Predicting Long-term Survival in Squamous Cell Carcinoma of the Tongue Base: Assessment of Evolving Treatment Strategies

by

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Contents

Abstract

Introduction: The treatment of squamous cell carcinoma of the tongue base has evolved with concomitant chemoradiation replacing surgery ± radiotherapy for advanced stages of disease. This study examines 10-year treatment outcomes in this patient population over the time-span of the changing treatment paradigm.

Methods: A cohort of 290 patients was followed for 3442 months (median15 months). Survival analysis was done using Kaplan- Meier curves and log-rank test for comparing sub-groups. Cox's proportional hazard models were used to determine the predictors of 10-year survival after treatment.

Results: The mean age of the cohort was 62.2 years (SD=12.4 years), 79.7% were males, and 86.4% had Stage III or IV disease at presentation. The overall median survival time was 16 months (95% CI=9.5, 22.5 months) with 23% of patients surviving the 10-year period. The 10-year disease specific and disease free survival was similar at 30 and 31 months respectively. Survival varied significantly ($P< 0.05$) with stage of disease on presentation. Survival probability at 10 years was 37% for stage I disease and 26%, 28% and 23% for stages II -IV respectively. Patients younger than 65 years had better overall survival when compared to those 65 or more: 29% versus 14%, respectively ($P<0.0001$). Similarly, females had better 10-year survival as compared to males, 31% vs. 21%, respectively; however, this difference was not statistically significant ($P>0.10$). A lateral location of the tumor had a better survival outcome when compared to a midline location of (27% or 28% versus 9%, $P<0.0025$). With univariate analysis 10-year survival of 54% was observed with chemoradiation, and 45% for surgey+radiotherapy ($P<0.0001$). Multivariate models demonstrated an independent effect of stage, gender, age, and initial

treatment modality on overall survival. Treatment with radiotherapy and chemotherapy reduced the risk of death over 10 years by 89% (HR=0.11; 95% CI=0.1, 0.2; P<0.0001) and surgery + radiotherapy reduced the risk of death over 10 years by 87% (HR=0.13; 95% CI=0.1, 0.2; P<0.0001).

Conclusion: Independent of cancer stage, gender, and age, treatment modality predicts 10-year survival of patients with base of tongue cancer. Similar survival is observed following chemoradiation and surgey+radiotherapy.

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1. Introduction

The management of squamous cell carcinoma of the tongue base is challenging. Tumors in this anatomical area remain relatively silent with nonspecific and vague complaints which results in relatively advanced stage of disease on presentation with a high incidence of cervical metastases. Clinical assessment of the tongue base can be difficult. The optimal treatment is controversial and has been undergoing an evolution in recent years. Local and regional control rates with radiation alone proved discouraging. Surgical resection, facilitated by advances in reconstruction techniques, with adjunctive radiotherapy, improved local and regional control. Over the last 10 to 15 years, combinations of chemotherapy and radiation have become the treatment of choice for advanced stages of disease in many institutions with the goal of organ preservation. The short-term outcome of radiation and chemotherapy protocols appear to be similar to those observed with surgery and radiotherapy. The disease control rates in the long-term have been questioned. This is recognized as a gap in knowledge. This study was undertaken to assess these evolving treatment strategies and specifically to address long-term predictors of survival (at 10 years post treatment) after the various treatment modalities.

2. Literature Review

2.1 Head and Neck Cancer

Head and neck cancer is the sixth most common cancer in the world accounting for 3-5% of all cancers. There are about 640,000 cases of head and neck cancer per year worldwide, with approximately 350,000 (more than half) deaths per year. Cancers of the oral cavity and pharynx are the most common type of head and neck cancer with approximately 485,000 cases per year.[1] Squamous cell carcinoma accounts for 90% of head and neck malignancies.[2]

Head and neck cancer incidence varies around the world. South Asia and parts of Central and South Europe have the highest incidence of head and neck cancer.[3] Oral cancer is the most common cancer in South Asian countries such as Sri Lanka, India, Pakistan, and Bangladesh[4] whereas, in Southeast Asian countries, including China, Malaysia, Indonesia and Singapore, nasopharyngeal cancer is one of the most prevalent cancers.[5] In North America, oropharyngeal carcinoma, associated with human papilloma virus (HPV) infection, is increasing[6] and tends to affect a younger age group.[7, 8] Head and neck cancer is more than twice as common in men than in women.[9] However, trends show that the incidence of head and neck cancer is increasing in women, while it is decreasing in men.[10] This may be because of increasing rates of drinking and smoking among women.[6-8] In Canada, it has been estimated that over 3,400 cases with oropharyngeal cancer will be diagnosed in 2012 and over 36,540 cases in the United States according to 2011 reports from the Canadian and American cancer registries.

Cancer data combines oral cavity sub-sites with oropharyngeal sub-sites, making the exact incidence of specific oral and pharyngeal primary site cancers somewhat difficult to determine.[11]

2.2 Oropharyngeal Cancer: Anatomical Considerations

The oral cavity is bound anteriorly by the vermillion border of the upper and lower lip and posteriorly by the anterior pillars (palatoglossal arches) of the palatine tonsils. The superior aspect of the oral cavity is bound by the hard and soft palates and inferiorly by the floor of the mouth, the lingual mucosa, and the anterior two-thirds of the tongue. The oral cavity is bounded posteriorly by the circumvallate papilla, which lie along the sulcus terminalis and separates the oral tongue from the base of tongue.

The pharynx connects the nasal and oral cavities to the esophagus and larynx. It is divided into three anatomical areas: the nasopharynx, the oropharynx, and the hypopharynx, the nasopharynx begins as an extension from the posterior aspect of the nasal cavity and extends from the nasal choana to the soft palate. The oropharynx extends from the soft palate to the level of the hyoid bone and is bound laterally by the tonsillar fossae and the tonsillar pillars (the palatoglossal and palatopharyngeal arches). The oropharynx includes the base of tongue, lateral and posterior pharyngeal walls, and the palatine tonsils. The hypopharynx extends from the level of the hyoid bone to the inferior aspect of the cricoid cartilage and includes the pyriform sinuses, postcricoid region, and posterior hypopharyngeal wall, the tongue has four pairs of intrinsic muscles, which interdigitate throughout the tongue. These muscles act to lengthen or shorten the tongue, curl the apex and edges, and flatten or round the dorsal surface. The intrinsic tongue

muscles originate and insert within the tongue itself. Extrinsic tongue muscles are genioglossus, hyoglossus, styloglossus, and palatoglossus. They act to protrude, depress, elevate, and retract the tongue. All motor function of the tongue is mediated by the hypoglossal nerve [cranial nerve XII (CN XII)]. Special sensory innervations (taste) are transmitted to the facial nerve via the chorda tympani nerve for the anterior two-thirds of the tongue. General sensation of the tongue is carried by the lingual nerve (a branch of the mandibular nerve CN V3), which itself is a branch of the trigeminal nerve (CN V). Most of the oropharynx is supplied with sensory and motor innervation through the glossopharyngeal (CN IX) and vagus (CN X) nerves. The hypoglossal nerve (CN XII) supplies motor innervation to the base of the tongue, and the trigeminal nerve (V2, V3) provides the motor and most of the sensory innervation to the soft palate. The sensory root of the facial nerve (CN VII), through the chorda tympani, supplies the taste buds in the anterior two-thirds of the tongue; the posterior third is innervated by the glossopharyngeal nerve (CN IX).

