially between the exposed (RT) and non-exposed (SX).

5.8.2.2 Exposure Assessment

It is not likely that patients who were treated with SX alone were categorized as RT alone or vice versa, since these treatments are administered under very difference circumstances, by different oncologists (surgical vs. radiation). As well, it was found that if a patient received any RT at all, they were at least listed in the OPIS database, whether or not their entry was accompanied by adequate information to categorize the intent of their therapy, could have led to incorrect exclusions (as mentioned in Section 1.7). As such, a critical concern with the treatment data was the issue of misclassification into curative versus palliative care. This could have occurred in situations where there were incorrect dates recorded for the start and end of treatment, and more importantly due to poor quality of RT dose information. As seen in Section 4.3.3, the data on RT dose was inadequate to be able to establish a dose response relationship. The presumed double counting of dose per fraction throughout a given RT schedule, led to doses that were clinically impossible to have been used to cure a patient with any H&NCa. As well, there were patients with missing dose information, and they had to be excluded, however, many of them were likely to have been treated curatively but were simply missing that data to include them in the study.

Despite these downfalls of having to rely on dose to categorize palliative vs. curative (for the RT patients), the potential misclassification that occurred is not likely to have drastically affected the risk estimate because if palliative patients were included as curative because their doses were overestimated, they likely would have died early in the follow-up period, and censored, without having experienced a stroke. As well, the potential bias of excluding patients that should have been considered curative is likely to have diluted our estimate of effect (biased towards the null) as opposed to inflating it. As such, if this study could have been free of this misclassification of the exclusion criteria, perhaps the risk estimate would have been higher.

A limitation to the use of two treatment groups as the 'exposed' and 'unexposed' is the fact that these two treatment regimens (RT versus SX) reflect two different patient profiles (overall health, stroke risk factors, HPV, etc.), and it raises the question as to whether it is appropriate to generate risk estimates comparing these two groups. On the other hand, this increases the generalizability of the results since directly comparing two treatment groups is easier to translate into practice.

5.8.2.3 Covariate Assessment

Due to the administrative source of data, information on lifestyle factors that could have likely been sources of confounding were not available such as alcohol consumption, and importantly, smoking. Chronic obstructive pulmonary disease and asthma were used as proxies for smoking, however this is not a perfect measure and the accuracy is not known. As such, smoking could be a source of possible unmeasured confounding; apart from being a compelling risk factor for stroke among the general population, smoking is an important risk factor for H&NCa, specifically for certain sites – and thus could drive the treatment options. Additionally, there was clinical oncological information that was not available for this study, such as stage of the cancer at diagnosis and HPV status of the tumour, which would have been useful in this analysis. The HPV *likely* categorization has not been validated, and the accuracy of this algorithm in correctly identifying HPV positive cancers is not known. As well, stage is an important determinant of treatment options, and it likely has an effect on the RT targeted region and

possibly the dose. Although ICES derived cohorts were used that implemented validated algorithms for identifying patients with: myocardial infarction, diabetes, hypertension, chronic obstructive pulmonary disease and asthma, the other risk factors including diagnoses that were used to populate the Elixhauser comorbidity index were based on individual ICD-9, 10 diagnostic codes. The presence of the code in the database translates into a diagnosis for that patient, however, a slight error in numbers could lead to a different condition altogether.

An important weakness in this study is the possibility of under-ascertainment of comorbidities (both for the index and the other covariates assessed). Both variables captured with individual codes, and those that were identified with algorithms through the ICES derived cohorts, are likely to not have captured everyone with these diseases. As well, the Elixhauser Index only captures a subset of all possible comorbid conditions, and among this patient population it seems unlikely that close to 77% of the sample have no comorbidities. This limitation could be the cause of residual confounding – where not having an appropriate measure for these covariates could be missing the overall health of these patients resulting in confounding that is not accounted for. An additional possible explanation for the counter-intuitive findings found in Section 4.3.1 and Section 4.3.2 regarding the risk of stroke attributed to chemotherapy and neck dissection, could therefore be residual confounding due to this limitation.

This measurement error would, again, not differ between exposure groups as it is likely random as opposed to systematic error. Since these were conditions that were not extremely common among this patient sample, it is not clear that effect estimates would be biased from these potential errors, and if so it would be towards the null.

5.8.3 Statistical Issues

The statistical approach implemented in this study is far more in depth and advanced compared to other studies examining this question. Only one previous study addressed the issue of competing risks of death, however this was only to account for the increased number of deaths in their cancer sample, compared to the general population (140). No previous studies have examined this clinical question with

such statistical rigor. However, a limitation to this study is due to the inability to use the proportional subdistribution hazard model in order to estimate the time-specific relative risks. This approach would have enabled adjusting for other covariates instead of relying on a crude estimate. As well, incorporating this model into the analysis would have yielded more comprehensive results (138).

5.8.4 Generalizability

The explicit aim of evaluating the risk stroke due to any radiation exposure, increases the generalizability of this study. The variety of treatments that can be used for a patient with H&NCa were all included in this analysis, contrary to most of the other studies in the current literature. A direct comparison of the risk of stroke between patients treated with RT and patients treated with SX is a result that can translate to clinical practice in a way that a comparison to the general population would not. As well, this was a population-based retrospective study, and was therefore not subject to patient enrollment and compliance, adding to the generalizability of the findings. The majority of the patients that were followed long enough to observe an event, were treated in the 1990s and technological advances have been made since, and these changes (particularly to RT) may limit how findings from this study can be applied to current day treatment recommendations.

