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Survival trends of patients with subglottic squamous cell carcinoma: A population based cohort study

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Abstract

Background: Subglottic squamous cell carcinoma is a rare subsite of laryngeal cancer, which is believed to behave more aggressively and portend a worse prognosis than other laryngeal cancer subsites (supraglottis and glottis). Our objective was to utilize a population-based cancer registry to report the overall survival and laryngectomy-free survival in patients diagnosed with subglottic squamous cell carcinoma, and to examine trends in outcomes over time. We also compared overall survival in patients treated with primary laryngectomy versus radiation.

Methods: We carried out a retrospective population-based study of patients with a new diagnosis of squamous cell carcinoma in the province of Ontario, Canada over a 15-year period (1995-2009). We identified patients with a new diagnosis of subglottic squamous cell carcinoma using the Ontario Cancer Registry. We determined demographics, comorbidity measures, staging, survival and primary treatment with laryngectomy using the linked population-based healthcare databases in Ontario. We first determined the overall survival and laryngectomy free survival of patients with subglottic cancer. In a secular trends study, we then examined the trends in overall survival and laryngectomy-free survival over the study period.

Results: A total of 4927 cases of laryngeal carcinoma were identified, with 89 patients defined as primary subglottic carcinoma (1.8%). Among the subglottic cohort, 68 (76.4%) were male, and the mean (25^{th}, 75^{th} percentile) age at diagnosis was 68 (60- 77 years). The 5-year overall survival was 47.2%, while the 5-year laryngectomy-free survival was 31.5%. No differences were observed in overall survival (OS) or laryngectomy-free survival (LFS) across years over the 15-year study period (p=0.42 OS, p=0.83 LFS). Thirteen patients (15%) were treated with primary laryngectomy. Primary treatment with laryngectomy was not associated with a different risk of mortality compared with radiation.

Conclusions: The overall survival and laryngectomy-free survival of patients with subglottic carcinoma is poor and has remained stable over time (1995-2009). Primary treatment with laryngectomy does not appear to improve overall survival compared with primary radiation.

Keywords

Subglottic, Overall Survival, Population-based, Laryngectomy-free survival, Squamous cell carcinoma

Summary for Lay Audience

Cancer that occurs below the level of the vocal cords, also known as subglottic cancer, is very rare. Subglottic cancer is thought to lead to a higher chance of death than cancer that occurs in the vocal cords or above the vocal cords, but we don't know for sure because it is so rare. Our goal with this study was to use a large database of patients with subglottic cancer to determine if it does have a higher chance of death than other vocal cord cancers and whether treatment with surgery or radiation is better. We looked at all patients in Ontario from 1995-2009 who were diagnosed with subglottic cancer. We searched the database for other factors that might contribute to the survival of patients with subglottic caner and impact their chance of cure. We used the data to determine how many patients were still alive at 5 years after a diagnosis of subglottic cancer and how many patients were still alive at 5 years and still retained their voice box (that is, they did not have to have it removed to cure the cancer).

In total we found 89 patients who had subglottic cancer in Ontario during our study period. At 5 years, 47.2% of patients were still alive and 31.5% of patients will still alive and still had their voice box. Over the 15 years of our study, we did not find that the chance of survival from subglottic cancer changed. Fifteen percent of patients were treated with surgery and the rest were treated with radiation. We found that the treatment chosen did not impact survival from subglottic cancer.

Patients with subglottic cancer have a lower chance of survival than patients with cancer in the vocal cords or above the vocal cords, and survival has not changed over the study timeframe 1995-2009. The treatment chosen for subglottic cancer does not

appear to impact survival at 5 years. More research is needed to improve the overall survival for patients with subglottic cancer and to determine the best treatment options.

Co-Authorship Statement The study presented here was designed and executed by S. Danielle MacNeil. This includes, but is not limited to, study conception, study design, data creation plan (DCP) production (appendix), data analysis, and manuscript production and editing. The supervisory committee as well as each of the co-authors provided regular feedback.

A version of the manuscript was submitted to the journal Current Oncology (citation below). Each co-author critically appraised the manuscript and provided important feedback for manuscript revision. Kuan Liu and Salimah Shariff also contributed to study design, acquisition and analysis of data and review of the manuscript.

Dr. Amit Garg was the primary supervisor and was involved in all aspects of the work. Dr. Amardeep Thind was a thesis committee supervisor and provided comprehensive feedback. I would like to acknowledge the other co-authors and reviewers who helped edit the final manuscript.

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Dedication

This thesis is dedicated to my family. Thank you for your ongoing love, patience and support.

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List of Abbreviations

LFS Laryngectomy free survival

CR Complete response

CRT Chemoradiotherapy

CT Computed tomography

DFS Disease-free survival

DSS Disease-specific survival

HPV Human papilloma virus

LC Local control

LSCC Laryngeal squamous cell carcinoma

MRI Magnetic resonance imaging

OS Overall survival

PET Positron emission tomography

PR Partial response

RFS Recurrence-free survival

RT Radiotherapy

SCC Squamous cell carcinoma

TL Total laryngectomy

TLM Transoral laser surgery

TNM Tumor, node, metastasis classification

CHAPTER ONE: OVERVIEW OF THESIS AND INTRODUCTION

1.1 Introduction

Squamous cell carcinoma (SCC) of the subglottis is rare, representing less than 5% of all laryngeal cancer.[1-3] In the past, defining primary subglottic cancer versus glottic cancer with subglottic extension was challenging due to poor imaging and laryngoscopy equipment.[4] The superior anatomic boundary of the subglottis has also been inconsistently defined, ranging from below the free edge of the true vocal cord to 5mm below the vocal cord to 1cm below the lateral margin of the ventricle, further complicating accurate classification of this disease subsite.[5] The rarity of the disease, the historic difficulty in defining primary versus secondary subglottic cancer as well as the changing definition of the superior boundary have made reporting treatment and survival outcomes of this rare carcinoma challenging.

Primary subglottic SCC is thought to herald a worse prognosis than the other subsites of laryngeal cancer secondary to advanced stage at presentation, propensity for paratracheal and upper mediastinal lymphatic spread, and the increased risk of stomal recurrence.[6-9] Historically, total laryngectomy has been employed as the standard of care for the treatment of subglottic carcinoma.[4] Laryngectomy involves removal of the entire larynx (voice box) and for most patients this surgical procedure results in a significant decline in their quality of life. Recent retrospective studies have demonstrated comparable survival outcomes for patients treated with primary radiotherapy.[10, 11] Most published reports on patients with subglottic carcinoma are small including less than 60 patients[6, 12-17], aside from two population based

studies[10, 18]. Only one published study reports on the outcome of laryngectomy-free survival.[12, 18-20] Most of these studies are also limited by institutional selection bias, and incomplete reporting of surgical data.[12, 18-20] Laryngectomy-free survival is an important outcome to report as the reason most patients pursue radiation is to preserve their larynx. We conducted a population-based study to determine the outcomes of patients with subglottic carcinoma and the secular trends in survival over time. Using the linked population-based databases in Ontario, we can determine the laryngectomy-free survival of this patient population following treatment with primary radiation. We were also able to compare the survival outcomes of patients treated primarily with surgery and radiation.

1.2 Thesis Overview

The thesis is structured into the following chapters: 2. Introduction to Laryngeal Cancer; 3. Literature Review of Subglottic Cancer; 4. Rationale and Research Approach; 5. Objectives and Hypothesis; 6. Patients and Methods; 7. Results; and 8. Discussion. In Chapter 2 we provide an overview of laryngeal cancer workup and epidemiology. We then describe the current treatment options for laryngeal cancer and discuss the prognosis and survival outcomes for laryngeal cancer highlighting a knowledge gap of reporting of survival outcomes with adequate sample size. In Chapter 3, we perform a scoping review of the literature on subglottic carcinoma to improve our understanding of subglottic squamous cell carcinoma, including the survival outcomes. We synthesize the existing literature on subglottic carcinoma and describe the limitations of the existing

studies. In Chapter 4, we state the rationale for our research approach. In Chapter 5 we provide our objectives and hypothesis. In Chapter 6 we describe our methods including the databases used, definition of outcomes and statistical methodology. Chapter 7 describes our results and in chapter 8 we discuss our findings and their implications. Finally, we conclude with a discussion of the strengths and weaknesses of this work and recommendations for future research.

CHAPTER 2: INTRODUCTION TO LARYNGEAL CANCER, TREATMENT AND OUTCOMES

2.1 Introduction

The larynx has three main functions: swallowing; speech; and respiration. It is responsible for protecting the airway, vocalization and protecting the lungs. With swallowing the larynx elevates and it is able to generate pressure with glottic closure which is important for straining and gastrointestinal function. Cancers of the larynx can impact all three physiologic functions to varying degrees. Worldwide, laryngeal cancer is the second most common head and neck cancer and it has an incidence of 157,000 new cases each year.[21] In the following sections we provide an overview of laryngeal cancer, including anatomy, epidemiology, histology, clinical evaluation, staging, treatment and survival outcomes.

2.2 Anatomy of the larynx

The larynx is composed of cartilage, ligaments, membranes and intrinsic and extrinsic laryngeal muscles. It contains three cartilaginous structures, which include the paired arytenoid, cuneiform and corniculate cartilages and three unpaired cartilaginous structures, the thyroid, cricoid and epiglottis.

Blood supply to the larynx is provided by the superior and inferior laryngeal arteries. The superior laryngeal artery, which arises from the superior thyroid artery, provides blood flow to the superior half of the larynx while the inferior half is supplied by the inferior

laryngeal artery, a branch of the inferior thyroid artery. Nervous innervation of the larynx is supplied by the superior laryngeal nerve and the recurrent laryngeal nerve. The superior laryngeal nerve provides sensation above the vocal folds and motor innervation to the cricothyroid muscle. The recurrent laryngeal nerve supplies both sensory and motor innervation to the glottis and below and the remaining of the laryngeal muscles.

The larynx is divided into three subsites, the supraglottis, glottis and subglottis. These anatomic subsites are based on embryologic development which results in clinically important difference between the subsites. The supraglottis is composed of the epiglottis, aryepiglottic folds, arytenoids and false cords. The supraglottis spans from the epiglottis to the laryngeal ventricle. The glottis is composed of the true vocal cords, anterior commissure, interarytenoid region and floor of the ventricle. The glottis extends inferiorly to 1cm below the apex of the ventricles. The subglottis starts 1 cm below the apex of the ventricle and extends to the inferior border of the cricoid cartilage. The border that divides the glottis from the subglottis has been inconsistently defined however, and this will be discussed in subsequent sections.

Due to the differences in embryologic development, the different subsites of the larynx have different patterns of lymphatic drainage. The supraglottis drains into bilateral lateral neck lymph node basins. Given the rich lymphatic drainage of the supraglottis, even early stage supraglottic cancers have a high propensity for lymphatic involvement. Clinically this results in a high incidence of unilateral or bilateral metastases (25-75% for all stages) at the time of diagnosis.[22] The glottis is devoid of lymphatics, so lymph

node involvement usually only occurs with advanced stage disease, and is more likely to be unilateral. Subglottic lymphatic drainage is most commonly to the central compartment lymph nodes.

The larynx is also composed of laryngeal membranes and spaces which clinically impact the spread of disease and treatment. These membranes (conus elasticus, quadrangular membrane and thyrohyoid membrane) provide anatomic barriers to spread of cancer which result in cancer spreading predictably through spaces that provide the least resistance. Two important spaces in the larynx are the preepiglottic space and the paraglottic space. Both spaces are rich with lymphatics and blood vessels and continuous with each other allowing spread between compartments.

Table 1 describes the subsites of the larynx and the regions of each subsite. The supraglottis extends from the tip of the epiglottis superiorly to the laryngeal ventricle. The laryngeal ventricle is a space bounded above by the false vocal cords and below by the true vocal cords. The subsites of the supraglottis are listed in Table 1. Depending of the subsite of the supraglottis that is involved there may or may not be anatomic barriers that prevent spread of cancer to other sites.

The glottic larynx encompasses the floor of the ventricle, the true vocal folds and extends to 1 cm below the free edge of the cord and the anterior commissure. As mentioned, the glottis contains few lymphatics which means cancers in the glottis

remain localized for longer periods of time. In addition, the thyroid cartilage prevents many early stage cancers in the submucosa from spreading.

The subglottis begins at the inferior limit of the glottis and extends to the inferior edge of the cricoid cartilage. The laryngeal subglottis is contained by the cricoid cartilage and the conus elasticus. Spread of malignant tumors beyond the boundaries of the subglottis is easily accomplished through the cricothyroid membrane anteriorly and laterally, and into the hypopharynx posteriorly.[9] Cancers arising in the subglottis have been known to have a unique circumferential pattern of intraluminal spread, with up to half of tumors involving a complete ring and over 90% involving at least two thirds of the circumference.[23] As a result subglottic cancers have a propensity for extralaryngeal extension.

Glottic cancers can spread from the glottis to the subglottis making the distinction between glottic tumors with secondary subglottic spread and primary subglottic tumors difficult.[6] In subglottic tumors the spread of the tumor is thought to be circumferential and inferior with superior spread less common.[24] Some have suggested that if the tumor grows into multiple regions, the region with the highest tumor volume is defined as the origin.

Table 1 Anatomic region and subsites of the larynx

Region of Larynx	Subsites
Supraglottis	Suprahyoid epiglottis (tip, lingual and laryngeal surfaces)

	Aryepiglottic fold
	Arytenoids
	Infrahyoid epiglottis
	False Cords
Glottis	True vocal folds
	Anterior commissure
	Posterior commissure
Subglottis	

2.3 Epidemiology of Laryngeal Cancer

Laryngeal carcinoma is the second most common malignancy of the head and neck and the eleventh most common form of cancer worldwide, comprising 1.1% of all new cancers.[25] Laryngeal cancer occurs more frequently with advancing age and among men.[26] The median age of diagnosis for patients with laryngeal cancer is 65 years and the median age at death is 68 years.[26] Men are more prone to the disease, with a 0.6% lifetime probability of developing laryngeal cancer, whereas for women the figure is significantly lower (0.1%).[27] Cancer incidence varies across geographical regions. In developing countries, the age-adjusted incidence in 2012 was 3.5 per 100000, compared to an incidence of 5.1 in more developed countries.[25] In Canada, the age-standardized incidence rates of laryngeal cancer has declined over the last decades in men from the 1988 high point of 11.6 per 100000 to 5.1 in 2017. A decrease in females was also observed, from 2.0 to 0.8.[27]

2.4 Laryngeal Cancer Histology and Classification

Ninety-five percent of laryngeal malignancies are squamous cell carcinomas (SCCs) arising from the stratified squamous epithelial lining of the larynx.[28, 29] Other laryngeal cancer pathologies include verrucous carcinoma, spindle cell carcinoma, glandular carcinomas (adenocarcinoma not otherwise specified (NOS), adenoid cystic, mucoepidermoid) [30-32], sarcomas (chondrosarcoma, fibrosarcoma and liposarcoma) [33], neuroendocrine tumors and metastatic disease.[22] Forty percent of laryngeal cancers will be diagnosed at an advanced stage (III or IV).[34] The glottis (51%) is the most common site for laryngeal cancer followed by the supraglottis (32%) and subglottis (2%).[35] In Ontario, population-based data has demonstrated that glottic cancers represent 64.8% of all laryngeal cancer diagnosed from 1995-2007, while supraglottic account for 28.2% and subglottic 1.8% of laryngeal cancer.[36]

There are a variety of histologic subtypes of laryngeal SCCs that have been shown to impact prognosis. Basaloid laryngeal SCC have characteristic “blue cells” on histology, they are more likely to be confused with other tumors and are associated with a poorer prognosis than typical laryngeal SCCs in most reports.[37] Verrucous carcinoma is a rare variant of SCC. It has an exophytic warty appearance and may be confused with squamous papilloma on clinical examination.[38] Although generally a less aggressive variant, Verrucous carcinoma is generally less aggressive than traditional SCC but is may contain small nests of traditional aggressive SCC. These tumors may be resistant to radiation, so surgical resection is generally preferred.[39] Papillary variant laryngeal SCC has an exophytic appearance, and a papillary-type growth pattern. These tumors are associated with human papillomavirus (HPV) viral infection and generally have a

good prognosis compared to traditional SCC. Local control and survival are excellent regardless of which treatment is chosen.[40, 41] Spindle cell variant is rare but can often be confused on histology with sarcoma, malignant melanoma and other malignant or benign spindle proliferations.[22] Survival rates are like traditional laryngeal SCC but they are locally aggressive.[42] Adenosquamous variant is another rare variant and it is challenging to differentiate them from salivary gland malignancies. On histology the characteristics are pseudoglandular structures and cystic degeneration. They are aggressive tumors and are associated with a poor prognosis.[43]

2.5 Risk Factors for laryngeal cancer

2.5.1 Tobacco and alcohol

The vast majority (85%) of laryngeal cancers can be attributed to tobacco and alcohol use.[44, 45] Compared with nonsmokers, current smokers have a 10- to 20- fold increased risk of laryngeal cancer.[46, 47] In addition to being a risk factor for the development of laryngeal cancer, smoking has also been identified as an independent risk factor for local recurrence and for recurrence at an earlier point than those who stopped smoking.[47] While the predominant risk factor for larynx cancer is smoking, alcohol is also an independent and synergistic risk factor.[44, 45]

2.5.2 Human Papillomavirus

Given that human papillomavirus (HPV) is associated with the majority cancer of the oropharynx, it was initially thought that HPV did not play a role in laryngeal cancer. However, new research is emerging that demonstrates the presence of HPV and/or the surrogate marker p16 in a minority of laryngeal tumours. A recent systematic review

demonstrated that laryngeal HPV-positive tumours may be associated with improved overall survival.[48] It is estimated that the prevalence of HPV ranges from 20% to 30% in laryngeal cancer; however, this percentage varies widely between studies and depends on the detection method used.[49, 50] More work is needed to determine the clinical relevance of HPV/p16-positive status in laryngeal cancer, as this remains controversial.[51-53]

2.5.3 Other risk factors

Other risk factors include carcinogens in the workplace such as asbestos, nickel compounds, wood dust, leather products, paint, diesel fume, textile dust, and glass-wool.[54-56] Dietary factors have also been noted, with red meat increasing the risk of laryngeal cancer, while a diet varied in fruit and vegetables potentially has a protective effect.[57, 58] In addition, the role that both gastroesophageal and laryngopharyngeal reflux play in the disease process is still controversial and under investigation.[59, 60] To date, only an association between tobacco and alcohol exposure and risk of laryngeal cancer has been established.

2. 6 Clinical Presentation and Diagnostic Workup

2.6.1 History and Physical Examination

Laryngeal cancer patients typically present with symptoms of hoarseness, voice changes, the sensation of something stuck in the throat, and discomfort in the throat. As the tumor grows, more severe symptoms including dyspnea (difficulty breathing), dysphagia (problems swallowing), odynophagia (pain with swallowing), hemoptysis (coughing up blood), referred pain to the ipsilateral ear, or weight loss (38). Symptoms

can vary based on the site of the larynx where the cancer is located (glottis, supraglottis or subglottis) and stage at presentation. Tumors of the glottic region typically present with hoarseness, referred ear pain (otalgia), dysphagia, chronic cough, stridor (noisy breathing) and hemoptysis. Whereas supraglottic tumors typically present with pressure symptoms such as lump in the throat or throat pain and a neck mass from cervical metastasis. Due to the early presentation of hoarseness, glottic tumors are generally detected at an earlier stage than supraglottic tumors.[28, 61, 62] Subglottic carcinoma may present with stridor and dyspnea on exertion. However, there are few early symptoms and most subglottic cancers present at an advanced stage.[6] It is important to assess the patient's comorbidities, and functional status. Particular attention should be placed on the patient's respiratory function, as this must be considered when determining the options for treatment.

When a patient presents in the outpatient clinic with a suspected laryngeal tumor, the assessment includes clinical examination as well as fiberoptic laryngoscopy investigation. Complete head and neck examination is important for identifying second primary malignancies, assessing dentition, identifying lymphadenopathy and determining nutritional status. Fiberoptic laryngoscopic examination allows for evaluation of the dynamic function of the larynx, such as the patency of the airway, the mobility of the vocal cords. This allows for determination of the extent of the tumor and accurate staging. Videolaryngoscopy with stroboscopy may also be performed to obtain information of the function and vibrating properties of the affected vocal cord and as a result the depth of tumor invasion.

2.6.2 Examination under general anesthesia

After clinical examination, the patient is consented for a general anesthetic where the tumor can be biopsied and assessed in more detail. Direct laryngoscopy also allows for palpation of the tumor and laryngeal structures. During the general anesthesia biopsies are taken for confirmation of the cancer diagnosis. The biopsies are examined by a pathologist to confirm cancer diagnosis. During the anesthetic the pharynx, larynx, hypopharynx and esophagus are carefully examined to rule out secondary primary tumors as well to allow for a better assessment of the extent of the tumor.

2.6.3 Diagnostic Imaging

Imaging of laryngeal tumors is helpful in determining the extent of disease including revealing regional (cervical) and distant (lung and liver) metastatic disease, cartilage invasion and extension to the laryngeal spaces. Patients should undergo diagnostic structural imaging, a CT or an MRI with contrast to determine the presence or absence of cervical lymph nodes, distant metastatic disease, cartilage invasion, preepiglottic or paraglottic space invasion and extralaryngeal spread as part of their initial stating workup. Both a CT and MRI are appropriate initial imaging modalities for the neck. A CT is useful in the assessment of submucosal disease, extralaryngeal extension, as well as cervical metastasis. CT can be particularly helpful in the detection of cartilage invasion.[63] CT may however overestimate cartilage invasion leading to overstaging of laryngeal cancer.[64] An MRI is better suited for visualizing soft tissue, including spread

to preepiglottic and paraglottic space. Both CT and MRI have an 87-93% accuracy in staging the neck.[65]

The most common sites of distant metastasis for laryngeal cancer are the lungs followed by the liver. A screening CT chest should be done to screen for lung metastasis or synchronous primary lung lesions especially in smokers. Abdominal CT or liver ultrasonography can also be done if there is increased suspicion. A PET/CT is helpful in detecting subtle metabolically active lesions/nodes and has been shown to change cancer management in 18-31% of cases.[66]

2.6.4 Additional tests and consultations

All patients should undergo routine pretreatment laboratory tests to assess for signs of metastatic disease, thyroid function and nutritional status.[65] Assessment by a multidisciplinary team is important in caring for patients with laryngeal cancer. The multidisciplinary team should include head and neck surgery, medical oncology, radiation oncology, dentistry, speech pathology, nutrition and social work. Each member of the multidisciplinary team will address specific needs of patients diagnosed with laryngeal cancer.

2.7 Staging of Laryngeal Cancer

The eighth edition of the AJCC TNM staging protocol, is currently in use (Tables 2 and 3).[67] Laryngeal cancer is staged according to the tumor, node, metastasis (TNM) classification updated by the UICC and AJCC. Staging information is gathered from the

physical examination, endoscopic evaluation and imaging. Accurate staging is essential in planning and assessing the appropriate treatment modalities and requirement for adjuvant therapy.

Table 2 TNM Staging for Laryngeal Cancer (AJCC 8th edition)[67]

Tis	Carcinoma in situ
T1	Supraglottis: tumor limited to one subsite of supraglottis with normal cord mobility
	Glottis: T1a, tumor limited to one vocal cord T1b, tumor limited to both vocal cords with normal vocal cord mobility
	Subglottis: tumor limited to subglottis
T2	Supraglottis: tumor invades mucosa of more than one adjacent subsite of supraglottis subsite or glottis or region outside supraglottis (eg, mucosa of base of tongue, vallecula, medial wall of pyriform sinus) without fixation of the larynx
	Glottis: tumor extends to supraglottis and/or subglottis and/or with impaired cord mobility

	Subglottis: tumor extends to vocal cord(s) with normal or impaired cord mobility
T3	Supraglottis: tumor limited to larynx with cord fixation and/or invades any of the following: postcricoid area, preepiglottic space, paraglottic space, and/or inner cortex of thyroid cartilage
	Glottis: tumor limited to the larynx with vocal cord fixation and/or invasion of paraglottic space and/or inner cortex of thyroid cartilage
	Subglottis: tumor limited to larynx with vocal cord fixation and/or inner cortex of the thyroid cartilage
T4	T4a, Moderately advanced local disease: tumor invades through the cricoid or outer cortex of the thyroid cartilage and/or invades tissues beyond the larynx (eg, trachea, soft tissues of the neck including deep extrinsic muscle of the tongue, strap muscles, thyroid or esophagus)
	T4b, Very advanced disease: tumor invades prevertebral space, encases carotid artery, or invades mediastinal structures
N0	No regional lymph node metastasis
N1	Metastasis in a single ipsilateral node, 3cm or smaller in greatest dimension extranodal extension (ENE) (-)

N2	A, Metastasis in a single ipsilateral lymph node, larger than 3 cm but not larger than 6 cm in greatest dimension and ENE (-)
	B, Metastases in multiple ipsilateral lymph nodes, none larger than 6 cm in greatest dimension and ENE (-)
	C, Metastases in bilateral or contralateral lymph nodes, none larger than 6 cm in greatest dimension and ENE(-)
N3	A, Metastasis in a lymph node, larger than 6 cmn in greatest dimension and ENE(-)
	B, Metastasis in any lymph node(s) with clinically overt ENE(+)
M0	No distant metastasis
M1	Distant metastasis

Table 3 Prognostic Stage Groups for Laryngeal Cancer

Stage 0	Tis	N0	M0
Stage I	T1	N0	M0
Stage II	T2	N0	M0
Stage III	T3	N0	M0
	T1	N1	M0
	T2	N1	M0
	T3	N1	M0

Stage IVA	T1	N2	M0
	T2	N2	M0
	T3	N2	M0
	T4a	N0, N1, N2	M0
Stage IVB	Any T	N3	M0
	T4B	Any N	M0
Stage IVC	Any T	Any N	M1

Different from other malignant tumors, the TNM classification of laryngeal carcinoma includes a functional component, i.e. vocal cord mobility to differentiate between T1, T2 and T3 laryngeal carcinoma. Vocal cord mobility is determined by flexible nasopharyngoscopy. Contrary to other head and neck tumors, the size of the tumor is not important for tumour staging. Rather, the involvement of adjacent structures impacts the tumour stage. Early stage laryngeal cancers are T1/T2 N0 (Stage I and II) and are characterized by small tumors with limited functional impact and minimal extension. These tumors are generally thought to require single modality treatment in the form of surgery alone or radiation alone. Advanced stage cancers T3/T4N1-3 are characterized by large tumors with significant impact on breathing, swallowing and speech. These tumors require multimodality treatment in the form of either primary surgery followed by radiation or primary treatment with a combination of chemotherapy and radiation.

2.8 Treatment options for laryngeal cancer

Treatment of laryngeal cancer depends on extent of the disease, baseline function of the patients, and the goal of preserving the patients' speech and swallowing function. Generally, monotherapy with surgery or radiation (RT) is preferred for early stage tumors (Stage 1 and 2). With increasing tumor size, chemoradiotherapy (CRT) or radical surgery (laryngectomy-removal of the larynx) combined with postoperative RT or CRT may be recommended. Together, RT or CRT are termed "laryngeal preservation" protocols.

Stage at presentation primarily determines the management of laryngeal cancer. In addition, a variety of other factors are also influence the decision-making including the patient's age, comorbidities, surgical access issues, the preferences of the treating multidisciplinary team and importantly, the desires of the patient.

For Stage 1 and 2 cancers, the options for treatment include radiotherapy or transoral laser microsurgery (TLM). For a small number of patients there is the option of open partial laryngeal surgery. This is now undertaken infrequently following the introduction of TLM. It should be noted that there have been no randomized trials comparing the efficacy of the two main treatment modalities, radiotherapy and TLM. However, several cohort studies demonstrate similar cure rates for early stage laryngeal cancer with the two treatment modalities.[68-70]

The main options for the treatment of advanced laryngeal cancer currently are total laryngectomy or chemoradiotherapy. Other options used less commonly include partial open laryngectomy, near total laryngectomy and TLM (for select cases only).

2.8.1 Radiotherapy for Laryngeal Cancer

Radiotherapy or chemoradiotherapy can yield comparable results with surgery in the treatment of subglottic carcinoma. Early-stage cases can be treated with radiation fields directed at the larynx with a 1 to 2 cm margin. Radiation fields for advanced-stage cases usually include the larynx, bilateral cervical, supraclavicular and upper mediastinal lymph nodes. Total dose ranges between 50 and 75 Gy.[71]

The main advantage of radiotherapy is that it can be administered to patients who are poor surgical candidates. Radiotherapy is also thought to have better voice outcomes. This hypothesis is based on the principle that the laryngeal structures are being “preserved”. This does not apply, however, if the laryngeal structures have already been destroyed by the malignant process. In addition, radiotherapy is a radical treatment so it can have a deleterious effect on the laryngeal structures especially in the long-term. To date, definitive comparison of voice outcomes between the two treatment methods has not been performed. However, an observational study has shown that quality of life outcomes for the two modalities appear to be similar.[72] Radiation is considered appropriate in treating T1, T2 and small T3 tumors.

Adjuvant radiation is considered postoperatively for advanced laryngeal cancer, positive or close surgical margins after surgical resection, positive node metastases, and perineural or lymphovascular invasion. Radiotherapy is ideally started within 6 weeks of surgery. Radiation can sometimes be used for palliative treatment of unresectable cancers.

Chemoradiation organ preservation strategies are used for advanced stage laryngeal cancer and have demonstrated that some larynges can be saved without compromising overall survival. In 1991, the Department of Veterans Affairs Laryngeal Cancer Study Group investigated whether induction chemotherapy and definitive radiation therapy with total laryngectomy (TL) reserved for salvage represented a better initial treatment approach for patients with advanced laryngeal cancer than TL with post-operative radiation therapy.[73] The conclusion was that induction chemotherapy and definitive radiation therapy can be effective in preserving the larynx in a high percentage of patients without compromising overall survival.[73]

In 2003, a randomized trial RTOG-9111 was published on concurrent chemoradiotherapy for laryngeal preservation.[74] This trial was updated at the 2006 American Society of Clinical Oncology annual meeting, and the findings confirmed the previous results: the 5-year laryngeal preservation rate was significantly better with concurrent chemoradiotherapy (83.6%) compared with induction chemotherapy (70.5%) or radiotherapy (RT) along (65.7%), without differences recorded in overall or disease-free survival.[75]

In addition, results of the “Meta-Analysis of Chemotherapy in Head and Neck Cancer” showed that concurrent chemoradiotherapy results in a significant 8% benefit in 5-year survival compared with RT alone, whereas adjuvant and induction chemotherapy did not improved survival.[76] Consequently, concurrent chemoradiotherapy appeared to be the most reasonable approach to preserve the larynx in patients with advanced laryngeal cancer. The current standard of care is definitive chemoradiation for stage III or IV disease to allow for potential organ preservation. Total laryngectomy is still indicated for salvage therapy (after radiation if there is persistent disease) and in advanced T4 lesions, including those with significant tongue base invasion or destruction of cartilage.[74, 75]

Concurrent chemoradiotherapy is however associated with significant acute and late toxicities because of its radiosensitization effects such as severe mucositis that may prevent oral feeding, leading to significant weight loss and often requiring a break in the radiation treatment.[77] In addition, radiation produces profound hypofunction of salivary gland tissue with consequent xerostomia, a major cause of distress. Furthermore, TL after failure of concurrent chemoradiation therapy is associated with high complication rates because of wound healing difficulties.[78]

Laryngeal preservation in the form of treatment with concurrent chemoradiation is an attractive option for patients who prefer not to have their larynx removed. However, the concept of organ preservation is not clearly defined. There has been little research into

what constitutes a preserved larynx. From an oncological perspective, the presence of a larynx that is free of oncologic disease is considered a preserved larynx. It has been suggested that organ preservation should include more than the presence of the organ in situ, but also an organ with useful function. Therapeutic radiation with concurrent chemotherapy can have not only acute but also chronic effects on the larynx and pharynx including: chondronecrosis resulting in an insensate larynx that does not protect the airway and causes chronic pain and inflammation; dysfunctional pharyngeal constrictors and muscle fibrosis resulting in impaired swallowing; narrowed airway resulting in shortness of breath; and chronic aspiration from post-radiation edema. Some considerations to assess whether a larynx is preserved and functional include whether the patient's voice is audible and clear, whether the patient can swallow all consistencies of food safely without signs of symptoms of aspiration, whether the patient has preserved lung function and is devoid of dyspnea at rest and on exertion, and whether the patient is pain free. As such, an assessment of end organ function once the patient is determined to be disease free would be appropriate. This can be achieved by using patient centered questionnaires, that address voice, swallowing, and quality of life. Laryngeal function has been poorly defined to date and is an active area of research.