The oral cavity and the pharynx are abundantly supplied with blood from most branches of the external carotid artery. The lymphatic drainage is primarily through lateral neck lymph nodes levels II and III, with central structures such as the tongue base, soft palate, and posterior pharyngeal wall draining to both sides of the neck. The posterior pharyngeal wall and tonsillar region also drain to the retropharyngeal nodes, which in turn drain to the upper level II nodes (submandibular triangle).[13, 14]

The oropharynx is surrounded on three sides by potential fascial spaces. The retropharyngeal space is an area of loose connective tissue lying between the buccopharyngeal fascia of the pharynx and the alar layer of the prevertebral fascia. It

extends from the skull base to the superior mediastinum and communicates with the parapharyngeal space laterally. The parapharyngeal space is defined by fascial planes extending from the skull base to the greater cornu of the hyoid bone and laterally to the pharyngeal walls. It has the shape of an inverted pyramid, and its boundaries include the skull superiorly, pterygomandibular raphe anteriorly, prevertebral fascia posteriorly, and the pharynx medially. The lateral boundary is the most complex and is formed by the fascia overlying the medial pterygoid muscle, a portion of the mandible, deep lobe of the parotid, and the posterior belly of the digastric muscle. This fascia extends superiorly, incorporating the stylomandibular ligament and fuses with the strong interpterygoid fascia to attach to the skull base in a line passing medial to the foramen ovale and spinosum. It also separates the parapharyngeal space from the infratemporal fossa and masticator space. The parapharyngeal space can be further divided by a layer of fascia running from the tensor veli palatini muscle to the styloid and its related structures into two compartments. The prestyloid compartment contains fat, variable portions of the deep lobe of the parotid, and a small branch of the trigeminal nerve to the tensor veli palatini. The poststyloid compartment contains the carotid artery, jugular vein, cranial nerves IX to XII, sympathetic chain, and lymph nodes.[15-19]

2.3 Epidemiology of Oropharyngeal cancer

2.3.1 Potentially Malignant Disorders:

Oral and pharyngeal cancer is a heterogeneous group of cancers that arise from the mucosa of the oral cavity, pharynx, larynx, nasal cavity and paranasal sinuses. In the

World Health Organization (WHO) Workshop, held in 2005, it was decided to use the term "potentially malignant disorders (PMD)" as it conveys that not all disorders described under this term may transform into cancer.[21] It is generally accepted that oral and pharyngeal cancer may arise from potentially malignant disorders (PMD).[20]

A precancerous lesion is a morphologically altered tissue in which oral cancer is more likely to occur than in its apparently normal counterpart. It is a generalized state associated with a significantly increased risk of cancer. Leukoplakia, erythroplakia, palatal lesion of reverse cigar smoking, oral lichen planus, and oral submucous fibrosis (SMF) were identified as PMD by the World Health Organisation's working group on Oral Cancer.[22] Leukoplakia is defined by the WHO working group as "a keratotic white patch or plaque that cannot be scraped off and cannot be characterized clinically or pathologically as any other disease"[23] Erythroplakia is defined as "a fiery red patch or bright red velvety plaques that cannot be characterized clinically or pathologically as any other definable disease".[24]

Nicotine stomatitis is an alteration of the palatal mucosa due to smoking. The palatal mucosa becomes thickened and hyperkeratotic, sometimes developing a fissured surface. The surface often develops popular elevations with red centers, which represent the inflamed openings of the minor salivary gland ducts. In some Southeast Asian and South American countries, individuals practice a habit known as reverse smoking in which the lit end of the cigarette or cigar is placed inside the mouth. This habit creates a more severe heat-related alteration of the palatal mucosa known as reverse smoker's palate, which has been associated with a significant risk of malignant transformation.[25, 26]

Lichen planus is an autoimmune disorder of the skin and/or mouth membranes with a strong female predilection (M:F = 1:2). Oral lichen planus is a T-cell-mediated autoimmune disease in which autocytotoxic CD8 + T cells trigger apoptosis of oral epithelial cells.[27, 28] The oral mucosa may be red, and might have blisters and ulcers with white lines. These lesions tend to be bilateral and symmetric. This distinguishes them from erythroleukoplakia. Oral lichen planus can be divided into six types: reticular, papular, plaque-like, erosive, atrophic, and bullous. The reticular, papular, and plaque-like types are usually painless and appear clinically as white keratotic lesions. The erosive, atrophic, and bullous forms are often associated with a burning sensation and in many cases can cause severe pain.[29]

Oral submucous fibrosis (OSMF) is a chronic disorder characterized by fibrosis of the lining mucosa of the upper digestive tract involving the oral cavity, oropharynx and frequently the upper third of the oesophagus. Except in early forms of the disease, the clinical presentation is characteristic due to fibrosis of lamina propria and submucosa with an increasing loss of tissue mobility.[30]

2.3.2 Known Risk Factors:

There are several known risk factors in the development of oral and pharyngeal cancer with the most studied and well established being the use of tobacco.[31,32] Smokers have been shown to be seven times more likely than non-smokers to develop leukoplakia. Further, the importance of tobacco is reinforced by the regression and/or disappearance

of many lesions following tobacco smoking cessation. A recent study shows that about 56% of leukoplakia regressed at three months and 78% regressed about a year after smoking cessation. [31, 33] There is an increased risk of head and neck cancer, ranging from a 5- to 25-fold, in cigarette smokers compared to non-smokers.[34, 35] There appears to be a dose-response relationship. A case-control study comparing 605 patients with head and neck cancer to 756 controls showed the relative risk of developing oral and pharyngeal cancer in tobacco users was more than sevenfold. The risk increased with the duration of smoking and gradually declined after smoking cessation.[36] In another study, patients who smoked more than one pack of cigarettes per day had a 13-fold increase in risk of head and neck cancer. The age of starting smoking (below 18 years of age) and the duration of smoking (over 35 years) were high risk factors. Cessation of smoking was associated with a significant decrease in relative risk. [37]

Epidemiologic studies also suggest that cigar and pipe smoking are associated with an increased incidence of head and neck cancer, [38, 39]and smokeless tobacco (both chewing tobacco and snuff) with an increased risk of cancer of the oral cavity and pharynx.[40,41] Second-hand smoke exposure may be a contributing factor. A study evaluated 59 patients with head and neck cancer who did not use tobacco and did not abuse alcohol. These patients had a significantly higher risk of exposure to environmental tobacco smoke in both the workplace and home than a control population without cancer. This relationship primarily occurred in women and those with tongue cancer.[42]

Alcohol consumption independently increases the risk of cancer in the upper aerodigestive tract.[43-45] The relative risk of developing head and neck cancer due to alcohol appears to be dose dependent.[44,45] One study reported a five- to six fold increased

risk for head and neck cancer with alcohol intake greater than 50 g/day versus less than 10 g/day.[45] Alcohol intake combined with tobacco smoking appear to have an interactive and multiplicative effect on the risk of developing head and neck cancer.[44,46] There is increasing evidence of the role of alcohol consumption in the development of oral cancer[31, 47]

A study undertaken by the International Head and Neck Cancer Epidemiology (INHANCE) Consortium, analyzed 11,221 patients with head and neck cancer and 16,168 controls showed a significant increase of oral and pharyngeal cancer among tobacco and alcohol users. It estimated the risks of smoking and alcohol use combined to be more than 64%, showing that the joint effect of tobacco and alcohol is responsible for a majority of head and neck cancers. This study also concluded that about 36% of head and neck cancers cannot be attributed to either tobacco or alcohol, particularly for the oral cavity and oropharyngeal cancer, among women and below the age 45.[31]