5.9 Contributions of this Study and Implications

The implications of this research relate to practical considerations in oncological treatment recommendations and follow-up schedules. As the risk of stroke does not decrease with time, patients are subject to RT-induced cerebrovascular events as far as 15 years after they have been treated. As such, recommendations could be made for regular follow-up among H&NCa survivors, which could include routine carotid imaging following treatment to detect any atherosclerotic progression. Huang et al. suggested screening patients for atherosclerosis prior to RT, in order to identify high risk patients that should be followed over time, in a cost effective way (74).

This was a novel study in that it used the largest sample of patients with H&NCa among all studies that evaluated the late effects of RT. As well, not only is it currently the only study that has been

done on an entire H&NCa cohort, including all ages and squamous cell carcinoma sites, no other study has used appropriate statistical methods to analyze this data, particularly considering the issue of competing risks.

Future research is necessary to establish whether or not a dose response relationship between RT and stroke actually exists. More information regarding the health and health-habits of the patients would also improve the strength of the research in this field; smoking is a strong contributive factor to the development of this cancer, as well as to the risk of stroke, and would likely be an important factor in this relationship. Finally, this study drives the notion that further research is required in order to clearly describe the risk of stroke across all treatment regimens, particularly, whether there is an added risk of stroke among patients treated with the younger modality of concurrent chemoradiation.

5.10 Conclusion

The changing etiology of H&NCa with a younger patient population and improved survival has led to patients living longer after diagnosis and treatment for the disease. RT to the head and neck can have severe late side effects, especially in patients with long survival times. Previously, the need to examine late effects of RT in patients with H&NCa may not have been warranted because individuals were likely to die of their disease, or other reasons due to the multitude of risk factors. As well as being biologically plausible, the current literature identifies vascular injury and subsequent stroke as possible outcomes following RT in various populations. As stroke and stroke-related events often result in devastation to the patient as well as substantial burden to the healthcare system, knowing the degree to which RT puts individuals at risk of stroke is an important question to answer. The existing literature has flawed designs, non-representative comparison groups, results that are simply not generalizable, and statistical methods that do not adequately address the complex nature of this data.

The most important finding of this study was the quantified increased risk of stroke following either RT alone or any RT treatment. These findings imply that any radiation exposure can increase one's risk of stroke, and even more so when RT is administered as the sole curative treatment modality. As

well, they fill an important gap in the literature and contribute a more appropriate statistical approach to addressing competing risks. Implications of this research are not to encourage SX over other treatments, but they speak to the need for adequate follow-up care among patients that were treated with RT, while nevertheless emphasizing the effectiveness of this treatment.

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Appendix A: Stroke Algorithm for Outcome Definition and Exclusion Criteria

As specified in both sections 3.4.2 and 3.5.2 Tu et al. published a validation study of an algorithm meant to identify patients that have ever had a stroke or transient ischemic attack, through Ontario administrative databases (59). We used this algorithm to identify prevalent and incident cases of all strokes and transient ischemic attacks that occurred prior to cancer diagnoses as an exclusion criteria, and a modified version was used to identify ischemic strokes and transient ischemic attacks as incident cases for outcome assessment. This section will provide a brief rationale for using this algorithm (expanded and amalgamated from sections 2.3, 3.4.2 and 3.5.2), an outline of its validity and appropriateness for this study as well as a thorough description of the algorithm used for outcome assessment and exclusion criteria.

As described in section 2.3, relying solely on hospitalization data to identify strokes would result in a gross underestimation of the number of prevalent and incident cases, as many people are not hospitalized for their stroke or transient ischemic attack, or may only see their family physician after the acute incident. Tu et al.'s objective was to determine if the addition of outpatient data to inpatient data would improve the accuracy of administrative data for the identification of prevalent stroke or transient ischemic attack in Ontario. They therefore tested a variety of different combinations of hospitalization, physician billing and emergency room data using an electronic chart review database from the Institute of Clinical Evaluative Sciences (Electronic Medical Record Administrative Data Linked Database (EMRALD)) as the reference standard. They used separate validation schemes for strokes (ischemic and hemorrhagic) and transient ischemic attacks, and reported the sensitivity, specificity, positive predictive values and negative predictive values for each scenario, while specifying the preferred algorithm where all of these statistics were optimized. Tables 19 and 20 are reproductions of tables from Tu et al.'s publication and show all of the validation statistics with the optimal algorithm in bold.

Table 19: Tu et al.'s Validation of Administrative Data Algorithms to Identify Patients with Stroke