2.8.2 Surgery for laryngeal cancer

Surgical approaches in treating laryngeal cancer range from microlaryngeal approaches to total laryngectomy. Treatment must consider the best approach for resecting the tumor while maximizing laryngeal function. The term “conservation laryngeal surgery” is

used to describe procedures that attempt to preserve speech and swallow through partial organ preservation. Patients can be considered for conservation laryngeal surgery if one functional cricoarytenoid joint and one laryngeal valve (epiglottic, false vocal cord or true vocal cord) can be reserved. Surgical approaches can further be divided into closed endoscopic and open procedures.

2.8.2.1 Transoral laser microsurgery

Transoral laser microsurgery (TLM) is one form of closed endoscopic surgery. This technique was first introduced in the 1970s and has been consistently evaluated for its oncologic effectiveness and functional outcomes with excellent results into the modern era.[79-81] This approach is often used in early-stage disease and has the benefit of reduced morbidity compared to open surgical management or nonsurgical strategies.[79] The tumor is resected using a laser (often carbon dioxide) coupled to an operating microscope. This is used in the treatment of T1, T2, and select T3 tumors. Contraindications include inadequate transoral access because of the patient's anatomy, including prominent teeth, trismus, large tongue and narrow mandibular arch. Further, the tumor cannot involve bilateral arytenoids nor have subglottic extension greater than 1cm. Advantages of transoral laser microsurgery (TLM) to open approaches include reduced patient morbidity, faster recovery, preservation of laryngeal function, and the possibility of avoiding tracheostomy. The TLM technique has challenged the traditional principle of en bloc resection, and when applied appropriately, offers equivalent oncologic outcomes regardless of whether the tumor is sectioned or removed en bloc.[80, 82, 83] Some authors have reported improved outcomes when

compared to radiotherapy for early laryngeal malignancy.[84] The importance of negative surgical margins cannot be overstated in order to achieve these outcomes.

For endolaryngeal surgery, advantages include treatment in a single sitting, minimal absence from employment, certainty of removal of the specimen and the ability to assess margins surgically. Importantly, it also allows further laryngeal surgery or radiotherapy in case of recurrence. The disadvantage of transoral laser surgery is that it can affect the voice quality and access is sometimes difficult. It also requires a general anesthetic and may need repeated operations for which patients may not be fit.

2.8.2.2 Transoral robotic surgery

Transoral robotic surgery (TORS) for the treatment of laryngeal cancer is a developing field. TORS has been most frequently applied in cancers of the oropharynx but it is now included as a method of closed endoscopic laryngeal surgery. TORS use in laryngeal cancers, particularly of the supraglottis, has been explored and it has favorable preliminary results.[85] Advancements in robotic technology, instrumentation and improvement in protocol must be made before TORS is used in routine treatment of laryngeal cancers.[86] Currently, TLM is usually superior to TORS for glottic cancer because of the improved access and superior cost profile.[87]

2.8.2.3 Vertical Hemilaryngectomy

This approach is used in the treatment of select T1, T2, T3 and rarely T4 glottic cancers. The involved vocal cord and a portion of the thyroid cartilage are removed en

bloc. Contraindications include fixed true cord, posterior commissures or interarytenoid involvement, cricoid cartilage involvement, and extralaryngeal spread. Variations on this approach include the frontolateral and posterolateral vertical hemilaryngectomy. Frontolateral vertical hemilaryngectomy can be used to treat lesions involving the anterior commissure and can involve up to one-third of the contralateral vocal cord. Posterolateral vertical hemilaryngectomy can be used for lesions that involve the unfixed ipsilateral arytenoid. Studies have found 83.1% for T1 and 67.2% for T2 5-year survival with this surgical approach.[88]

While reported control rates after open partial laryngeal surgery for small tumors are probably as good as the other modalities, there is only a very limited role for open partial surgery for T1 and small T2 tumors. This is because the approach carries more morbidity with poorer outcomes than TLM or TORS. Its only role is for a patient whose access transorally is not possible, and who has refused radiotherapy. In addition, there may also be a limited role in low volume recurrences following radiotherapy.[89]

2.8.2.4 Supraglottic laryngectomy

Supraglottic laryngectomy can be considered in T1, T2 and T3 supraglottic tumors. This procedure involves removal of the structures superior to the true vocal cords. Surgical resection leaves a portion of the thyroid cartilage and both arytenoid cartilages. The patients must have bilateral vocal cord mobility, lack of cartilage involvement, limited base of tongue involvement, no pyriform sinus involvement, and good pulmonary reserve. Many patients will have some degree of aspiration immediately after the procedure; therefore, good baseline lung function is critical.

2.8.2.5 Supracricoid partial laryngectomy

Select T2, T3 and T4 glottic and transglottic cancers are candidate for a supracricoid laryngectomy. This procedure includes the same resection of supraglottic laryngectomy with the addition of the true vocal cords and entire thyroid cartilage. The cricoid cartilage, hyoid bone and at least one arytenoid are preserved. This procedure is adequate in treating tumors that extend to the preepiglottic and paraglottic space. The remaining surgical defect is reconstructed using a cricohyoidopexy (if the epiglottis is removed) or cricohyoidoepiglottopexy (if the epiglottis is preserved). Again, pulmonary function is important as with supracricoid laryngectomy. One recent study showed a 5 year local control rate of 94%.[90] This technique can also be used in the salvage setting with success in appropriately selected patients.[91]

2.8.2.6 Near Total laryngectomy

Near total laryngectomies are done in select large T3 and T4 lesions that are not candidates for the above-mentioned procedures. One hemilarynx and the anterior portion of the contralateral cord are resected. The ipsilateral cricoid and the proximal trachea can be removed. Unlike the previously mentioned procedures, a permanent tracheostomy is needed. Contraindications include tumor involvement of the interarytenoid and postcricoid and inability to preserved two-thirds of the contralateral vocal cord. Studies have found that disease control rates were comparable in near total laryngectomy compared to total laryngectomy/laryngopharyngectomy.[92] This procedure is not routinely performed.

2.8.2.7 Total laryngectomy

Total laryngectomy involves complete removal of the larynx. It was first successfully performed by Theodor Billroth in 1873.[93] The procedure removes the larynx, hyoid bone, thyroid cartilage, cricoid cartilage and proximal traches. A portion of the pharynx and base of tongue may also be resected. There is mobilization of the trachea and once the trachea is entered it is sutured to the skin, completely separating the trachea from the pharynx. The pharyngeal mucosa is closed using a running suture. Primary total laryngectomy is indicated in advanced disease that is not amenable to partial laryngectomy, concurrent chemoradiation or radiotherapy alone. Specifically, tumors that have penetrated through cartilage, invasion into the extralaryngeal soft tissue of the neck and extensive involvement of the base of tongue are suitable indications for this procedure. Also, pulmonary status and medical comorbidities and cognitive function may define the treatment options for a given patient. Total laryngectomy is an effective treatment for advanced cancers but has an overall recurrence rate of 37% in stage II and IV glottis tumors.[94] Swallowing, with appropriate reconstruction is usually excellent and a primary or secondary tracheoesophageal puncture for voice rehabilitation should be considered in patients undergoing total laryngectomy.

Salvage total laryngectomy (TL) is indicated for chemoradiation, radiation, or partial laryngeal surgical failures. Salvage TL can be technically more difficult and caries a higher postoperative complication rate but has produced favorable outcomes in several studies.

2.8.3 Treatment outcomes

There is debate whether laryngeal cancer is best treated with radiation, chemoradiation or primary surgery. Options for treatment are largely determined by the stage of the disease, but many times there are multiple acceptable standard-of-care treatments for the same cancer. Single modality treatment with surgery or radiation is considered acceptable primary treatment for early glottic or supraglottic cancers. The modality of therapy selected is largely determined by the surgical and radiation experience of the treating physicians and considering the functional impact of the treatment. The goal is always to minimize morbidity of treatment and the number of treatment modalities used) and maximize therapeutic outcomes. When surgery is thought to leave good voice and swallowing function, such as in selected glottis and supraglottic tumors, surgery is limited and the likelihood of adjuvant chemoradiotherapy is low (triple modality therapy). Surgery has the benefit of pathologically staging the neck, assessing the primary tumor and neck for negative features (perineural invasion, lymphovascular invasion and extracapsular extension) and potentially being a shorter and more cost-effective treatment option.[95, 96] However, when the likelihood of triple modality therapy or loss of function are high, nonsurgical modalities are preferred when oncologic outcomes are not compromised.

2.9 Laryngeal Cancer Prognosis and Outcomes

The primary objectives of laryngeal cancer treatment are cure, long-term survival and the preservation of a functional larynx. This has led to a variety of definitions of laryngeal cancer outcomes.

2.9.1 Overall Survival for Laryngeal Cancer

Overall survival is defined as the rate at which patients with laryngeal cancer survive from all causes. Mortality events are due to deaths from cancer and other causes.

2.9.2 Disease-specific survival of laryngeal cancer

Disease-specific survival of laryngeal cancer is defined as the rate of survival from laryngeal cancer. Deaths are from laryngeal cancer treatment related complications, primary cancer progression or cancer recurrence. Other deaths are commonly treated as a censored event.

2.9.3 Laryngectomy-free survival of laryngeal cancer

Laryngectomy-free survival is defined as the number of patients with laryngeal cancer who survive with an intact larynx. This can be defined as the number of surviving patients who have not undergone a laryngectomy.

2.9.4 Laryngo-esophageal dysfunction-free Survival

Complications following laryngeal preservation protocols can include aspiration, hoarseness, aphonia and stridor. Over time that larynx can become non-

functional and some patients require a tracheostomy for pulmonary toilet (suctioning of secretions from the lungs) and airway protection. Laryngectomy for an incompetent larynx is required in some situations even in the absence of cancer. Furthermore, complications from a pharyngeal and esophageal perspective can result in failure to achieve esophageal speech or speech with tracheoesophageal prosthesis. Esophageal stenosis resulting in gastrostomy (feeding) tube dependence can also occur. Although laryngeal preservation is an important component of quality of life, even though the larynx may be present it is not necessarily functional following radiotherapy +/- chemotherapy. This has led experts in the area to propose the outcomes of laryngo-esophageal dysfunction-free survival. Events for this outcome would include death, local relapse, totally laryngectomy, tracheostomy at >= 2 years or feeding tube at >= 2 years.[97]

2.10 Surveillance for Recurrence of Laryngeal Cancer

Close follow-up is needed for patients with laryngeal cancer. Traditional tenets of surveillance of laryngeal cancer center on clinical symptoms, office-based or operative laryngoscopy and biopsy and imaging studies such as CT or MRI. Although the timing of surveillance is not standardized across centers, clinic visit intervals are often every 2-3 months during the first 2 years and 6-8 months during years 3-5. Current National Comprehensive Cancer Network Guidelines recommend baseline posttreatment imaging of the primary within 6 months followed by further reimaging as indicated based on signs and symptoms.[98] Most recurrences occur in the first 2 years after treatment.

Patients without evidence of disease 5 years after treatment can be examined annually or more frequently if significant risk factors such as tobacco abuse are present.

CHAPTER THREE: LITERATURE REVIEW OF SUBGLOTTIC CANCER

3. 1 Introduction to Subglottic cancer

Subglottic carcinoma is a rare variant of laryngeal cancer. It is traditionally thought that subglottic carcinoma has a worse prognosis than tumors arising in other subsites of the larynx (supraglottis and glottis), owing to its tendency to present in advanced stages, with a high incidence of cartilage invasion and extralaryngeal spread. The incidence of subglottic carcinoma varies among series, mainly because there is no uniform definition of the upper boundary of the subglottis. The extent of the tumor may be difficult to define because subglottic carcinoma may spread through the submucosa without visible mucosal changes. There is also a rich lymphatic network in the subglottis draining to the prelaryngeal and paratracheal lymph nodes, which are usually not involved by cancers arising in other laryngeal subsites. Current literature indicates that early stage subglottic carcinoma can be treated using radiotherapy or chemoradiotherapy with high locoregional control and survival rates. In advanced stage subglottic carcinoma, a combination of surgery followed by radiotherapy or chemoradiotherapy likely results in comparable outcomes as in advanced carcinoma from the rest of the larynx. We performed a scoping literature review to determine the following:

a) Anatomic boundaries and definition of the subglottic larynx

b) Incidence and epidemiology of subglottic carcinoma

c) Stage presentation of subglottic carcinoma

d) Treatment regimens for subglottic carcinoma

e) Survival outcomes including locoregional control, disease specific survival, overall survival, and laryngectomy free survival.

f) Propensity for stomal recurrence

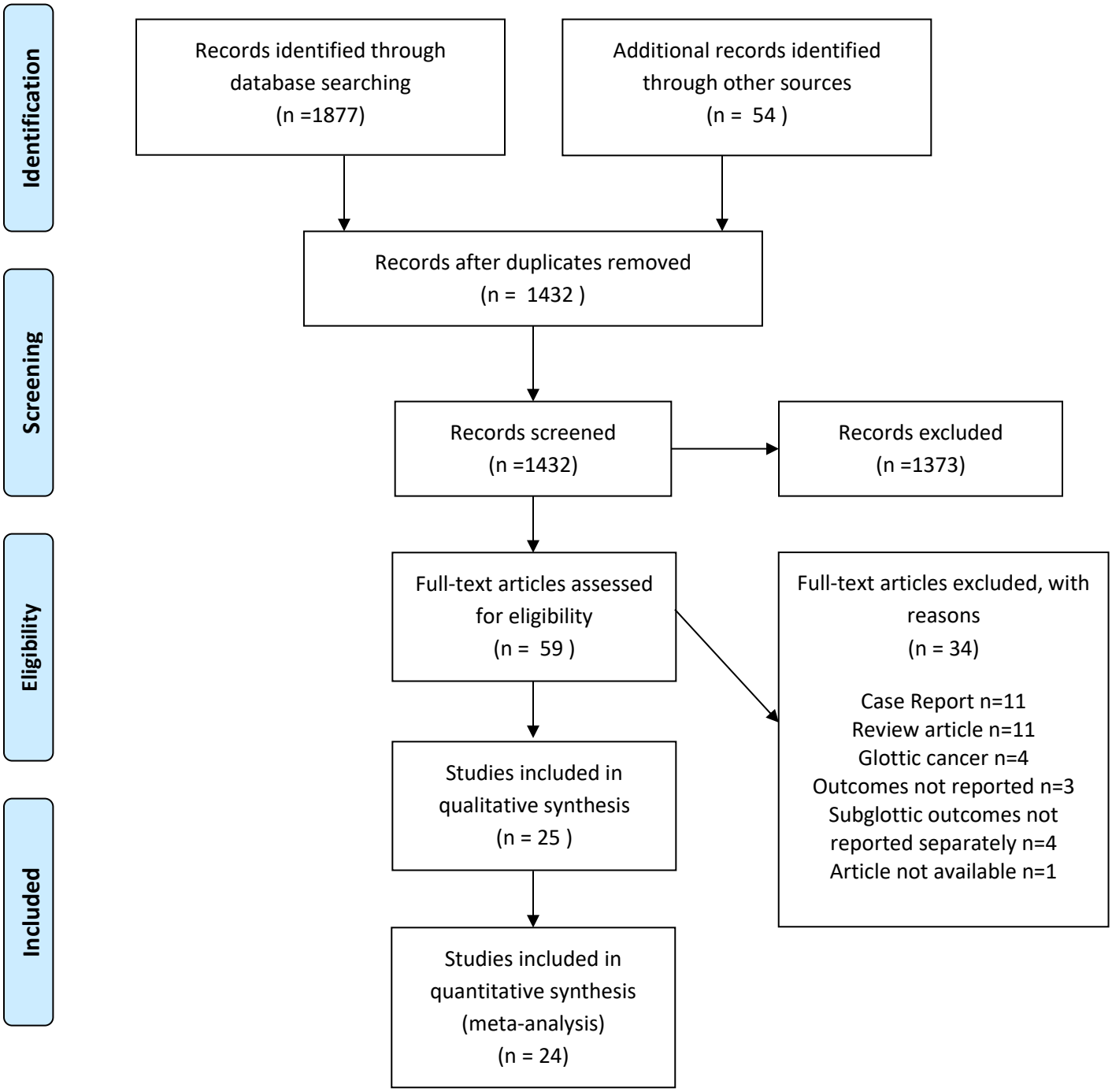
g) Quality of life outcomes

3.2 Literature Search Strategy

We performed a literature search to retrieve all articles on subglottic cancer. We included all single arm and comparative studies which reported on the incidence and outcomes of patients with subglottic cancer. The literature search performed on September 1, 2020 and retrieved 1244 citations. Randomized controlled trials, observational studies, case series and case reports (more than 3 patients) were included. The study population was limited to patients diagnosed with squamous cell carcinoma of the subglottis, excluding other histologies. We excluded non-English articles. We excluded patients with primary glottic cancer with subglottic extension. All treatment interventions were included. We reported on the incidence of subglottic carcinoma, the treatment modalities used and survival outcomes including: overall survival; disease-specific survival; locoregional control; and larynx preservation.

The search strategy is outlined in Appendix A. From the MEDLINE search we retrieved 940 titles, from EMBASE 618 titles and from CINAHL 319 titles. The reference lists of all included articles were also reviewed. Once we removed duplicates the number of titles were 1432 titles. The full papers of 59 studies were reviewed. The PRISMA flow diagram is outlines in figure 1.

Figure 1 Prisma Flow Diagram



Excluded articles and reasons for exclusion are listed in table 4. Included articles are listed in table 5.

Table 4 Excluded articles and reasons for exclusion

Author (year)	Title	Reason for Exclusion
Berger G (1985)[99]	Primary subglottic carcinoma masquerading clinically as T1 glottic carcinoma--a report of nine cases.	Glottic Cancer
Bryce DP (1975)[9]	The laryngeal subglottis.	Review article
Calem WS (1961)[100]	Subglottic carcinoma with extensive tracheal involvement.	Case Report
Chiesa F (2001)[101]	Surgical treatment of laryngeal carcinoma with subglottis involvement	Glottic Cancer
Coskun H (2018)[102]	Prognosis of subglottic carcinoma: Is it really worse?	Review article
De Souza RP (2007)[103]	Value of computed tomography for evaluating the subglottis in laryngeal and hypopharyngeal squamous cell carcinoma	Outcomes not reported
Delaere P (2007)[104]	Organ preservation surgery for advanced unilateral glottis and subglottic cancer	Glottic cancer and non-epidermoid histology
Dogan E (2014)[105]	Elective superior mediastinal dissection for laryngeal carcinoma involving subglottis	Subglottic outcomes not reported separately

Ferlito A (2000)[106]	The pathology and management of subglottic cancer	Review article
Flynn JM (1964)[107]	Subglottic carcinoma of the larynx	Case Report
Gorphe P (2016)[108]	Laryngo-esophageal Dysfunction-free Survival in a Preservation Protocol for T3 Laryngeal Squamous-cell Carcinoma	Subglottic outcomes not reported separately
Hamauchi S (2020)[109]	Chemoradiotherapy for high-risk stage II laryngeal cancer	Glottic cancer
Hanna EY (1994)[110]	Subglottic cancer.	Case Report
Harris HH (1968)[111]	Surgical limits in cancer of the subglottic larynx	Review article
Harrison DF (1971)[7]	The pathology and management of subglottic cancer	Review article
Harrison DF (1975)[112]	Laryngectomy for Subglottic Lesions	Outcomes not reported
Huang YC (1993)[113]	The management of advanced subglottic carcinoma with stomal invasion	Case report
Jones RD (1991)[114]	An iridium-192 applicator for the treatment of stomal recurrence following tracheostomy for subglottic carcinoma	Case report
Joseph ST (2018)[115]	Endoscope-assisted conservative resection and reconstruction in recurrent subglottic carcinoma	Case report
Kennedy KS (1992)[116]	Subglottic and tracheal malignancies	Review article
Lassaletta L (1998)[117]	Synchronous glottis glandular cell tumor and subglottic spindle cell carcinoma	Case report
Liang J (2020)[118]	Which risk factors are associated with stomal recurrence after total laryngectomy for laryngeal cancer? A meta-analysis of the last 30 years	Review article

Lucioni M (2018)[119]	Management of paratracheal lymph nodes in laryngeal cancer with subglottic involvement	Subglottic outcomes not reported separately
Lund WS (1974)[120]	Classification of subglottic tumors and discussion of their growth and spread	Review article
Nhembe F (2010)[121]	Subglottic carcinoma treated with surgery and adjuvant photodynamic therapy	Case report
Porter GC (1999)[122]	Submucosal squamous cell carcinoma of the subglottis	Case report
Saleh EM (1992)[23]	Computed tomography of primary subglottic cancer: clinical importance of typical spread	Outcomes not reported
Sessions DG (1975)[123]	Laryngeal carcinoma involving anterior commissure and subglottis.	Review article
Stell (1975) [124]	The behaviour of cancer affecting the subglottic space	Article not available
Succo G (2017)	Supratracheal partial laryngectomy: indications, oncologic and functional results	Subglottic outcomes not reported separately
Vermund H (1970)[4]	Role of radiotherapy in Cancer of the larynx as related to the TNM system of staging	Review article
Wakisaka M (2003)[125]	A case of subglottic carcinoma effectively treated with intraluminal irradiation using low dose rate iridium-192	Case report
Wang ZY (2017)[126]	Influence of risk factors on stomal recurrence after total laryngectomy for laryngeal carcinomas: A meta-analysis	Review article
Yamasaki T (2016)[127]	Use of a videolaryngoscope with a tube guide for metal stent placement to subglottic tracheal tumor	Case report

Table 5 Articles included in literature review and patient characteristics

Included Study	Type of Study	Subglottis Definition (upper border)	Treatment[a]		Year of Treatment	Stage		Histology	Mean Age, years	Gender	Median Follow-Up Time, years
			Surgery	RT		I/II	III/IV			Male/ Female	
Cassidy R (2012)[128][b]	Single centre Retrospective Review	1cm below cords	0	18	1977-2009	7	12	All SCC	NR	NR	NR
Dahm JD (1998)[129][c]	Single centre Retrospective Review	5mm below cords	15	12	1955-1988	19	9	All SCC	62.9	23/5	5
Gairola A (1992)[130]	Single centre Retrospective Review	5mm below cords	6	2	1981-1190	1	7	7/8 cases SCC	49.8	6/2	1.5
Garas J (2006)[131]	Single centre Retrospective Review	5mm below cords	9	6	1976-2001	3	12	All SCC	22-74	13/2	3
Guedea F (1991)[20]	Single centre Retrospective Review	NR	0	6	1964-1985	3	3	All SCC	64.8	NR	3
Hata M (2013)[71]	Single centre Retrospective Review	Tumor primarily in subglottis	0	19	1993-2010	9	19	All SCC	68	18/1	5
Haylock BJ (1993)[15]	Single centre Retrospective Review	5mm below cords	0	23	1976-1990	13	10	NR	67	12/11	5
Hill-Madsen L (2019)[10]	Danish Cancer Registry	5mm below cords	12	134	1971-2015	70	75	All SCC	66	123/23	10
Jumaily M (2020)[11]	NCDB Database	NR	205	344	2004-2014	219	330	All SCC	62	459/90	2.8
Komatsubara Y (2020)[132]	Single centre Retrospective Review	NR	2	9	1995-2019	9	2	All SCC	69	11/0	5
Lee KC (2020)[133]	SEER database	NR	0	37	2005-2015	37	0	All SCC	67	NR	5
Marchiano E (2016)[18][d]	SEER database	NR	456	277	1973-2011	126	219	All SCC	65.7	705/184	5
Nahavandipour A (2019)[134]	Danish Cancer Registry	5 mm below cords	142		1980-2014	NR		NR	60	NR	20
Paisley S (2001)[12]	Single centre Retrospective Review	5mm below cords	0	43	1971-1996	23	20	NR	68.8	35/8	4.2
Santoro R (2000)[135]	Single centre Retrospective Review	5mm below cords	35	6	1969-1993	17	32	NR	69	49/0	5
Sessions DG (1975)[1][e]	Single centre Retrospective Review	5mm below cords	3	0	NR	1	2	5 SCC	NR	NR	3
Shaha AR (1982)[2]	Single centre Retrospective Review	5mm below cords	16	0	1956-1980	3	13	NR	60	13/3	5
Smee RI (2008)[6]	Single centre Retrospective Review	NR	6	4	1967-2003	6	4	All SCC	69.2	8/2	2

Strome SE (1999)[19]	Single centre Retrospective Review	1cm below ventricle	2	8	1964-1994	5	4	All SCC	NR	5/5	5
Su WF (2003)[136]	Single centre Retrospective Review	NR	2	3	1991-2002	3	2	All SCC	59	4/1	2.5
Vlckova (2019)[137]	Single centre Retrospective Review	NR	1	3	2009-2013	4	0	NR	NR	NR	0.5
Warde P (1987)[138]	Single centre Retrospective Review	Below true vocal cords	0	23	1971-1982	9	14	All SCC	64	19/4	4
Weiss B (2018)	Single centre Retrospective review	NR	13	0	1986-2018	4	9	NR	NR	NR	5
Yu H (2019)[17]	Single centre Retrospective Review	Subglottic tumor	21	0	2005-2010	12	9	20/21	63	19/2	5
Zhu F (2019)[b]	NCDB	NR		249	2004-2014	249	0	NR	69	NR	3.1

NR Not Reported
NCDB National Cancer Database
SCC Squamous Cell Carcinoma
[a] Treatment was defined as primary treatment. Numbers do not add up to total number of patients in each study as some patients declined treatment.
[b] Abstract only
[c] 1patient no treatment (denied by patient)
[d] Stage unknown in 30 patients. Staging was only available from 2004 and onward.
[e] 2 patients did not receive treatment

We assessed the methodologic quality using the New-Castle Ottawa scale (Appendix B) for cohort studies, where a higher score reflects better methodology. The study quality of most studies was poor (Table 6), with only 9 studies with a score of 6 or more. A large number of studies lost points for the category "comparability" as they did not account for confounding factors that impacted survival such as stage, age and patient comorbidity.

Table 6 Assessment of methodologic quality of included articles using the Newcastle-Ottawa Scale

Study	Selection	Comparability	Outcome	Total Score

Cassidy R (2013)[128]	3	0	1	3
Dahm JD (1998)[129]	3	1	3	6
Gairola A (1992)[130]	1	0	1	2
Garas J (2006)[131]	3	0	2	4
Guedea F (1991)[20]	3	0	3	5
Hata M (2013)[71]	2	0	2	5
Haylock BJ (1993)[15]	2	0	2	4
Hill-Madsen (2019)	3	2	3	8
Jumaily M (2020)[11]	3	2	3	8
Komatsubara Y (2020)[132]	2	0	1	3
Lee KC (2020)	4	2	3	9
Marchiano E (2016)	4	2	3	9
Nahavandipour A (2019)[134]	4	1	3	8
Paisley S (2001)[12]	3	0	3	6
Santoro R (2000)[135]	4	2	2	8
Sessions DG (1975)[1]	3	1	1	5
Shaha AR (1982)[2]	4	0	3	7
Smee RI (2008)[6]	4	0	3	7

Strome SE (1999)[19]	4	0	2	6
Su WF (2003)[136]	4	0	2	6
Vlckova K (2019)[137]	1	1	2	4
Warde P (1987)[138]	3	0	3	5
Weiss B (2018)[3]	1	0	3	3
Yu H (2019)	2	1	3	6
Zhu F (2019)[139]	4	2	3	9

3.3 Anatomic boundaries and definition of the subglottic larynx

The subglottic larynx is located between the vocal folds and the trachea. Despite this simple definition, the anatomic boundaries of the subglottis are controversial. The laryngeal ventricle clearly separates the supraglottic and glottis regions, whereas the glottis and subglottic regions are fused with no visible boundary, because they have a common embryological origin. There is general agreement that the inferior border of the subglottis is the inferior border of cricoid cartilage but there is no agreement about the superior border, which is considered to be an imaginary line passing 5mm below the free margins of the vocal folds by some authors[16] and from 0 to 1 cm below the vocal folds by others.[24] It may also be defined as 1 cm below the apex of the laryngeal ventricle.

Ferlito and Rinaldo (2000) published a review of subglottic carcinoma in 2000 and they reported the many different definitions of the upper border of the subglottis according to various authors.[24] Today, there is still no clear definition of the superior border, which

makes our understanding of the nature of subglottic carcinoma difficult and reporting data regarding subglottic carcinoma inconsistent.

As demonstrated in our review (Table 5), 13 studies did not specify the boundaries of the subglottis, with some authors either not reporting a definition or simply stating that the tumor was "primarily in the subglottis". The majority of the papers reported the superior border of the subglottis as starting 5mm below the level of the cords while 2 papers reported the superior border as 1 cm below the level of the ventricle.

This variable definition in the superior border of the subglottis may result in some cancers that are in fact glottic cancers being misclassified as subglottic cancers (misclassification bias). As described below, glottic cancer may have improved survival compared to subglottic carcinoma therefore, this misclassification of subglottic tumors may impact the survival outcomes reported in our review. In the future, explicitly defining the boundaries of the subglottis and excluding those glottic cancers that exhibit subglottic extension will allow for a more accurate estimate of survival outcomes.

3.4 Epidemiology of Subglottic Carcinoma

Cancer arising from the subglottic larynx is rare, ranging from 0-8.7% of all laryngeal cancers (Table 7). We performed a pooled analysis of the proportion of subglottic carcinoma amongst all laryngeal cancers and found the proportion of subglottic carcinoma to be 2.1% (95% CI 1.4-3.0%) (Figure 2). As described above the difference in reported proportion may relate to the different criteria adopted for the definition of

subglottic cancer (Table 5). The rarity of primary subglottic cancer has been attributed to decreased mucosal trapping in the upper airway and a consequent minimal contact with potential carcinogens.[24] Whereas, the glottis and supraglottis have direct contact with potential inhaled carcinogens, the subglottic mucosal is partially protected from exposure by the vocal cords which overhang the subglottic mucosa. This theory, however, has not been demonstrated in animal or human studies.