Multiple types of viral infections have an established relationship with increased risk of head and neck cancer, including Epstein-Barr virus (EBV), human papillomavirus (HPV), and human immunodeficiency virus (HIV). Nasopharyngeal carcinoma is one of the most common cancers in southern China. Several studies support the role of EBV as the primary etiologic agent in the pathogenesis of nasopharyngeal carcinoma.[48-51]

There are multiple other risk factors that have been linked to head and neck cancer including, betel nut chewing, occupational exposure or environmental toxins, radiation, poor oral hygiene and periodontal disease, genetic factors, dental prostheses or poorly fitting dentures, diet and multiple vitamin deficiencies.[57-82]

2.5 Human Papilloma Virus and Oropharyngeal Cancer:

There has been a gradual change in the demographics of head and neck carcinoma. The incidence of oropharyngeal carcinoma has been increasing despite declining tobacco consumption and decreasing incidence of cancers at other head and neck sites. It is now clear that the incidence of human papillomavirus (HPV)-associated oropharyngeal cancers is rising. The incidence of oropharyngeal cancer initially remained constant and then began to rise.[1,2]

Epidemiologic and molecular evidence has established a causal role for HPV, specifically, HPV 16, in patients with head and neck cancer, particularly those arising in the base of the tongue and the tonsils. These HPV associated head and neck cancers are seen in younger patients, who typically are nonusers of tobacco and alcohol. Patients with HPV positive oropharyngeal cancer are approximately 10 years younger when compared to HPV negative patients.[52-54] Multiple studies have found that there is an approximately two- to threefold increase in the incidence of squamous cell carcinoma of the head and neck among patients who are infected with HPV.[55, 56]

Several cohort studies from the 1990s suggested that approximately 50% of oropharyngeal squamous cell carcinomas were attributable to HPV, while more recent studies suggest that HPV may account for more than 70 to 80 % of these malignancies.[1,2]

Over the last decade understanding of the bio-pathology of head and neck squamous cell carcinoma and the significant role of HPV has been established. HPV-associated oropharyngeal carcinoma has recently been recognized as a unique subtype of head and neck squamous cell carcinoma.[6] A systematic review and meta-analysis revealed that

HPV-associated HNSCC is mainly located in the oropharynx and that HPV16 accounts for the vast majority of these carcinomas.[7,8]

Head and neck squamous cell carcinomas were considered a uniform group of cancer; incidence and anatomical distribution were mainly attributed to demographic differences in the habit of exposure to smoking or chewing tobacco and alcohol consumption. This view has changed due to refinements of the molecular techniques that allow for the recognition of new subtype of head and neck cancer that differ not only in etiology, but also in pathogenesis and clinical outcomes.[9,10] HPV status has a profound effect on patient prognosis, and it may soon guide therapy. Accordingly, HPV status will become a standard component in the diagnostic reporting of all oropharyngeal carcinomas.[9] There are very important and significant differences between HPV related oropharyngeal cancers and other head and neck cancers resulting from other risk factors (eg, tobacco, alcohol).[11] These include:

Epidemiologic factors: Patients with HPV positive oropharyngeal cancer are approximately 10 years younger when compared to HPV negative patients.[12,13,14] Many of the patients seen with this entity are in their late thirties or early forties. This difference in patient age has major implications in terms of performance status, comorbidities, and ultimately, prognosis.

Anatomic location: HPV associated tumors predominantly arise in the base of the tongue or the tonsillar region, although a small percentage of tumors at other sites are also HPV positive. Why the oropharynx is more susceptible to HPV transformation than other sites is unclear. Like the uterine cervix, the oropharynx offers easy access for infection. The

tonsils contain deep invaginations of the mucosal surface believed to favor the capture and processing of antigens, which may facilitate viral access to basal cells.

Clinical stage at presentation: Multiple studies have shown that HPV associated oropharyngeal cancer is more likely to present with a relatively early stage (T1/T2) primary tumor, but relatively advanced disease in the neck (N2/N3), often with a large cystic lymph node that is sometimes mistaken for a benign cyst. Despite the biologic aggressiveness of HPV positive cancer, these tumors appear to have a better prognosis than head and neck cancers not associated with HPV with a lower rate of distant metastases. In a retrospective analysis of a randomized trial, the incidence of distant metastases was lower in HPV positive as opposed to HPV negative patients (9 versus 15 percent)[15] Similar results were observed in another large retrospective series, in which the incidence of distant metastases was also lower in HPV positive compared with HPV negative tumors (10 versus 15 percent, respectively), although the difference was not statistically significant.[16] In the HPV positive group, distant metastases developed later in patients with an HPV associated cancer and in a much different pattern than in HPV negative patients.[16]

Second malignancy: A study that included 318 patients with oropharyngeal cancer found that those whose tumors were HPV associated based upon immunostaining for p16 were significantly less likely to have a second malignancy. [16] The decrease in second malignancies included prior tumors, synchronous lesions, and metachronous second primary lesions (11 versus 20, 1 versus 9, and 6 versus 13 percent, respectively).

These findings have led to a new and meaningful subdivision of conventional head and neck squamous-cell carcinoma in two main prognostic and therapeutic groups:

i) Keratinizing Head and Neck Squamous Cell Carcinoma (HNSCC) mainly occurring in elderly men that are heavy smokers and drinkers, HPV16-negative, being associated with an aggressive course of disease.

ii) Non-keratinizing Head and Neck Squamous Cell Carcinoma (HNSCC) occurring in younger men between 40 and 60 years that are non-smokers and non-drinkers, HPV16- positive, being associated with improved prognosis. The main risk factors are number of sexual partners, oral-genital sex, oral-anal sex, and marijuana use. Among the unusual variants of HNSCC, papillary and lymphoepithelial-like are mostly related to HPV-16 infection, whereas the spindle and acantholytic types are mainly associated with tobacco and alcohol.

The current available methods in detecting HPV include serum antibody against several HPV epitypes, type-specific and consensus (broadspectrum) polymerase chain reaction (PCR) assay, real-time PCR to quantify viral load, type-specific DNA in situ hybridization (ISH), and immunohistochemical (IHC) detection of surrogate markers, particularly a known biomarker of HPV E7 oncoprotein function, the cyclin-dependent-kinase inhibitor p16 protein. As recommended at the 2008 meeting of the task force of the National Cancer Institute's head and neck steering committee, the choice of HPV assays depends on how the information obtained is to be used.[17] HPV serology and PCR-based methods have been mostly used for the study of the natural history of HPV infection. A weakness of the nonquantitative PCR-based assay is that it cannot distinguish oncogenic virus from biologically irrelevant (transcriptionally inactive) virus. These methods need to be refined and more sophisticated forms may become available soon for clinical use.

Compared with the traditional smoking-associated head and neck squamous cell carcinoma, HPV-related oropharyngeal carcinoma has a favorable natural history and responds better to treatment. Consequently, patients with this cancer have better long-term survival than those with HPV-unrelated head and neck squamous cell carcinoma (eg, 5-year overall survival rate of >80% versus >40% for patients with stage III-IV tumors), and hence they are more likely to experience chronic therapy-induced morbidity. Therefore, changes in evaluation, staging, and treatment are needed for this patient group. However, attempts to change the treatment for HPV-associated oropharyngeal carcinoma should take place in a closely monitored clinical trial setting.[18]

2.4 Squamous Cell Carcinoma of the Tongue Base

Management of squamous cell carcinoma of the tongue base (BOT) is challenging and controversial for all medical disciplines involved in treating this disease including Head and Neck Surgical Oncologists, Medical Oncologists and Radiation Oncologists. Nonspecific and vague complaints on presentation, in conjunction with the complex anatomic location, makes precise clinical examination challenging. This contributes to the delay in diagnosis and advanced stage of disease identified on presentation. As the majority of patient present with late stage disease, a multidisciplinary approach is usually advised. Advanced disease is a reflection of the relatively silent anatomical location and biological aggression. The management of tongue base cancer has improved significantly during the past decade. Currently, most patients can be treated using an organ-preservation approach that optimizes oncologic and quality-of-life outcomes. Continued

advances in radiation therapy delivery and the increasing incorporation of concomitant chemotherapy into the management of these cancers have led to excellent local control and potentially lower rates of distant metastasis.