Rule Description	Sensitivity % (95% CI)	Specificity % (95% CI)	PPV % (95% CI)	NPV % (95% CI)	Prevalence estimate
1. CIHI code	36.9 (27.6-46.2)	99.8 (99.7-99.9)	80.9 (69.6-92.1)	98.7 (98.4-99.0)	0.9%
2. CIHI or NACRS or SDS	45.6 (36.0-55.3)	99.7 (99.5-99.8)	73.4 (62.6-84.3)	98.9 (98.6-99.2)	1.3%
3. CIHI or 1 OHIP	74.8 (66.4-83.1)	97.6 (97.2-98.1)	39.9 (33.0-46.8)	99.5 (99.3-99.7)	3.9%
4. CIHI or NACRS or SDS or 1 OHIP	75.7 (67.4-84.0)	97.5 (97.1-98.0)	39.2 (32.4-46.0)	99.5 (99.3-99.7)	4.0%
5. CIHI or 2 OHIP in 1 yr	**60.2 (50.7-69.6)**	**99.2 (99.0-99.5)**	**62.0 (52.5-71.5)**	**99.2 (98.9-99.4)**	**2.0%**
6. CIHI or NACRS/SDS or 2 OHIP in 1 yr	62.1 (52.8-71.5)	99.1 (98.8-99.4)	59.3 (50.0-68.5)	99.2 (99.0-99.5)	2.2%
7. CIHI or 2 OHIP in 2 yrs	61.2 (51.8-70.6)	99.2 (99.0-99.5)	61.8 (52.3-71.2)	99.2 (98.9-99.4)	2.0%
8. CIHI or 2 OHIP in 3 yrs	61.2 (51.8-70.6)	99.2 (99.0-99.5)	61.8 (52.3-71.2)	99.2 (98.9-99.4)	2.0%
9. CIHI or 3 OHIP in 1 yr	49.5 (39.9-59.2)	99.4 (99.2-99.7)	65.4 (54.8-75.9)	98.9 (98.7-99.2)	1.6%
10. CIHI or 3 OHIP in 2 yrs	50.5 (40.8-60.1)	99.4 (99.2-99.7)	65.8 (55.4-76.3)	99.0 (98.7-99.2)	1.6%
11. CIHI or 3 OHIP in 3 yrs	50.5 (40.8-60.1)	99.4 (99.2-99.6)	65.0 (54.5-75.5)	99.0 (98.7-99.2)	1.6%

Table 20: Tu et al.'s Validation of Administrative Data Algorithms to Identify Patients with Transient Ischemic Attack

Rule Description	Sensitivity % (95% CI)	Specificity % (95% CI)	PPV % (95% CI)	NPV % (95% CI)	Prevalence estimate
1. CIHI code	18.5 (10.1-27.0)	99.8 (99.7-99.9)	60.0 (40.8-79.2)	98.7 (98.4-99.0)	0.5%
2. CIHI or NACRS or SDS	42.0 (31.2-52.7)	99.5 (99.3-99.7)	56.7 (44.1-69.2)	99.0 (98.8-99.3)	1.2%
3. CIHI or 1 OHIP	72.8 (63.2-82.5)	98.2 (97.8-98.6)	40.1 (32.2-48.1)	99.5 (99.4-99.7)	2.9%
4. CIHI or NACRS or SDS or 1 OHIP	76.5 (67.3-85.8)	98.1 (97.7-98.5)	39.5 (31.8-47.1)	99.6 (99.4-99.8)	3.1%
5. CIHI or 2 OHIP in 1 yr	44.4 (33.6-55.3)	99.3 (99.1-99.5)	50.7 (39.1-62.3)	99.1 (98.8-99.4)	1.4%
6. CIHI or NACRS/SDS or 2 OHIP in 1 yr	**53.1 (42.2-64.0**	**99.0 (98.8-99.3)**	**47.8 (37.5-58.1)**	**99.2 (99.0-99.5)**	**1.8%**
7. CIHI or 2 OHIP in 2 yrs	44.4 (33.6-55.3)	99.3 (99.1-99.5)	50.7 (39.1-62.3)	99.1 (98.8-99.4)	1.4%
8. CIHI or 2 OHIP in 3 yrs	44.4 (33.6-55.3)	99.2 (99.0-99.5)	49.3 (37.8-60.8)	99.1 (98.8-99.4)	1.5%
9. CIHI or 3 OHIP in 1 yr	35.8 (25.4-46.2)	99.6 (99.4-99.8)	58.0 (44.3-71.7)	98.9 (98.7-99.2)	1.0%
10. CIHI or 3 OHIP in 2 yrs	35.8 (25.4-46.2)	99.6 (99.4-99.8)	58.0 (44.3-71.7)	98.9 (98.7- 99.2)	1.0%
11. CIHI or 3 OHIP in 3 yrs	35.8 (25.4-46.2	99.6 (99.4-99.8)	58.0 (44.3-71.7)	98.9 (98.7-99.2)	1.0%

CIHI refers to the presence of a diagnostic code of stroke or TIA in the CIHI database, and *OHIP* refers to the presence of procedural code accompanied by a stroke or TIA diagnostic code in the OHIP database

Both ICD-9 &10 codes and OHIP codes used are as follows:

Table 21: Codes used to Identify Strokes from Inpatient and Outpatient Data

	ICD-9 codes	ICD-10 codes	OHIP codes
Hemorrhagic Stroke	430, 431	I60.0, I60.1, I60.2, I60.3, I60.4, I60.5, I60.6, I60.7, I60.8, I60.9, I61.0, I61.1, I61.2, I61.3, I61.4, I61.5, I61.6, I61.8, I61.9	432
Ischemic Stroke	434.0, 434.1, 434.9, 436	I63.0, I63.1, I63.2, I63.3, I63.4, I63.5, I63.8, I63.9, I64	436
Transient Ischemic Attack	435.8, 435.9	G45.0, G45.1, G45.2, G45.3, G45.8, G45.9	435

For stroke identification in this study, the optimal algorithm was used for both exclusion criteria and outcome assessment: the presence of a CIHI stroke code or 2 OHIP stroke diagnosis codes within one year.

Tu et al. identified algorithm 6 as optimal for identifying transient ischemic attacks, however the National Ambulatory Care Reporting System (NACRS) database only holds patient information after 2000, is therefore not applicable to the patient population for this study and required using an algorithm that did not use this database while optimizing the validity statistics– the same algorithm used for strokes.

Stroke & Transient Ischemic Attack - Outcomes

Since the hypothesized biologic mechanism by which radiotherapy can cause a stroke is only specified for ischemic strokes (whereby an injured carotid artery would lead to an embolism in the brain), it does not suit the purposes of this project to include hemorrhagic strokes in the outcome assessment. The algorithms were therefore only run (separately) for ischemic strokes (where the codes for hemorrhagic strokes were omitted) and for transient ischemic attacks.