Table 7 Published studies reporting the proportion of those with laryngeal cancer where the primary location was subglottic

Author (Year)	No of laryngeal cancers	No of subglottic cancers	Proportion (%)	Remarks
Bittesini (1991)[140]	650	2	0.3	These tumors included adenoid cystic carcinomas
Dahm (1998)[13]	2201	39	1.8	In this series 28 tumors (71.8%) were squamous cell carcinomas and 4 (10.3%) were chondrosarcomas. The other tumors included sarcoma (n=2), small cell carcinoma (n=2), adenoid cystic carcinoma, lymphoma and undifferentiated carcinoma
Garas (2006)	1098	15	1.37	All squamous cell carcinoma, tumors originating in the glottis with subglottic extension excluded
Hata (2013)[71]	319	19	6.0	All squamous cell carcinoma
Haylock (1993)	263	23	8.7	Some patients may have had glottic cancer with subglottic extension given high incidence of hoarseness on presentation

Komatsubara (2020)	280	11	3.9	All squamous cell carcinoma
Kleinsasser (1991)[141]	~2000	0	0	Other malignant tumors were not considered
Lederman (1970)[142]	2035	140	6.9	Tumors were included that originated from the undersurface of the vocal cord which would now be classified as glottic cancers using TNM staging
Lee KC (2020)	3221	37	1.15	Only early stage T1/T2N0 laryngeal cancer treated with radiation were included
MacNeil (2015)[36]	4927	89	1.81	Administrative data so coding errors may have been present.
Nahavandipour (2019)	8748	142	1.62	Administrative data so coding errors may have been present. Tumors in addition to squamous cell carcinoma were included
Paisley (2002)[12]	2908	55	1.9	All tumors were squamous cell carcinomas
Santoro (2000)	3000	49	1.6	Other malignant tumors included
Shaha (1982)[2]	2180	22	1.01	All tumors were squamous cell carcinomas
Silvestri (1992)[143]	455	1	0.2	The tumor was a squamous cell carcinoma
Stell (1975)[124]	1011	42	4.1	Tumors also originated from the undersurface of the vocal cords and would now be classified as glottic cancers using TNM staging
Su (2003)	96	5	5.2	All squamous cell carcinoma

Yu (2019)[17]	1815	23	1.3	Tumors in addition to squamous cell carcinoma were included

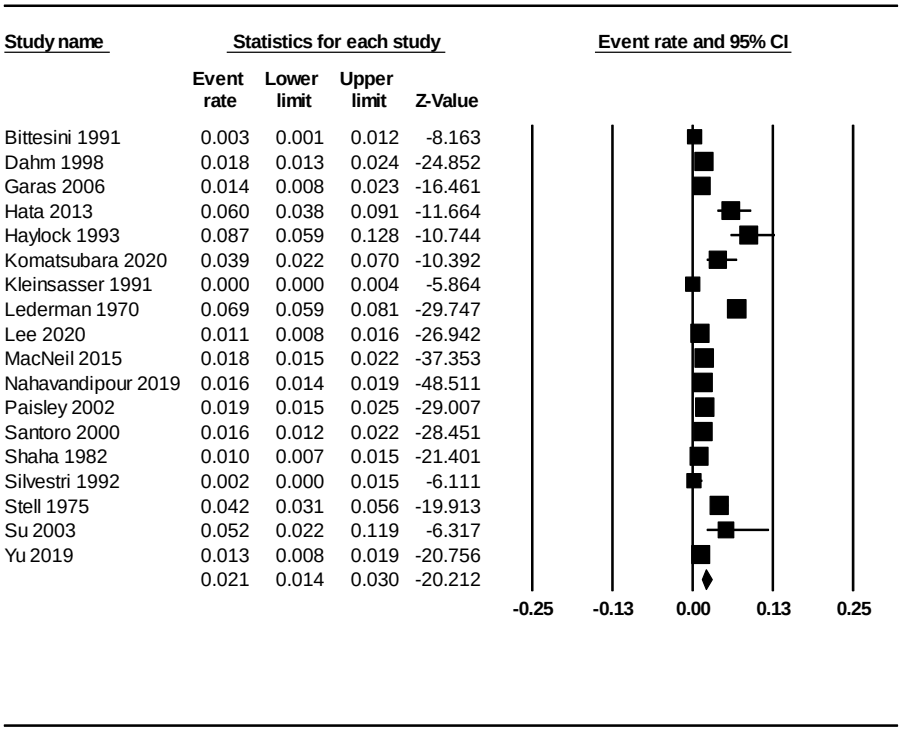


Figure 2. Forest Plot of the proportion of those with laryngeal cancer where the primary location was subglottic

For several reasons, it is difficult to establish the true proportion of subglottic carcinoma. First, as previously mentioned, there is no uniform definition of the upper border of the subglottic region. Second, in some reports, subglottic carcinoma and glottic carcinomas with subglottic extension were grouped together. Third, it is not always possible to

distinguish between primary glottis and primary subglottic cancers with extension into neighboring region(s) and consequently, to determine the true origin of the tumor inside the larynx. Fourth, cancers other than squamous cell carcinoma, such as adenoid cystic carcinoma or chondrosarcoma, are reported together in some series. Tumors with different histologies have completely different clinical behaviors and should be reported separately.

Nahavandipour A et al (2019) used the Danish Cancer Registry to determine the trends in incidence of laryngeal cancer in the Danish population from 1980 to 2014. They found decreasing incidence in for the groups supraglottic cancer with an average annual percent change (AAPC) of -2.4 % (95% CI -3.5; -1.2%) and glottic cancer with an AAPC of -4.8% (95% CI -6.6%; -2.9%) but no change in incidence for subglottic cancer with an AAPC pf -1.1% (95% CI -2.8; 0.7).[134] No other studies have examined the trends in incidence of subglottic cancer over time. Some authors have suggested that the subglottic larynx is protected from the common carcinogens that cause glottic and supraglottic cancer. With the decreasing incidence of smoking and other inhaled carcinogens, many studies have shown that laryngeal cancer overall is decreasing in incidence. The stable incidence in subglottic cancer over time may indicate that this region of the glottis is not as susceptible to inhaled carcinogens however further studies with large numbers of patients are needed to demonstrate causation.

3.5 Stage Presentation of Subglottic Carcinoma

As described in the staging of laryngeal cancer in the sections above, the stage of subglottic cancer is dependent on the extent of the primary tumor, the presence of nodal

disease as well as the presence of distant metastasis. Subglottic tumors can spread locally invading into the surrounding structures of the larynx or regionally through the lymphatics into the cervical lymph nodes. Strome (1999) examined the invasion patterns of 10 patients with subglottic carcinoma.[19] In this study, cartilage invasion was rare. Cancer spread was usually submucosal with paraglottic invasion, which occurred in the early stages of the disease and extralaryngeal extension, which occurred easily through potential spaces.[19] Similarly, Olofsson (1995) found that extralaryngeal spread through the cricothyroid membrane was common in subglottic tumors and glottic tumors with subglottic extension.[144] In the study by Olofsson (1995), other features of subglottic tumors were extensive circumferential growth and cartilage invasion.[144] A high rate of cartilage invasion was also demonstrated by Kurita et al (1985) who conducted a histopathological study of 51 serially sectioned laryngectomy specimens.[145] The incidence of cartilage invasion was highest in subglottic carcinomas; thyroid cartilage invasion was present in 67% and cricoid cartilage invasion was present in 33%.[145]

With respect to nodal spread of disease Liu et al (2006) examined 18 fresh cadavers and found that the inferior surface of the vocal folds have a large number of lymphatic vessels and collecting chambers.[146] These lymphatic vessels anastomosed with each other to form a dense network, which connects with the subglottic lymphatic system. Lymphatic drainage of the subglottic region proceeds though the prelaryngeal (Delphian), pretracheal and paratracheal nodes and drainage patterns are to bilateral lymph nodes.[147]

Some have suggested that subglottic carcinoma is more likely to present with advanced stage disease compared to the other subsites of laryngeal cancer. We found no large studies that examined the stage of presentation for all subsites of laryngeal cancer. In those studies that reported on early and advanced stage subglottic cancer, summarizing the findings we found 562 patients presented with early stage disease while 798 presented with advanced stage disease (ratio early/advanced 0.70). Previous population based work by our group has demonstrated that glottic cancer presents with a ratio of 3.11 early stage to advanced stage (544 patients early stage/175 patients with advanced stage) and supraglottic cancer at a ratio of 0.34 early stage to advanced stage (71 patients early stage/ 208 patients advanced stage).[36] Therefore, subglottic cancer based on our pooled analysis appears to present at more advanced stage than glottic cancer but less advanced than supraglottic cancer. As described in the laryngeal section above, similarities between the supraglottis and the subglottis include rich lymphatics, bilateral lymph node drainage basins and lack of anatomic barriers to local spread. Given the possible misclassification of some glottic cancers as subglottic cancers, this may account for the higher ratio of early stage to advanced stage in subglottic compared to supraglottic cancers.

3.6 Treatment of Subglottic Cancer

Treatment of subglottic carcinoma varies according to the stage of the disease. Several studies have demonstrates that early-stage subglottic carcinoma can be managed with a single modality treatment, whereas advanced-stage disease requires combined treatment.[2, 6, 12-16, 18, 20, 71, 101, 128, 136, 148] In our scoping review, we found

the treatments used and reporting of outcomes varied greatly amongst the studies (Table 8). There were very few head to head comparisons of primary surgery versus radiation. In addition, the treatment regimens for laryngeal cancer have changed over the years. For example, studies included patients treated with antiquated radiation techniques, and patients treated with neoadjuvant radiation before surgery (no longer used at most centres). Further, transoral surgery techniques for excision of small laryngeal cancers have improved, partial laryngectomy techniques described above have largely fallen out of favour. Several studies reported outcomes for patients treated with partial laryngectomy techniques. Chemotherapy was not considered standard of care for advanced laryngeal cancer until the publication of the RTOG 91-11 study in 2003 which demonstrated acceptable survival outcomes and laryngeal preservation for patients with advanced laryngeal cancer. [74] The description of treatment outcomes below is limited to more recent studies using contemporary treatment practices.

3.6.1 Surgical Treatment

As summarized in table 5, surgery was used as primary treatment for subglottic cancer in 798 patients. Surgery can be used as a single modality treatment in early stages. Depending on the location of the primary tumor, a total laryngectomy is frequently required. However, in selected cases, extended partial laryngectomies can provide similar oncologic results while preserving laryngeal functions. In the case of advanced-stage subglottic carcinoma a wide-field total laryngectomy is required, owing to the high incidence of extralaryngeal spread. Jumaily studied the NCDB and assess 205 patients undergoing surgical treatment for subglottic cancer.[11] In this group, 76 patients were

treatment with surgery alone, 77 patients with surgery followed by postoperative radiation and 52 patients by surgery followed by postoperative chemoradiation. Total laryngectomy accounted for 80.5% of the cases, partial laryngectomy 8.3% and transoral laser surgery for 11.2% of cases. Marchiano examined the SEER database and found that the majority of patients with subglottic cancer were treated with surgery followed by radiation (317 (38.8%)), while 139 patients (17.0%) were treated with surgery alone.[31] They found that surgery alone was used for 9 patients with early stage disease and 23 patients with advanced stage disease. Surgery and radiotherapy was used for 18 patients with early stage disease and 66 patients with advanced stage disease. However, the SEER database does not report of the extent of surgery.

There were two studies that reported on patients with subglottic cancer only treated with surgery.[3, 17] Yu examined 21 patients, of which 12 had early stage disease and were treated with a mix of vertical hemilaryngectomy, transoral laser microsurgery and supracricoid laryngectomy, the other 7 patients underwent total laryngectomy.[17] All patients with advanced stage laryngeal cancer in this study were treatment with total laryngectomy.[17] Weiss reported on 17 patients with subglottic cancer, of which 13 patients treated with transoral laser microsurgery, and 3 were treated with laryngectomy.[3]

From our review of the literature, options for surgical treatment of subglottic cancer which yield acceptable survival outcomes include transoral laser microsurgery, vertical partial laryngectomy, supracricoid laryngectomy and total laryngectomy. Early stage

subglottic cancers are amenable to microsurgery, vertical partial laryngectomy and supracricoid laryngectomy, whereas advanced stage subglottic cancer requires total laryngectomy. The data reported in the literature to date on the surgical outcomes for patients with subglottic cancer are limited by lack of surgical detail for population based studies, low numbers of patients in single centre studies, and inconsistent use of adjuvant treatment following surgery. A comparison of the survival outcomes for patients treated with surgery versus radiation is listed in table 8 however caution should be used in comparing the results given the representativeness and selection of both cohorts. Due to the heterogeneity of the data meta-analysis could not be performed for survival comparing different treatment regimens. Accepting the limitations of the included studies the 5 year overall survival for patients treated with surgery range was 46.4-73.9%. One study reported 5 year overall survival separately for early stage and advanced stage subglottic cancer which found 63% for early stage and 57% for advanced stage.

3.6.2 Chemoradiation Treatment

Early-stage cases can be treated with radiation fields directed at the larynx with a 1- to 2-cm margin.[128] Radiation fields for advanced-stage cases usually include the larynx, bilateral cervical, supraclavicular, and upper mediastinal lymph nodes and total dose usually ranges between 50 and 75 Gy.[12, 71, 128]

Nine studies reported on the survival outcomes of patients with subglottic cancer treated with radiation. Three were population based studies, the rest were single centre

retrospective reviews. Hill-Marsden reported on 146 patients from the Danish Cancer Registry, 134 (92%) patients were treated with primary RT and 10 (7%) with RT and surgery in combination.[10] Over the study period the provided RT dose increased due to changing practices over time. Patients were treated with different radiotherapy regimens including standard RT regimens, accelerated RT and accelerated hyperfractionated RT. In a study by Marchiano et al using the SEER database, primary radiotherapy was used in 277 patients.[18] The SEER database is limited by lack of information on chemotherapy administered or radiotherapy regimens and whether they changed over time. Jumaily et al used the NCDB database to study 549 patients treated for sublgottic cancer, 344 of which were treated with primary radiation.[11] The remainder of the studies reporting survival by treatment type were single centre case series.

Unfortunately, due to the heterogeneity of the data we were not able to perform meta-analysis for any of the survival outcomes by treatment. The survival results by treatment are summarized in table 8. Based on the studies presented in Table 8, the 5 year overall survival for patients treated with primary radiation ranged from 26-57.5%. For patients with stage I/II disease 5 year overall survival range was 57-63%. For advanced stage disease 5 year overall survival was 38% as reported in Jumaily et al.[11]

Visual inspection of the data in Table 8 demonstrates that 5 year overall survival appears to be lower for patients treated with primary radiation versus primary surgery. However, the data needs to be interpreted with caution for the following reasons:

1) The definition of subglottic cancer differs amongst the studies which may impact the survival if some of the tumors are misclassified as primary glottic cancers with subglottic extension;

2) There is selection bias in the patients treated with surgery and radiation, as the data reported are limited to population-based and single centre studies. There are no randomized trials comparing surgery and radiation for subglottic cancer and the studies that report head to head comparisons do not specify the selection criteria for each treatment.

3) The treatment practices for radiation and surgery have evolved over time which makes comparison of survival outcomes between studies challenging.

4) Details of the extent of surgery is lacking in some studies as well as the indications and extent of adjuvant treatment. These factors may impact long-term survival.

Table 8 Survival Outcomes of Subglottic Carcinoma by Treatment

Study	Treatment	LRC	DSS	OS 5 year
Haylock (1993)[15]	RT		78.3%	57.5%
Hill-Madsen (2019)[10]	RT (1% patients treated with Sx	42	49	38%
Jumaily (2020)[11]	Surgery			
	I/II			63
	III/IV			57

	RT or CRT			
	I/II			57
	III/IV			38
Lee (2020)[133]	RT		84.3	62.2
	I/II			
Marchiano	Surgery		62.4	46.7
(2016)[18]	Surgery +RT		55.1	46.4
	RT		56.7	44.3
Paisley (2002)[12]	RT	56	66.9	50.3
Warde	RT		61	26
(1987)[138]				
Yu (2019)[17]	Surgery		73.9	73.9
Zhu (2020)[139]	Surgery			47
	RT			29

RT: radiation

CRT: chemoradiation

LRC: Locoregional Control

OS: Overall Survival

DSS: Disease Specific Survival

3.7 Survival Outcomes of Subglottic Carcinoma

Traditionally, subglottic carcinoma is regarded as an aggressive tumor with a worse prognosis compared with other laryngeal subsites. Possible explanations for the apparent “worse prognosis” include a predilection for cartilage invasion and

extralaryngeal spread, a high incidence of paratracheal and mediastinal lymph node metastases (which may be left untreated during surgical or radiotherapeutic treatment), thyroid gland involvement, and stomal recurrence. In addition, these tumors usually remain asymptomatic until advanced stages, because submucosal spread through potential spaces (ie paraglottic space) is common and may cause a delay in diagnosis.

There is controversy in the literature about the prognosis and treatment results of subglottic carcinoma. Some reports indicate very low survival and locoregional control rates when compared with other laryngeal subsites, whereas others observed comparable outcomes, despite unfavorable features listed above. As described in Table 9, the 5 year overall survival range was 26-80%. When only population-based studies were included the 5 year overall survival range was 41.5-48.7%. 5 year disease free survival range was 25-90% when all studies were included and 53.7-57% when only population-based studies were included. Finally, local regional control ranges from 53.7-57% in the two studies that reported it. Hill-Madsen et al. were the only authors to report laryngectomy free survival in their population based study in Denmark. They reported 5 year LFS of 37% (95% CI 29-45).[10] Previous population-based research by our group using Ontario administrative data found a 5 year overall survival for patients with glottic and subglottic cancer was 67.1% and 39.5%, respectively.[36] Five-year laryngectomy free survival was 55.5% for glottic cancer patients and 28.0% for supraglottic cancer patients.[36] This suggests that the survival of patients with subglottic cancer may not be worse than the other laryngeal sites, and the survival outcomes lie somewhere between glottic and supraglottic cancer. Of note, the data reported in many of the

studies is heterogenous and confounding factors that are known to impact survival of patients with laryngeal cancer such as age, stage, comorbidity, and treatment completion are not adjusted for.

Table 9. Literature review of subglottic carcinoma treatment and survival outcomes

Series	No of patients	Stage		Treatment Protocol		5-year LRC (%)	5-year DSS (%)	5-year OS (%)	Stomal Recurrence
		I/II	III/IV	RT	Surgery				
Cassidy (2012) [128]	18	7	12	14	5	83	66	44	NR
Dahm (1998)[a] [13]	28	19	9	10	17	61.5	46.2	58	NR
Gairola (1992)[b] [130]	8	1	7	5	3	NR	NR	37.5	12.5
Garas(2006)[c] [131]	15	3	12	6	9	NR	25	NR	NR
Guedea[d] (1991)[20]	6	3	3	6	0	NR	NR	33	16.7
Hata(2013)[e][71]	19	9	10	15	4	74	63	80	NR
Haylock(1993)[15]	23	13	10	23	0	NR	78.3	57.5	NR
Hill-Madsen (2019)[f][10]	146	70	75	134	12	47 (38-55 95% CI)	57 (48-65 95%CI)	43 (35-51 95% CI)	NR

Jumaily(2020)[11]	549	219	330	344	205	NR	NR	48.2	NR
Komatsubara(2020)[132]	11	9	2	9	2	NR	61.4	NR	9.1
Lee[g] (2020)[133]	37	37	0	37	0	NR	68	39.6	NR
Marchiano[h](2016)[18]	889	126	219	277	456	NR	53.7	41.5	NR
Nahavandipour[i] (2019)[134]	142	NR	NR	NR	NR	NR	NR	45	NR
Paisley(2002)[12]	43	23	20	43	0	56	66.9	50.3	NR
Santoro(2000)[135]	49	17	32	6	25	NR	NR	56	43.9
Sessions(1975)[1]	5	1	2	0	3	NR	NR	66.7	NR
Shaha(1982)[2]	16	3	13	16	0	NR	NR	77	NR
Smee (2008)[6]	10	6	4	4	6	90	NR	NR	NR
Strome(1999)[19]	10[f]	5	4	3	6	NR	NR	50	NR
Su[j](2003)[136]	5	3	2	3	2	NR	NR	80	NR

Warde (1987)[138]	23	9	14	22	0	74	61	26	NR
Weiss(2018)[3]	13	4	9	0	13	46	90	79	NR
Yu (2019)[17]	21	12	9	0	21	NR	73.9 (54.1-93.7)	73.9 (54.1-93.7)	4.8
Zhu (2010)[139]	249	249	0	NR	NR	NR	NR	31 (10yr)	NR
Pooled results	2335	562[l]	798	968	799				

Abbreviations: TL-Total laryngectomy; PL-partial laryngectomy; RT-radiation; CRT-chemoradiation; Sx- Surgery undefined; NR-not reported; LRC-Locoregoinal Control; DSS-Disease Specific Survival; OS-Overall Survival.

Shaded studies represent crude survival rates not proportionate survival.

[a] No difference in survival amongst treatment groups. 5-year overall survival 44% RT

alone, 50% Surgery alone, 100% combined therapy. 1 patient opted for palliative care.

Crude survival rates reported.

[b] RT used as neoadjuvant treatment in 4 patients with planned laryngectomy after.

Reported as crude survival rate at 3 years.

[c] 3-year crude survival reported for patients treated with TL 0%, TL + adjuvant RT 40%, RT 33.3%, and RT + salvage TL 0%.

[d] 4-year crude overall survival reported. One patient had carcinoma in situ

[e] 5-year crude survival for patients treated with CRT 100% and RT 92%. 4 surgical patients were treated with pre-op RT and planned surgery

[f] 10 patients in surgery group treated with neoadjuvant RT and planned surgery

[g] All patients had Stage I/II subglottic cancer

[h] Population-based SEER study in which no further detail on extent of surgery. Some Surgery patients treated with adjuvant radiation.

[i] OS estimation from KM curve at 5 years

[J] 2.5 year crude survival rate

[k] 10 yr OS reported

[l] Studies that only included early stage cancers were excluded from pooled result

3.8 Stomal Recurrence

Stomal recurrence is one of the most feared types of recurrence during patients with laryngeal carcinoma. The reported incidence of stomal recurrence ranges from 4.8-43.9%.[17, 20, 130, 132, 149] The pathogenesis of stomal recurrence is still unknown but various factors, such as tumor site and stage, positive tracheal margins, thyroid gland invasion, tumoral implants, prior tracheostomy, and paratracheal lymph node metastases are considered possible causes.[150] As indicated in Table 9, the majority of the studies did not report stomal recurrence, and the studies that did report on stomal recurrence have a small sample size. Therefore, given the limitation of reporting in stomal recurrence no conclusions can be made regarding the incidence relative to other laryngeal cancer sites, or the risk factors for stomal recurrence.

3.9 Quality of Life Outcomes

Only one study reported on voice and swallowing outcomes in patients treated for subglottic cancer.[137] They compared voice and swallowing outcomes in patients

treated for all three subsites of laryngeal cancer, glottic, supraglottic and subglottic. They found that the voice outcomes were worst in the glottic cancer group. In the subglottic group, the number of patients with "bad voice" did not change pre-and post-treatment.[137] Among the patients with subglottic cancer, the number of patients with "no swallowing dysfunction" increased after treatment.[137] This study is limited by reporting of a non-validated instrument for measurement of voice and swallowing outcomes, small numbers of patients with subglottic cancer (n=4) and incomplete follow-up data.

CHAPTER FOUR: RATIONALE FOR RESEARCH APPROACH

4.1 Limitations of existing studies

There are several methodological limitations of the existing studies on survival outcomes of patients with subglottic carcinoma. Furthermore, there is only one population-based study that reports on laryngectomy-free survival.[10] These limitations are summarized here:

I. Study centers: most prior studies were institutional case series limited to a single center which limits study generalizability.

II. Sample size: most prior studies were limited by small sample size (less than 50 people). Small sample size can limit adjustment for important confounding factors because of concerns about over-fitting in statistical models. Over-fitting in a statistical model occurs when it has more variables than the amount of available data, which results in uncertain results.

III. Type of treatment: the types of treatments administered in previous studies varied from study to study. In some of the previous studies there was no data on chemotherapy. Furthermore, the methods of radiotherapy have changed in recent years. Only one study examined the trends in survival over time.[134]

IV. Study design: All the existing studies are observational in nature. Most are institutional reviews which are limited by selection bias, institutional bias, or referral bias in which the baseline characteristics of the patients who present at that institution may not be representative of the entire population of patients with subglottic cancer, thus the results may not be generalizable. Most studies did not report whether all sequential patients were included in their results.

V. Clinically important outcomes: As outlined above, one of the most important outcomes in laryngeal cancer is “laryngectomy-free survival”. To determine whether organ (laryngeal) preservation protocols are effective, the composite outcome of laryngectomy-free survival must be reported.

4.2 Relevance of Proposed Research

Although patients who present with subglottic cancer are rare, having accurate survival and prognostic data can help with future treatment decision making as well as with patient counseling. Given the low numbers of patients with subglottic cancer, treatment protocols from patients with laryngeal cancer in other subsites are being applied to patients with subglottic cancer. It is important to ensure that we are aware of the survival outcomes for patients with subglottic cancer so that we know if improvements in treatment or escalation of treatment is required. The results from this study are intended

to provide needed information about the survival outcomes of patients with subglottic carcinoma in the province of Ontario, Canada. The results will also add to the literature at large to provide results on the clinically important outcome of laryngectomy-free survival on a population level for patients with subglottic carcinoma.

4.3 Assessment of Possible Research Methodologies

Randomized control trials (RCTs) are generally considered to be the gold standard in evidence-based medicine (EBM). A properly designed large RCT allows researchers to compare different therapies, while also minimizing confounding from known and unknown confounding variables, which are, usually, balanced across two comparative groups following randomization. In oncology, RCTs have advanced the care for patients by enabling researchers to answer important questions regarding the efficacy of a therapy aimed at driving evidence based decision-making.

RCTs do have limitations however. They can be costly to conduct, may require a large number of patients to detect small differences in treatment effect, may take a long time to finish depending on patient accrual time and the outcomes investigated, and tend to have participating patients who are highly selected and do not represent actual clinical populations.[151] Due to these limitations, obtaining evidence through other means, such as prospective multi-institutional observational studies, may be required.

Although RCTs have long been considered the first choice for evidence generation in medicine, due to their high level of internal validity and ability to provide the least biased

estimates of risk, there are many instances where results from experimental studies are not indicative of real-life application. Observational studies are a source of evidence generation that can answer research questions that are less suited for an RCT. For example, observational studies can be more appropriate in instances of rare disease, when it is unethical to randomly assign the intervention of interest, when it is impossible to randomize the factor of interest, or when it is impractical to assign the intervention.[151] Additionally, observational studies have the advantage of being less costly and labor intensive to carry out than an experimental study and can provide initial evidence to support the implementation of a future RCT.[152]

Observational studies play an important role in evidence-based medicine in the generation of primary evidence for practice guideline construction and policy driven decision-making. The use of administrative data in observational studies has the advantage of being inexpensive to use, contains information on very large populations and provides information on outcomes requiring a longer follow-up time.[153] However, limitations in observational studies exist, which if not properly accounted for can lead to erroneous results. The inability to randomly allocate patients to different therapies can lead to confounding, which occurs when there are imbalances between confounding variables among patient groups.[153] A confounding variable is defined as a variable that is associated with the primary variable of interest (independent variable) and associated with the outcome of interest (dependent variable), but is not an intermediate variable in the causal pathway between the independent variable and dependent variable.[154] Adjustment for confounding is very important, as any imbalance in

confounders has the potential to change the magnitude or even direction of an estimated treatment effect. However, a properly designed study using appropriate analytical methods can help reduce inaccurate estimates of the association between treatment and outcome that is caused by measured confounding variables.[153]

4.4 Our Research Approach

To determine whether primary radiation or primary surgery is superior for the treatment of subglottic carcinoma, the highest level of evidence would be achieved by a randomized clinical trial (RCT) comparing patients with subglottic carcinoma treated with radiation (with or without chemotherapy) versus primary surgery (laryngectomy). The small numbers of patients diagnosed every year with subglottic cancer (76 patients diagnosed in the province of Ontario from 1995-2007)[36] and the high cost associated with running an RCT render this study design infeasible. For these reasons, we conducted a population-based retrospective observational study to determine the survival outcomes of patients with this disease.

4.4.1 Secular Trends

Secular trends are defined as “the changing pattern of disease in populations over time”.[155] Analyses for secular trends are useful for rapidly providing evidence for hypothesis generation and preliminary research. Possible reasons for changes in trends over time can be classified as artifactual, and real. Artifactual changes may be errors in the numerator due to changes in the recognition of disease, changes in the classification of causes of death, changes in accuracy of reported age at death. There

may also be errors in the denomination due to error in the enumeration of the population. Real changes include changes in age distribution of the population, changes in survivorship and changes in incidence of disease resulting from genetic factors and environmental factors. Secular trends can be used to determine if an intervention such as a change in treatment practice has resulted in better or worse survival over time. Interpreting secular trends requires care. Outcomes are compared over several years or decades, such observations are especially susceptible to biased conclusions. Threats to correct interpretation of secular trends include changes in disease definitions, altered categorization of disease, establishment of new disease entities, changes in disease outcomes, more accurate diagnostic techniques, and an updated understanding of disease etiology. Furthermore, demographic changes, changes in living conditions, lifestyle changes, landscape changes, catastrophes and migration can also impact interpretation of secular trends.

The limitations associated with using secular trends for this project are as follow:

I. Changes in the patients' susceptibility to disease would diminish the number of cases of the disease. For laryngeal cancer reduced susceptibility would be the declining incidence in smoking over time, a known risk factor for laryngeal cancer.

II. Change in disease definitions. As mentioned previously the anatomic boundary of the subglottis has been the source of much controversy. This may have resulted in misdiagnosis of patients with subglottic cancer as glottis cancer and vice versa.

III. Secular trends do not capture the point that the incidence of the disease or treatment of the disease changes. The publication of the RTOG-9111 study in 2003 resulted in most centers moving away from primary laryngectomy for the treatment of advanced stage laryngeal cancer in favor of organ preservation protocols combing chemotherapy with radiation with the goal of laryngeal preservation.[74] Secular trends studies will not capture the time point where treatment practice changed rather a trend over time may be observed.

IV. “Ecologic fallacy”- a term used to represent the fact that associations observed at the level of the group or population may not represent the association at the individual level. Analyses of secular tends are unable to differentiate which factor is likely to be the true cause of the outcome of interest and establish a causal relationship between the exposure and outcome of interest on an individual level.

V. Changes in diagnostic methods. In the setting of subglottic carcinoma, improved CT scanners and MRI scanner may have resulted in more patients being diagnosed with advanced stage disease over time (due to greater pick up of cartilage invasion) resulting in more patients being treated with dual modality treatment (surgery followed by radiation or a combination of radiation and chemotherapy).

4.4.2 Regression-Based Modeling

Multivariable regression modeling is a traditional analytical approach used in observational studies to account for confounding bias. Regression-based modeling

allows investigators to estimate the association between a treatment and outcome, while keeping other covariates in the model constant.[154] As long as the number of outcomes of interest in the study sample is large, regression modeling using either, linear regression for continuous outcomes, or logistic regression for binary outcomes, has the advantage of adjusting for a substantial number of confounding variables. However, there are some limitations to regression-based models, some of which include: they do not account for confounders which are not included in the model, they are unable to provide accurate estimates of association when there is insufficient overlap among covariates between treatment groups, and they are bound by the assumptions of the regression model chosen.[156]

4.4.3 Strengths of Ontario's Health Administrative Data

The Institute for Clinical and Evaluative Sciences (ICES) is a not for profit organization which houses the large population-based databases in Ontario, Canada. Ontario currently has approximately 13 million residents who have universal access to hospital and physicians care. The organization links the databases using personal health number such that demographic, socioeconomic, treatment and outcome data is available for individual patient populations. ICES captures all residents of Ontario with minimal selection bias and loss to follow-up. Access to these linked databases allows researchers to study rare populations of patients with high statistical power and low cost. Compared to large population-based databases in the United states (SEER and NCDB), the main advantage of ICES is that it has physician billing codes and robust survival outcome such that all patient who underwent a surgical procedure are captured.