2.4.1 Epidemiology

Cancer data combines oral cavity sites with oropharyngeal sites, making the exact incidence of specific oropharyngeal primary site cancers somewhat difficult to determine.[10] The American Cancer Society estimates that a total of 9,040 people, 5,870 men and 3,170 women were diagnosed in 2012 with 1,780 people dying of the disease in the same year. From 2000 to 2009, the median age at diagnosis for cancer of the tongue was 61 years. India has one of the world's highest incidences of oral cancer. Their reported overall tongue base cancer rate is 5.5 per 100,000 compared to 4.4 in the USA.[83,84] American figures show 0.1% diagnosed under age 20; 2.2% between 20 and 34; 7.1% between 35 and 44; 22.9% between 45 and 54; 26.5% between 55 and 64; 21.9% between 65 and 74; 15.0% between 75 and 84; and 4.3% 85+ years of age. The annual percentage change (APC) of this disease is 0.5 from 1975–2003 which represents an increasing trend of statistical significance, however, fortunately there is a decreasing mortality. The decrease in mortality is most apparent in the period 1990–1999 represented by an APC of a negative value at -2.4.[84] Base of tongue cancer normally accounts for one-third of all squamous cell carcinoma of the tongue. The one exception to this is India, where SCC of the BOT is three times greater than SCC of the oral tongue.[85] According to 2011 reports from the Canadian and American cancer registries, it has been estimated that over 3,400 cases with oral and pharyngeal cancer will be diagnosed in

Canada in 2012 and over 36,540 cases in the United with approximately one-third of these will be expected to arise in the oropharynx.

Tongue base is considered the second most common subsite behind the tonsillar regions, representing between 20 and 35% of oropharyngeal lesions. The vast majority of cases are squamous cell carcinomas. Although incidence of the disease is low, an increase as well as tendency of appearance in younger ages has been noted in recent years. This has been mainly attributed to HPV infection. Squamous cell carcinoma of the tongue base is generally considered an aggressive disease with poor prognosis.

2.4.2 Clinical Presentation

Patients with tongue base cancer tend to present with advanced disease because early lesions are usually asymptomatic. Pain and dysphagia are the most common presenting symptoms. Neck node enlargement is usually present at presentation but is identified as the primary symptom in only 30% of the patients. Other symptoms include otalgia, foreign-body sensation, dysarthria, hemoptysis, and weight loss. Trismus and numbness in the distribution of V3 should alert clinicians of the possible involvement of the masticator space and mandible.[16]

Cancer of the tongue base remain virtually silent with nonspecific and vague complaints which results in relatively advanced stage of disease on presentation with a high incidence of cervical metastases. Clinical assessment of the tongue base can be difficult. Mackle et al. report 21% of their patient population presenting with T1/2, and 79% with T3/4 disease.[86] Gourin et al. quote 91% of their patients with T3/4 disease,[87] and Krus et al. quote 81%.[89]

There are a myriad of features which may indicate tongue base pathology. Mackle et al.[23] report pain being the main feature of tongue base disease with 76% of patients with severe throat pain and only 16% presenting with a mass. These presenting features differ markedly with Gorsky et al. who report 73% of patients presenting with a neck mass.[90] Twenty percent of patients present with bleeding and 10% have oral pain. Sixty percent of patients have symptoms of dysphagia, 45% dysphonia and 36% with otalgia. Mulwafu et al. report that their patient population present with neck mass in 40% of cases and 33% had unilateral otalgia.[91] A unilateral persistent throat pain associated with smoking has been reported to be an ominous predictor of disease. Patients may also have bilateral palpable lymphadenopathy given the midline anatomical location and the high propensity for regional lymph node metastases.[92]

2.4.3 Clinical Evaluation and Staging

A comprehensive history, including a review of systems, past medical history, dental history, and social and family history, is essential in planning the proper therapy. Tongue base cancer patients tend to have a prolonged history of tobacco and alcohol abuse and consequently suffer from cardiac, pulmonary, and liver disease.

A complete physical and a thorough head and neck examination should be routinely performed on all patients. Systematic visualization of all the mucosal surfaces of the upper aerodigestive tract is essential due to the field cancerization phenomenon. This examination is greatly facilitated by the use of a fiberoptic nasopharyngoscope, especially in patients with trismus. The mandibular range of motion and cranial nerve function are also examined, with deficiencies indicating extension into the mandible, parapharyngeal,

or masticator spaces. Palpation of the primary tumor to judge the extent of the lesion and submucosal spread is always performed. All the neck levels are systematically evaluated, and size, location, and fixation of nodes are noted. The patient's dentition is also assessed because restoration or extraction may be required before initiation of treatment.

The extent of the tumor, neck metastasis, distant metastasis, and the medical condition of the patient should be assessed completely before a treatment plan is implemented. The following radiologic studies are recommended:

Chest radiograph: to evaluate the lungs for metastasis, second primary tumors, and chronic changes associated with tobacco use.

Computed tomography (CT) and magnetic resonance imaging (MRI): Imaging is essential. They are indicated in the assessment of advanced-stage tumors or when involvement of the mandible, parapharyngeal space, prevertebral fascia, neck nodes, or retropharyngeal nodes is suspected. CT scanning is better suited for evaluating bony structures. MRI is best at evaluating soft tissue involvement, such as the tongue base, parapharyngeal space, or prevertebral fascia.[93] Because of the incidence of multiple primary tumors occurring simultaneously, a careful search for other primary tumors of the upper aerodigestive tract is indicated.

Panorex of the mandible: This helps in select cases in detecting mandibular involvement and assessing the dentition of the patient.

Other considerations: Barium swallow may performed on patients with dysphagia if esophagoscopy is not planned. Angiography with the balloon test occlusion and cerebral blood flow evaluation should be considered if the tumor involves the carotid and resection is contemplated. Positron emission tomography (PET) scan is now used

extensively in cancer of the aerodigestive tract. Positron emission tomography has been investigated as an imaging modality for recurrent oropharyngeal cancer[94] however its exact role in cancer at various oropharyngeal sub-sites is not clear.

Laboratory evaluation of oropharyngeal cancer patients includes a complete blood count, blood chemistry, liver function tests, and an electrocardiogram. Nutritional evaluation may be included in this regimen if indicated by the patient's physical status.

Tissue diagnosis is obtained with fine-needle aspiration of enlarged nodes and/or biopsy of the oropharyngeal lesion. This can usually be performed in the office or clinic, but biopsy should be reserved for endoscopy in patients with trismus, tenuous airway, or lesions that are not easily accessible transorally.

Examination under anesthesia and panendoscopy should be considered when the assessment of submucosal spread and invasion of surrounding structures such as the prevertebral fascia and mandible is suspected, especially in patients with trismus. This exam may be necessary if a second primary cancer is suspected. Biopsies are performed at the end of the examination and/or endoscopy to allow the examination to proceed unhindered by bleeding from the biopsy site.