In identifying strokes as an outcome measure, it is important to attempt to maximize sensitivity (the ability of the algorithm to detect patients that actually had a stroke) and positive predictive value (the

probability that the strokes identified by the algorithm are true strokes). The algorithms selected have less than ideal sensitivities (60.2% - stroke, 44.4% - TIA) when validated against chart reviews, however in a previous American study that used a different combination of both inpatient and outpatient information to identify various comorbid conditions through administrative data, a much higher sensitivity was found for both stroke and transient ischemic attack (91%, 61% respectively) (153). This study's results are relevant to this project since similar to the approach for stroke detection in this project, their objectives were to identify incident cases within a given time period, thus presumably increasing the sensitivity for this study's outcomes. Our approach is also likely to capture more strokes since stroke death, as identified through the registrar general's cause of death, was included as an identification of stroke for this project, whereas Tu et al. did not include this source in their algorithms.

Due to the low positive predictive values (62.0% - stroke, 50.7% - TIA), in order to increase the precision of identifying stroke and transient ischemic attack outcomes, the algorithm was slightly modified: CIHI diagnosis or 2 OHIP diagnoses within 1 year, where at least one of the OHIP codes were billed by physicians of the following specialties: neurosurgery, internal medicine, vascular surgery, neurology, physical medicine, cardiology and emergency medicine. Based on clinical expertise, these specialties are more likely to provide accurate diagnoses of stroke simply because if a patient is referred to any of these specialists whereby the physician is billing a consultation or procedure with a stroke or TIA diagnosis associated with it, it would be more reliable in the eyes of clinicians. As well, positive predictive value is a function of the prevalence of the disease, and in previous studies, head and neck cancer populations were found to have 5 to 9 times higher risk of stroke than comparable healthy populations (75,77); as such, having a patient sample that is hypothesized to have a higher prevalence of stroke, will yield a more favorable positive predictive value than was cited by Tu et al.

Stroke & Transient Ischemic Attack - Exclusion Criteria

Since the aim of the exclusion criteria was to create a clean patient sample whereby none of the included patients would have suffered an event that would put them at a much higher risk of recurrent cerebrovascular event compared to the general population, ischemic strokes, hemorrhagic stroke, transient ischemic attack (and carotid endarterectomy/stent which were found using standard methods for extracting procedures from administrative databases) using the algorithm as specified by Tu et al. was appropriate since they showed it was optimal in identifying prevalent ischemic strokes, hemorrhagic strokes and transient ischemic attacks. Therefore all codes listed above were extracted from CIHI and OHIP for the patient sample. However, the issue with low sensitivities is of particular concern for the exclusion criteria since we are no longer concerned with incident cases, but prevalent cases. To address this concern a priori, previous carotid endarterectomies and carotid stents were used as an additional exclusion criteria to omit patients that may have been on the diseased path to a stroke or transient ischemic attack (or had one of either prior to the procedure which could not be captured using this algorithm).

In aiming to address the low positive predictive value in this case, the modification of using at least one OHIP code billed by a specialist (see above) was also used for identifying patients to be excluded. As well, the same argument can be made regarding a hypothesized higher prevalence of stroke among this diseased patient population thus increasing the positive predictive value for the purposes of this study.

Appendix B: Codes to Identify Carotid Endarterectomies or Carotid Stents

CIHI		OHIP	
Carotid Endarterectomy			
50.02	Incision of other vessels of head and neck	R792	Endarterectomy, with or without bypass graft
50.12	Endarterectomy of other vessels of head and neck		
50.22	Resection of other vessels of head and neck with anastamosis		
50.32	Resection of other vessels of head and neck with replacement		
50.52	Other excision of other vessels of head and neck		
1JE50	Dilation, carotid artery		
1JE57	Extraction, carotid artery		
1JE80	Repair, carotid artery		
1JE87	Excision partial, carotid artery		
Carotid Stent			
1JE76MXXXA	Bypass, carotid artery using autograft bypass terminating in carotid artery [e.g. Carotid-carotid]	J058	Vascular stenting
1JE76MXXXN	Bypass, carotid artery using synthetic material bypass terminating in carotid artery [e.g. Carotid-carotid]		

Appendix C: Codes to Identify Surgical Treatment for Head and Neck Cancer

CIHI	
Codes	**Procedure**
Neck Dissection	
52.2	regional lymph node excision
52.3	radical excision of cervical lymph nodes
52.31	radical neck dissection, unqualified
52.32	radical neck dissection, unilateral
52.33	radical neck dissection, bilateral
88.5	excision and reconstruction of mandible
88.52	total mandibulectomy with reconstruction
88.53	other total mandibulectomy
1MC87	Excision partial, lymph node(s), neck region NEC (cervical)
1MC89	Excision total, lymph node(s), neck region NEC (cervical)
1MC91	Excision radical, lymph node(s). neck region NEC (cervical)
Other Head and/or Neck Surgical Procedure	
37	operations on tongue
37.0	excision or destruction of lesion or tissue of tongue
37.01	excision of lingual frenum
37.09	other local excision of tongue
37.1	partial glossectomy
37.2	complete glossectomy
37.3	radical glossectomy
39.2	excision of lesion or tissue of palate
39.21	local excision or destruction of lesion or tissue of palate
39.22	wide excision or destruction of lesion or tissue of palate
39.3	excision of other parts of mouth
39.31	labial frenumectomy
39.39	other excision of mouth
39.62	excision of uvula
39.69	other operations on uvula nec
39.99	other operations on oral cavity
40.92	excision of lesion of tonsil and adenoid
41.2	excision or destruction of lesion or tissue of pharynx
41.23	pharyngectomy (partial)
41.29	other excision or destruction of lesion or tissue of pharynx
41.99	other operations on pharynx nec
42	excision of larynx
42.0	excision or destruction of lesion or tissue of larynx
42.09	other excision or destruction of lesion or tissue of larynx