This data is thought to be reliable given the financial remuneration for submission and encoding of the data. We have used these data sources to assess the secular trends of laryngeal cancer sites previously.[36]

4.4.4 Limitations of Ontario's Health Administrative Data

In cancer research the main limitations of using administrative data in Ontario are the lack of staging and treatment details. Staging data is available in Ontario from 2005 onwards thus limiting the analysis that can be performed prior to 2005. Additionally, nuances about the patient presentation such as airway obstruction, feeding limitations, and ECOG score are not captured by the databases. Some administrative data codes have been validated for use in research, but the vast majority have not, therefore coding errors may occur. This is a consideration in the classification of subglottic cancer as some patients may have been inappropriately misclassified as subglottic but were glottic cancer with subglottic extension.

4.5 Population-based Survival Outcomes Analyses Considerations

4.5.1 Strengths of Population-based Survival Outcomes Analysis

There are several strengths associated with using population databases for survival analysis. In the province of Ontario, there is very little migration out of the province, therefore, loss to follow-up or the requirement to censor for loss to follow-up is not a major concern. Vital statistics are reliably captured, and we can be certain that the patient is living if there is no death record in ICES.

4.5.2 Limitations of Population-based Survival Outcomes Analysis

There are several analytic challenges to consider when conducting population-based survival outcome analyses in oncology patients. First, while the outcome of mortality is reliably captured the cause of death is not. Using ICES data, the outcome of overall survival or mortality is reliable however, the outcome of disease-specific mortality is not. Patients with laryngeal cancer often have several competing risks. Second, OHIP billing codes for surgical treatment are reliable however, billing codes for radiation and chemotherapy are not reliable. Therefore, several assumptions about treatment are usually made. We assume that patients who have no billing record for surgery were treated with radiation, however some of these patients may have received no treatment. Third, there are several confounders that must be adjusted for in survival analysis of patients with laryngeal cancer. Data on some of these confounders is available but confounders such as stage of disease is variable and there is no smoking or alcohol use data in ICES. Fourth, while reporting of pathology to Ontario Cancer Registry is reliable as there is mandatory reporting of all pathology specimens, reporting of the site of the cancer may not be accurate.

4.6 Rationale

Given the current state of the literature, the study conducted here is novel and meets an information need. We have considered other study methods to determine the survival outcomes of patient with subglottic carcinoma but given the low incidence, a retrospective population-based design is the best available. We have considered the data and coding limitations of using administrative databases, however given the risk of

selection bias with institutional reviews administrative data that captures all patients diagnosed with subglottic cancer in the province of Ontario will help reduce selection bias. The majority of cancer patients in Ontario are treated at a high volume cancer centre whereas in other countries, high numbers of patients are treated at low volume cancer centres. As well as the methodology of secular trends will allow us to explore changes in the survival trends with the introduction of chemotherapy and new radiotherapy techniques.

CHAPTER FIVE: RESEARCH QUESTIONS AND FRAMEWORK

5.1 RESEARCH QUESTIONS

5.1.1 Survival Outcomes of Patients with Subglottic Cancer

Among all patients with a diagnosis of subglottic carcinoma over a 15-year period (1995-2009) in the province of Ontario, Canada what is the 5-year overall survival and 5-year laryngectomy free survival?

Hypothesis: We expect overall survival will be low and similar to population-based reports in the literature.[18] We expect laryngectomy-free survival will be lower than overall survival and lower to that reported for other subsites of laryngeal cancer (glottis and supraglottic).[36]

5.1.2 Secular Trends in Overall Survival and Laryngectomy-free Survival of Patients with Subglottic Cancer

Over the 15-year period (1995-2009) in the province of Ontario, Canada has the 5-year overall survival and 5-year laryngectomy-free survival improved in patients with subglottic cancer? Is there an association between the introduction of chemotherapy protocols in 2003 and improved radiation techniques and secular trends in laryngectomy-free survival over the 15-year period from 1995-2009?

Hypothesis: We expect that improved radiation techniques, the addition or chemotherapy to radiation protocols, improved perioperative management of patients with laryngeal cancer, decreasing incidence of smoking will be associated with a higher

5-year overall survival in patients with subglottic cancer. The RTOG-9111 study published in 2003 found that chemotherapy had a survival benefit when used concurrently with radiation.[74] We expect that the laryngectomy-free survival in patients treated in era after 2003 will be improved compared to the eras before the study was published.

5.1.3 Survival of patients treated with primary surgery versus primary radiation

Among patients with subglottic cancer in the province of Ontario is primary treatment with surgery associated with a better 5-year overall survival than primary treatment with radiation (+/- chemotherapy).

Hypothesis: We expect based on previous research on patients with glottic and supraglottic cancer that primary treatment with surgery will result in an improved 5-year overall survival.

5.2 RESEARCH FRAMEWORK

In order to address these questions, we conducted a retrospective population-based cohort study of all consecutive patients diagnosed in subglottic squamous cell carcinoma over a 15-year period (1995-2009) in Ontario, Canada to determine the 5-year overall survival, 5-year laryngectomy-free survival, secular trends in overall and laryngectomy-free survival and to determine if treatment with surgery is associated with improved overall survival.

CHAPTER SIX: PATIENTS AND METHODS

6.1 Overview of Study Methodology

We performed a retrospective population-based study to assess the secular trends in subglottic squamous cell cancer in Ontario, Canada. Study conduct and reporting follow guidelines (STROBE) for observational studies (Appendix C).[157] The study was approved by the Sunnybrook Health Sciences Centre Research Ethics Board according to a pre-specified protocol (Appendix D and E). However, numbers of participants were suppressed in the case of five or fewer participants (reported as ≤ 5) to comply with privacy regulations for minimizing the chance of identification of a study participant.

6.2 Study Population

Residents of Ontario (2014 population estimate: 13, 678,700)[158] have universal access to hospital care and physician services. Encounters are recorded in large population-based health care databases, many of which are held at the Institute for Clinical Evaluative Sciences (ICES).

6.3 Data Sources

We used five linked databases accessed through ICES.

I. Ontario Cancer Registry (OCR), which records data on all patients with non-skin cancers diagnosed in Ontario (mandatory reporting) [159, 160].

II. Discharge Abstract Databases held by the Canadian Institute for Health Information (CIHI-DAD), which records all admissions to hospitals and includes information about diagnoses and procedures performed.

III. Ontario Health Insurance Plan Databases (OHIP), which contains information on all fee-for-service physician claims for inpatients and outpatient services. Each claim record include information about the physician, service provided and diagnostic information.

IV. Registered Persons Database (RPDB), which contains vital statistics about all permanent residents of Ontario.

V. National Ambulatory Care Reporting System Database (NACRS), which collects data on ambulatory care visits, including day surgery, outpatient clinics, cancer clinics, and emergency department visits.

The databases were linked using unique encoded identifiers (encrypted Ontario health care numbers that are unique to each resident eligible for health care services paid by the government) available starting July 1991, after the assignment of new health care numbers in Ontario. We previously used these data sources to study secular trends in other conditions.[36, 161] For the present work, we used the OCR to identify laryngeal cancer patients (subsite subglottis), and the CIHI-DAD, NACRS, OHIP and RPDB databases to define patient's characteristics, baseline comorbidities, and patient outcomes. Diagnoses were identified using International Classification of Disease, 9th revision (pre-2002) and 10th revision (post-2002) codes, while procedures were identified using the Canadian Classification of Diagnostic, therapeutic, and Surgical

Procedures (pre-2002) and the Canadian Classification of Health Interventions (post-2002) codes.

The Canadian Institute for Health Information Discharge Abstract Database, Same Day Surgery and National Ambulatory Care Reporting System (CIHI-DAD, SDS, NACRS) databases collect demographic, diagnostic and procedural variable for inpatients, emergency department and outpatient visits. Diagnostic and inpatient procedural codes used the 9th version of the International Classification of Disease system (ICD-9) prior to 2002 and the 10th version (ICD-10) thereafter.

The Ontario Health Insurance Plan (OHIP) captures information on inpatients, outpatient and laboratory services based on billing claims from Ontario physicians. We used OHIP diagnostic codes to identify baseline conditions and both procedural and diagnostic codes to define our outcomes.

The Registered Persons Database (RPDB) captures demographic information on Ontario residents including their sex, date of birth, postal code and vital status. We used the RPDB to ascertain baseline demographics, exclusion criteria and potential confounders.

6.4 Patients

All patients diagnosed with laryngeal cancer and SCC on histology during 1995 – 2009 in the province of Ontario, Canada were reviewed retrospectively. To allow for a

complete 3-year look-back for baseline comorbidities, cohort accrual began on January 1, 1995. We restricted our cohort to patients who were residents of Ontario and who had a histologic diagnosis of squamous cell carcinoma. A prior validation study found a sensitivity of 89.8% and a positive predictive value of 96.8% for the diagnostic code for laryngeal cancer in the registry compared with a clinical database.[162] The date of the laryngeal cancer diagnosis (“index date”) served as the start time for follow-up.

Patients were further divided into supraglottic, glottic and subglottic cancers. Staging data were available only for the subpopulation diagnosed from 2005 to 2009. Registry staging ranged from I to IV and was derived from either the American Joint Committee on Cancer staging manual (6th or 7th edition).[5] We classified patients staged I and II as “early-stage”. According to both versions of the staging manual, early-stage grouping includes only patients with local disease and excludes patients with regional or distant metastases. Patients staged III and IV were classified as “advanced-stage”. This group included patients with advanced local disease and patients with regional or distant metastasis. Patients who underwent laryngectomy within 3 months of the initial diagnosis were treated with primary laryngectomy. We assumed that 3 months would allow enough time to capture those patients whose treatment was delayed for other medical problems, but it was too soon for radiation failure to be identified (assuming 6-7-week course of radiation). Those who underwent laryngectomy after 3 months were chemo/radio-therapy failures and required a salvage laryngectomy. Those not treated with primary laryngectomy were assumed to have been treated with primary radiation.

6.5 Outcomes

We categorized the study period into three eras: 1995-1999; 2000-2004; 2005-2009. We selected these eras to correspond with the availability of staging data, which initiated in 2004; this allowed for division of the cohort into three approximately equal periods. We determined 5-year mortality after a subglottic cancer diagnosis for each of the three eras and the rate per 100 person years. We assessed two primary outcomes in the 5 years following a new diagnosis of laryngeal cancer: overall survival and laryngectomy-free survival. We defined overall survival as the proportion of patients alive 5 years from the date of diagnosis censoring for patients who were lost to follow-up before 5 years. Laryngectomy-free survival as the proportion of patients alive 5 years from the date of diagnosis with an intact larynx, censoring for patients who were lost to follow-up. Deaths (including out-of-hospital mortality) are well ascertained in the RPDB, which provides accurate mortality data for all Ontario residents.[163]

6.6 Statistical Analysis

6.6.1 Cohort demographics

Patients with a diagnosis of subglottic cancer were divided into three eras: 1995-1999; 2000-2004; 2005-2009. For each era and for the 15-year time period the mean age with standard deviation, age (≤64, >65), sex, Charlson comorbidity group (0, 1 , ≥2), and treatment (laryngectomy, salvage laryngectomy and radiation) were reported. To determine whether there was a difference in demographic characteristics among the patients in each era, the Kruskal-Wallis test for continuous variable was used.

6.6.2 Survival Outcomes of Patients with Subglottic Cancer

We determined the crude 5-year mortality of patients after a subglottic cancer diagnosis and calculated the rate per 100py. Kaplan-Meier plots adjusting for age (≤64, >65), Charlson comorbidity (0, 1, ≥2) and sex (male/female) were generated for both 5-year overall survival and 5-year laryngectomy free survival.

6.6.3 Secular Trends in Overall Survival and Laryngectomy-free Survival of Patients with Subglottic Cancer

We divided patients into three eras, and generated Kaplan-Meier plots for both 5-year overall survival and 5-year laryngectomy free survival. We used the log rank test to determine whether there was a difference in survival amongst the three eras for each outcome.

6.6.4 Survival of patients treated with primary surgery versus primary radiation

We used the PHREG Procedure in SAS to perform a Cox proportional-hazards regression model to investigate the association between treatment with surgery versus radiation and survival adjusting for the influence of potential confounders (age, sex and Charlson Comorbidity Index).

SAS software package (version 9.3: SAS Institute, Cary, NC, USA) was used for all statistical analysis. We interpreted 2-tailed p values less than 0.05 as statistically significant.

CHAPTER SEVEN: RESULTS

7.1 Cohort Description and Demographics

From 1995 – 2009, a total of 4,977 patients with a diagnosis of laryngeal cancer were identified. Out of those, 50 patients were excluded for insufficient information leaving 4,927 patients; 1371 (27.83%) were diagnosed supraglottic cancer, 3201 (64.97%) with glottic cancer and 89 (1.81%) with subglottic cancer (Figure 3).

Out of 89 patients with subglottic cancer, 31 patients were diagnosed between 1995 – 1999, 31 patients were diagnosed between 2000 – 2004 and 27 patients were diagnosed between 2005 – 2009. Baseline characteristics are reported in Table 7. Mean age at the time of diagnosis was 68 years and 68 (76.4%) patients were males. A total of 13 (14.6%) patients underwent primary laryngectomy, 15 (16.9%) patients underwent salvage laryngectomy and 61 (68.5%) patients did not undergo laryngectomy within 5 years of diagnosis. There was no difference in the number of patients who underwent laryngectomy over the three time periods (p=0.23).

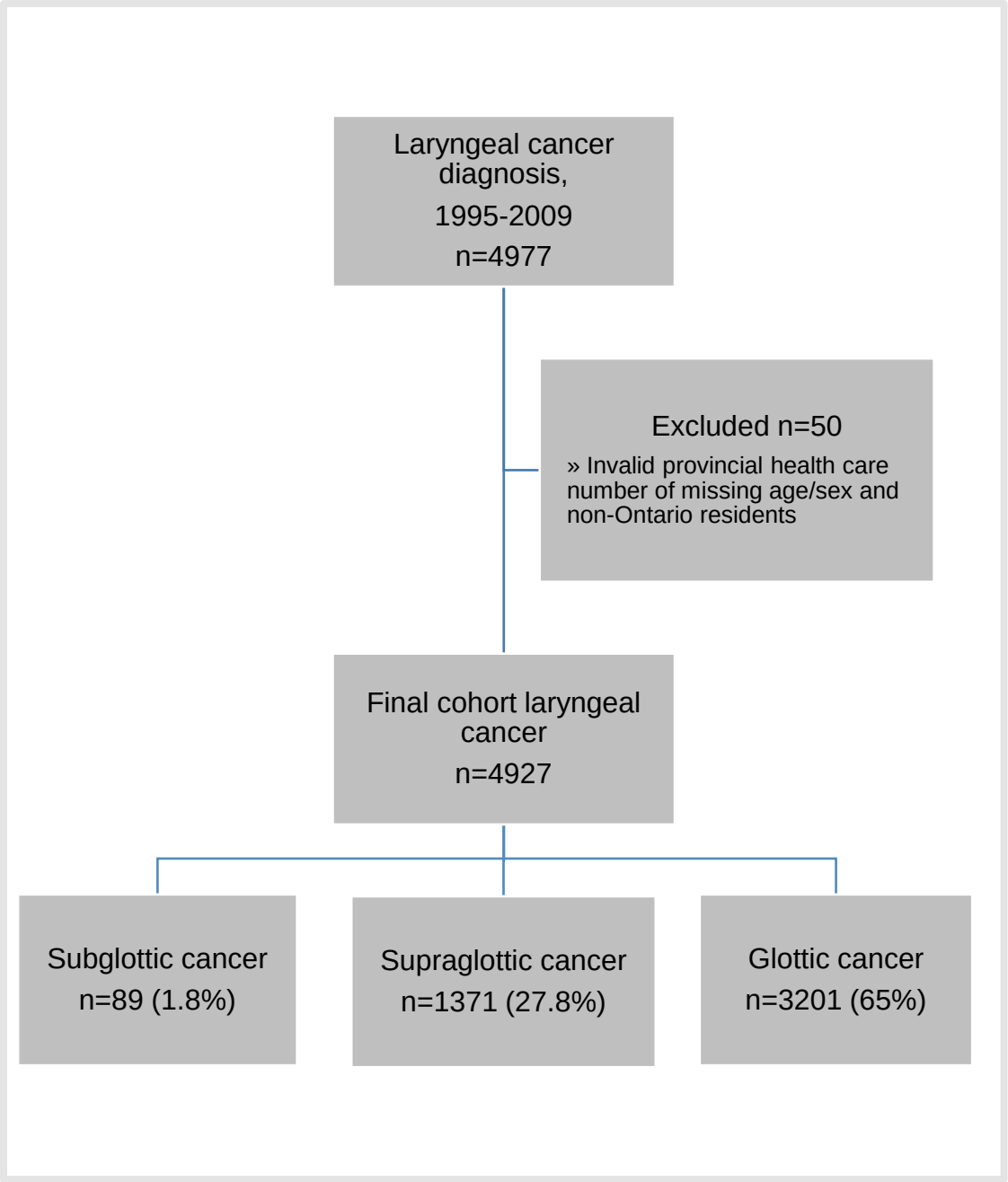


Figure 3 Selection of patients for subglottic cancer cohort

Table 10. Baseline characteristics of subglottic squamous cell cancer patients in Ontario, 1995-2009

Year of Diagnosis	**1995-2009 (N=89, %)**	**P value‡**
Age Mean (SD)	68.0 (11.1)	0.958
<65	32 (35.9)	0.99
≥65	57 (64.0)	
Sex Men		0.417
Male	68 (76.4)	
Female	21 (23.6)	
Charlson Comorbidity Index		0.826
0	19 (21.3)	
1	≤5 (4.5)	
≥2	8 (9.0)	
N/A	58 (65.2)	
*Stage**		
I/II	12	
III/IV	≤15	
Treatment		0.228
Primary Laryngectomy**	13 (14.6)	
Radiation†	61 (68.5)	

Salvage Laryngectomy ┼┼	15 (16.9%)

*Stage: Staging information was only available for 2005-2009

**Primary laryngectomy was defined as those patients undergoing laryngectomy within 3 months of the date of diagnosis

┼Radiation codes were not available, therefore we assumed that if patients did not have a primary laryngectomy they were treated with radiation however patients who received no treatment may also have been included in this group

┼┼Salvage laryngectomy was defined as those patients undergoing laryngectomy after 3 months of date of diagnosis

‡Kruskal-Wallis test used to compare patient demographics amongst patients in three eras (1995-1999, 2000-2004, 2005-2009). Data not shown for privacy reasons as several cells were ≤5.

7.2 Survival Outcomes of Patients with Subglottic Carcinoma

Table 11 outlines 5-year mortality after diagnosis of subglottic cancer. Five-year mortality was 58.06% (18/31) from 1995 – 1999, 41.94% (13/31) from 2000 – 2004 59.26% (16/27) from 2005 – 2009. For the entire cohort, 5-year overall survival was 47.2%, and 5–year laryngectomy-free survival was 31.5% (Figures 4 and 5).

Table 11: Five-year mortality after subglottic cancer diagnosis

Year of Diagnosis	No of Patients	5-year mortality	Rate per 100 person years
1995-1999	31	18 (58.1%)	19
2000-2004	31	13 (41.9%)	12

2005-2009	27	16 (59.3%)	20

Figure 4: Kaplan Meier plot depicting the five-year laryngectomy free survival

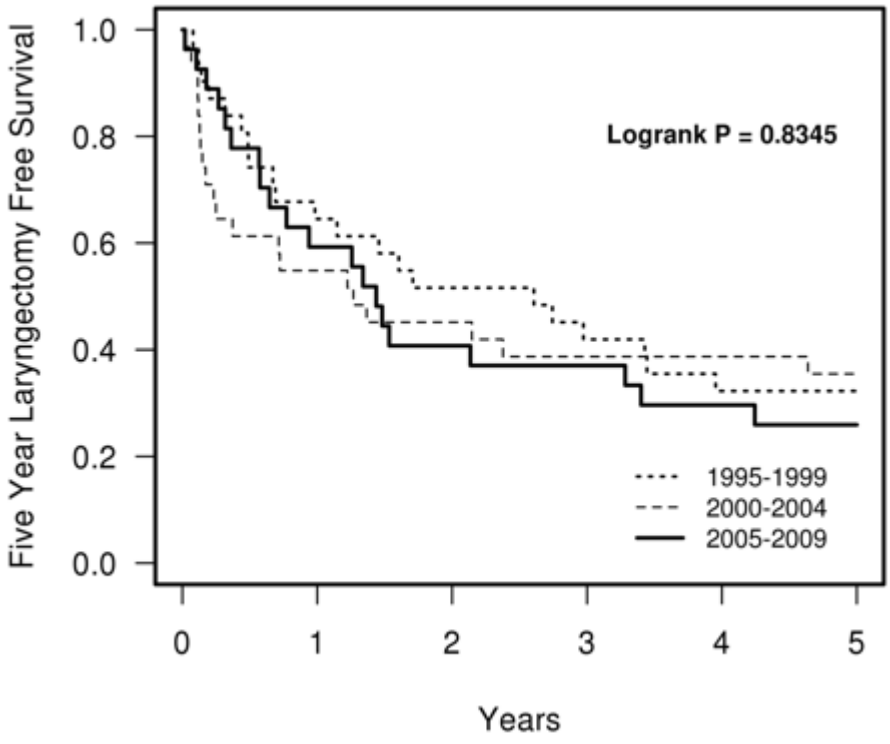
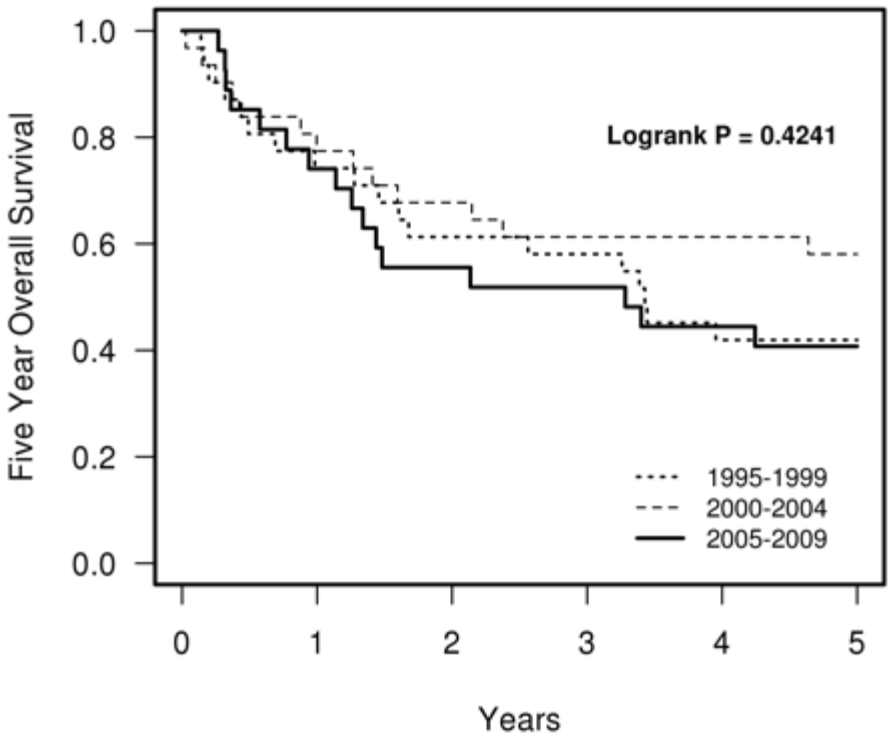


Figure 5: Kaplan Meier plot depicting the five-year overall survival



7.3 Secular trends in Overall Survival and Laryngectomy-free survival in patients with subglottic cancer

Comparing the five year overall and five-year laryngectomy free survival in patients for the three eras (1995-1999, 2000-2004, 2005-2009) there was no difference according to the log rank test after adjusting for age, sex and Charlson comorbidity status (figure 4 and 5).

7.4 Survival of patients treated with surgery versus radiation

Results from the adjusted cox regression model indicate that age (65 years or older vs 64 years or younger) is a significant predictor of 5-year mortality (Hazard Ratio[HR]: 2.57; Confidence Interval[CI]: 1.25 – 5.26; Table 13). No significant differences were

observed in 5-year mortality in patients treated with primary laryngectomy versus primary radiation (HR: 1.21; 95%CI: 0.55 - 2.67).

Table 12. Unadjusted hazard ratio of 5-year mortality after diagnosis of subglottic squamous cell carcinoma

Variable	**Unadjusted Hazard Ratio (95% CI)**	**95% Confidence Interval**
Age		
<65	1.0 (reference)	
≥65	2.76	1.37-5.55
Sex		
Female	1.0 (reference)	
Male	1.16	0.58-2.34
Charlson Comorbidity Index		
0	1.0 (reference)	
1	1.62	0.50-5.26
≥2	2.25	0.99-5.07
Treatment		
Radiation	1.0 (reference)	

Primary Laryngectomy	1.33	0.61-2.88

Table 13. Adjusted hazard ratio of 5-year mortality after diagnosis of subglottic squamous cell carcinoma

Variable	**Adjusted* Hazard Ratio (95% CI)**	**95% Confidence Interval**
Age		
<65	1.0 (reference)	
≥65	2.57	1.25-5.26
Sex		
Female	1.0 (reference)	
Male	1.26	0.62-2.56
Charlson Comorbidity Index		
0	1.0 (reference)	
1	1.09	0.32-3.67
≥2	1.97	0.86-4.50
Treatment		

Radiation	1.0 (reference)	
Primary Laryngectomy	1.21	0.55-2.67

* Adjusted for age (<=64, >65), Charlson comorbidity (0, 1, >=2), and sex (male, female)

CHAPTER EIGHT: DISCUSSION

8.1 Summary of Findings in Survival of Subglottic Cancer

In the Canadian province of Ontario, subglottic squamous cell carcinoma represented 1.8% of all new diagnoses of laryngeal cancer from 1995-2009. The 5-year overall survival was 47.3% compared to 57.4% for the other laryngeal subsites.[36] Over this 15 year period, we observed no improvement in overall survival or laryngectomy-free survival. Furthermore, we found no difference in survival comparing patients treated with primary laryngectomy versus radiotherapy.

8.2 Subglottic Carcinoma Characteristics

The demographic characteristics of the patients in our study are consistent with that reported in other studies.[6, 15, 36, 131] Subglottic carcinoma in our cohort represented 1.8% of all laryngeal squamous cell carcinoma. Other studies have found that this incidence ranges from 1.0-8.7% of laryngeal SCC, although the majority of studies report a range from 1-1.6%.[1, 6, 15] Variability in the definition of primary subglottic cancer over time and inclusion of other histologic cancers in the definition of subglottic cancer is likely the reason for the discrepancy in incidence reported in this study compared to other series.[1, 13, 20, 164]

Primary subglottic carcinoma is usually asymptomatic early in the disease process and traditionally thought to present in advanced stage (50-64% of patients).[6, 18, 19, 165] However, we found an even distribution between those patients presenting with early

stage and advanced stage disease. The small number of patients in our series and lack of staging information prior to 2005 likely accounts for this variability in stage presentation. The largest reported study of patients with subglottic squamous cell carcinoma demonstrated a 58.4% (219/375) rate of advanced stage presentation.[18] Taken together, this data indicated that patients are slightly more likely to present with advanced stage disease than early stage disease.

8.3 Subglottic Carcinoma Treatment

The treatment options for primary subglottic carcinoma include surgery (laryngectomy or partial laryngectomy), radiation (+/-chemotherapy) or combination therapy. Direct extralaryngeal extension, a circumferential pattern of intraluminal spread and cartilage invasion result in few patients being candidates for partial laryngectomy as primary treatment.[120] With the exception of few patients undergoing partial- or hemi-laryngectomy, the majority of the patients in other studies underwent total laryngectomy (Table 11). There was significant variability in other studies with respect to primary treatment administered (Table 11). Some authors treated patients with primary surgery[2, 18, 131, 135] while others treated most patients with primary radiotherapy[12, 15, 20, 71, 138]. Furthermore, the indications for combined modality treatment, adjuvant radiation and salvage laryngectomy were often not reported.

In our study, 13 (14.6%) patients underwent primary laryngectomy. Other reports in the literature demonstrate 31-81% of patients treated with primary total laryngectomy and 10-30% of patients treated with partial laryngectomy.[4, 6, 19, 131] We were not able to

determine whether any patients had partial laryngeal surgery in our cohort. In our study, 68.5% of the patients underwent non-surgical management. Other studies reported 12-100% of patients treated with primary radiotherapy.[4, 12, 15, 19, 20, 71, 131] We did not have access to radiation or chemotherapy billing codes, therefore we assumed that if patients did not have a primary laryngectomy they were treated with radiation, however some of these patients may have been treated with palliative intent. Our reported rate of salvage laryngectomy was 24.6%, however this number may be larger as some of the patients in our denominator may have been palliated. It remains unclear from our data and other studies what proportion of patients treated with primary radiation require salvage laryngectomy and whether organ-preservation protocols improve laryngectomy-free survival.

8.4 Survival Outcomes

We reported 5-year overall survival of 47.2%for all patients with a diagnosis of subglottic SCC. Previous studies have reported 5-year overall survival ranging from 25-80% (Tables 8 and 9). Some have suggested that a higher rate of local recurrence particularly at the peristomal region or a high rate of distant metastatic spread up to 32% is responsible for the poor overall survival, however the data is unclear.[13] Previous studies (Tables 8 and 9) suggest that combined modality treatment either surgery plus radiation, chemotherapy plus radiation or radiation followed by salvage surgery offers a survival benefit however, the small sample sizes prevent definitive conclusions.[6, 19, 71] We were unable to determine whether patients in our cohort

received combined modality treatment due to limitations of our databases. Our results do however suggest that there may be no survival benefit with primary laryngectomy.

We demonstrated no change in overall survival or laryngectomy free survival from 1995-2009 (Figures 4 and 5). These results are consistent with previous work by our group and others demonstrating no change in overall survival in patients with glottic and supraglottic carcinomas.[35, 36, 166, 167] Although large randomized trials have demonstrated an improved laryngectomy-free survival for patients with glottic and supraglottic carcinoma treated with concurrent chemoradiation, this benefit has not been demonstrated in population-based studies.[35, 36, 166] The reasons for this are unknown but may be related to patient selection for laryngeal preservation protocols. Additionally, the difficulty in defining primary subglottic carcinoma versus glottic carcinoma with subglottic extension as well as the evolving definition of the superior boundary of the subglottis may have influenced survival trends over the study period.

8.5 Strengths and Limitations

To our knowledge, this is largest study reported in the literature on the outcome of laryngectomy-free survival in patients with subglottic carcinoma. Our survival outcome is robust, accounting for all patients with a diagnosis of subglottic carcinoma in the province of Ontario, Canada. That is, there is no selection bias which is inherent to institutional reviews of survival outcomes. Procedural and diagnostic codes were well-documented.[162] Our study has limitations. We only had T-stage and N-stage information available for 2005 – 2009 and thus the stage analysis was limited.

Furthermore, disease specific survival was not calculated because cause of death has a low sensitivity in cancer registries and population databases. We assumed that patients who did not receive a primary laryngectomy were treated with primary radiation. Some of these patients may have been treated with palliative intent or they may not have undergone any treatment. Lack of radiation and chemotherapy treatment codes limited this analysis.

8.6 Conclusions

Subglottic carcinoma has a low incidence and has a poor prognosis compared to other laryngeal cancer subsites. The reason for poor overall survival in patients with this subsite of laryngeal cancer is unknown but does not appear to be associated with advanced stage at presentation. Overall there was no difference in 5-year mortality rate between patients treated with primary laryngectomy and those treated without laryngectomy. Thus, laryngeal preservation therapy may be considered as a primary option for suitable patients. More research is needed to determine which patients are suitable for laryngeal preservation treatment protocols versus primary laryngectomy.