The staging systems for tongue base cancer are all clinical, based on the best possible estimate of the extent of disease before treatment. The assessment is based on physical examination, endoscopy, and imaging studies. The tumor must be confirmed histologically, and any other pathologic data obtained from a biopsy may be included. The American Joint Committee on Cancer has designated staging by TNM classification to define oropharyngeal cancer. (Appendix A)

2.4.2 Treatment Options and Outcome

The management of squamous cell carcinoma of the tongue base is controversial. In the past local and regional control rates with radiation alone proved discouraging. Surgical resection facilitated by advances in reconstruction techniques, with adjunctive radiotherapy, improved local and regional control. Over the last ten to 15 years, combinations of chemotherapy and radiation have become the treatment of choice for advanced stages of disease in many institutions with the goal of organ preservation. Surgery is reserved for treatment failures. [95,96]

The optimal treatment of tongue base cancer has been undergoing an evolution in recent years. Primary radiation has replaced primary surgery as the treatment of choice in most centers. Primary radiation therapy allows optimization of oncologic and quality-of-life outcomes. Chemotherapy has evolved as an important part of the management strategy, especially in the presence of locoregionally advanced disease. Also, for most patients with neck disease beyond N1, planned neck dissection is often advised with reports of improved locoregional control.[83,97]

Controversy persists within the literature as the traditional treatment for advanced head and neck cancer is surgery with postoperative radiotherapy. Surgical intervention has equivalent survival statistics to radiation but confers significant disability. Hamoir[98] argues that significant advances have been observed in reconstructive surgical procedures through the use of microvascular free flaps routinely, which allows a more functional restoration of the surgical defect. The most aggressive surgical intervention, a total glossectomy, is still advocated in the literature. Bova et al. consider this procedure to be an oncologically sound surgical procedure in advanced disease.[99]

A recent paper by Jones et al presents an ominous 30-year experience where comparisons were made between the treatment strategies of radiation versus surgery. In terms of observed survival, treating locally advanced (T3-4) at presentation offered no survival advantage over palliation alone. Treating early disease (T1-2) doubled the survival rate for up to 4 years, but by 5 years this survival advantage was lost. Jones concluded that radiotherapy and surgery were equivalent at controlling this disease.[100]

There are several radiotherapeutic options. Mendenhall et al. used external beam techniques with hyperfractionation, with local control rates for T1 96%, T2 91%, T3 81% and T4 38% and 5-year survival rates for Stage III 65% and Stage IV 42%. Late stage cancers showed improved control rates with the introduction of platinum based chemotherapy.[101] Aldelstein et al[102]compared radiotherapy alone to radiotherapy and cisplatin. In 295 patients overall 3-year survival improved from 23 to 37% with the addition of chemotherapy. Further trials have employed chemotherapeutic combinations such as carboplatin, 5-fluorouracil and leucovorin.[102] The optimal scheduling and delivery of radiotherapy is not clear; good outcomes have been reported with a variety of techniques. A range of protocols using external beam radiation therapy with conventional fractionation, various hyperfractionation schemes, and the use of brachytherapy has also been studied and reported. Even among the radiation oncologists, there is still some debate regarding the optimal approach. Thus, a multidisciplinary approach is essential to achieve good outcomes.[96] The overall prognosis is poor for a number of reasons, including delay in diagnosis, advanced stage at presentation, and increased overall age and poor general health at the time of diagnosis.[103]

Transoral laser microsurgery (TLM) offers an alternative for organ preservation and function, sparing radical surgical approaches to the primary tumor site. Indications for treatment of the neck and other adjuvant therapy such as radiation remain unchanged compared with open surgical techniques. Therefore, in assessing the effectiveness of TLM the focus of analysis should be on 1) local control, 2) establishing that regional and distant spread is not increased compared with other treatment modalities and 3) functional results. The benefits of TLM to patients include safety, shorter periods of hospitalization, organ preservation, and improved functional and cosmetic results.[104] The evidence base for long-term survival and functional outcomes for tongue base cancer treated with TLM have yet to be established but preliminary results are encouraging.[105] Complications after open surgery include fistula formation, flap failure, abscess formation, osteonecrosis, and osteomyelitis, and rates can be as high as 16% to 41%.[106-110] Compared with conventional open surgery, Grant et al reported TLM is relatively safe. TLM is not associated with the same degree of functional disability that can accompany conventional open surgery or indeed radical radiotherapy. They reported in a series of 618 patients with base of tongue cancer treated with TLM that the postoperative hemorrhage rate was 5%. This was contrasted to a rate of 2.8% for upper aerodigestive tract tumors.[104] Steiner and others reported postoperative bleeding in 3.1% of 600 patients treated with TLM with the highest rates seen in the oropharnyx (6.4%) and supraglottis (7%). In patients treated with TLM for carcinoma of the tongue base Steiner reported a postoperative hemorrhage rate of 10%.[105]

The strong opinions of physicians and patients about ideal treatments make randomization of a sufficient number of patients challenging (a large cohort is needed to

measure potentially small differences in outcomes). Consequently, retrospective studies are still the best resource for determining treatment outcomes of base of tongue cancer.[111]

3. Objectives

The purpose of this analysis is to determine the predictors of 10-year survival in patients with base of tongue cancer registered with the population based tumor registry of the Province of Manitoba. The treatment of squamous cell carcinoma of the tongue base has changed over the last two decades. Prospective data comparing treatment outcomes for this disease site is not available. The evaluation of a population based historical cohort of patients with squamous cell carcinoma of the tongue base, where no patients are excluded from evaluation, is considered valuable in assessing the outcomes of various treatment strategies used in treating this disease. Information on the long-term outcome (>5 years) by stage of disease at presentation, and treatment modality is limited.

3.Methods

For 35 years, the data of all patients with oropharyngeal cancer has been collected prospectively in the population based Manitoba Cancer Registry. This data, with appropriate institutional and ethics approval, was transferred to an electronic data base and stored for further study and analysis.

From these databases, a cohort of 290 patients with a biopsy proven squamous cell carcinoma of the base of tongue were selected out of 430 patients reviewed. One hundred and forty patients with incorrect site coding, other pathology, insufficient clinical data, or seen in consultation only after treatment elsewhere were excluded.

Patients were analyzed for demographic factors, treatments modalities, and treatment outcomes. Patients were staged based on the clinical presentation at the time of the initial consultation according to the TNM classification as formulated by the American Joint Committee on Cancer.[112]

Data were evaluated using the Chi-square contingency table method and the T-test where appropriate. Survival analysis using Kaplan-Meier curves and log-rank test for comparing sub-groups was used. Patients were censored if they lived up to 120 months to determine the 10-year survival outcomes. Multivariate models employing Cox's proportional hazard models were used to determine the predictors of 10-year survival after treatment of advanced oral cancer including age, gender, T- and N-staging, location, surgical margin and treatment modalities.

4. Results

The baseline characteristics of the study population are presented in Apendix B. Two hundred and thirty-one patients (79.3%) of this cohort were males, and 59 patients (20.3%) were females. One hundred and eighty-two patients (62.8%) were younger than 65 years. Tobacco use was recorded as an etiologic factor in 210 (72%) and alcohol in 150 (52%). Thirty patients(11.1%) presented with midline lesionThirty-eight patients (14.1%) presented with T1 disease, while 95 patients (35.2%), 67(24.8%), 70(25.9%) presented with T2, T3 and T4 lesions respectively. Sixty-six patients (24.4%) presented with N0, while 44(16.3%), 134(49.6%), and 26 (9.6%) presented with N1, N2, and N3 respectively. Eight patients (3.0%) presented with distant metastasis. The stage distribution on presentation is shown in Figure 1. Eighty-six percent of patients presented with advanced stages (III,IV) of disease.