42.1	hemilaryngectomy (anterior) (lateral)
42.2	other partial laryngectomy
42.21	epiglottidectomy
42.22	vocal cordectomy
42.29	other partial laryngectomy nec
42.3	complete laryngectomy
42.4	radical laryngectomy
1EE87	Excision partial, mandible
1EE91	Excision radical, mandible
1EM87	Excision partial, maxillary alveolar ridge
1EN87	Excision partial, mandibular alveolar ridge
1EN91	Excision radical, mandibular alveolar ridge
1EQ87	Excision partial, soft tissue of head and neck
1FB87	Excision partial, hard palate
1FB91	Excision radical, hard palate
1FC87	Excision partial, soft palate
1FD87	Excision partial, gingiva
1FG87	Excision partial, oral and buccal mucosa
1FH87	Excision partial, floor of mouth
1FJ87	Excision partial, tongue
1FJ91	Excision radical, tongue
1FQ87	Excision partial, uvula
1FX87	Excision partial, oropharynx
1FX91	Excision radical, oropharynx
1GA87	Excision partial, glottis
1GA89	Excision total, glottis
1GB87	Excision partial, supraglottis
1GE87	Excision partial, larynx NEC
1GE89	Excision total, larynx NEC
1GE91	Excision radical, larynx NEC
1MB87	Excision partial, lymph node(s), deep cervical

OHIP	
Codes	**Procedure**
Neck Dissection	
r910	neck lymph nodes - limited dissection
r915	neck lymph nodes - comprehensive dissection
Other Head and/or Neck Surgical Procedure	
M081	Total laryngectomy
M082	Laryngectomy - laryngofissure
M084	Laryngectomy - segmental
Z323	Laryngoscopy with removal of lesion(s)
Z502	Excision of lesion less than 2 cms of oral cavity or pharynx
S003	Excision of lesion 2 to 4 cms of oral cavity or pharynx
S006	Excision of lesion over 4 cms of oral cavity or pharynx
S005	Composite resection of lesion of oral cavity and/or oropharynx with partial resection of madible
S007	Extended composite resection of lesion of oral cavity and oropharynx with partial resection of madible and resection of maxilla
S018	Partial glossectomy
S067	Partial pharyngectomy
S068	Pharyngo-laryngectomy

Appendix D: Study Covariates - Databases & Relevant Administrative Database Codes

Variables	Database	Codes
Age at diagnosis	OCR	
Sex	OCR	
Cancer site	OCR	
Date of cancer diagnosis (year)	OCR	
Ischemic Heart Disease	CIHI & OHIP	See Appendix E
Myocardial Infarction	OMID**	ICD-9: 410 ICD-10: I21
Peripheral Vascular Disease	CIHI	ICD-9: 4438, 4439 ICD-10: I738, I739
Asthma	ASTHMA***	ICD-9: 493 ICD-10: J45 493
Atrial Fibrillation	CIHI	ICD-9: 4273 ICD-10: I480, I481
Chronic Obstructive Pulmonary Disease	COPD***	ICD-9: 491, 492, 496 ICD-10: J41, J43, J44 491, 492, 496
Hypertension	HYPER***	ICD-9: 401, 402, 403, 404, 405 ICD-10: I10, I11, I12, I13, I15 401, 402, 403, 404, 405
Diabetes	ODD***	ICD-9: 401, 402, 403, 404, 405 ICD-10: I10, I11, I12, I13, I15 401, 402, 403, 404, 405
HPV status: Cancer site (oropharynx) Year of diagnosis (>2000) Age (≤55)	 OCR OCR OCR	
Elixhauser Comorbidity Index	CIHI	See Appendix F

* Codes from these databases were retained for both procedures and diagnoses
** This ICES-derived cohort was based on data from CIHI only
*** These ICES-derived cohorts were based on data from both CIHI and OHIP

Appendix E: Algorithm to Identify Patients with Ischemic Heart Disease

Tu et al. also developed an algorithm to identify patients that have ischemic heart disease (IHD) from administrative data (104). This algorithm involves using both diagnoses in CIHI and OHIP for ischemic heart disease, but also procedures that were likely caused by a diagnosis of IHD including: percutaneous coronary intervention (PCI) and coronary artery bypass graft surgery (CABG). Multiple algorithms were tested for their sensitivity, specificity, positive predictive value and negative predictive value, and where these statistics were optimized was the algorithm that was deemed most appropriate for use.

For this study Tu et al.'s optimal algorithm was used to identify patients with IHD, and it is outlined as follows: two physician billing codes that include either a diagnosis of IHD or procedural codes for PCI or CABG or one hospital discharge abstract that include either a diagnosis of IHD or procedural codes for PCI or CABG. Table 22 denotes the CIHI and OHIP codes that were used to identify the diagnoses and procedures used for this algorithm.