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APPENDICES

Appendix A. Literature Review Search Strategy

To collect all studies related to subglottic cancer, we searched MEDLINE (January 1960 to September 2020), EMBASE January 1947 to September 2020, and CINAHL (1981-2020). Reference lists of all included studies were also manually searched for additional reports. The following key words were used for the comprehensive search: cancer, carcinoma, malignancy, squamous cell cancer, subglotti*. For MEDLINE the search strategy was (("neoplasms"[MeSH Terms] OR "neoplasms"[All Fields] OR "cancer"[All Fields]) OR ("carcinoma"[MeSH Terms] OR "carcinoma"[All Fields]) OR ("neoplasms"[MeSH Terms] OR "neoplasms"[All Fields] OR "malignancy"[All Fields])) AND (subglottic[All Fields] OR subglottica[All Fields] OR subglottical[All Fields] OR subglottically[All Fields] OR subglottice[All Fields] OR subglottictracheal[All Fields] OR subglottid[All Fields] OR subglottie[All Fields] OR subglottig[All Fields] OR subglottik[All Fields] OR subglottis[All Fields] OR subglottisch[All Fields] OR subglottische[All Fields] OR subglottischen[All Fields] OR subglottischer[All Fields] OR subglottisches[All Fields] OR subglottiscope[All Fields] OR subglottiscopes[All Fields] OR subglottises[All Fields] OR subglottisk[All Fields] OR subglottiske[All Fields]) with limits human and English, result 940 titles. For EMBASE the search strategy was (subglottic*.mp AND (cancer.mp or malignant neoplasm/)) limits English and humans results 618 titles. We search CINAHL for “subglottic*” and retrieved 319 results from 1981-2020, using limits of English-language, human subjects and adult.

Appendix B. NewCastle-Ottawa Quality Assessment Scale for Cohort Studies

Note: A study can be awarded a maximum of one star for each numbered item within the Selection and Outcome categories. A maximum of two stars can be given for Comparability

Selection

1) Representativeness of the exposed cohort
   a) truly representative of the average_____(describe) in the community *****
   b) somewhat representative of the average____in the community *****
   c) selected group of users eg nurses, volunteers
   d) no description of the derivation of the cohort

2) Selection of the non-exposed cohort
   a) drawn from the same community as the exposed cohort *****
   b) drawn from a different source
   c) no description of the derivation of the non-exposed cohort

3) Ascertainment of exposure
   a) secure record (eg surgical records) *****
   b) structured interview *****
   c) written self-report
   d) no description

4) Demonstration that outcome of interest was not present at start of study
   a) yes *****
   b) no

Comparability

1) Comparability of cohorts on the basis of the design or analysis
   a) study controls for_____(select the most important factor) *****
   b) study controls for any additional factor ***** (This criteria could be modified to indicate specific control for a second important factor.)

Outcome

1) Assessment of outcome
   a) independent blind assessment *****
   b) record linkage *****
   c) self report
   d) no description

2) Was follow-up long enough for outcomes to occur
   a) yes (select an adequate follow up period for outcome of interest) *****

b) no

3) Adequacy of follow up of cohorts

a) complete follow up - all subjects accounted for *

b) subjects lost to follow up unlikely to introduce bias - small number lost - > _% (select an adequate %) follow up, or description provided of those lost) *

c) follow up rate <__% (select an adequate %) and no description of those lost

d) no statement

Appendix C. Checklist of Recommendations for Reporting of Observational Studies Using the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Guidelines

	Item No	Recommendation	Location
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	84
Objectives	3	State specific objectives, including any prespecified hypotheses	86
Methods			
Study design	4	Present key elements of study design early in the paper	88
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	90
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	92
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	N/A
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	93
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	88
Bias	9	Describe any efforts to address potential sources of bias	92
Study size	10	Explain how the study size was arrived at	92

Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	92
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	92
		(*b*) Describe any methods used to examine subgroups and interactions	92
		(*c*) Explain how missing data were addressed	92
		(*d*) If applicable, explain how loss to follow-up was addressed	N/A
		(*e*) Describe any sensitivity analyses	
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	95
		(b) Give reasons for non-participation at each stage	96
		(c) Consider use of a flow diagram	96
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	96
		(b) Indicate number of participants with missing data for each variable of interest	96
		(c) Summarise follow-up time (eg, average and total amount)	97
Outcome data	15*	Report numbers of outcome events or summary measures over time	97
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	101
		(*b*) Report category boundaries when continuous variables were categorized	98
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N/A
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	102
Discussion			
Key results	18	Summarise key results with reference to study objectives	104

Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	107
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	106
Generalisability	21	Discuss the generalisability (external validity) of the study results	106
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	5

*Give information separately for exposed and unexposed groups.

Appendix D: Secular Trends in Laryngeal Carcinoma: Incidence, Treatment and Survival

Number of Study	2014 0906 036 000
Team Contacts	**S. Danielle MacNeil** **Salimah Shariff** **Stephen Hall** **Amit Garg** **Jamie Fleet** **John Yoo** **Eric Winquist** **Amardeep Thind** **Kuan Liu**
PIA Approved?	Yes
Last Modified on/by:	April 23, 2013 (DM) April 3, 2013 (DM) March 28, 2013 (DM) March 19, 2013 (AG, JF, SS) March 18, 2013 (DM) May 30, 2013 (DM) June 10, 2013 (DM) June 12, 2013 (DM) June 19, 2013 (DM) July 5, 2013 (DM) Feb 15, 2014 (DM)

Study Description	**Objectives of this Project (Incidence and Trends)** To assess the secular (annual) trends in incidence of laryngeal carcinoma. To assess the secular (annual) trends in treatment of laryngeal carcinoma. To assess secular (annual) trends in 2, 3 and 5 year survival laryngeal carcinoma. To determine if there is improved 2, 3 and 5 year survival and laryngectomy free survival for patients with laryngeal cancer who have been treated with chemotherapy and radiotherapy versus radiation alone **Hypotheses**: The incidence of laryngeal carcinoma will have decreased over the past 19 years, secondary to the decreased rate of smoking. The treatment practices will have shifted from primary radiotherapy and primary surgery to primary chemoradiotherapy and transoral laser surgery. There will be improved survival for patients with advanced stage disease treated with primary surgery. **Main population of interest**: Patients 18 years of age and older with a diagnosis of laryngeal carcinoma, treated with surgery, radiation and/or chemotherapy in the province of Ontario from 1991 to 2010. **Main outcomes of interest**: Outcomes are incidence (number of patients diagnosed with laryngeal cancer per year in the province of Ontario), primary treatment type and 5-year survival.
Accrual period	January 1, 1991 to December 31, 2010. Beginning of Accrual Period: **January 1, 1991** End of Accrual Period: **December 31, 2010**
Max Follow-up Date	The last day of accrual period is December 31, 2010.
Databases Used	RPDB, CIHI-DAD, OHIP, OCR, ODD, HYPERTENSION
Defining the Cohort	
Inception Date	January 1, 1991

Description of Selection Process for Cohort of Interest	▪ *Begin with patients who have a diagnosis of laryngeal carcinoma according to OCR from January 1, 1991 to December 31, 2010 (see Appendix A for applicable diagnostic codes)* *Inclusion Criteria* • *All patients with diagnosis of laryngeal carcinoma* • *Squamous cell histology* • *Begin with all patients in OCR with diagnosis of laryngeal carcinoma during accrual period* • *The date of diagnosis in the OCR is referred to as the index date.* **Exclusion Criteria** ▪ Patients with invalid or missing IKN, age, or sex (data-cleaning step) ▪ Patients that are non-Ontario residents (data-cleaning step) ▪ Death on or before index date
Index date	Date of diagnosis in OCR
Look-back window from index date	Fixed 5 year look-back window from index date (to determine exclusion criteria).

Baseline Patient Characteristics	**PATIENT CHARACTERISTICS** ▪ Assessed at the time of index date, sample Table 2 for format **1. Year of Index Date (report calendar year)** **2. Gender (female, N(%))** **3. Age at index date** ▪ Mean age (years) ▪ Median age (years) ▪ Standard deviation for age (years) ▪ Age categories (crude number) ▪ <50 years ▪ 50-59 years ▪ 60-69 years ▪ 70-79 years ▪ >=80 years ***4. Socioeconomic status*** • Income quintile, for missing impute as 3 (median income) ***5. Residency status, rural or urban (report only categorical number (%)), for 'missing', code this as urban*** ***6. Cancer treatment centre (report only categorical number (%))*** ***7. Charlson Comorbidity Index (CCI)*** • Use 5-year look back window to calculate • Possible scores are 0, 1, 2, >=3 • No hospitalization or missing values to be denoted '0' ***8. Elixhauser*** • Use 5-year look back window to calculate Elixhauser,using ICES algorithm ***9. ADG*** • ***1991-use DAD for 1 year look back*** • ***Use 1 year look back 1992-1996*** • ***Use 5 year look back 1997-2010*** • ***Record ADG sum as groupings 1-12, 13-20, 20-34*** ***10. Comorbidities*** • ***Use Appendix C to define comorbidities*** ***11. Previous treatment for Head and Neck Cancer*** • Use 5-year look back window to calculate • Number of patients with past history of radiotherapy treatment or follow-up in 5 year period prior to index date and diagnosis of head and neck cancer (Appendix B)

- Number of patients with past history of major head and neck cancer resection in 5 year period prior to index date and diagnosis of head and neck cancer (Appendix B)

12. Tumor stage

- Crude number stage 1-4 and percent

13. Tumor site (Appendix D)

Laryngeal (total and for each subsite)

- Glottis
- Supraglottis
- Subglottis

*crude number and percent of larynx cancer cases reported by age group and per year

Outcomes	**OUTCOMES** **Complete Tables 1 and 2 for feasibility. Once all investigators have signed off on Tables 1 and 2 then proceed with remaining tables.** **1. Treatment trends (Appendix E)** ▪ For each cancer site as well as for total sample per year determine number of patients who received each treatment type ▪ Group 1 :Laryngectomy, primary treatment based on surgery, no other treatments administered for 5 years post surgery ▪ Group 2: Non-laryngectomy surgery, primary treatment based on surgery, no other treatments administered for 5 years post surgery ▪ Group 3: Open surgery followed by Radiation, surgery and radiation therapy administered within 4 months ▪ Group 4: Endoscopic surgery followed by radiation, endoscopic surgery followed by radiation administered within 4 months ▪ Group 5a: Open Surgery followed by radiation, radiation therapy administered from 4 months to 5 years after surgery ▪ Group 5b: Endoscopic surgery followed by radiation, radiation therapy administered from 4 months to 5 years after surgery ▪ Group 6: Open surgery followed by Chemoradiation, surgery followed by chemotherapy and radiation therapy both administered within 4 months of surgery ▪ Group 7: Endoscopic surgery followed by chemoradiation, endoscopic surgery followed by chemotherapy and radiation both administered within 4 months. ▪ Group 8a: Open Surgery followed by chemoradiation, chemoradiation administered from 4 months to 5 years after surgery ▪ Group 8b: Endoscopic surgery followed by chemoradiation, chemoradiation administered from 4 months to 5 years after surgery ▪ Group 9: Radiotherapy, primary treatment based on radiotherapy without chemotherapy, no other treatments administered for 5 years post radiation ▪ Group 10: Concurrent Chemotherapy and Radiotherapy, primary treatment based on radiotherapy with chemotherapy, chemotherapy followed by radiation administered within 2 months, no other treatments administered for 5 years ▪ Group 11: Radiotherapy followed by surgery, radiotherapy followed by surgery administered within 6 months ▪ Group 12: Radiotherapy followed by surgery, radiotherapy followed by surgery administered 6 months to 5 years after treatment ▪ Group 13: Concurrent Chemotherapy and radiotherapy followed by surgery , chemotherapy and radiation therapy administered within 2

months, followed by surgery administered within 6 months of last treatment

- Group 14: Concurrent chemotherapy and radiotherapy followed by surgery, chemotherapy and radiation administered within 2 months, followed by surgery administered 6 months to 5 years of last treatment
- Group 15: Chemotherapy only, no other treatment administered within 5 years
- Group 16: No treatment given or data not available

- See Tables 2-7 for format

2. Trends in Surgery (Appendix F)

- For entire cohort of patients
- For each cancer site as well as for total sample per year
- Report number of patients who had OHIP billing code for surgery
- Crude number and percent of procedures per year
- Include procedures that occur on the same day
- For each surgical procedure record if one procedure for each group occurred eg. For neck dissection group if R910, R911 and R915 were recorded for same patient, this is recorded as one neck dissection procedure for that patient (yes/no procedure for each surgical procedure group).
- See Tables 8, 9 and 10 for format

3. 5 year overall survival

- Figure 1: K-M 5 year overall survival all laryngeal cancer (3 eras 1991-1996, 1997-2002, 2003-2007)

- Figure 2: K-M 5 year overall survival glottic cancer (3 eras 1991-1996, 1997-2002, 2003-2007)

- Figure 3: K-M 5 year overall survival supraglottic cancer (3 eras 1991-1996, 1997-2002, 2003-2007)

- Calculate survival from date of diagnosis in OCR to date of death in RPDB

4. 5 year Overall Survival Survival for Early and Advanced Stage Laryngeal Cancer

- Figure 4: K-M 5 year overall survival all laryngeal cancer 2004-2007, early stage and advanced stage in same graph

- Figure 5: K-M 5 year overall survival glottic cancer 2004-2007, early stage and advanced stage in same graph

- Figure 6: K-M 5 year overall survival supraglottic cancer 2004-2007, early stage and advanced stage in same graph

- Calculate survival from date of diagnosis in OCR to date of death in RPDB

5. 5 year Overall Survival Comparing Treatment Groups

- Figure 7: K-M 5 year overall survival early glottic cancer 2004-2007 for 6 treatment groups.

- Figure 8: K-M 5 year overall survival advanced stage glottic cancer 2004-2007 for 6 treatment groups

- Figure 9: K-M 5 year overall survival early stage supraglottic cancer, 2004-2007 for 6 treatment groups

- Figure 10: K-M 5 year survival advanced stage supraglottic cancer, 2004-2007 for 6 treatment groups

- Calculate survival from date of diagnosis in OCR to date of death in RPDB

6. 5 year laryngectomy free survival

- Figure 11: K-M 5 year laryngectomy free survival all laryngeal cancer (3 eras 1991-1996, 1997-2002, 2003-2007)

- Figure 12: K-M 5 year laryngectomy free survival glottic cancer (3 eras 1991-1996, 1997-2002, 2003-2007)

- Figure 13: K-M 5 year laryngectomy free survival supraglottic cancer (3 eras 1991-1996, 1997-2002, 2003-2007)

- Calculate survival from date of diagnosis in OCR to date of death in RPDB

  - Exclude patients who have had a laryngectomy (OHIP code: M081, M084, S068;) at any time between date of diagnosis and 5 years from date of diagnosis.

7. 5 year Laryngectomy free Survival for Early and Advanced Stage Laryngeal Cancer

- Figure 14: K-M 5 year laryngectomy free survival all laryngeal cancer 2004-2007, early stage and advanced stage in same graph
- Figure 15: K-M 5 year laryngectomy free survival glottic cancer 2004-2007, early stage and advanced stage in same graph
- Figure 16: K-M 5 year laryngectomy free survival supraglottic cancer 2004-2007, early stage and advanced stage in same graph
- Calculate survival from date of diagnosis in OCR to date of death in RPDB
- Exclude patients who have had a laryngectomy (OHIP code: M081, M084, S068;) at any time between date of diagnosis and 5 years from date of diagnosis.

8. 5 year Laryngectomy free Survival Comparing Treatment Groups

- Figure 17: K-M 5 year laryngectomy free survival early glottic cancer 2004-2007 for 6 treatment groups.
- Figure 18: K-M 5 year laryngectomy free survival advanced stage glottic cancer 2004-2007 for 6 treatment groups
- Figure 19: K-M 5 year laryngectomy free survival early stage supraglottic cancer, 2004-2007 for 6 treatment groups
- Figure 20: K-M 5 year laryngectomy free survival advanced stage supraglottic cancer, 2004-2007 for 6 treatment groups
- Calculate survival from date of diagnosis in OCR to date of death in RPDB
- Exclude patients who have had a laryngectomy (OHIP code: M081, M084, S068;) at any time between date of diagnosis and 5 years from date of diagnosis.

9. Proportional Hazard Analysis of the Predictors of Local Surgery versus Radiation Therapy Among Patients with Early-Stage Laryngeal Cancer

- Use data 2004-2010
- Use only treatment groups “local surgery” and “radiation”
- Local surgery: groups 2, 5b, 8b
- Radiation: groups 4, 9, 11, 12
- See table 11 for format

10. **Proportional Hazard Analysis of the Predictors of Laryngectomy versus Radiation Therapy Among Patients with Advanced-Stage Laryngeal Cancer**

    - Use data 2004-2010
    - Use only treatment groups “laryngectomy” and “radiation”
    - Laryngectomy: groups 1, 3, 5a, 6, 8a
    - Radiation: groups 4, 7, 9, 10, 11, 12, 13, 14
    - See table 12 for format

11. **Hazard Ratio Model Predicting 5 year overall survival among patients with early-stage laryngeal cancer**

    - Use data 2004-2007
    - Adjust for age, ADG comorbidity score and year of diagnosis
    - See table 13 for format

12. **Hazard Ratio Model Predicting 5 year laryngectomy free survival among patients with early-stage laryngeal cancer**

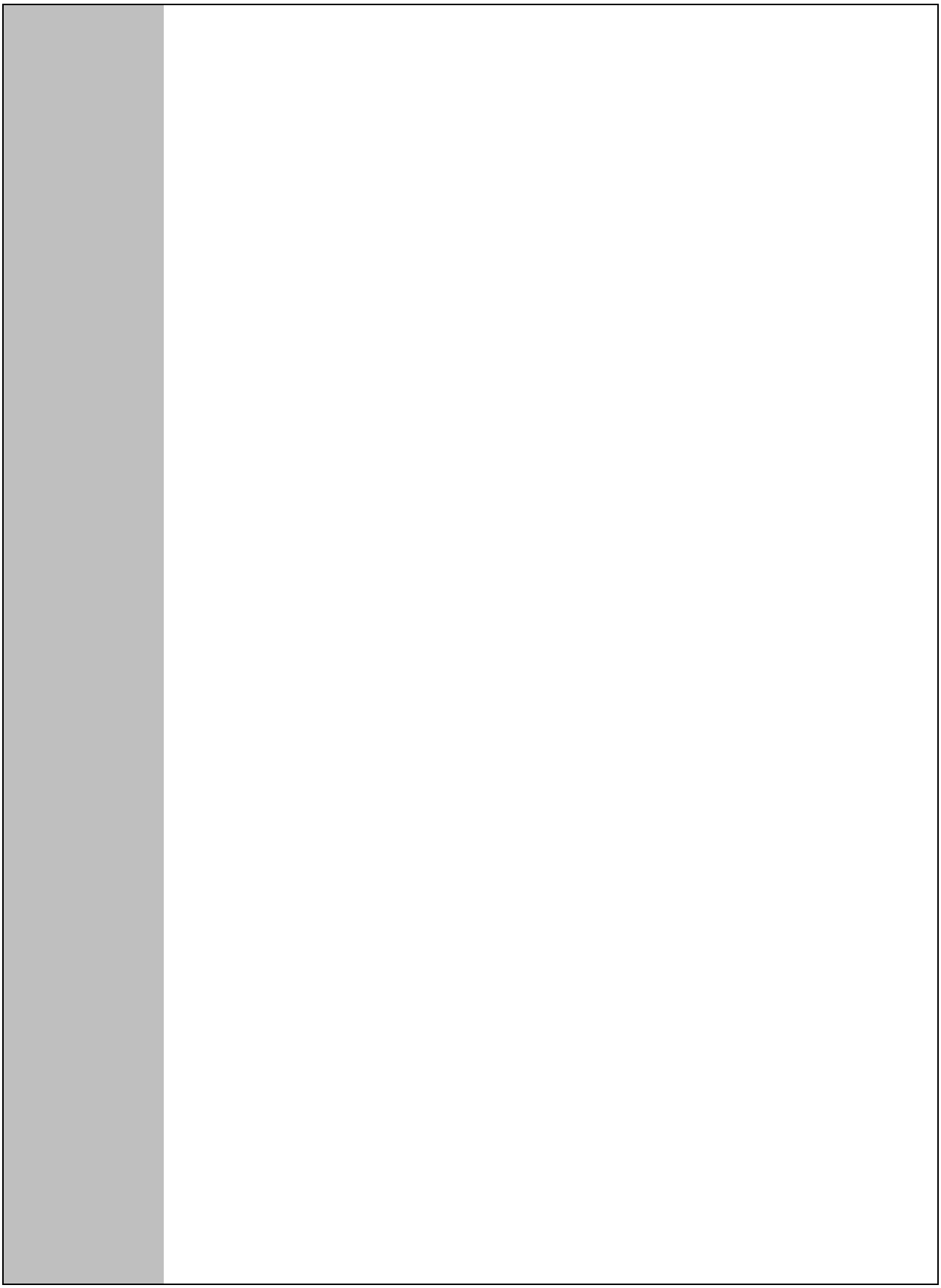
    - Use data 2004-2007
    - Adjust for age, ADG comorbidity score and year of diagnosis
    - See table 14 for format

13. **Hazard Ratio Model Predicting 5 year overall survival among patients with advanced stage laryngeal cancer**

    - Use data 2004-2007
    - Adjust for age, ADGcomorbidity score and year of diagnosis
    - See table 15 for format

14. **Hazard Ratio Model Predicting 5 year laryngectomy free survival among patients with advanced stage laryngeal cancer**

    - Use data 2004-2007
    - Adjust for age, ADG comorbidity score and year of diagnosis
    - See table 16 for format



Appendix A: Diagnostic codes and histologic codes for inclusion of patients with Laryngeal Carcinoma

Microsoft Excel 97 - 2004 Sheet

Appendix B: Previous History of Head and Neck Radiotherapy or Major Head and Neck Surgery for Head and Neck Cancer

Microsoft Excel 97 - 2004 Worksheet

Appendix C: Comorbidities

COMORBIDITIES.doc

Appendix D: Tumor Subsites

Microsoft Excel 97 - 2004 Sheet

Appendix E: Type of treatment

Microsoft Excel 97 - 2004 Sheet

Appendix F : Type of Surgery

Microsoft Excel 97 - 2004 Sheet

Table 1. Cohort selection	
Diagnosis of laryngeal carcinoma (OCR) and histology of squamous cell carcinoma (Appendix A)	N =
• Invalid IKN, missing date of birth, missing sex	N =
• Non-Ontario Residents	N=
• Death on or before index date	N =
Number of patients in cohort	N =
# of patients with diagnosis of glottic cancer	N =
# of patients with diagnosis of supraglottic cancer	N =
# of patients with diagnosis of subglottic cancer	N =

Table 1: Demographics of laryngeal cancer patients, 1991-2010

Variable		1991-1996	1997-2002	2003-2010	P value
Demographics					
Gender	N=, (%)				
Female	N=, (%)				
Male	N=, (%)				
Age					
Median (IQR)	Median (25^{th}, 75^{th})				
Mean (SD)	Mean (SD)				
<50	N=, (%)				
50-59	N=, (%)				
60-69	N=, (%)				
70-79	N=, (%)				
>=80	N=, (%)				
Socioeconomic status					
Low					
2					
3					
4					
High					
Residency Status					
Urban					
Rural					
Cancer Treatment Centre					
1					
2					
3					
4					
5					
6					
7					
8					
9					
10					

11					
12					
13					
Co-morbidity (5 years prior to index date)					
Charlson Comorbidity Index					
Median (IQR)	Median (25^{th}, 75^{th})				
0					
1					
2					
>=3					
Elihxauser					
0					
1					
2					
3					
>=4					
ADG					
0-12					
13-20					
21-34					
Comorbidities					
Abdominal aortic aneurysm repair/aortic bypass					
Alcoholism					
Arrhythmia					
Cancer					
Carotid endarterectomy					
Chronic kidney disease					
Chronic liver disease					
Chronic lung disease					
Coronary artery disease					
Dementia					
Diabetes mellitus					
Gastrointestinal Bleeding					
Heart failure					
HIV					

Hypertension					
Myocardial Infarction (MI)					
Peripheral vascular disease					
Pneumonia					
Stroke/Transient ischemic attack (TIA)					
Previous Treatment for Head and Neck Cancer (5years prior to index date)					
Radiation	N (%)				
Surgery	N (%)				
Tumor Stage (All cancers)					
I					
II					
III					
IV					
Tumor Stage (Glottis)					
I					
II					
III					
IV					
Tumor Stage (Supraglottis)					
I					
II					
III					
IV					
Tumor Site					
Glottis					
Supraglottis					
Subglottis					

Table 2: Treatment Trends Early Stage Laryngeal Cancer, 2004-2010

Variable	2004	2005	2006	2007	2008	2009	2010
Laryngectomy Groups 1, 3, 5a, 8a, 6							
Local Surgery Groups 2, 5b, 8b							
Radiation Groups 4, 9, 11, 12 +radiation (NACRS)							
Chemoradiation groups 7, 10, 13, 14 + chemoradiation (NACRS)							
Chemotherapy Group 15 + chemo (NACRS)							
No treatment (group 16)							

Table 3: Treatment Trends Advanced Stage Laryngeal Cancer, 2004-2010

Variable	2004	2005	2006	2007	2008	2009	2010
Laryngectomy Groups 1, 3, 5a, 8a, 6							
Local Surgery Groups 2, 5b, 8b							
Radiation Groups 4, 9, 11, 12 +radiation (NACRS)							
Chemoradiation groups 7, 10, 13, 14 + chemoradiation (NACRS)							
Chemotherapy Group 15 + chemo (NACRS)							
No treatment (group 16)							

Table 4: Treatment Trends Early Stage Glottic Cancer, 2004-2010

Variable	2004	2005	2006	2007	2008	2009	2010
Laryngectomy Groups 1, 3, 5a, 6, 8a							
Local Surgery Groups 2, 5b, 8b							
Radiation Groups 4, 9, 11, 12 +radiation (NACRS)							
Chemoradiation groups 7, 10, 13, 14 + chemoradiation (NACRS)							
Chemotherapy Group 15 + chemo (NACRS)							
No treatment (group 16)							

Table 5: Treatment Trends Advanced Stage Glottic Cancer, 2004-2010

Variable	2004	2005	2006	2007	2008	2009	2010
Laryngectomy Groups 1, 3, 5a, 6, 8a							
Local Surgery Groups 2, 5b, 8b							
Radiation Groups 4, 9, 11, 12 +radiation (NACRS)							
Chemoradiation groups 7, 10, 13, 14 + chemoradiation (NACRS)							
Chemotherapy Group 15 + chemo (NACRS)							
No treatment (group 16)							

Table 6: Treatment Trends Early Stage Supraglottic Cancer, 2004-2010

Variable	2004	2005	2006	2007	2008	2009	2010
Laryngectomy Groups 1, 3, 5a, 6, 8a							

Local Surgery Groups 2, 5b, 8b							
Radiation Groups 4, 9, 11, 12 +radiation (NACRS)							
Chemoradiation groups 7, 10, 13, 14 + chemoradiation (NACRS)							
Chemotherapy Group 15 + chemo (NACRS)							
No treatment (group 16)							

Table 7: Treatment Trends Advanced Stage Supraglottic Cancer, 2004-2010

Variable	**2004**	**2005**	**2006**	**2007**	**2008**	**2009**	**2010**
Laryngectomy Groups 1, 3, 5a, 6, 8b							
Local Surgery Groups 2, 5b, 8b							
Radiation Groups 4, 9, 11, 12 +radiation (NACRS)							
Chemoradiation groups 7, 10, 13, 14 + chemoradiation (NACRS)							
Chemotherapy Group 15 + chemo (NACRS)							
No treatment (group 16)							

Table 8: Surgical Procedures (All Laryngeal Cancer)																				
Variable	**1991**	**1992**	**1993**	**1994**	**1995**	**1996**	**1997**	**1998**	**1999**	**2000**	**2001**	**2002**	**2003**	**2004**	**2005**	**2006**	**2007**	**2008**	**2009**	**2010**
Total Number of patients																				
Total Number of Procedures																				
Laryngectomy																				
Non-laryngectomy																				
Neck Dissection																				
Regional Flap																				
Free flap																				

Table 9: Surgical Procedures (Glottic Cancer)																				
Variable	**1991**	**1992**	**1993**	**1994**	**1995**	**1996**	**1997**	**1998**	**1999**	**2000**	**2001**	**2002**	**2003**	**2004**	**2005**	**2006**	**2007**	**2008**	**2009**	**2010**
Total Number of patients																				
Total Number of Procedures																				
Laryngectomy																				
Non-laryngectomy																				
Neck Dissection																				
Regional Flap																				
Free flap																				

Table 10: Surgical Procedures (Supraglottic Cancer)

Variable	1991	1992	1993	1994	1995	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010
Total Number of patients																				
Total Number of Procedures																				
Laryngectomy																				
Non-laryngectomy																				
Neck Dissection																				
Regional Flap																				
Free flap																				

Figure 1: K-M 5 year overall survival all laryngeal cancer (3 eras 1991-1996, 1997-2002, 2003-2007)

Figure 2: K-M 5 year overall survival glottic cancer (3 eras 1991-1996, 1997-2002, 2003-2007)

Figure 3: K-M 5 year overall survival supraglottic cancer (3 eras 1991-1996, 1997-2002, 2003-2007)

Figure 4: K-M 5 year overall survival all laryngeal cancer 2004-2007, early stage and advanced stage in same graph

Figure 5: K-M 5 year overall survival glottic cancer 2004-2007, early stage and advanced stage in same graph

Figure 6: K-M 5 year overall survival supraglottic cancer 2004-2007, early stage and advanced stage in same graph

Figure 7: K-M 5 year overall survival early stage glottic cancer 2004-2007 for 6 treatment groups.

Figure 8: K-M 5 year overall survival advanced stage glottic cancer 2004-2007 for 6 treatment groups

Figure 9: K-M 5 year overall survival early stage supraglottic cancer, 2004-2007 for 6 treatment groups

Figure 10: K-M 5 year overall survival advanced stage supraglottic cancer, 2004-2007 for 6 treatment groups

Figure 11: K-M 5 year laryngectomy free survival all laryngeal cancer (3 eras 1991-1996, 1997-2002, 2003-2007)

Figure 12: K-M 5 year laryngectomy free survival glottic cancer (3 eras 1991-1996, 1997-2002, 2003-2007)

Figure 13: K-M 5 year laryngectomy free survival supraglottic cancer (3 eras 1991-1996, 1997-2002, 2003-2007)

Figure 14: K-M 5 year laryngectomy free survival all laryngeal cancer 2004-2007, early stage and advanced stage in same graph

Figure 15: K-M 5 year laryngectomy free survival glottic cancer 2004-2007, early stage and advanced stage in same graph

Figure 16: K-M 5 year laryngectomy free survival supraglottic cancer 2004-2007, early stage and advanced stage in same graph

Figure 17: K-M 5 year laryngectomy free survival early glottic cancer 2004-2007 for 6 treatment groups.