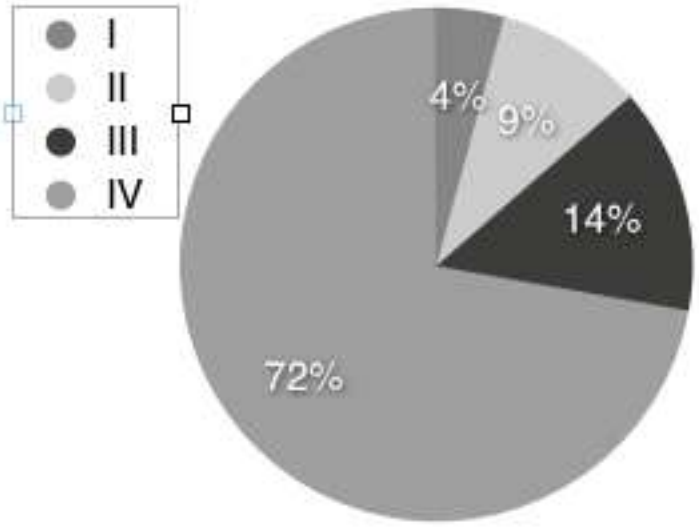

Figure 1. Clinical staging (n=290)

Surgery was used as a single treatment modality in 15 patients (5.3%), 94 patients (33.5%) were treated with radiotherapy alone, and 35 (12.5%) received surgery and adjunctive radiotherapy. A combination of chemotherapy and radiotherapy was delivered to 56 patients (19.9%), and 10 (3.6%) were treated with all 3 modalities. Seventy-one patients (25.3%) received no or palliative treatment. Treatment by stage of disease is shown in Figure 2. Radiotherapy, and radiotherapy and chemotherapy were the most frequent treatment modalities for advanced stages of disease ($P<0.0001$).

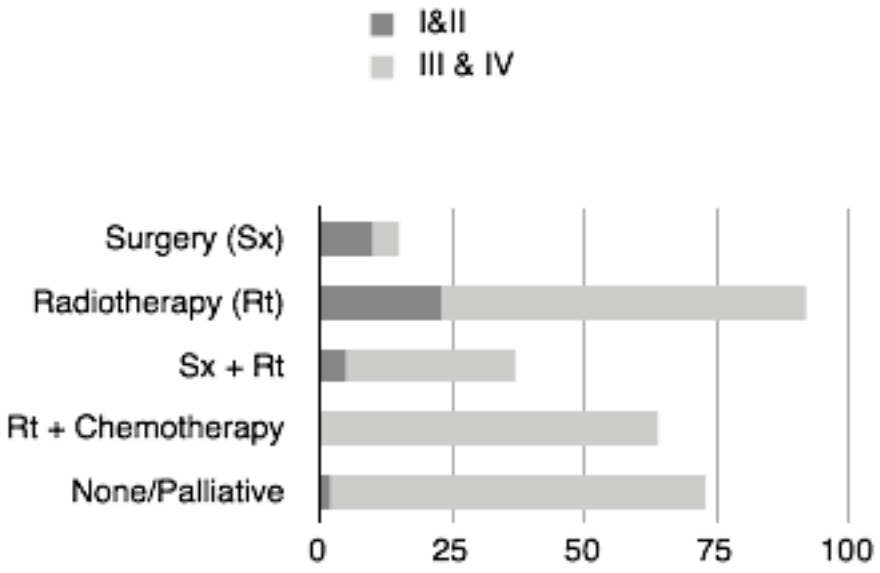

Figure 2. Treatment modality by stage of disease.

Radiotherapy was delivered by standard fractionation to a median dose of 6600 cgy (mode: 7000 cgy). Chemotherapy was cisplatinum based. In patients treated with surgery

margins were clear in 22 (71.0%), close (<2mm) in 4(12.9%), and five (16.1%) had involved margins.

In the patients treated with curative intent 9 had persistent disease and 80 recurred. The sites of recurrence are summarized in Figure 3 with local regional failure predominating and the neck identified as the single commonest site of treatment failure.

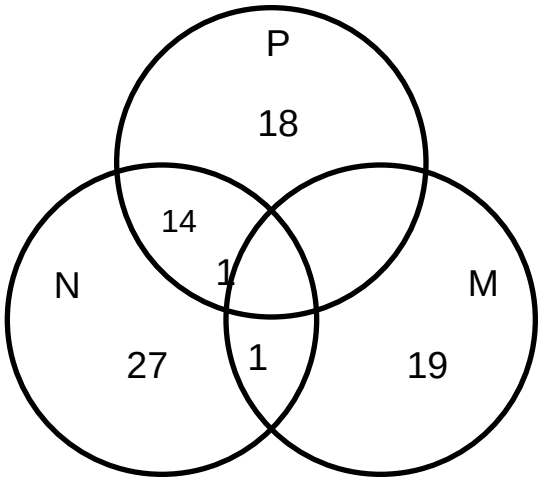

Figure 3. Venn diagram showing initial sites of treatment failure. (P= Primary N= Neck, M=Distant Metastasis)

Twenty-two patients died during the time period of the study. Death was attributed to the base of tongue in 143 (65%), second primaries in 18(8%) and other causes in 34 (15%). The cause of death was not recorded in 17 (8%).

The overall median survival time was 16 months (95% CI=9.5, 22.5 months) with 23% of patients surviving the 10-year period. When disease-specific survival was considered 39% of the patients survived the 10-year period and median survival

time was 30 months (95% CI=16.9, 43.1 months). Ten-year disease-free survival, on the other hand, was 31% and median survival time was 11 months (95% CI=6.6, 15.4 months). Overall and disease specific survival are shown in Figure 4.

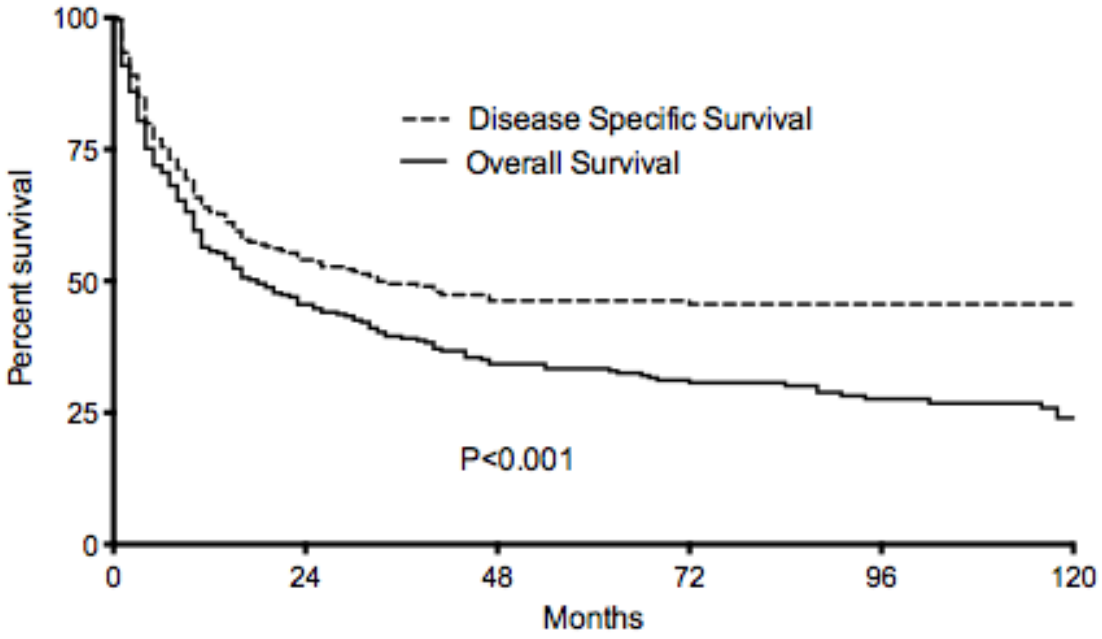

Figure 4. Disease specific and overall survival.