Table 22: CIHI and OHIP used for Algorithm to Identify Patients with Ischemic Heart Disease

	Ischemic Heart Disease	**Percutaneous Coronary Intervention**	**Coronary Artery Bypass Graft Surgery**
CIHI Codes	410, 411, 412, 413, 414, I20, I21, I22, I23, I24, I25	4802, 4803, 4809, 1IJ50, 1IJ57GQ	481, 1IJ76
OHIP Codes	410, 412, 413	Z434, G298	R742, R743

Appendix F: ICD-9 and ICD-10 Coding Algorithms for Elixhauser Comorbidities

Comorbities	ICD-9 codes	ICD-10 codes
Congestive heart failure	398.91, 402.01, 402.11, 402.91, 404.01, 404.03, 404.11, 404.13, 404.91, 404.93, 425.4–425.9, 428.x	I09.9, I11.0, I13.0, I13.2, I25.5, I42.0, I42.5–I42.9, I43.x, I50.x, P29.0
Cardiac arrhythmias	426.0, 426.13, 426.7, 426.9, 426.10, 426.12, 427.0–427.4, 427.6–427.9, 785.0, 996.01, 996.04, V45.0, V53.3	I44.1–I44.3, I45.6, I45.9, I47.x–I49.x, R00.0, R00.1, R00.8, T82.1, Z45.0, Z95.0
Valvular disease	093.2, 394.x–397.x, 424.x, 746.3–746.6, V42.2, V43.3	A52.0, I05.x–I08.x, I09.1, I09.8, I34.x–I39.x, Q23.0–Q23.3, Z95.2–Z95.4
Peripheral vascular disorders	093.0, 437.3, 440.x, 441.x, 443.1–443.9, 447.1, 557.1, 557.9, V43.4	I70.x, I71.x, I73.1, I73.8, I73.9, I77.1, I79.0, I79.2, K55.1, K55.8, K55.9, Z95.8, Z95.9
Pulmonary circulation disorders	415.0, 415.1, 416.x, 417.0, 417.8, 417.9	I26.x, I27.x, I28.0, I28.8, I28.9
Hypertension, uncomplicated	401.x	I10.x
Hypertension, complicated	402.x–405.x	I11.x–I13.x, I15.x
Paralysis	334.1, 342.x, 343.x, 344.0–344.6, 344.9	G04.1, G11.4, G80.1, G80.2, G81.x, G82.x, G83.0–G83.4, G83.9
Other neurological disorders	331.9, 332.0, 332.1, 333.4, 333.5, 333.92, 334.x–335.x, 336.2, 340.x, 341.x, 345.x, 348.1, 348.3, 780.3, 784.3	G10.x–G13.x, G20.x–G22.x, G25.4, G25.5, G31.2, G31.8, G31.9, G32.x, G35.x–G37.x, G40.x, G41.x, G93.1, G93.4, R47.0, R56.x
Chronic pulmonary disease	416.8, 416.9, 490.x –505.x, 506.4, 508.1, 508.8	I27.8, I27.9, J40.x–J47.x, J60.x–J67.x, J68.4, J70.1, J70.3
Diabetes, uncomplicated	250.0–250.3	E10.0, E10.1, E10.9, E11.0, E11.1, E11.9, E12.0, E12.1, E12.9, E13.0, E13.1, E13.9, E14.0, E14.1, E14.9
Diabetes, complicated	250.4–250.9	E10.2–E10.8, E11.2–E11.8, E12.2–E12.8, E13.2–E13.8, E14.2- E14.8
Hypothyroidism	240.9, 243.x, 244.x, 246.1, 246.8	E00.x–E03.x, E89.0
Renal failure	403.01, 403.11, 403.91, 404.02, 404.03, 404.12, 404.13, 404.92, 404.93, 585.x, 586.x, 588.0, V42.0, V45.1, V56.x	I12.0, I13.1, N18.x, N19.x, N25.0, Z49.0–Z49.2, Z94.0, Z99.2
Liver disease	070.22, 070.23, 070.32, 070.33, 070.44, 070.54, 070.6, 070.9, 456.0–456.2, 570.x, 571.x, 572.2–572.8, 573.3, 573.4, 573.8, 573.9, V42.7	B18.x, I85.x, I86.4, I98.2, K70.x, K71.1, K71.3–K71.5, K71.7, K72.x–K74.x, K76.0, K76.2–K76.9, Z94.4

Peptic ulcer disease excluding bleeding	531.7, 531.9, 532.7, 532.9, 533.7, 533.9, 534.7, 534.9	K25.7, K25.9, K26.7, K26.9, K27.7, K27.9, K28.7, K28.9
AIDS/HIV	042.x–044.x	B20.x–B22.x, B24.x
Lymphoma	200.x–202.x, 203.0, 238.6	C81.x–C85.x, C88.x, C96.x, C90.0, C90.2
Metastatic cancer	196.x–199.x	C77.x–C80.x
Solid tumor without metastasis	140.x–172.x, 174.x–195.x	C00.x–C26.x, C30.x–C34.x, C37.x–C41.x, C43.x, C45.x–C58.x, C60.x–C76.x, C97.x
Rheumatoid arthritis/collagen vascular disease	446.x, 701.0, 710.0–710.4, 710.8, 710.9, 711.2, 714.x, 719.3,720.x, 725.x, 728.5, 728.89, 729.30	L94.0, L94.1, L94.3, M05.x, M06.x, M08.x, M12.0, M12.3, M30.x, M31.0–M31.3, M32.x–M35.x, M45.x, M46.1, M46.8, M46.9
Coagulopathy	286.x, 287.1, 287.3–287.5	D65–D68.x, D69.1, D69.3–D69.6
Obesity	278.0	E66.x
Weight loss	260.x–263.x, 783.2, 799.4	E40.x–E46.x, R63.4, R64
Fluid and electrolyte disorders	253.6, 276.x	E22.2, E86.x, E87.x
Blood loss anemia	280.0	D50.0
Deficiency anemia	280.1–280.9, 281.x	D50.8, D50.9, D51.x–D53.
Alcohol abuse	265.2, 291.1–291.3, 291.5–291.9, 303.0, 303.9, 305.0, 357.5, 425.5, 535.3, 571.0– 571.3, 980.x, V11.3	F10, E52, G62.1, I42.6, K29.2, K70.0, K70.3, K70.9, T51.x, Z50.2, Z71.4, Z72.1
Drug abuse	292.x, 304.x, 305.2– 305.9, V65.42	F11.x–F16.x, F18.x, F19.x, Z71.5, Z72.2
Psychoses	293.8, 295.x, 296.04, 296.14, 296.44, 296.54, 297.x, 298.x	F20.x, F22.x–F25.x, F28.x, F29.x, F30.2, F31.2, F31.5
Depression	296.2, 296.3, 296.5, 300.4, 309.x, 311	F20.4, F31.3–F31.5, F32.x, F33.x, F34.1, F41.2, F43.2