Figure 18: K-M 5 year laryngectomy free survival advanced stage glottic cancer 2004-2007 for 6 treatment groups

Figure 19: K-M 5 year laryngectomy free survival early stage supraglottic cancer, 2004-2007 for 6 treatment groups

Figure 20: K-M 5 year laryngectomy free survival advanced stage supraglottic cancer, 2004-2007 for 6 treatment groups

Table 11: Predictors of Local Surgery vs Radiation Therapy Among Patients with Early-Stage Laryngeal Cancer, 2004-2010

Category	OR (95% CI)
Year of Diagnosis	
2004	
2005	
2006	
2007	
2008	
2009	
2010	
Gender	
Male	
Female	
Age	
<70	
>=70	
Socioeconomic Status	
Low	
2	
3	
4	
High	

Subsite	
Glottic	
Supraglottic	
Charlson Comorbidity Index	
0	
1	
2	
>=3	
ADG	
0-12	
13-20	
20-34	
Individual Comorbidities	
Alcoholism	
Arrhythmia	
Chronic liver disease	
Chronic lung disease	
Coronary Artery Disease	
Dementia	
Diabetes	
Heart Failure	
Hypertension	

Table 12: Predictors of Laryngectomy vs Radiation Therapy Among Patients with Advanced-Stage Laryngeal Cancer, 2004-2010

Category	OR (95% CI)
Year of Diagnosis	
2004	
2005	
2006	
2007	
2008	
2009	
2010	
Gender	
Male	
Female	
Age	
<70	
>=70	
Socioeconomic Status	
Low	
2	
3	
4	

High	
Subsite	
Glottic	
Supraglottic	
Charlson Comorbidity Index	
0	
1	
2	
>=3	
ADG	
0-12	
13-20	
20-34	
Individual Comorbidities	
Alcoholism	
Arrhythmia	
Chronic liver disease	
Chronic lung disease	
Coronary Artery Disease	
Dementia	
Diabetes	
Heart Failure	
Hypertension	

Table 13: Hazard Ratio Model Predicting 5 year overall survival among patients with early-stage cancer, 2004-2007

Category	OR (95% CI)
Treatment	
Local Surgery	
Radiation	
Subsite	
Glottic	
Supraglottic	

Table 14: Hazard Ratio Model Predicting 5 year laryngectomy free survival among patients with early-stage cancer, 2004-2007

Category	OR (95% CI)
Treatment	
Local Surgery	
Radiation	
Subsite	
Glottic	
Supraglottic	

Table 15: Hazard Ratio Model Predicting 5 year Overall Survival Among Patients with Advanced-stage laryngeal cancer, 2004-2007	
Category	OR (95% CI)
Treatment	
Local Surgery	
Radiation	
Subsite	
Glottic	
Supraglottic	

Table 16: Hazard Ratio Model Predicting 5 year laryngectomy Free Survival Among Patients with Advanced-stage laryngeal cancer, 2004-2007	
Category	OR (95% CI)
Treatment	
Local Surgery	
Radiation	
Subsite	
Glottic	
Supraglottic	

Appendix E: ICES Project-Specific Privacy Impact Assessment Form

INSTITUTE FOR CLINICAL EVALUATIVE SCIENCES

PROJECT-SPECIFIC PRIVACY IMPACT ASSESSMENT FORM

(FOR ALL ICES PROJECTS)

A. PROJECT TITLE

Secular Trends in Laryngeal Carcinoma: Incidence, Treatment and Survival

B. THE PROJECT

Select the PHIPA Section that applies to this project as the privacy implications are different.

1) Please indicate below whether this Project falls into PHIPA Section 45i and/or 45ii OR Section 44(iii). (see "Completing PIAs" document and/or Reference*)

Section 45:

i)	The purpose of the project is analysis or compiling statistical information related to evaluation, monitoring, planning, resource allocation, service delivery and management of the health care system;	☒ **Y**	Sec. 45 i)
	and/or		
ii)	This project is creating infrastructure or a framework for the activity above?		
	or		
		☐ **Y**	Sec. 45 ii)

Section 44:

iii)	Research purpose other than activities listed in Section 45 above (see "Completing PIAs" document or contact Privacy Office).	☐ **Y**	Sec. 44 iii)

2) Has an electronic PIA and Proposal been submitted to the Program Administrator? (A DCP may be an acceptable substitute in some circumstances) ☒ **Y**

3) Is data planned for use in this project to be linked with other data sets? ☒ **Y**

4) Is the rationale for the planned data linkage described in the proposal (or in the DCP?) **If not, please append.**

☒ **Y** ☐ **N**

5) From a Process and/or Technology perspective, is this project :

- Introducing a novel methodology or direction? ☐ **Y**
- Introducing significant changes from an existing project? ☐ **Y**
- Implementing a new remote implementation? ☐ **Y**
- Introducing a new technology? ☐ **Y**

If yes, security consultation with CISO may be of benefit for this project

6) Is this a trainee / student / fellow project? ☒ **Y** ☐ **N**

7) If you answered "yes" in question 6, please identify the student's designation below:

☐ **MSc** ☐ **PhD** ☒ **Other** ICES@Western Faculty Scholar

8) Name the project participants / staff and provide contact details here.
Use pull-down lists under role to describe each person's activity.

At least one ICES scientist must be named for all projects as Investigator or Co-investigator.
Include affiliations/qualifications for all scientists who are <u>not</u> ICES scientists/adjunct scientists. You may provide affiliations/qualifications on an attached sheet or electronically.

NAME / AFFILIATION/ QUALIFICATIONS	ROLE	PHONE	E-MAIL
Amit Garg	Co-investigator		
Salimah Shariff, PhD	Co-investigator		
Stephen Hall, MD, MSc	PI		
S. Danielle MacNeil, MD, MSc	Co-PI		
John Yoo, MD	Co-investigator		
Amardeep Thind, MD, PhD	Co-investigator		
Eric Winquist, MD, MSc	Co-investigator		
Jamie Fleet, BSc	Co-investigator		
Kuan Liu, MMath	PB		
	PI		
	PI		
	PI		
	PI		
	PI		

9) Please name team members who will have **access to the individual-level data**.

(Have you provided names and related qualifications as requested above?)

Kuan Liu, Analyst, ICES@Western

10) What types of data are being used? (check all that apply)

Identify those, which are being linked to administrative datasets.

Type	To be linked
☒ ICES Administrative Data	
☐ Survey	☐
☐ Registry	☐
☐ Primary clinical	☐
☐ Chart abstraction	☐
☐ Electronic Health Record	☐
☐ Web-based data collection	☐
☐ Other: (Please indicate below)	☐

11) What databases are being used? (check all that apply)

Indicate dates of data to be used. (Note: *Year* means year for which data is summarized. Fiscal year is defined as: 1 April 2008 – 31 March 2009 = fiscal 2008.

Type	Fiscal year	
Administrative Databases	**Year**	
☒ CIHI-DAD	1991	to 2010
☐ CIHI-SDS		to
☐ CIHI-NACRS		to
☐ CIHI-CCRS		to
☐ CIHI-NRS		to
☐ ODB		to
☒ OHIP	1991	to 2010

☐ HCD	to
☐ LOC	to
☐ OMHRS	to
☒ RPDB	N/A
☐ CAPE	N/A
☐ IPDB	N/A
☐ CPDB	N/A
☐ Other	
☐	
☐	

Composite Databases (i.e., OHIP + CIHI + ODB)	**Day/Month/Yr**
☐ Asthma*	
☐ CHF *	
☐ COPD*	
☒ Hypertension	
☐ MOMBaby	
☒ ODD	
☐ OMID	
☐ PIBD*	
☐ Other	
☐	

* Permission/notification required before use of asterisked datasets. Please contact Director, Information Management for details.

Restricted Databases – Registry – Permission Required

☐ CCN* (approval required)	to	
☒ OCR** (approval required)	January 1, 1991	to December 31, 2010
☐ RCSN † (approval required)	to	
☐ EFFECT✱(approval required)	to	
☐ OBSP** (approval required)		
☐ Cytobase** (approval required)		
Others: (Please indicate below)		
	to	
	to	

* Note: all studies planning use of CCN data must be approved by an external process through Program Lead - CardioDIP

** All studies planning use of Cancer Care Ontario databases (ie, OCR, OBSP, Cytobase) must be logged and submitted to Cancer Care Ontario by Chief Privacy Officer (contact for details) and approved by additional process.

† Written application for use of Stroke Data is required

✱Written application / approval required by Program Lead - CardioDIP

Surveys	Linked
☐ OHS*	☐
☐ NPHS*	☐
☐ CCHS*	☐
☐ PCAS	☐
☐ OTHER:	☐

* **Restricted to MOHLTC mandated and/or funded projects.**

Other Databases	Year	
☐ ARIS	to	
☐ MIS	to	
☐ OTR	to	
☐ Custom Clinical dataset		to

☐ Others: (Please indicate below)
to

12) i) Is probabilistic linkage planned? ☐ **Y** ☒ **N**

ii) Please list any personal health information/data that will be collected and / or used in this study, which *potentially*, alone or *in combination*, could be associated *with increased risk to privacy* (identification of the individual).

☒ Birth date ☒ Postal Code ☐ Other (list below)

C. DATA SECURITY/PRIVACY IMPACT

A. Internal Projects:

1) Complies with all ICES policies / procedures ☒ **Y**

Describe perceived need for modification:

None

B. External Projects (e.g. Chart abstraction, EHM/EMR, primary data collection) have special privacy and security data concerns.

ICES Staff Research Coordinator and/or Analyst should be designated for these projects.

☐ **Y**

1) Complies with all ICES policies / procedures

Describe perceived need for modification:

2) MRNs sent to hospitals in password-protected Excel files ☐ **Y**

(see SOP DM005)

3) For primary data collection projects using laptops/USB key/mobile devices:

- Encryption software in place. ☐ **Y**
- 2 levels of unique passwords must comply with ICES password policy. ☐ **Y**
- Anonymization at collection point: collected under unique study number. ☐ **Y**
- Data collection tool complies with ICES standards for primary databases on laptops. (see Mobile Devices Policy) ☐ **Y**

☐ **Y** ☐ **N**

4) Are complete copies of reports / tests required?

If Yes:

- Limited numbers of reports may be scanned where abstraction difficult or untenable. Consult the Privacy Office. ☐ **Y**
- Paper reports / tests will be de-identified; assigned a unique number only and couriered to ICES. ☐ **Y**

5) Append methods describing encryption methods and protections, if you plan to transmit data back to ICES. ☐ **Y**

D. PUBLIC BENEFIT

(Legislation requires completion of this section)

1) What is the public benefit of this Data use: (eg. Research that contributes to the effectiveness, quality, equity and efficiency of health care in Ontario) that are expected / anticipated from the project? Identify any potential impact.

The purpose of this project is to determine the incidence, treatment trends and 5 year survival of patients with laryngeal cancer treated in the province of Ontario from 1991-2010. Laryngeal cancer is divided into three subsites: subglottic; supraglottic and glottic. Several randomized controlled trials performed more than twenty years ago have demonstrated improved 5-year survival and improved laryngectomy-free survival when chemotherapy is added to radiotherapy. The method of delivering radiothrapy has changed since these landmark studies (specifically, the current method is IMRT versus conventional radiation). Additionally, the last 10 years has seen a rise in minimally invasive surgery for laryngeal cancer. The proposed project will determine whether changes in treatment for laryngeal cancer has influenced the 2, 3 and 5 year survival and laryngectomy-free survival from 1991-2010. This project has the potential to change the treatment practices of laryngeal cancer in Ontario.

E. ESTIMATION OF HARM

(Legislation requires completion of this section)

Note: Cell sizes less than or equal to 5 cannot be reported without prior written approval from the President and CEO of ICES.

1) Please describe the level at which the results will be reported (e.g. level of individuals, institution or region – smallest units)

The results will be reported at the aggregate level and results less than 5 will be supressed and reported as <=5.

2) Describe any reasonably foreseeable harms that may arise from the use of the data. Are there any ways this study might identify, stigmatize, or otherwise harm patients, practitioners or institution(s)? How will these reasonably foreseeable harms be addressed?

None

F. ALTERNATIVES

(Legislation requires completion of this section)

1) Is it possible to do this research without using personal health information?

☐ **Y** ☒ **N**

2) Were any alternative methods considered / rejected as less privacy-invasive for achieving the desired objectives? If so, please describe briefly (this provides a means of assessing any real / potential privacy-adverse impact which may be challenged by external sources). ☒ **Y** ☐ **N**

Randomized controlled trials were not considered feasible due to the high cost and long-term nature of these studies.

G. TIMEFRAME, DATA RETENTION/DESTRUCTION

1) What is the proposed time frame of the project:

- Anticipated start-up date: 01/05/2013 (dd/mm/yyyy)
- Anticipated completion date: 30/05/2014 (dd/mm/yyyy)

2) Retention and disposal policies.

Stipulate retention prior to dataset destruction period.

Notification to PI to be sent on: Jan-13 (mm/yy)

- Document shredding. ☒ **Y**
- Destruction of electronic media (magnetic and optical disks, cartridges, CDs). ☒ **Y**
- Dataset Destruction date: 30/05/2018 (dd/mm/yy):

H. FINANCIAL INFORMATION

1) What is the funding source for this study?

ICES – Core Budget *

* Do not use unless expenditures have been pre-approved and included in the ICES core budget.

- Ministry Workplan (MOHLTC)* ☐ **Y**
- ICES Funded (non-MOHLTC/non-grant)* ☐ **Y**

Externally Funded

- MOHLTC Program Funded (Special Projects) ☐ **Y**
- CCO ☐ **Y**
- Peer Reviewed Grant (Specify Source) [ ] ☐ **Y**
- External Contract ☐ **Y**
- MOHLTC Third Party Funded (MOHLTC funds held at another institution.)
- Other funding source (Specify Source) [ICES@Western Faculty Scholars Program] ☐ **Y**
  ☒ **Y**

2) PAW: Have you completed and submitted a Project Activation Worksheet? ☒ **Y**

NOTE: A project TRIM number will not be assigned unless the budget section of the PAW is completed.

I. ETHICS APPROVAL STATUS

- Ethics approval sought by President and CEO and Chief Privacy Officer (anonymized data studies with administrative data) ☒ **Y**
- Chart abstraction study – ethics approval obtained (append copies of REB approval) ☐ **Y**
- Clinical study – ethics approval obtained (append copies of REB approval) (Include patient consent form ***if applicable***.) ☐ **Y**

J. COMPLIANCE WITH CORPORATE RULES FOR ALL STAFF

Is a data-sharing agreement required for this project? ☐ **Y** ☒ **N**

- If yes:
    - Has the Privacy Office and the Program Administrator been notified? **OR** ☐ **Y** ☐ **N**
    - Data sharing agreements have been signed. ☐ **Y** ☐ **N**
- Confidentiality agreements have been signed by ALL project staff. ☒ **Y**
- All project participants have been familiarized with ALL ICES privacy and confidentiality policies and procedures. ☒ **Y**
- Copies of proposal, Privacy Impact Assessment form and Project Activation Worksheets have been filed with the Program Administrator. Electronic copies of each of these have been sent to the ICES Privacy Office. ☒ **Y**
- If external Ethics approval has been sought, append copy to documents ☐ **Y**
- Cell sizes less than or equal to 5 cannot be reported (any exceptions must be approved in writing by ICES President and CEO). ☒ **Y**
- Your interest in the disclosure of the data for your research purpose will not result in actual, perceived or potential conflict of interest with your other duties as researcher. ☒ **Y**
- You have received and agree with ICES Media Relations Policy ☒ **Y**
- You have read and agree with the ICES Conflict of Interest Policy ☒ **Y**

K. SOP'S AND POLICIES

- You and your project team have reviewed all current Policies and SOP's applicable to this project ☒ **Y** ☐ **N**

If you selected "N" please find the up-to-date SOP's and Polices at the following locations:

- ICES Intranet – under “Policies and Forms”
- ICES Research Practice site

- For access to the documents, please contact your Program Administrator.
- For questions about a specific Policy or SOP, please contact the owner listed on the document.

_____ _____

Signature of Investigator / Scientist Date (dd/mm/yy)

_____ _____

Signature of Scientific Program Leader Date (dd/mm/yy)

_____ _____

Signature of Site Director, if applicable Date (dd/mm/yy)

_____ _____

CEO Approval Date (dd/mm/yy)

_____ _____

Privacy Office Approval Date (dd/mm/yy)

This section is for the use of Ontario Cancer Registry

_____ _____

Signature Date (dd/mm/yy)

on behalf of

☐ CCO

☐ Cancer Research Program

***Reference:**

For more information, please refer to the *Personal Health Information Protection Act* (PHIPA) which is found at:
http://www.e-laws.gov.on.ca/html/statutes/english/elaws_statutes_04p03_e.htm

The Regulation to the Act (Reg. 329/04) can be found at:

http://www.e-laws.gov.on.ca/html/regs/english/elaws_regs_040329_e.htm

APPENDIX F Curriculum vitae

Schulich School of Medicine & Dentistry

Professional Curriculum Vitae

MAY 24, 2021

DR. S. DANIELLE MACNEIL

MD, MSc, FRCSC

Assistant Professor - Department of Otolaryngology - Head & Neck Surgery

Assistant Professor - Department of Oncology

PERSONAL SUMMARY

Name	S. Danielle MacNeil
Date of Birth	1978 Apr 12
Languages	English, Understood, Spoken, Read, Written

EDUCATION AND QUALIFICATIONS

Degrees and Diplomas

2013 - present	Master of Science, Western University, Epidemiology and Biostatistics, Master's Thesis, EPIDEMIOLOGY, London, Ontario, Canada
2006	Bachelor of Science, Dalhousie University, Medicine, Bachelor's - Equivalent, Halifax, Nova Scotia, Canada
2006	Doctor of Medicine, Dalhousie University, Medicine, Doctor (Medical), Halifax, Nova Scotia, Canada
2002	Master of Science, Dalhousie University, Pathology, Master's Thesis, Halifax, Nova Scotia, Canada
1999	Bachelor of Science, University of Guelph, Biological Science, College of, Bachelor's - Honours, Guelph, Ontario, Canada

Research Training

2013 - 2015	Western University, ICES Faculty Scholars, Population database subject, Supervisor: Amit Garg, Ontario, Canada

Specialized Training

2018	Course Participant, Department of Oncology, Meditation and Leadership Retreat, Ontario, Canada
2012	University of Alberta, Advanced Head and Neck Oncology and Microvascular Reconstruction Fellow, Edmonton, Alberta, Canada
2011	Royal College of Physicians and Surgeons of Canada, Fellow, Canada
2011	University of British Columbia, Otolaryngology Residency, British Columbia, Canada

Qualifications, Certifications and Licenses

2019	Ontario Core Indigenous Cultural Safety Health Course Certificate, Indigenous Cultural Safety Ontario, Certificate, Ontario, Canada
2019	CIHR Institute of Gender and Health Core Competency Module for Sex and Gender in Biomedical Research. CIHR, License, Ontario, Canada
2019	CIHR Institute of Gender and Health Core Competency Module for Sex and Gender in Primary Data Collection with Human Participants, CIHR, License, Ontario, Canada

APPOINTMENTS

Academic Appointments

2016 - 2022	Assistant Professor, Otolaryngology - Head & Neck Surgery, Schulich School of Medicine & Dentistry, The University of Western Ontario
2013 - 2015	Lecturer, Otolaryngology - Head & Neck Surgery, Schulich School of Medicine & Dentistry, The University of Western Ontario
2016 - 2022	Assistant Professor, Department of Oncology, Schulich School of Medicine & Dentistry, The University of Western Ontario
2013 - 2015	Lecturer, Department of Oncology, Schulich School of Medicine & Dentistry, The University of Western Ontario

Clinical Appointments

2013 - 2022	Otolaryngologist, London Health Sciences Centre, Otolaryngology - Head and Neck Surgery

POSITIONS HELD & LEADERSHIP EXPERIENCE

Academic Positions

2019 - present Associate Scientist, Lawson Health Research Institute, London, Ontario, Canada

Clinical Positions

2019 - present CCO Ontario Head and Neck Cancer Advisory Committee

2019 - present LRCP Head and Neck Cancer Survivorship Committee Chair

2019 - present Chair Head and Neck Disease Site Team, London Regional Cancer Program, London, Ontario, Canada

2019 - present South West Regional Cancer Program Surgical Champion

HONOURS AND AWARDS

Honours

Received

2019	AAO Cochrane Scholars Award, Recipient of 2019 AAO Cochrane Scholars Award to receive funding to attend the Cochrane Colloquium in Santiago, Chile in October 2019. American Academy of Otolaryngology, $3,300, Type: Research award, International
2012	Top Paper, Canadian Society of Otolaryngology Annual Meeting, Toronto, Ontario, Canada
2011	Lavell H. Leeson, Award for resident achieving highest academic standing, Division of Otolaryngology, University of British Columbia, Type: Distinction, British Columbia, Canada
2011	A.W.D. Bill Knox, Award for outstanding postgraduate surgical study, Department of Surgery, University of British Columbia, Type: Distinction, British Columbia, Canada
2010	Research Grant Award, Branch for International Surgery Research Grant Award, University of British Columbia, British Columbia, Canada
2009	Research Award, Division of Otolaryngology Research Award, University of British Columbia, British Columbia, Canada
2004	Research Scholarship, Dalhousie Medical Research Foundation B.Sc. (Medicine), Dalhousie University, Halifax, Nova Scotia, Canada
2003	Research Scholarship, Dalhousie Medical Research Foundation B.Sc. (Medicine), Dalhousie University, Halifax, Nova Scotia, Canada
2003	Research Grant, Category A Research Grant, IWK Health Centre, Canada
2002	John G. Quinlan, Memorial Bursary, Canada
2001	Research Placement Grant, Aquanet Educational Research Placement Grant, Canada
2000	Graduate Scholarship, Dalhousie University Graduate Scholarship, Dalhousie University, Halifax, Nova Scotia, Canada
1995	Entrance Scholarship, York University Entrance Scholarship, Toronto, Ontario, Canada
1995	Science Scholarship, York University Science Scholarship, Toronto, Ontario, Canada
1995	Entrance Scholarship, Rotary Club University Entrance Scholarship, Rotary Club, Canada
1995	Entrance Bursary, Royal Canada Legion University Entrance Bursary, Royal Canada Legion, Canada

Teaching Awards

Received

2018 Department of Otolaryngology-Head and Neck Surgery Faculty Teaching Award, Level: Postgraduate, Scope: Department, Western University, Schulich School of Medicine & Dentistry

SERVICE AND ADMINISTRATION

Professional Affiliations and Activities

Professional Associations

2007 - present	American Academy of Otolaryngology-Head and Neck Surgery
2006 - present	Canadian Society of Otolaryngology-Head and Neck Surgery
2003 - present	Canadian Medical Association

2018 - present	Chair, Awards Committee CSO
2018 - present	Chair, CSO Women in Otolaryngology Committee

2019 - 2021	Consultant, AAO-HNS/F- WIO Leadership Development and Mentorship

2018 - present	Member, American Head and Neck Society- Survivorship Committee
2018 - present	Member, PGE Committee
2018 - present	Member, Competency Committee
2018 - present	Member, American Head and Neck Society- Women in Head and Neck Surgery
2018 - 2020	Member, AMOSO Opportunities Fund Committee
2018 - 2020	Member, Selection Committee Vice-Dean of Dentistry
2018 - 2020	Member, SRTP Committee
2018 - present	Member, American Head & Neck Society Women in Otolaryngology
2018 - present	Member, American Head & Neck Society
2018 - present	Member, IFOS Head and Neck Oncology Scientific Program Committee

Peer Review Activities

Journal Reviewer

2020 - present	Manuscript Reviews, BMJ Open
2017 - present	Manuscript Reviews, PLOS ONE
2017 - present	Manuscript Reviews, Manuscript reviewer CMAJ
2016 - present	Manuscript Reviews, Manuscript reviewer JAMA- Otolaryngology
2015 - present	Manuscript Reviews, Manuscript reviewer Clinical Case Reports
2015 - present	Manuscript Reviews, Manuscript reviewer Medicine Journal
2015 - present	Manuscript Reviews, Manuscript reviewer current oncology
2011 - present	Manuscript Reviews, Journal of Otolaryngology-Head and Neck Surgery

2009 - present Manuscript Reviews, Laryngoscope

Administrative Committees

International

AHNS

2018 - present **Member**, Survivorship/Supportive Care/Rehabilitation Service, Total Number of Meetings: 4, Total Hours: 4

2018 - present **Member**, Women in Head and Neck Surgery Service, Total Number of Meetings: 4, Total Hours: 4

American Academy of Otolaryngology-Head and Neck Surgery

2019 - present **Member**, WIO Leadership Development and Mentorship, Total Number of Meetings: 2, Total Hours: 2

American Society of Head and Neck Surgery

2020 **Member**, AHNS Women in HNS Margaret F. Butler Award Selection Committee, Total Number of Meetings: 1, Total Hours: 2
Main Activities: Review and selection of award recipient

Association of Women Surgeons

2018 - present **Member**, Association of Women Surgeons, Total Number of Meetings: 3, Total Hours: 3

International Federation of ORL Societies

2020 - 2021 **Member**, IFOS Vancouver 2021 Physician Health, Wellness and Diversity Committee, Total Number of Meetings: 2, Total Hours: 3

2019 - 2021 **Member**, IFOS 2021 Head and Neck Oncology Scientific Program Committee, Total Number of Meetings: 4, Total Hours: 8
Main Activities: Planning committee member for head and neck oncology for scientific program

National

Canadian Society of Otolaryngology

2018 - 2021 **Chair**, CSO Poloquin Awards, Total Number of Meetings: 8, Total Hours: 40

2017 - present **Chair**, CSO Women in Otolaryngology, Total Number of Meetings: 13, Total Hours: 24

2016 - present **Member**, CSO Collaborative Research Committee Core Group, Total Number of Meetings: 33, Total Hours: 33

2016 - present **Member**, CSO Collaborative Research Committee Head and Neck Group, Total Number of Meetings: 33, Total Hours: 33

2015 - 2016 **Member**, Poloquin Resident Research Award Committee, Total Number of Meetings: 2, Total Hours: 10
Main Activities: Review and judge resident abstract and manuscripts. Panel member for resident oral presentation competition. Attend one administrative meeting per year.

Local

AMOSO

2018 - present **Member**, AMOSO Opportunities Fund Sub-Committee, Total Number of Meetings: 4, Total Hours: 16

Western University

2018 - 2019 **Member**, Selection Committee Vice-Dean of Dentistry, Total Number of Meetings: 2, Total Hours: 10
Main Activities: Selection committee member including interviews of vice-dean of dentistry
Contribution: 20

Western University Department of Otolaryngology

2016 - present **Member**, Postgraduate Committee, Total Number of Meetings: 28, Total Hours: 80
Main Activities: Attend 6 meetings per year.

2016 - 2019 **Member**, Summer Research Training Program, Total Number of Meetings: 4, Total Hours: 8
Main Activities: Attend 2 meetings per year.

Other

Dalhousie University

2004 **Council Member**, Research Opportunities in Medical Training Committee

University of British Columbia

2009 **Council Member**, Residency Selection Interview Committee

2009 **Council Member**, Residency Training Committee, Division of Otolaryngology

University of Guelph

1998 **Council Member**, Human Rights Coordinator Hiring Committee

1998 **Council Member**, Student Health and Dental Plan Implementation Committee

1998 **Council Member**, University Centre Board of Directors

1998 **Council Member**, University Senate

1997 **Council Member**, Women's Campus Safety Initiatives Committee

RESEARCH AND SCHOLARLY ACTIVITIES

Grants

Peer Reviewed

Applied Grants

2018 Sep - 2020 Sep **Role:** Principal Applicant	**Title:** Geographic disparities in survival amongst head and neck cancer patients **Funding Source:** Canadian Institutes of Health Research (CIHR)
Principal Investigator: Danielle MacNeil	
Grant Total: $370,000 **Industry Grant:** N	

2018 Sep - 2020 Sep **Role:** Co-Applicant	**Title:** A Phase II Randomized Trial of Treatment De-Escalation for HPV-Associated Oropharyngeal Squamous Cell Carcinoma: Radiotherapy vs. Trans-Oral Surgery (ORATOR II) **Funding Source:** CIHR
Principal Investigator: Anthony Nichols	
Grant Total: $1,140,000 **Industry Grant:** N	

2018 Mar - 2020 Mar **Role:** Principal Applicant	**Title:** Survivorship after Head and Neck Cancer Randomized Controlled trial evaluating patient care and adherence to follow-up **Co-Investigators:** David Palma **Funding Source:** CCSRI
Principal Investigator: Danielle **MacNeil**	
Grant Total: $194,400 **Industry Grant:** N	

Past Grants

2019 Feb - 2019 May **Role:** Principal Applicant **Principal Investigator: Danielle MacNeil** **Grant Total:** $1,000 **Industry Grant:** N	**Title:** eCornell Women in Leadership- Cornell University **Funding Source:** Cornell University

2018 Apr - 2019 Apr **Role:** Principal Investigator **Principal Investigator: Danielle MacNeil** **Grant Total:** $15,000 **Industry Grant:** N	**Title:** Head and Neck Survival Outcomes: Impact of Time to Treatment Initiation **Funding Source:** Department of Otolaryngology-Head and Neck Surgery Research Fund Pilot Study

2018 Jan - 2019 Jan **Role:** Principal Applicant **Principal Investigator: Danielle MacNeil** **Grant Total:** $29,468 **Industry Grant:** N	**Title:** Geographic Disparities Head and Neck Cancer **Funding Source:** London Regional Cancer Program Catalyst Grant

2017 May - 2018 Apr **Role:** Co-Investigator **Principal Investigator:** Brian Rotenberg **Grant Total:** $27,630 **Industry Grant:** N	**Title:** Medical grade cocaine and perioperative morbidity following ambulatory endoscopic sinus surgery – a population analysis **Funding Source:** St. Joseph's Hospital Foundation

2016 Apr - 2016 Apr **Role:** Principal Applicant **Principal Investigator: Danielle MacNeil** **Grant Total:** $1,000 CAD **Industry Grant:** N	**Title:** 2016 Master Class on Writing Research for Publication **Funding Source:** Schulich School of Medicine & Dentistry

2016 Mar - 2019 Mar **Role:** Co-Investigator **Principal Investigator: Danielle MacNeil** **Grant Total:** $113,650 CAD **Member Share:** $11,365.00 **Industry Grant:** N	**Title:** Clinical Health Informatics Program Grant

2014 Jul - 2016 Jun **Role:** Co-Principal Investigator **Principal Investigator:** Dr. **Danielle MacNeil** **Grant Total:** $196,244 CAD **Member Share:** $14,000.00 **Industry Grant:** N	**Title:** ICES Surgery Provincial Program **Co-Investigators:** Chris Vinden, Blayne Welk, Sumit Dave, Luc Dubois, Eric Frechette, Sarah Jones, Richard Malthaner, Jacob McGee, Stephen Paulter, Dave Nagpal **Funding Source:** AMOSO Innovation Fund

2014 Jan - 2017 Jan **Role:** Principal Investigator **Principal Investigator: Danielle MacNeil** **Grant Total:** $195,000 CAD **Industry Grant:** N	**Title:** Treatment and Outcomes in Head and Neck Cancer Patients: Developing a Population-Based Reserach Program in Surgical Oncology **Funding Source:** Academic Medical Oraniztion of Southwestern Ontario (AMOSO). Opportunities Fund

2013 Jul - 2014 Jun **Role:** Principal Investigator	**Title:** Secular Trends Laryngeal Cancer **Co-Investigators:** Amit Garg John Yoo
Principal Investigator: Danielle MacNeil	
Grant Total: $29,319 **Industry Grant:** N	**Funding Source:** London Regional Cancer Program Catalyst Grant

Non-Peer Reviewed

Past Grants

2019 Sep - 2020 Sep **Role:** Principal Applicant	**Title:** ORATOR III: A Phase II RCT Comparing TOS to Radiotherapy for HPV Negative Oropharynx cancer
Principal Investigator: S. Danielle MacNeil	
Grant Total: $15,000 CAD **Member Share:** $15,000.00 **Industry Grant:** N	

PUBLICATIONS

Peer Reviewed Publications

Journal Article

Published

1. COVIDSurg Collaborative, GlobalSurg Collaborative . SARS-CoV-2 vaccination modelling for safe surgery to save lives: data from an international prospective cohort study. Br J Surg, 2021 Mar 24, **Coauthor**, DOI: 10.1093/bjs/znab101.