The 10-year overall survival probabilities for each category of the risk factors examined in the study are presented in Appendix C. Patients younger than 65 years had better overall survival when compared to those 65 or more: 29% versus 14% respectively (P<0.0001). Similarly, females had a better 10-year survival as compared to males, 31% vs. 21%, respectively; however, this difference was not statistically significant (P>0.10). Both lateral locations (right or left) had better survival outcomes when compared

to middle/anterior location of the cancer (27% or 28% versus 9%, P<0.0025). All staging systems were statistically significant in prediction of 10-year survival (P<0.05). (Figure5) Combined treatment showed better 10-year survival where surgery combined with radiotherapy had 45% survival, radiotherapy combined with chemotherapy had 54% and all three combined had 44% 10-year survival. (P<0.0001). (Figure 6)

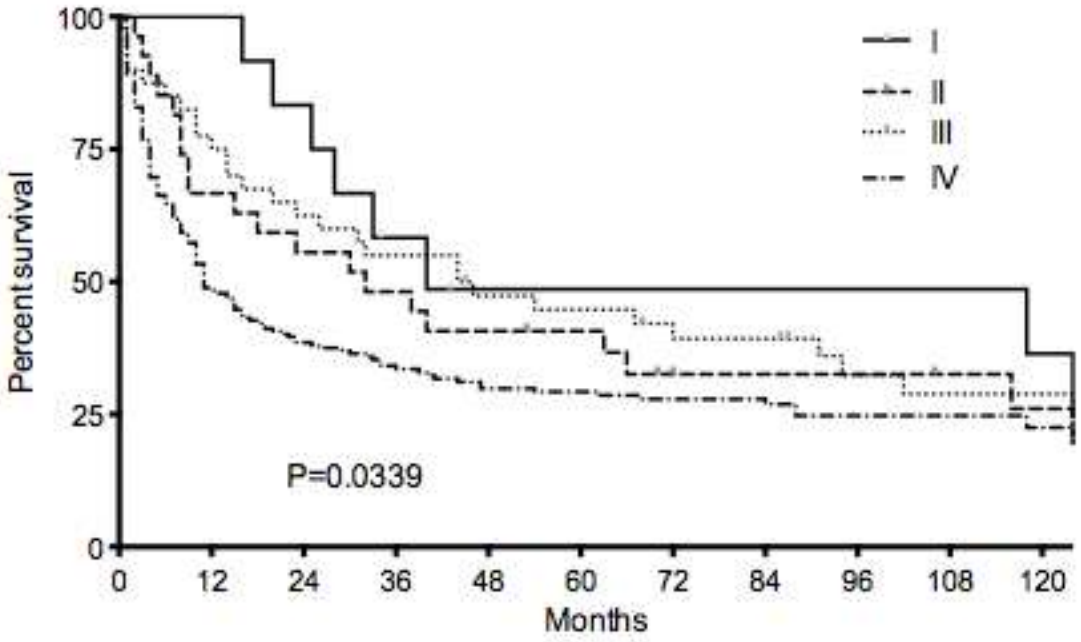

Figure 5. Overall survival by stage of disease.

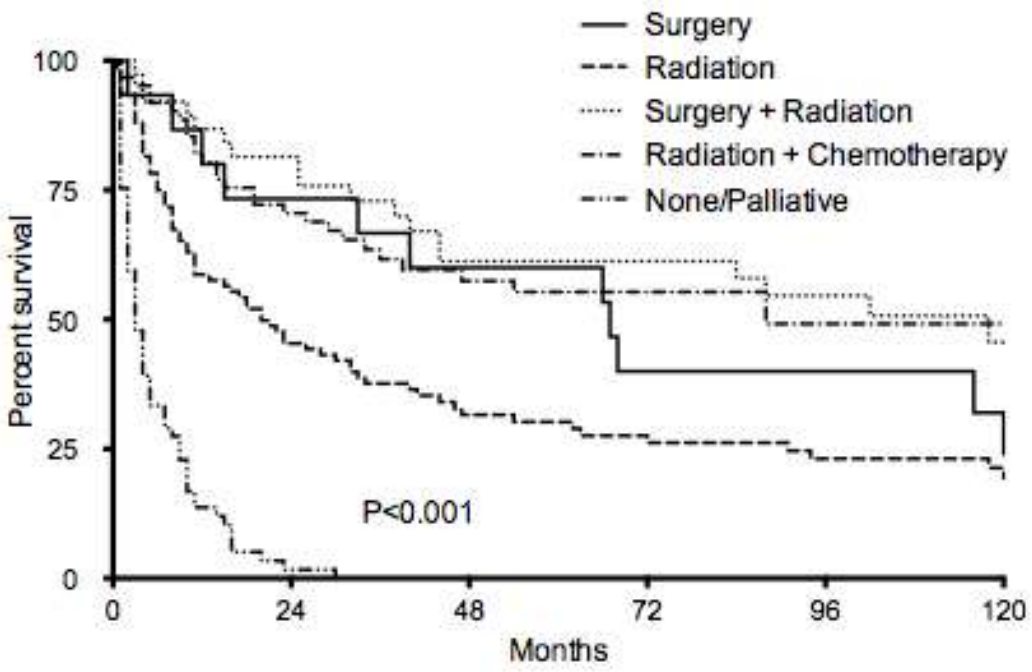

Figure 6. Overall survival by initial treatment modality

Multivariable Cox's proportional hazard modeling results are presented in Table 1. where T2, T3, T4 and N2/N3 were all statistically significant (P<0.5-<0.0001). Male gender had 50% increased risk of death within 10 years (P<0.5), while older age (> 65 years) had only marginally statistically significant increase in risk of death by 40% (P<0.10). All treatment modality enhanced survival over the 10-year period of the study by 65-89% when compared to no treatment/palliative treatment and were all statistically significant (P<0.001-<0.0001). It appears that combined treatment had better effect on survival, where combined treatments reduced the risk of death by 87-89% over 10 years. Treatment with surgery and radiotherapy

reduced the risk of death over 10 years by 87% (HR=0.13; 95% CI=0.1, 0.2; P<0.0001). Treatment with radiotherapy and chemotherapy reduced the risk of death over 10 years by 89% (HR=0.11; 95% CI=0.1, 0.2; P<0.0001). Treatment with surgery, radiotherapy and chemotherapy also reduced the risk of death over 10 years by 89% (HR=0.11; 95% CI=0.03, 0.30; P<0.0001)