(120)

Appendix G: Ethics Approval

QUEEN'S UNIVERSITY HEALTH SCIENCES AND AFFILIATED TEACHING HOSPITALS RESEARCH ETHICS BOARD ANNUAL RENEWAL

Queen's University, in accordance with the "Tri-Council Policy Statement 2, 2010" prepared by the Interagency Advisory Panel on Research Ethics for the Canadian Institutes of Health Research, Natural Sciences and Engineering Research Council of Canada and Social Sciences and Humanities Research Council of Canada requires that research projects involving human participants be reviewed annually to determine their acceptability on ethical grounds.

A Research Ethics Board composed of:

Dr. A.F. Clark, Emeritus Professor, Department of Biomedical and Molecular Sciences, Queen's University (Chair)
Dr. H. Abdollah, Professor, Department of Medicine, Queen's University
Dr. C. Cline, Assistant Professor, Department of Medicine, Director, Office of Bioethics, Queen's University, Clinical Ethicist, Kingston General Hospital
Dr. R. Brison, Professor, Department of Emergency Medicine, Queen's University
Dr. M. Evans, Community Member
Ms. J. Hudacin, Community Member
Dr. B. Kisilevsky, Professor, School of Nursing, Departments of Psychology and Obstetrics and Gynaecology, Queens's University
Dr. J. MacKenzie, Pediatric Geneticist, Department of Paediatrics, Queen's University
Mr. D. McNaughton, Community Member
Ms. P. Newman, Pharmacist, Clinical Care Specialist and Clinical Lead, Quality and Safety, Pharmacy Services, Kingston General Hospital
Ms. S. Rohland, Privacy Officer, ICES-Queen's Health Services Research Facility, Research Associate, Division of Cancer Care and Epidemiology, Queen's Cancer Research Institute
Dr. A. Singh, Professor, Department of Psychiatry, Queen's University
Ms. K. Weisbaum, LL.B. and Adjunct Instructor, Department of Family Medicine (Bioethics)

has reviewed the request for renewal of Research Ethics Board approval for the project **What Should we be Telling Patients About the Rate of Stroke and Carotid Vascular Disease After Radiation Treatment for Squamous Cell Carcinoma of the Head and Neck?** as proposed by **Dr. Stephen Frederick Hall** of the **Department of Otolaryngology,** at **Queen's University** . The approval is renewed for one year, effective **August 09, 2013.** If there are any further amendments or changes to the protocol affecting the participants in this study, it is the responsibility of the principal investigator to notify the Research Ethics Board. Any unexpected serious adverse event occurring locally must be reported within 2 working days or earlier if required by the study sponsor. All other adverse events must be reported within 15 days after becoming aware of the information.

Albert F. Clark.
_____Date: July 17, 2013
Chair, Research Ethics Board
Renewal 1[ ] Renewal 2 [X] Extension [ ] **Code# OTOL-045-11 Romeo file# 6006201**

Amendment Acknowledgment/Approval Letter

January 23, 2014

Dr. Stephen Frederick Hall
Department of Otolaryngology
Queen's University
Kingston ON K7L 3N6

RE: File #6006201 OTOL-045-11 What Should we be Telling Patients About the Rate of Stroke and Carotid Vascular Disease After Radiation Treatment for Squamous CellCarcinoma of the Head and Neck?

Dear Dr. Hall:

I am writing to acknowledge receipt of the following:

- Addition of Erin Arthur's, MSc student, Dept of Public Health Sciences to the study team. CORE certificate submitted

I have reviewed the amendment and hereby give my approval. Receipt of this will be reported to the Queen's University Health Sciences and Affiliated Teaching Hospitals Research Ethics Board.

Yours sincerely,

Albert L. Clark.