2. Roshanov PS, Sessler DI, Chow CK, Garg AX, Walsh MW, Lam NN, Hildebrand AM, Biccard BM, Acedillo RR, **MacNeil SD**, Lee VW, Szczeklik W, Mrkobrada M, Thabane L, Devereaux PJ. Predicting myocardial injury and other cardiac complications after elective noncardiac surgery with the Revised Cardiac Risk Index: the VISION study. Can J Cardiol, 2021 Mar 23, **Coauthor**, DOI: 10.1016/j.cjca.2021.03.015.

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4. Shi LL, McMullen C, Vorwald K, Nichols AC, **MacNeil SD**, Wadsworth JT, Chung CH, Wang X, Patel KB. Survival outcomes of patients with subglottic squamous cell carcinoma : a study of the National Cancer Database. Eur Arch Otorhinolaryngol, 2021 Mar 1, **Coauthor**, DOI: 10.1007/s00405-021-06712-w.

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7. Di Gravio EJ, Lang P, Kim HAJ, Chinnery T, Mundi N, **MacNeil SD**, Mendez A, Yoo J, Fung K, Mymryk JS, Barrett JW, Read N, Venkatesan V, Kuruvilla S, Mendez LC, Winquist E, Mitchell S, Mattonen SA, Nichols AC, Palma DA. Modern treatment outcomes for early T-stage oropharyngeal cancer treated with intensity-modulated radiation therapy at a tertiary care institution. Radiat Oncol, 2020 Nov 10; 15 (1): 261, **Coauthor**, DOI: 10.1186/s13014-020-01705-1.

8. Hayler R, Low TH, Fung K, Nichols AC, **MacNeil SD**, Yoo J. Implantable Doppler Ultrasound Monitoring in Head and Neck Free Flaps: Balancing the Pros and Cons. Laryngoscope, 2020 Nov 3, **Coauthor**, DOI: 10.1002/lary.29247.

9. Ruicci KM, Meens J, Plantinga P, Stecho W, Pinto N, Yoo J, Fung K, **MacNeil D**, Mymryk JS, Barrett JW, Howlett CJ, Boutros PC, Ailles L, Nichols AC. TAM family receptors in conjunction with MAPK signalling are involved in acquired resistance to PI3Kα inhibition in head and neck squamous cell carcinoma. J Exp Clin Cancer Res, 2020 Oct 15; 39 (1): 217, **Coauthor**, DOI: 10.1186/s13046-020-01713-9.

10. Dwyer CD, Qiabi M, Fortin D, Inculet RI, Nichols AC, **MacNeil SD**, Malthaner R, Yoo J, Fung K. Idiopathic Subglottic Stenosis: An Institutional Review of Outcomes With a Multimodality Surgical Approach. Otolaryngol Head Neck Surg, 2020 Oct 13: 194599820966978, **Coauthor**, DOI: 10.1177/0194599820966978.

11. Kassirian S, Dzioba A, Hamel S, Patel K, Sahovaler A, Palma DA, Read N, Venkatesan V, Nichols AC, Yoo J, Fung K, Mendez A, **MacNeil SD**. Delay in diagnosis of patients with head-and-neck cancer in Canada: impact of patient and provider delay. Curr Oncol, 2020 Oct 1; 27 (5): e467-e477, **Senior Responsible Author**, DOI: 10.3747/co.27.6547.

12. Lang P, Contreras J, Kalman N, Paterson C, Bahig H, Billfalk-Kelly A, Brennan S, Rock K, Read N, Venkatesan V, Sathya J, Mendez LC, **MacNeil SD**, Nichols AC, Fung K, Mendez A, Winquist E, Kuruvilla S, Stewart P, Warner A, Mitchell S, Theurer JA, Palma DA. Preservation of swallowing in resected oral cavity squamous cell carcinoma: examining radiation volume effects (PRESERVE): study protocol for a randomized phase II trial. Radiat Oncol, 2020 Aug 14; 15 (1): 196, **Coauthor**, DOI: 10.1186/s13014-020-01636-x.

13. Mundi N, Ghasemi F, Zeng PYF, Prokopec SD, Patel K, Kim HAJ, Di Gravio E, **MacNeil D**, Khan MI, Han MW, Shaikh M, Mendez A, Yoo J, Fung K, Gameiro SF, Palma DA, Mymryk JS, Barrett JW, Boutros PC, Nichols AC. Sex disparities in head & neck cancer driver genes: An analysis of the TCGA dataset. Oral Oncol, 2020 Mar 5; 104: 104614, **Coauthor**, DOI: 10.1016/j.oraloncology.2020.104614.

14. Butskiy O, Rahmanian R, **MacNeil SD**, Anderson DW. Pharyngoesophageal reconstruction with the gastric pull-up: Functional outcomes in a cohort of 49 patients. Clin Otolaryngol, 2020 Mar 1; 45 (2): 297-301, **Coauthor**, DOI: 10.1111/coa.13503.

15. Nichols AC, Lang P, Prisman E, Berthelet E, Tran E, Hamilton S, Wu J, Fung K, de Almeida JR, Bayley A, Goldstein DP, Eskander A, Husain Z, Bahig H, Christopoulous A, Hier M, Sultanem K, Richardson K, Mlynarek A, Krishnan S, Le H, Yoo J, **MacNeil SD**, Mendez A, Winquist E, Read N, Venkatesan V, Kuruvilla S, Warner A, Mitchell S, Corsten M, Rajaraman M, Johnson-Obaseki S, Eapen L, Odell M, Chandarana S, Banerjee R, Dort J, Matthews TW, Hart R, Kerr P, Dowthwaite S, Gupta M, Zhang H, Wright J, Parker C, Wehrli B, Kwan K, Theurer J, Palma DA. Treatment de-escalation for HPV-associated oropharyngeal squamous cell carcinoma with radiotherapy vs. trans-oral surgery (ORATOR2): study protocol for a randomized phase II trial. BMC Cancer, 2020 Feb 14; 20 (1): 125, **Coauthor**, DOI: 10.1186/s12885-020-6607-z.

16. Black M, Ghasemi F, Sun RX, Stecho W, Datti A, Meens J, Pinto N, Ruicci KM, Khan MI, Han MW, Shaikh M, Yoo J, Fung K, **MacNeil D**, Palma DA, Winquist E, Howlett CJ, Mymryk JS, Ailles L, Boutros PC, Barrett JW, Nichols AC. Spleen tyrosine kinase expression is correlated with human papillomavirus in head and neck cancer. Oral Oncol, 2020 Feb 1; 101: 104529, **Coauthor**, DOI: 10.1016/j.oraloncology.2019.104529.

17. Patel KB, Low TH, Partridge A, Nichols AC, **MacNeil SD**, Yoo J, Fung K. Assessment of shoulder function following scapular free flap. Head Neck, 2020 Feb 1; 42 (2): 224-229, **Coauthor**, DOI: 10.1002/hed.25992.

18. Kamel Hasan O, De Brabandere S, Rachinsky I, Laidley D, **MacNeil D**, Van Uum S. Microscopic Positive Tumor Margin Increases Risk for Disease Persistence but Not Recurrence in Patients with Stage T1-T2 Differentiated Thyroid Cancer. J Thyroid Res, 2020 Jan 1; 2020: 5287607, **Coauthor**, DOI: 10.1155/2020/5287607.

19. Pinto N, Prokopec SD, Ghasemi F, Meens J, Ruicci KM, Khan IM, Mundi N, Patel K, Han MW, Yoo J, Fung K, **MacNeil D**, Mymryk JS, Datti A, Barrett JW, Boutros PC, Ailles L, Nichols AC. Flavopiridol causes cell cycle inhibition and demonstrates anti-cancer activity in anaplastic thyroid cancer models. PLoS One, 2020 Jan 1; 15 (9): e0239315, **Coauthor**, DOI: 10.1371/journal.pone.0239315.

20. **MacNeil SD**, Rotenberg B, Sowerby L, Allen B, Richard L, Shariff SZ. Medical use of cocaine and perioperative morbidity following sinonasal surgery-A population study. PLoS One, 2020 Jan 1; 15 (7): e0236356, **Principal Author**, DOI: 10.1371/journal.pone.0236356.

21. Sahovaler A, Eibling DE, Bruni I, Duvvuri U, **MacNeil SD**, Nichols AC, Yoo J, Fung K, Roth K. Novel minimally invasive transoral surgery bleeding model implemented in a nationwide otolaryngology emergencies bootcamp. J Robot Surg, 2019 Dec 1; 13 (6): 773-778, **Coauthor**, DOI: 10.1007/s11701-019-00920-7.

22. Ruicci KM, Meens J, Sun RX, Rizzo G, Pinto N, Yoo J, Fung K, **MacNeil D**, Mymryk JS, Barrett JW, Boutros PC, Ailles L, Nichols AC. A controlled trial of HNSCC patient-derived xenografts reveals broad efficacy of PI3Kα inhibition in controlling tumor growth. Int J Cancer, 2019 Oct 15; 145 (8): 2100-2106, **Coauthor**, DOI: 10.1002/ijc.32009.

23. Nichols AC, Theurer J, Prisman E, Read N, Berthelet E, Tran E, Fung K, de Almeida JR, Bayley A, Goldstein DP, Hier M, Sultanem K, Richardson K, Mlynarek A, Krishnan S, Le H, Yoo J, **MacNeil SD**, Winquist E, Hammond JA, Venkatesan V, Kuruvilla S, Warner A, Mitchell S, Chen J, Corsten M, Johnson-Obaseki S, Eapen L, Odell M, Parker C, Wehrli B, Kwan K, Palma DA. Radiotherapy versus transoral robotic surgery and neck dissection for oropharyngeal squamous cell carcinoma (ORATOR): an open-label, phase 2, randomised trial. Lancet Oncol, 2019 Oct 1; 20 (10): 1349-1359, **Coauthor**, DOI: 10.1016/S1470-2045(19)30410-3.

24. Ruicci KM, Plantinga P, Pinto N, Khan MI, Stecho W, Dhaliwal SS, Yoo J, Fung K, **MacNeil D**, Mymryk JS, Barrett JW, Howlett CJ, Nichols AC. Disruption of the RICTOR/mTORC2 complex enhances the

response of head and neck squamous cell carcinoma cells to PI3K inhibition. Mol Oncol, 2019 Oct 1; 13 (10): 2160-2177, **Coauthor**, DOI: 10.1002/1878-0261.12558.

25. So T, Sahovaler A, Nichols A, Fung K, Yoo J, Weir MM, **MacNeil SD**. Utility of clinical features with fine needle aspiration biopsy for diagnosis of Warthin tumor. J Otolaryngol Head Neck Surg, 2019 Aug 29; 48 (1): 41, **Senior Responsible Author**, DOI: 10.1186/s40463-019-0366-3.

26. Arifin AJ, Lam S, **MacNeil SD**. A case report of a primary lymphoma of the tongue presenting as trigeminal neuralgia. J Otolaryngol Head Neck Surg, 2019 Aug 5; 48 (1): 37, **Senior Responsible Author**, DOI: 10.1186/s40463-019-0360-9.

27. Sahovaler A, Krishnan RJ, Yeh DH, Zhou Q, Palma D, Fung K, Yoo J, Nichols A, **MacNeil SD**. Outcomes of Cutaneous Squamous Cell Carcinoma in the Head and Neck Region With Regional Lymph Node Metastasis: A Systematic Review and Meta-analysis. JAMA Otolaryngol Head Neck Surg, 2019 Apr 1; 145 (4): 352-360, **Senior Responsible Author**, DOI: 10.1001/jamaoto.2018.4515.

28. Ghasemi F, Prokopec SD, **MacNeil D**, Mundi N, Gameiro SF, Howlett C, Stecho W, Plantinga P, Pinto N, Ruicci KM, Khan MI, Yoo J, Fung K, Sahovaler A, Palma DA, Winquist E, Mymryk JS, Barrett JW, Boutros PC, Nichols AC. Mutational analysis of head and neck squamous cell carcinoma stratified by smoking status. JCI Insight, 2019 Jan 10; 4 (1), **Coauthor**, DOI: 10.1172/jci.insight.123443.

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30. Mundi N, Prokopec SD, Ghasemi F, Warner A, Patel K, **MacNeil D**, Howlett C, Stecho W, Plantinga P, Pinto N, Ruicci KM, Khan MI, Han MW, Yoo J, Fung K, Sahovaler A, Palma DA, Winquist E, Mymryk JS, Barrett JW, Boutros PC, Nichols AC. Genomic and human papillomavirus profiling of an oral cancer cohort identifies TP53 as a predictor of overall survival. Cancers Head Neck, 2019 Jan 1; 4: 5, **Coauthor**, DOI: 10.1186/s41199-019-0045-0.

31. Alwithenani R, DeBrabandere S, Rachinsky I, **MacNeil SD**, Badreddine M, Van Uum S. Performance of the American Thyroid Association Risk Classification in a Single Center Cohort of Pediatric Patients with Differentiated Thyroid Cancer: A Retrospective Study. J Thyroid Res, 2019 Jan 1; 2019: 5390316, **Coauthor**, DOI: 10.1155/2019/5390316.

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36. Roshanov PS, Walsh M, Devereaux PJ, **MacNeil SD**, Lam NN, Hildebrand AM, Acedillo RR, Mrkobrada M, Chow CK, Lee VW, Thabane L, Garg AX. External validation of the Revised Cardiac Risk Index and update of its renal variable to predict 30-day risk of major cardiac complications after non-cardiac surgery: rationale and plan for analyses of the VISION study. BMJ Open, 2017 Jan 9; 7 (1): e013510, **Coauthor**, DOI: 10.1136/bmjopen-2016-013510.

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39. Rohin Krishnan, **S. Danielle MacNeil**, Monall S Malvankar-Mehta. Comparing sutures versus staples for skin closure after orthopaedic surgery:systematic review and meta-analysis. BMJ Open, 2016 Jan 20; 6 (1), **Coauthor**

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41. Yeh DH, Tam S, Fung K, **MacNeil SD**, Yoo J, Winquist E, Palma DA, Nichols AC. Transoral robotic surgery vs. radiotherapy for management of oropharyngeal squamous cell carcinoma - A systematic review of the literature. Eur J Surg Oncol, 2015 Dec 1; 41 (12): 1603-14, **Coauthor**, DOI: 10.1016/j.ejso.2015.09.007.

42. **MacNeil SD**, Liu K, Garg AX, Tam S, Palma D, Thind A, Winquist E, Yoo J, Nichols A, Fung K, Hall S, Shariff SZ. A Population-Based Study of 30-day Incidence of Ischemic Stroke Following Surgical Neck Dissection. Medicine (Baltimore), 2015 Aug 1; 94 (33): e1106, **Principal Author**, DOI: 10.1097/MD.0000000000001106.

43. Chang BA, **MacNeil SD**, Morrison MD, Lee PK. The Reliability of the Reflux Finding Score Among General Otolaryngologists. J Voice, 2015 Jun 25, **Coauthor**, DOI: 10.1016/j.jvoice.2014.10.009.

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47. Botto, F, **Macneil, D**. Myocardial injury after noncardiac surgery: a large, international, prospective cohort study establishing diagnostic criteria, characteristics, predictors, and 30-day outcomes. Anesthesiology, 2014 Mar 1; 120 (3): 564-78, **Coauthor**, DOI: 10.1097/ALN.00000000.

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49. Nichols AC, Yoo J, Hammond JA, Fung K, Winquist E, Read N, Venkatesan V, **MacNeil SD**, Ernst DS, Kuruvilla S, Chen J, Corsten M, Odell M, Eapen L, Theurer J, Doyle PC, Wehrli B, Kwan K, Palma DA. Early-stage squamous cell carcinoma of the oropharynx: radiotherapy vs. trans-oral robotic surgery (ORATOR)--study protocol for a randomized phase II trial. BMC Cancer, 2013 Mar 20; 13 (133): 133, **Coauthor**, DOI: 10.1186/1471-2407-13-133.

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51. **MacNeil SD**, Moxham JP. Review of floor of mouth dysontogenic cysts. The Annals of otology, rhinology, and laryngology, 2010 Mar 1; 119 (3): 165-73, **Principal Author**

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53. **MacNeil SD**, Westerberg BD, Romney MG. Toward the development of evidence-based guidelines for the management of methicillin-resistant Staphylococcus aureus otitis. Journal of otolaryngology - head & neck surgery = Le Journal d'oto-rhino-laryngologie et de chirurgie cervico-faciale, 2009 Aug 1; 38 (4): 483-94, **Principal Author**

54. **MacNeil SD**, Fernandez CV. Attitudes of research ethics board chairs towards disclosure of research results to participants: results of a national survey. Journal of medical ethics, 2007 Sep 1; 33 (9): 549-53, **Principal Author**

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Invited Editorial

Published

1. **MacNeil SD**, Fernandez CV. Offering results to research participants. BMJ (Clinical research ed.), 2006 Jan 28; 332 (7535): 188-9, **Principal Author**

Case Reports

Published

1. van der Woerd BD, **MacNeil SD**. Sialocutaneous fistula to the external auditory canal repaired with superficial parotidectomy and temporoparietal flap: A case report. 2017 Oct 1, **Senior Responsible Author**, DOI: 10.1097/MD.0000000000007038.

2. Ioanidis KE, **MacNeil SD**, Tay KY, Wehrli B. An atypical lipomatous tumor mimicking a giant fibrovascular polyp of the hypopharynx: A case report. 2017 Oct 1, **Senior Responsible Author**, DOI: 10.1097/MD.0000000000006927.

3. Best CA, Dhaliwal S, Tam S, Low TH, Hughes B, Fung K, **MacNeil SD**. Spontaneous intrathyroidal hematoma causing airway obstruction: A case report. 2016 Aug 1, **Senior Responsible Author**, DOI: 10.1097/MD.0000000000003209.

4. Nichols AC, Chan-Seng-Yue M, Yoo J, Agrawal SK, Starmans MH, Waggott D, Harding NJ, Dowthwaite SA, Palma DA, Fung K, Wehrli B, **Macneil SD**, Lambin P, Winquist E, Koropatnick J, Mymryk JS, Boutros PC, Barrett JW. A case report and genetic characterization of a massive acinic cell carcinoma of the parotid with delayed distant metastases. 2013 Apr 3 Case Rep Oncol Med, **Coauthor**, DOI: 10.1155/2013/270362.

Journal Article, Meta-Analysis

Published

1. Sahovaler A, Kim MH, Mendez A, Palma D, Fung K, Yoo J, Nichols AC, **MacNeil SD**. Survival Outcomes in Human Papillomavirus-Associated Nonoropharyngeal Squamous Cell Carcinomas: A Systematic Review and Meta-analysis. JAMA Otolaryngol Head Neck Surg. 2020 Dec 1, 146. (12): p.1158-1166, **Senior Author**, DOI: 10.1001/jamaoto.2020.3382.

ABSTRACTS

Abstracts Published

Peer Reviewed

Published

1. Samargandy L, De Brabandere S, Van Uum S, **MacNeil D**, Rachinsky I. Long-term outcomes of distant metastasis from differentiated thyroid cancer and prognostic factors associated with disease-specific survival. Thyroid. American Thyroid Association; 2019 Oct 30, Illinois, United States; 2019. **Coauthor**

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3. Samargandy L, De Brabandere S, Van Uum S, **MacNeil D**, Rachinsky I. Prognostic factors of disease progression in patients with metastatic differentiated thyroid carcinoma. Thyroid. American Thyroid Association; 2019 Oct 30; Chicago, Illinois, United States; 2019. **Coauthor**

Abstracts Presented

1. **D. MacNeil**, A. Nichols, K. Fung, J. Yoo, A. Garg, E. Winquist, S. Hall, Secular Trends in the Treatment and Survival of Laryngeal Carcinoma, 2014, Ontario, Canada, **Presenter**
2. J. Theurer, A. Nichols, E. Winquist, D. Palma, J. Barrett, C. Howlett, K. Fung, **D. MacNeil**, J. Yoo, Targeted Treatment of PIK3CA Mutations in Head and Neck Cancer: A Feasibility Study, 2014, Ontario, Canada, **Presenter**
3. S. Um, N. Mundi, J. Barrett, **S.D. MacNeil**, K. Fung, J. Yoo, J. Mynryk, A. Nichols, Role of the Viral Oncoprotein E5: Is E5 the Forgotten Oncogene? 2013, Ontario, Canada, **Presenter**
4. **MacNeil SD**, O'Connell DA, Seikaly H, Harris J. Reduced Hospital Stay Following Total Thyroidectomy using a Parathyroid Hormone Algorithm. Canadian Society of Otolaryngology Annual Meeting. Toronto, ON (Top Paper Oral Presentation). 2012 May, **Presenter**
5. **MacNeil SD**, Seikaly H, Logan H, Grosvenor A, Wolfaardt J, Dobrovolsky W, Ansari K, O'Connell DA. 3D Digital Planning and Medical Modelling: A new and Improved Method of Maxillary and Mandibular Reconstruction. Canadian Society of Otolaryngology Annual Meeting. Toronto, ON . 2012 May, **Presenter**
6. **MacNeil SD**, Seikaly H, Yu J, Grosvenor A, Osswald M, Wolfaardt J, Ansari K. Secondary Maxillary Reconstruction with a Digitally Designed and Prefabricated Fibular Free Flap. Canadian Society of Otolaryngology Annual Meeting, Toronto, ON . 2012 May, **Presenter**

7. **S.D. MacNeil**, H. Harris, D. O'Connell, H. Seikaly, Reduced Hospital Stay Following Total Thyroidectomy using a Parathyroid Hormone Algorithm, 2012, Alberta, Canada, **Presenter**
8. **S.D. MacNeil**, H. Seikaly, A. Grosvenor, M. Osswald, J. Wolfaardt, W. Dobrovolsky, K. Ansari, D. O'Connell, 3D Digital Planning and Medical Modeling: A New and Improved Method of Mandibular Reconstruction, 2012, Alberta, Canada, **Presenter**
9. **S. D. MacNeil**, H. Seikaly, J. Yu, A. Grosvenor, M. Osswald, W. Dobrovolsky, K. Ansari, Secondary Maxillary Reconstruction with a Digitally Designed and Prefabricated Fibular Free Flap, 2012, Alberta, Canada, **Presenter**
10. Hernandez-Lee J, **MacNeil SD**, Anderson D. Validation of a Quality of Life Scale for Benign Thyroid Disease. Canadian Society of Otolaryngology Annual Meeting. Victoria, BC . 2011 May, **Presenter**
11. Rahmanian R, Anderson DW, **MacNeil SD**, Finley R, Ling H, Yee J. Outcomes of Gastric Pull-Up Reconstruction Following Resection of Hypopharyngeal and Cervical Esophageal Carcinoma. Canadian Society of Otolaryngology Annual Meeting. Victoria, BC . 2011 May, **Presenter**
12. J. Hernandez-Lee, D. Anderson, **S. D. MacNeil**, Validation of a Quality of Life Scale for Benign Thyroid Disease, 2011, British Columbia, Canada, **Presenter**
13. R. Rahmanian, D. Anderson, **D. MacNeil**, R. Finley, H. Ling, J. Yee, Outcomes of Gastric Pull-up Reconstruction Following Resection of Hypopharyngeal and Cervical Esophageal Carcinoma, 2011, British Columbia, Canada, **Presenter**
14. Moxham JP, **MacNeil SD**, Kibblewhite DK. Transforming Growth Factor Beta-1 and Oncostatin-M Exhibit Synergy in Osteoinduction. COSM Western Section Meeting. Orlando, FL. 2010 Feb, **Presenter**
15. **D. MacNeil**, A.R. Javer, B. Westerberg, R. Irvine, Systematic Review Assessing the Effectiveness of Cocaine for Local Anesthesia and Vasoconstriction, 2010, British Columbia, Canada, **Presenter**
16. **MacNeil SD**, Romney MG, Westerberg BW. Towards the development of evidence-based guidelines for the treatment of Methicillin-resistant Staphylococcus aureus (MRSA) otitis. University of British Columbia Department of Surgery Chung Research Day. 2009 Nov, **Presenter**
17. **MacNeil SD**, Moxham JP. Systematic review of floor of mouth dermoid cysts. COSM Western Section Meeting. Las Vegas NV. 2009 Jan, **Presenter**
18. **D. MacNeil**, A. Mallinson, J. Galo, N. Longridge, Vestibular Evoked Myogenic Potential (VEMP) Abnormalities in Patients with Visual Vestibular is Match, 2009, British Columbia, Canada, **Presenter**
19. **S. Danielle MacNeil**, The Reliability of the Reflux Finding Score Among General Otolaryngologists, 2008 Jun 1, Canadian Society of Otolaryngology, Alberta, Canada, **Presenter**
20. **D. MacNeil**, The Reliability of the Reflux Finding Score Among General Otolaryngologists, 2008, British Columbia, Canada, **Presenter**
21. **MacNeil SD**, Fernandez CV. Informing Research Participants of Research Results: Analysis of Canadian University-based Research Ethics Board Policies. Ethics of Bioethics Conference. Schenetady, NY. 2005 Apr, **Presenter**

22. **MacNeil SD**, Pohajdak B, Wright JR. The Development of Tilapia (Oreochromis niloticus) Chimeras and Short-term Culture of Undifferentiated Embryo Cells. Department of Pathology Research Seminar, Dalhousie University. Halifax, NS. 2002 Apr, **Presenter**

Posters Presented

1. Lina Samargandy, Sarah Nixey, Stan Van Uum, **Danielle MacNeil**, Irina Rachinsky, Long term outcomes of distant metastasis from differentiated thyroid cancer and prognostic factors associated with disease-specific survival, 2019 Oct 30, Chicago, Illinois, United States, **Co-Author**
2. Lina Samargandy, Sarah Nixey, Stan Van Uum, **Danielle MacNeil**, Irina Rachinsky, Prognostic factors of disease progression in patients with metastatic differentiated thyroid carcinoma, 2019 Oct 30, Chicago, Illinois, United States, **Supervisor**
3. Hamilton S, Weir M, Nichols A, Fung K, Yoo J, Zeman-Pocrnich C, **MacNeil D**, A retrospective study of the natural history of thyroid nodules with indeterminate cytopathology, 2019 Oct 30, Chicago, Illinois, United States, **Supervisor**
4. Rucci K, Means J, Sun R, Rizzo G, Pinto N, Yoo J, Fung K, **MacNeil D**, Barrett JW, Boutros P, Ailles L, Nichols A, A Controlled Trial of HNSCC Patient-derived Xenografts Reveals Broad Efficacy of PI3K-alpha Inhibition in Control Tumor Growth, 2019 Jun 3, **Co-Author**
5. Mundi N, Prokopec S, Ghasemi F, Warner A, **MacNeil D**, Howlett C, Boutros P, Nichols A, Genomic and Human Papillomavirus Profiling of an Oral Cancer Cohort Identifies TP53 as a Predictor of Overall Survival, 2019 Jun 3, **Co-Author**
6. Kim L, Sahovaler A, Fung K, Nichols A, Yoo J, **MacNeil D**, The Prevalence of HPV in Non-Oropharyngeal Head and Neck Squamous Cell Carcinomas and its Implications: A Systematic Review, 2019 Jun 3, Canadian Society of Otolaryngology, **Supervisor**
7. Dwyer C, **MacNeil D**, Nichols A, Yoo J, Inculet R, Qiabi M, Malthaner R, Fung K, Idiopathic Subglottic Stenosis: An Institutional Review of Surgical Treatment Outcomes, 2019 Jun 3, Canadian Society of Otolaryngology, **Co-Author**
8. Risk factors and Outcomes of metastatic cutaneous Squamous Cell Carcinoma in the Head and Neck Region: Systematic Review and Meta-analysis, 2018 Jun 16, 72nd CSOHNS Annual Meeting, Quebec, Canada, **Supervisor**
9. Dr. Laura Kim, Radiologic Assessment of the Lateral Scapula and Scapular Tip for Dental Implant Suitability in Patients Undergoing Mandibular Reconstruction, 2018 Jun 16, 72nd CSOHNS Annual Meeting, Quebec, Canada, **Co-Author**
10. Dr. Axel Sahovaler, Finding Unknown Primaries: A Canadian Head and Neck Surgery Referral Center Experience, 2018 Jun 16, 72nd CSOHNS Annual Meeting, Quebec, Canada, **Co-Author**
11. Dr. Axel Sahovaler, Decreasing Morbidity of the FAMM Flap: Comparing Traditional and Modified Harvesting Techniques, 2018 Jun 16, 72nd CSOHNS Annual Meeting, Quebec, Canada, **Co-Author**
12. F. Ghasemi, High-throughput Testing in Head and Neck Squamous Cell Carcinoma Identifies Agents with Preferential Activity in HPV-positive and Negative Cell Lines, 2018 Jun 16, 72nd CSOHNS Annual Meeting, Quebec, Canada, **Co-Author**

13. F. Ghasemi, Mutational Analysis of Head and Neck Squamous Cell Carcinoma Stratified by Smoking Status Identified NSD1 Mutations as a Biomarker of Survival, 2018 Jun 16, 72nd CSOHNS Annual Meeting, Quebec, Canada, **Co-Author**
14. Dr. A. Nichols, Genomic and Human Papillomavirus Profiling of a Canadian Oral Cancer Cohort, 2018 Jun 16, 72nd CSOHNS Annual Meeting, Quebec, Canada, **Co-Author**
15. Dr. H. Ernst, RAPSTOR: Development of a Rapid Standardized OR for Thyroid Surgery, 2018 Jun 16, 72nd CSOHNS Annual Meeting, Quebec, Canada, **Co-Author**
16. Dr. A. Sahovaler, Novel Minimally Invasive Pharyngeal Surgery (MIPS) Hemorrhage Model Implemented in a Nationwide Otolaryngology Emergencies Bootcamp: Importance and Outcomes, 2018 Jun 16, 72nd CSOHNS Annual Meeting, Quebec, Canada, **Co-Author**
17. F. Ghasemi, Repurposing Albendazole: New Potential as a Chemotherapeutic Agent with Preferential Activity Against HPV-negative Head and Neck Squamous Cell Cancer, 2017 Jun 11, 71st CSOHNS Annual Meeting, Saskatchewan, Canada, **Co-Author**
18. S. Kassirian, Delay in Diagnosis of Oral Cavity Carcinoma: The Impact of Referral Source, 2017 Jun 11, 71st CSOHNS Annual Meeting, Saskatchewan, Canada, **Supervisor**
19. Dr. Benjamin van der Woerd, Sialocutaneous Fistula to the External Auditory Canal Repaired with Superficial Parotidectomy and Temporoparietal Flap: A Case Report, 2017 Jun 11, 71st CSOHNS Annual Meeting, Saskatchewan, Canada, **Supervisor**
20. J. Athayde, Thyroid Lobectomy versus Total Thyroidectomy in the Treatment of Well-Differentiated Thyroid Cancer 1-4cm in Size: A Systematic Review and Meta-Analysis, 2017 Jun 11, 71st CSOHNS Annual Meeting, Saskatchewan, Canada, **Supervisor**
21. C. Best, **D. MacNeil**, Echocardiogram changes following parathyroidectomy in patients iwth primary hyperparathyroidism: A systematic review and meta-analysis, 2016 Jul 17, International Conference on Head and Neck Cancer, Seattle, Washington, United States, **Co-Author**
22. H. Low, K. Patel, A. Partridge, **D. MacNeil**, A. Nichols, J. Yoo, K. Fung, Shoulder Function after Scapular Free Flap, 2016 Jul 17, International Conference on Head and Neck Cancer, Seattle, Washington, United States, **Co-Author**
23. K. Patel, H. Low, A. Partridge, **D. MacNeil**, A. Nichols, J. Yoo, K. Fung, Shoulder Function After Scapula Free Flap, 2016 Jun 12, 70th CSOHNS Annual Meeting, Prince Edward Island, Canada, **Co-Author**
24. A. Nichol, M. Black, K. Ruicci, N. Pinto, J. Barrett, J. Yoo, K. Fung, **D. MacNeil**, Syk as a Novel Therapeutic Target in HNSCC, 2016 Jun 12, 70th CSOHNS Annual Meeting, Prince Edward Island, Canada, **Co-Author**
25. **D. MacNeil**, K. Ioanidis, Case Report: An Atypical Lipomatous Tumour Mimicking a Giant Fibrovascular Polyp of the Hypopharynx, 2016 Jun 12, 70th CSOHNS Annual Meeting, Prince Edward Island, Canada, **Supervisor**
26. A. Nichols, M. Black, J. Barrett, J. Yoo, K. Fung, **D. MacNeil**, E. Qinquist, D. Palma, Xenograft Directed Care for Recurrent and Metastatic Head and Neck Cancer: Description of a Novel Clinical Trial, 2016 Jun 12, 70th CSOHNS Annual Meeting, Prince Edward Island, Canada, **Co-Author**

27. K. Patel, H. Low, A. Partridge, **D. MacNeil**, A. Nichols, J. Yoo, K. Fung, The Incidental Thyroid lesion in Parathyroid Disease Management, 2016 Jun 12, CSO 2016, Prince Edward Island, Canada, **Co-Author**
28. C. Best, **D. MacNeil**, Echocardiogram Changes Following Parathyroidectomy in Patients with Primary Hyperparathyroidism: A Systematic Review and Meta-analysis, 2016 Jun 12, 70th CSOHNS Annual Meeting, Prince Edward Island, Canada, **Supervisor**
29. C. Best, S. Dhaliwal, S. Tam, H. Low, K. Fung, B. Hughes, **D. MacNeil**, Spontaneous, Slowly Expanding Intrathyroidal Hematoma Causing Airway Obstruction: A Case Report, 2016 Jun 12, CSO 2016, Prince Edward Island, Canada, **Supervisor**
30. Zhang TW, Low TH, Yeh D, Araslanova R, Hammond JA, Palma DA, Read N, Fung K, **MacNeil SD**, Nichols AC, Yoo J, Venkatesan V, Outcomes of Stage II Glottic Cancer in a Single Institution: Conventional vs. Intensity Modulated Radiotherapy, 2015 Sep 7, Canadian Radiation Oncology (CARO) Conference, Ontario, Canada, **Co-Author**
31. Zhang TW, Low TH, Yeh D, Araslanova R, Hammond JA, Palma DA, Read N, Fung K, **MacNeil SD**, Nichols AC, Yoo J, Venkatesan V, Outcomes in T1 Glottic Cancer Treated with Radiotherapy: A Single Institution Experience, 2015 Sep 7, Canadian Radiation Oncology (CARO) Conference, Ontario, Canada, **Co-Author**
32. S. Tam, J. Theurer, A. Grewal, S. Hawkins, **D. MacNeil**, A. Nichols, J. Yoo, K. Fung, Dysphagia Following Salvage Neck Dissection: A Prospective Cohort Study, 2015 Jun 8, 69th CSOHNS Annual Meeting, Winnipeg, Manitoba, Canada, **Co-Author**
33. P. Doyle, K. Fung, J. Theurer, **D. MacNeil**, J. Yoo, Exploring the Functional Influence of Flap Reconstruction on Tracheosophageal Voice Production, 2015 Jun 7, 69th CSOHNS Annual Meeting, Winnipeg, Manitoba, Canada, **Co-Author**
34. T. H. Low, A. Partridge, P. Doyle, J. Theurer, K. Fung, A. Nichols, **D. MacNeil**, J. Yoo, Patient and Observer Assessment of Donor Site Scars for Head and Neck Reconstruction- Implications for Donor Site Selection, 2015 Jun 7, 69th CSOHNS Annual Meeting, Winnipeg, Manitoba, Canada, **Co-Author**
35. K. Patel, **D. MacNeil**, K. Liu, J. Shariff, J. Yoo, A. Nichols, K. Fung, A. Garg, Survival of Patients with Subglottic Squamous Cell Carcinoma, 2015 Jun 7, 69th CSOHNS Annual Meeting, Winnipeg, Manitoba, Canada, **Supervisor**
36. S. Tam, T. H. Low, J. Theurer, A. Partridge, K. Fung, A. Nichols, **D. MacNeil**, J. Yoo, The Infraclavicular Pedicled Adipofascial Flap for Recontouring the Neck following Neck Dissection, 2015 Jun 7, 69th CSOHNS Annual Meeting, Winnipeg, Manitoba, Canada, **Co-Author**
37. **S. Danielle MacNeil**, Samantha Tam, Kyan Liu, Amit X Garg, Amardeep Thind, Eric Winquist, John Yoo, Anthony Nichols, Kevin Fung, Stephen Hall, Salimah Z Shariff, Incidence of perioperative ischemic stroke after neck dissection, 2015, Boston, Massachusetts, United States, **Poster Presenter**
38. Murphy R, O'Connell DA, Seikaly H, Harris J, **MacNeil SD**. Locoregional Recurrence in Free Flap Surgery for Advanced Stage Head and Neck Cancer. International Conference on Head and Neck Cancer. Toronto, ON. 2012 Jul, **Presenter**

39. **MacNeil SD**, Yu J, Grosvenor A, Osswald M, Dobrovolsky W, Ansari K, O'Connell DA, Wolfaardt J, Seikaly H. Maxillary Reconstruction with Digital Pre-Planning and Prefabrication of Fibular Free Flaps. International Conference on Head and Neck Cancer. Toronto, ON . 2012 Jul, **Presenter**
40. **MacNeil SD**, Osswald M, Wolfaardt J, Ansari K, O'Connell DA, Grosvenor A, Harris J, Seikaly H. Digital Planning Improves the Accuracy of Mandibular and Maxillary Reconstruction. International Conference on Head and Neck Cancer. Toronto, ON. 2012 Jul, **Presenter**
41. Towles R, **MacNeil SD**, Berean K, Anderson D, Garnis C. The Molecular Characterization of Anaplastic Thyroid Cancer. Department of Surgery Chung Research Day. Vancouver, BC. 2010 Oct, **Presenter**
42. **MacNeil SD**, Moxham JP, Kozak FK. Nasopharyngeal foreign bodies may mimic lower airway locations. ABEA: COSM. May 2008. Orlando, FA. 2010, **Presenter**
43. **MacNeil SD**, Moxham JP, Kozak FK. Nasopharyngeal foreign bodies may mimic lower airway locations. 2010, COSM: ABEA, Orlando, Florida, United States, **Presenter**
44. **MacNeil SD**, Westerberg BW, Romney MG. Topical antibiotics for the treatment of Methicillin-resistant staphylococcus aureus otorrhea: a systematic review of the literature. Canadian Society of Otolaryngology Annual Meeting. Montreal, QC. 2007 May, **Presenter**
45. Kent J, **MacNeil SD**, Javer A. Eosinophilic Angiocentric Fibrosis (EAF) causing bilateral complete nasal obstruction: Case Report and Review of the Literature. Canadian Society of Otolaryngology Annual Meeting. Montreal, QC. 2007 May, **Presenter**
46. **MacNeil SD**, Westerberg BW, Romney MG. Topical antibiotics for the treatment of Methicillin-resistant staphylococcus aureus otorrhea: a systematic review of the literature. 2007, Canadian Society of Otolaryngology Annual Meeting 2007, Montreal, Quebec, Canada, **Presenter**
47. **MacNeil SD**, Wright E. Multi-Port Technique for Drainage of Unilateral Frontal Sinusitis. Canadian Society of Otolaryngology Annual Meeting. Kelowna, BC. 2006 May, **Presenter**
48. **MacNeil SD**, Fernandez CV. Informing Research Participants of Research Results: An Analysis of the Attitudes of Canadian University-based Research Ethics Board Chairs. IWK Health Centre Department of Pediatrics Research Day. Halifax, NS. 2005 Apr, **Presenter**
49. **MacNeil SD**, Kodish E, Fernandez CV. Informing Research Participants of Research Results: An Analysis of Pediatric Informed Consent Conference in Randomized Controlled Trials. IWK Health Centre Department of Pediatrics Research Day. Halifax, NS. 2004 May, **Presenter**
50. **MacNeil SD**, Kodish E, Fernandez CV. Informing Research Participants of Research Results: An Analysis of Pediatric Informed Consent Conference in Randomized Controlled Trials. Faculty of Medicine Research Day. Halifax, NS. 2003 Dec, **Presenter**
51. **MacNeil SD**, Lu X, Pohajdak B, Wright JR. The Development of a Tilapia (Oreochromis niloticus) Embryonic Stem Cell Line. Aquanet I Conference. Halifax, NS. 2001 Sep, **Presenter**

PRESENTATIONS

Plenary Presentations

National

1. **Co-Author**, Functional Outcomes Following Pharyngoesophageal Reconstruction with the Gastric Pull Up, Canadian Society of Otolaryngology, Presenters: Butskiy O, Rahmanian R, **MacNeil D**, Anderson D, 2019 Jun 4, Canada, Scientific Presentation

Conference Presentation

Provincial

1. **Organizer**, Survivorship, London Regional Cancer Program Multidisciplinary Retreat, 2019 Mar 5, London, Ontario, Canada, Scientific Presentation

2. **Presenter**, Survivorship, McGill University, 2018 Nov 12, Montreal, Quebec, Canada, Scientific Presentation

National

1. **Co-Author**, Gender Disparity in Head and Neck Cancer Driver Genes: An Analysis of the TCGA Dataset, Canadian Society of Otolaryngology, Presenters: Mundi N, Ghasemi F, **MacNeil D**, Fung K, Yoo J, Nichols A, 2019 Jun 4, Scientific Presentation

2. **Presenter**, ORATOR 3, London Regional Cancer Program Multidisciplinary Retreat, 2019 Jan 12, Toronto, Ontario, Canada, Scientific Presentation

3. **Supervisor**, Prevalence of Obstructive Sleep Apnea in Head and Neck Patients: A Systematic Review, 72nd CSOHNS Annual Meeting, Presenters: Dr. Krupal Patel, 2018 Jun 19, Quebec, Canada, Scientific Presentation

4. **Supervisor**, Functional Outcomes in Early (T1/T2) Supraglottic Cancer: A Systematic Review, 72nd CSOHNS Annual Meeting, Presenters: Dr. Benjamin van der Woerd, 2018 Jun 18, Quebec, Canada, Scientific Presentation

5. **Supervisor**, Diagnostic Delay in Head and Neck Cancer Patients, 72nd CSOHNS Annual Meeting, Presenters: Dr. Shannan Hamel, 2018 Jun 18, Quebec, Canada, Scientific Presentation

6. **Supervisor**, Safety of Outpatient Parathyroidectomy for Primary Hyperparathyroidism in a Cohort of Unilateral Neck Explorations, 72nd CSOHNS Annual Meeting, Presenters: Dr. Chris Dwyer, 2018 Jun 17, Quebec, Canada, Scientific Presentation

7. **Supervisor**, Total Thyroidectomy versus Thyroid lobectomy for the treatment of low risk well-differentiated thyroid cancer 1-4 cm in size: a systematic review, 72nd CSOHNS Annual Meeting, Presenters: Dr. Axel Sahovaler, 2018 Jun 17, Quebec, Canada, Scientific Presentation

8. **Supervisor**, Inclusion of Clinical Features in the Diagnosis of Warthin's Tumor, 72nd CSOHNS Annual Meeting, Presenters: Dr. Thomas So, 2018 Jun 16, Quebec, Canada, Scientific Presentation

9. **Co-Author**, The Initial Transoral Robotic Surgery Experience in a Canadian Series, 71st CSOHNS Annual Meeting, Presenters: Dr. David Yeh, 2017 Jun 12, Saskatchewan, Canada, Scientific Presentation

10. **Co-Author**, Shouldering the Load of Mandible Reconstruction: 74 Cases of Oromandibuar Reconstruction with the Scapula Tip Free Flap, 71st CSOHNS Annual Meeting, Presenters: Dr. David Yeh, 2017 Jun 12, Saskatchewan, Canada, Scientific Presentation

11. **Co-Author**, The practicality of 3D Printing for Mandibular Reconstruction, International Conference on Head and Neck Cancer, Presenters: J. Prasad, A. Partridge, D. Yeh, K. Fung, A. Nichols, **D. MacNeil**, J. Yoo, 2016 Jul 19, Seattle, Washington, United States, Scientific Presentation

12. **Co-Author**, Prior Radiotherapy and age strongly predict survival after salvage surgery for recurrent oral cavity squamous cell carcinoma- A recursive partitioning analysis, International Conference on Head and Neck Cancer, Presenters: S. Tam, R. Araslanova, H. Low, K. Fung, **D. MacNeil**, D. Palma, A. Nichols, 2016 Jul 18, Seattle, Washington, United States, Scientific Presentation

13. **Co-Author**, The mutational landscape of analplastic thyroid cancer, International Conference on Head and Neck Cancer, Presenters: A. Nichols, S. Lai, S. Prokopec, N. Pinto, M. Chan, W. Faquin, M. Black, J. Yoo, C. Howlett, K. Fung, **D. Macneil**, J. Koropatncik, A. Datti, F. Vizeocoumar, K. Patel, C. Garnis, K. Berean, J. Mymryk, J. Rocco, D. Palma, J. Barrett, D. Wheeler, G. Clayman, P. Boutros, 2016 Jul 18, Seattle, Washington, United States, Scientific Presentation

14. **Presenter**, Does Parathyroidectomy Reverse Mortality Risk in Patients with Primary Hyperparathyroidism? A Systematic review and Meta-Analysis, International Conference on Head and Neck Cancer, Presenters: **Danielle MacNeil**, Rohin Krishnan, Monali Malvankar-Mehta, John Costella, John Yoo, 2016 Jul 17, Seattle, Washington, United States, Scientific Presentation

15. **Co-Author**, Treatment of Early Stage Supraglottic Squamous Cell Carcinoma: Meta-Analysis Comparing Primary Surgery Versus Primary Radiotherapy, International Conference on Head and Neck Cancer, Presenters: K. Patel A. Nichols, K. Fung, J. Yoo, **D. MacNeil**, 2016 Jul 17, Seattle, Washington, United States, Scientific Presentation

16. **Co-Author**, Analysis of Clinical variables associated with plate extrusion in Oromandibular reconstruction, International Conference on Head and Neck Cancer, Presenters: J. Prasad, A. Nichols, K. Fung, **D. MacNeil**, J. Theurer, D. Lee, D. Yeh, J. Yoo, 2016 Jul 17, Seattle, Washington, United States, Scientific Presentation

17. **Co-Author**, Patient Eligibility for Osseointegrated Implant-Based Rehabilitation Following Bony Reconstruction of the Oral Cavity, 70th CSOHNS Annual Meeting, Presenters: J. Theurer, C. Aragon, K. Fung, **D. MacNeil**, A. Nichols, J. Yoo, 2016 Jun 14, Prince Edward Island, Canada, Scientific Presentation

18. **Co-Author**, The Practicality of 3D Printing for Mandibular Reconstruction, 70th CSOHNS Annual Meeting, Presenters: J. Prasad, J. Yoo, K. Fung, **D. MacNeil**, A. Nichols, H. Low, A. Partridge, 2016 Jun 14, Prince Edward Island, Canada, Scientific Presentation

19. **Supervisor**, Treatment of Early Stage Supraglottic Squamous Cell Carcinoma: Meta-analysis Comparing Primary Surgery versus Primary Radiotherapy, 70th CSOHNS Annual Meeting, Presenters: K. Patel, A. Nichols, K. Fung, J. Yoo, **D. MacNeil**, 2016 Jun 13, Prince Edward Island, Canada, Scientific Presentation

20. **Co-Author**, A Continuing Epidemic of Human Papillomavirus Related Oropharyngeal Cancer in Southwestern Ontario, 70th CSOHNS Annual Meeting, Presenters: A. Nichols, S. Dhaliwal, J. Basmaji, J. Yoo, K. Fung, **D. Macneil**, J. Barrett, J. Mymryk, 2016 Jun 12, Prince Edward Island, Canada, Scientific Presentation

21. **Co-Author**, An Oral Cavity Wait Time Improvement Initiative: Do Wait Times in Surgeyr and Post-operative Radiation Matter? 70th CSOHNS Annual Meeting, Presenters: A. Nichols,N. Mundi, S. Dhaliwal, J. Basmaji, J. Yoo, K. Fung, **D. Macneil**, D. Palma, 2016 Jun 12, Prince Edward Island, Canada, Scientific Presentation

22. **Co-Author**, TORS vs. RT: Development of a Decision board for patients with early Oropharyngeal Cancer, 70th CSOHNS Annual Meeting, Presenters: G. Scott, A. Louie, **D. MacNeil**, A. Nichols, D. Palma, J. Yoo, K. Fung, 2016 Jun 12, Prince Edward Island, Canada, Scientific Presentation

23. **Co-Author**, Detection of Circulating Thyroid Tumor DNA in Patients with Thyroid Nodules, 70th CSOHNS Annual Meeting, Presenters: -K. Patel, N. Cormier, J. Barrett, J. Yoo, **D. MacNeil**, I. Radchinsky, W. stecho, A. Nichols, 2016 Jun 12, Prince Edward Island, Canada, Scientific Presentation

24. **Co-Author**, Highly Effective Agents Identified by High-throughput Screening of Genetically Characterized Anaplastic Thyroid Cancer Cell Lines, 70th CSOHNS Annual Meeting, Presenters: N. Pinto, M. Black, J. Yoo, **D. MacNeil**, K. Fung, A. Datti, J. Barrett, A. Nichols, 2016 Jun 12, Prince Edward Island, Canada, Scientific Presentation

25. **Co-Author**, Patterns of Failure in Laryngeal Cancer-Glottic versus Supraglottic, 69th CSOHNS Annual Meeting, Presenters: D. Yeh, H. Low, T. Zhang, V. Venkatesan, K. Fung, **D. MacNeil**, A. Nichols, J. Yoo, 2015 Jun 9, Manitoba, Canada, Scientific Presentation

26. **Co-Author**, Highly Effective Agents Identified in Genetically Characterized Anaplastic Thyroid Cancer Cell Lines, 69th CSOHNS Annual Meeting, Presenters: N. Pinto, M. Black, J. Yoo, **D. MacNeil**, K. Fung, A. Datto, J. Barrett, A. Nichols, 2015 Jun 8, Winnipeg, Manitoba, Canada, Scientific Presentation

27. **Co-Author**, High Throughput Screening for Drug Discovery in Head and Neck Squamous Cell Carcinoma, 69th CSOHNS Annual Meeting, Presenters: M. Black, N. Pinto, J. Yoo, **D. MacNeil**, K. Fung, A. Datti, J. Barrett, A. Nichols, 2015 Jun 8, Winnipeg, Manitoba, Canada, Scientific Presentation

28. **Co-Author**, Frequency of HPV16 Prevalence and PIK3CA Hot Spot Mutations in early-stage Laryngeal Squamous Cell Carcinoma, 69th CSOHNS Annual Meeting, Presenters: M. Black, N. Pinto, J. Yoo, **D. MacNeil**, K. Fung, A. Nichols, 2015 Jun 8, Winnipeg, Manitoba, Canada, Scientific Presentation

29. **Co-Author**, Targeted Therapeutics: Optimization of a PIK3CA Mutational Analysis Pathway, 69th CSOHNS Annual Meeting, Presenters: J. Theurer, E. Qinquist, D. Palma, J. Yoo, **D. MacNeil**, K. Fung, C. Howlett, A. Nichols, 2015 Jun 7, Winnipeg, Manitoba, Canada, Scientific Presentation

30. **Co-Author**, Prospective Evaluation of Neck and Shoulder Function After unilateral neck Dissection, 69th CSOHNS Annual Meeting, Presenters: H. Low, M. Ehsan, T. Overend, B. Chesworth, **D. MacNeil**, A. Nichols, J. Yoo, K. Fung, 2015 Jun 7, Manitoba, Canada, Scientific Presentation

31. **Presenter**, The Control of Anaplastic Thyroid Carcinoma Cell Lines by Oncolytic Poxviruses, Presenters: N. Mundi, A. Nichols, S. Um, J. Barrett, G. Rizzo, M. Black, **D. MacNeil**, K. Fung, J. Yoo, J. Koropatnick, J. Mymryk, 2014, Ontario, Canada, Scientific Presentation

32. **Presenter**, The Impact of Standardized Pre-Printed Order Sets on Post-Laryngectomy Physician Orders, Presenters: S. Ansari, L. Sowerby, J. Yoo, **D. MacNeil**, J. Franklin, A. Nichols, K. Fung, 2014, Ontario, Canada, Scientific Presentation

33. **Presenter**, Targeting PIK3CA in Head and Neck Cancers with BYL719, An Alpha Specific PI3K Inhibitor, Presenters: G. Rizzo, A. Nichols, M. Black, J. Barrett, J. Yoo, K. Fung, **D. MacNeil**, 2014, Ontario, Canada, Scientific Presentation

34. **Presenter**, Infraclavicular Free and Pedicled Flaps - A Novel Flap With Broad Applications in Head and Neck Surgery, Presenters: D. Angel, J. Yoo, K. Fung, **D. MacNeil**, A. Nichols, 2014, Ontario, Canada, Scientific Presentation

35. **Presenter**, Vestibular Evoked Myogenic Potential (VEMP) Abnormalities in Patients with Visual Vestibular Mismatch. Canadian Society of Otolaryngology Annual Meeting. Halifax, NS. Presenters: **MacNeil SD**, Mallinson A, Galo J, Longridge N. 2009 May

36. **Presenter**, The reliability of the reflux finding score among general Otolaryngologists. Canadian Society of Otolaryngology Annual Meeting. Jasper, AB. Presenters: **MacNeil SD**, Morrison M, Lee PK. 2008 Jun

37. **Presenter**, Diagnosis of Upper Aerodigestive Foreign Bodies: A Major Gap in Medical School Education, Presenters: **D. MacNeil**, 2008, British Columbia, Canada, Scientific Presentation

38. **Presenter**, Disclosure of research results: demonstrating greater respect for research participants. Dalhousie University Medical School Summer Research Seminar Series. Halifax, NS. Presenters: **MacNeil SD**, Fernandez CV. 2005 Jun

39. **Presenter**, Informing Research Participants of Research Results: An Analysis of the Attitudes of Canadian University-based Research Ethics Board Chairs. Canadian Pediatrics Society 82nd Annual Conference. Vancouver, BC. Presenters: **MacNeil SD**, Fernandez CV. 2005

40. **Presenter**, The Development of Tilapia (Oreochromis niloticus) Chimeras and Short-term Culture of Undifferentiated Embryo Cells. Aquanet II Conference. Moncton, NB. Presenters: **MacNeil SD**, Pohajdak B, Wright JR. 2002 Sep

41. **Presenter**, The development of tilapia germ-line chimeras from embryonic stem cell cultures. Department of Pathology Research Seminar, Dalhousie University, Halifax, NS. Presenters: **MacNeil SD**, Lu X, Pohajdak B, Wright JR. 2001 Apr

International

1. **Co-Author**, Early mortality with immune checkpoint inhibitors (IOs) in solid tumors: an inconvenient truth? 2018 ASCO Annual Meeting, Presenters: E. Winquist, **D. MacNeil**, 2018 Jun 1, Toronto, Ontario, Canada, Scientific Presentation

2. **Presenter**, Does Parathyroidectomy Reverse Mortality Risk in Patients with Primary Hyperparathyroidism? A Systematic review and Meta-Analysis. International Conference on Head and Neck Cancer, 2016 Jul 1

3. **Presenter**, Treatment of Early Stage Supraglottic Squamous Cell Carcinoma: Meta-Analysis Comparing Primary Surgery Versus Primary Radiotherapy. International Conference on Head and Neck Cancer, 2016 Jul 1

4. **Co-Author**, Infraclavicular Pedicled Adipofascial Flap for Recontouring the Neck following Neck Dissection, ASOHNS ASM2016, Presenters: Tsu-Hui (Hubert) Low1
Samantha Tam2, Allison Partridge2, Kevin Fung2, Anthony Nichols2, Danielle MacNeil2, and John Yoo2, 2016 Mar 6, Melbourne, Australia, Scientific Presentation

5. **Co-Author**, A surgical algorithm for management of retrosternal goitre Expanding role of video-assisted thoracoscopic surgery, ASOHNS ASM2016, Presenters: Tsu-Hui (Hubert) Low1
Kevin Fung2, Anthony Nichols2, Danielle MacNeil2, Richard Inculat3, and John Yoo2, 2016 Mar 6, Melbourne, Australia, Scientific Presentation

6. **Co-Author**, Shoulder Function after Scapular Free Flap, ASOHNS ASM2016, Presenters: Tsu-Hui (Hubert) Low1
Allison Partridge2, Krupal Patel2, Kevin Fung2, Anthony Nichols2, Danielle MacNeil2, and John Yoo2, 2016 Mar 6, Melbourne, Australia, Scientific Presentation

7. **Presenter**, Informing Research Participants of Research Results: An Analysis of Pediatric Informed Consent Conference in Randomized Controlled Trials. American Society of Hematology. San Diego, CA. Presenters: **MacNeil SD**, Kodish E, Fernandez CV. 2003 Dec

Student Presentation

National

1. **Co-Author**, NSD1 is a Biomarker of Survival in HPV-Negative Head and Neck Squamous Cell Carcinoma, Canadian Society of Otolaryngology, Presenters: Ghasemi F, Prokopec S, **MacNeil D**, Mundi N, Fung K, Yoo J, Barrett J, Nichols A, 2019 Jun 2, Scientific Presentation

Workshop

National

1. **Presenter**, The Development of a Head and Neck Cancer Survivorship Care Program: Practical Applications Within Existing Resources, Canadian Society of Otolaryngology, Presenters: O'Connell D, Arsenault M, Nayer S, Roth K, **MacNeil D**, 2019 Jun 3, Scientific Presentation

2. **Facilitator**, Mentorship in Otolaryngology-Head and Neck Surgery: Improving Ourselves and Our Colleagues, Presenters: **MacNeil D**, Seikaly H, Gowrishankar M, Chan Y. 2019 Jun 2, Scientific Presentation

3. **Facilitator**, Asymptomatic Primary Hyperparathyroidism: An Update on Surgical Indications and Surgical Advances, 71st CSOHNS Annual Meeting, Presenters: Dr. John Yoo, Dr. Jeffrey Harris, Dr. Paul Kerr, 2017 Jun 13, Saskatchewan, Canada, Scientific Presentation

4. **Facilitator**, How to Produce High Quality Clinical Research Using Canadian Health Administrative Databases, 71st CSOHNS Annual Meeting, Presenters: Dr. Jason Beyea, Dr. Antoine Eskander, Dr. Steve Hall, 2017 Jun 13, Saskatchewan, Canada, Scientific Presentation

5. **Panelist**, Beavertail modification of the Radial Forearm Free Flap: Indications. Technique and Functional Outcomes, 69th CSOHNS Annual Meeting, Presenters: E. Fung, J. Tibbo, **D. MacNeil**, K. Richardson, J. Harris, H. Seikaly, 2015 Jun 7, Manitoba, Canada, Scientific Presentation

6. **Panelist**, Using Electronic Data for Research in Otolaryngology- Head and Neck Surgery, 69th CSOHNS Annual Meeting, Presenters: S. Hall, A. Eskander, K. MacDonald, **D. MacNeil**, 2015 Jun 7, Manitoba, Canada, Scientific Presentation

Continuing Medical Education

Courses

Instructor - CME Course

2017 Sep 16	C-Star, 6th Annual Emergencies in Otolaryngology Head & Neck Surgery Boot Camp 2017, Total Hours: 7

Organizer - CME course

2019 Nov 29	Lamplighter Best Western, LRCP Head and Neck Disease Site Team Annual Retreat, Total Hours: 4
2019 Mar 5	LRCP, LRCP Head and Neck Cancer Survivorship Retreat, Total Hours: 3

Presenter - Faculty Development Course / Workshop

2015 Jun 9	Winnipeg, Patterns of Failure in Laryngeal Cancer- Glottis vs Supraglottic, Total Hours: 1
2015 Jun 8	Winnipeg, Highly Effective Agents Identified in Genetically Characterized Anaplastic Thyroid Cancer Cell Lines, Total Hours: 1
2015 Jun 8	Winnipeg, Head and Neck Surgery 2 continued, Total Hours: 1
2015 Jun 8	Winnipeg, Frequence of HPV16 Prevalence and PIK3CA Hot Spot Mutations in Early-stage Laryngeal Squamous Cell Carcinoma, Total Hours: 1
2015 Jun 7	Winnipeg, Beavertail Modification of the Radical Forearm Free Flap: Indications, Technique and Functional Outcomes, Total Hours: 1
2015 Jun 7	Winnipeg, Using Electronic Data for Research in Otolaryngology-Head and Neck Surgery, Total Hours: 1
2015 Jun 7	Winnipeg, Targeted Therapeutics: Optimization of a PIK3CA Mutational Analysis Pathway, Total Hours: 1

Presenter - Grand Rounds

2016 Oct 16	Head and neck, Krupal Patel, Total Hours: 1
2013 Mar	Anaplastic Thyroid Cancer Guidelines, Total Hours: 1
2010 Mar - present	Treating the difficult unexplained chronic cough. Total Hours: 1
2010 Jan - present	What is the impact of fellowship on residency education? Total Hours: 1
2008 Oct - present	Vestibular Evoked Myogenic Potentials. Total Hours: 1
2007 Dec - present	Dermoid cysts of the floor of the mouth. Total Hours: 1

Lecturer- Workshop

2015 Jun 7	Winnipeg, Using Electronic Data for Research in Otolaryngology-Head and Neck Surgery, Total Hours: 1

Graduate Education

Courses

Examiner- Graduate Student Theses

2016 Dec 6	Title: A Longitudinal Study to Investigate Changes in Functional Ability and Concerns in Head Neck Cancer Patients Undergoing Neck Dissection PhD Convocation Title: Program: Health and Rehabilitation Sciences Degree: Master of Science, Mariya Ehsan, Total Hours: 1

SUPERVISION AND MENTORING

Mentorship

Undergraduate

2016 - 2017	Shayan Kassirian, Supervisor, Schulich School of Medicine & Dentistry, Otolaryngology - Head & Neck Surgery
2015 - 2017	Thomas So, Supervisor, Schulich School of Medicine & Dentistry, Otolaryngology - Head & Neck Surgery
2015 - 2017	Jonathan Athayde, Supervisor, Schulich School of Medicine & Dentistry, Otolaryngology - Head & Neck Surgery
2014	Ronghbo Zhu, Supervisor, Schulich School of Medicine & Dentistry, Otolaryngology - Head & Neck Surgery
2014	Rochelle Johnstone, Supervisor, Schulich School of Medicine & Dentistry, Otolaryngology - Head & Neck Surgery

Research Assistant

2017 - present	Shannan Hamel, Supervisor, Schulich School of Medicine & Dentistry, Otolaryngology - Head & Neck Surgery

OTHER ACTIVITIES

Other Noteworthy Activities

1995 Grade 9 Royal Conservatory of Music, Canada