Albert Clark, Ph.D.
Chair
Health Sciences Research Ethics Board

Appendix H: Regression Diagnostics

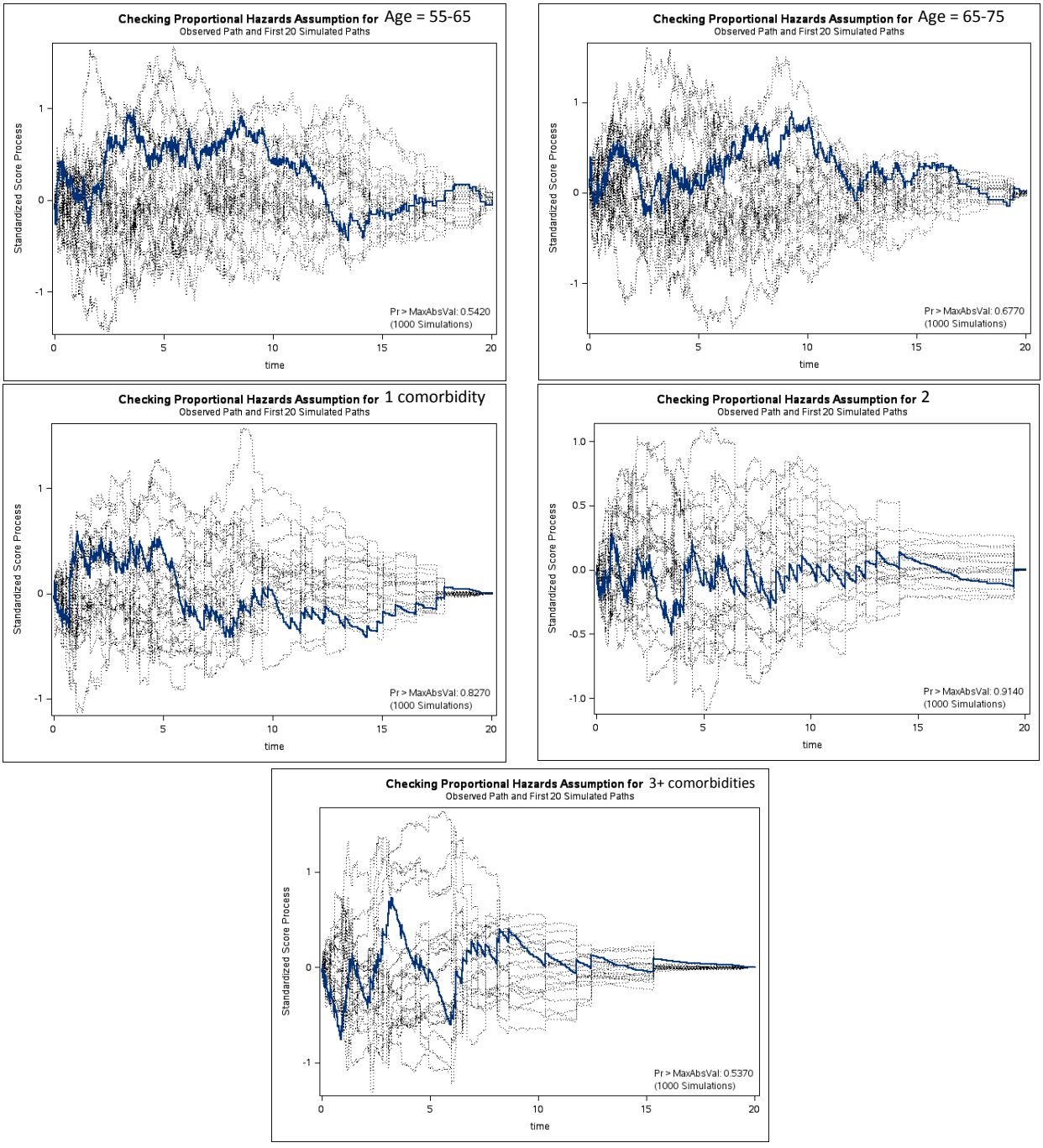

Figure 17: Observed Standardized Score Process for Testing the Proportional Hazards Assumption by Non-Reference Category Levels of Covariates

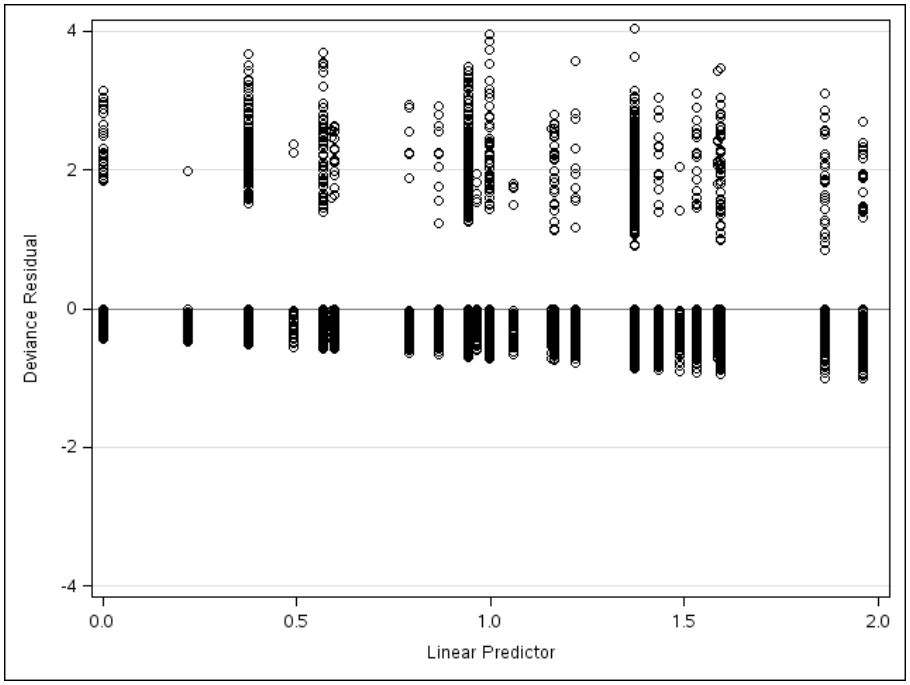

Figure 18: Testing for Outlying Observations with Deviance Residuals