Variable	Hazard Ratio	95% CI	P-value
Included in the Model			
Male vs. Female	1.5	(1.03, 2.3)	0.0283
Age 65+ years vs. <65 years	1.4	(1.0, 1.9)	0.0556
T2 vs. T1	1.9	(1.1, 3.3)	0.0148
T3 vs. T1	2.4	(1.3, 4.2)	0.0022
T4 vs. T1	4.2	(2.3, 7.5)	0.0000
N2/N3 vs. N0	1.6	(1.1, 2.2)	0.0093
Surgery vs. Palliative/no treatment	0.35	(0.2, 0.7)	0.0032
Radiotherapy vs. Palliative/no treatment	0.38	(0.3, 0.6)	0.0000
Surgery Radiotherapy vs Palliative/no treatment	0.13	(0.1, 0.2)	0.0000
Radiotherapy + Chemotherapy vs. Palliative/no treatment	0.11	(0.1, 0.2)	0.0000
Surgery + Radio + Chemo vs. Palliative/no treatment	0.11	(0.03, 0.30)	0.0000
Excluded from the Model			
Location			0.1738
N1 vs. N0			0.5232

Table 1. Cox's proportional hazard model predicting 10-year overall survival

5. Discussion

This historical cohort study of patients with squamous cell carcinoma of the base of tongue has similarities to previously reported studies and reviews. The age and sex distribution and advanced stage of diseases at presentation are consistent with previous reviews.[86-89,103] In contrast to these studies this review reports results of a population based historical cohort making this a unique contribution to this area of study. The fact that all patients with biopsy proven squamous cell carcinoma of the tongue base, within the defined geographic area and time frame of the study , are included in the review eliminates a major source of bias apparent in single institution reviews reporting on the outcome of a single treatment modality. Another defining aspect of this study is the duration of follow-up. Most studies report 2-5 year outcome following the treatment protocol used at their institution .[95, 88, 111, 100, 102,122] Reports of outcome beyond 5 years are infrequent. In a selected cohort treated at Memorial Sloan Kettering with radiation and neck dissection for node positive patients, 10 year disease free and overall survival of 67% and 52 % are reported.[109,116] In this series 72% had T1 and T2 lesions, compared to 49% in our cohort. The largest contemporary review of squamous cell carcinoma of the tongue base is reported by Zhen and coworkers.[103] They extracted and pooled data from 16,188 patients entered in National Cancer Data Base in the United States. The 10 year overall and disease specific survival was 12.2% and 29.4% respectively. In this review 78% of patients had Stage III and IV disease comparable to the 86% with advanced disease in the Manitoba cohort. The findings in the current review are more in keeping

with the latter study. These two reviews do not include outcome data by either stage of disease or treatment modality beyond 5 years. This is reported in our review and appears to be a unique contribution to the literature.

It is generally accepted that tongue base tumors have a relatively poor outcome. This is attributed to the advanced stage of disease on presentation and the anatomic location.[123] If detected early, 5 year survival in the order of 50 to 70% is reported.[100,103] Survival for Stage III and IV disease is in the order of 20-30%.[100, 92,102] Jones and coworkers[10] , in a detailed review of 165 patients treated in Liverpool concluded that there was no statistically significant evidence that treatment of advanced disease with curative intent is any better than no active treatment in terms of survival at 5 years. The Manitoba study shows a statistically significant difference in overall survival by stage of disease at 10 years. A positive impact on outcome with treatment versus no treatment is clearly identified in the current study. All treatment modalities enhanced survival over the 10-year period by 65-89% when compared to no or palliative treatment. We conclude that there is a long-term survival advantage to treating squamous cell carcinoma of the tongue base. Also it is noteworthy that this study is one of the few to compare different treatment modalities.

The single most frequent treatment modality used in this series was radiation. Radiation was used as a single modality for all stages of disease. Early stage disease was generally treated with a single modality and most frequently radiation (58%). Radiation and surgery are reported to provide comparable survival in early stage disease by some investigators. [96, 100, 116, 118] It is noted that the radiation series generally include surgical management of the neck. The present study suggests that surgery is superior for disease

control. This is consistent with the observations of Zhen et al[103] where surgery with or without radiation had higher survival rates than radiation alone. The majority of patients with advanced stages of disease in this series were treated, in decreasing order of frequency, with none or palliative means (30%,) radiation alone (29%), radiation and chemotherapy (27%), and surgery and radiation (13%). Treatment of advanced tongue base cancer is considered controversial. This controversy is reflected in the present series with the wide range of treatments selected for this patient population. The evolution of treatment strategies is also observed.

Radiation alone was used more frequently towards the start of this study. Poor local control rates with radiation alone, as observed in the Manitoba cohort, prompted a change in treatment strategy. Through the middle part of the time period of this study surgery with adjunctive radiotherapy was used more frequently for advanced disease with improvement in local and regional control when compared to radiation alone. This mirrors other reports in the literature.[115-117] The problem with combined surgery and radiotherapy when applied to the tongue base is the associated severe morbidity. Resection of more than half of the tongue base combined with high dose of adjunctive radiotherapy leads to severe dysphagia and dysarthria leaving patients dependent on alternative methods of feeding, usually by gastrostomy. Other morbidities include aspiration, recurrent chest infections, and disfigurement.[118] The concept of organ preservation with a combination of radiation and chemotherapy was applied to the tongue base with evidence of improved disease control when compared to radiation alone. [95, 111, 102, 121] This was achieved with reported reasonable functional outcomes. The benefit of adding chemotherapy to radiation has been confirmed with an absolute benefit of 6.5% at

5 years.[124] Recent studies [125-127] show high rates of local and regional control with this approach.

The Manitoba study provides comparative data on different treatment modalities for tongue base carcinoma at 5 and 10 years post treatment. This has not been previously reported. This study shows, when compared to no treatment; that both radiotherapy + chemotherapy and surgery + adjunctive radiotherapy, have a significant and comparable impact on outcome at 5 and 10 years. The question of the durability of the response to radiation and chemotherapy is addressed.

Important questions remained to be answered. We do achieve organ preservation with chemoradiation; however the real concern should be functional preservation. A significant number of patients do have severe problems with deglutition after chemoradiation. Functional data needs to be collated with these more traditional outcomes to facilitate treatment selection in this population. This work has started at CancerCare Manitoba and preliminary data suggests reasonable function outcomes following chemoradiation for advanced oropharyngeal cancer.[128]

Advanced laboratory and clinical investigations conducted during the past few decades along with technological advances have significantly improved our knowledge of the biology of head and neck squamous cell carcinoma (HNSCC), established new multimodality treatment regimens, improved surgical and radiation therapy methods, and refined management of HNSCC originating in different subsites to optimize tumor control while preserving organs and functions. Because these research efforts have been evolving, the epidemiology and demographics of HNSCC have been changing, particularly during the last decade, mainly because of the appearance and the rising

incidence of human papillomavirus (HPV)-related carcinoma.[9,10 51-54] Current clinical literature fully supports HPV-associated oropharyngeal squamous cell carcinoma as a unique entity: it is histologically distinct, affects an unambiguous patient population with defined risk factors and may warrant divergent clinical management compared with HNSCC associated with traditional risk factors (i.e. smoking and alcohol). Although epidemiological and clinical studies support HPV positive oropharyngeal squamous cell carcinomas (OPSCC) as a distinct clinical entity, the pathobiology of HPV-associated OPSCC initiation and progression is poorly understood. A more detailed understanding of molecular events associated with HPV+ OPSCC progression is therefore a prerequisite for improved staging and diagnostic/prognostic stratification, as well as for the design of novel therapeutic strategies specific for this population. Consequently, it is important to reevaluate the overall management paradigms and redirect some research endeavors to address emerging needs.

6. Conclusions

Carcinoma of the tongue base comprises a difficult to manage disease entity. Despite recent advances in treatment options, prognosis remains relatively poor. This poor prognosis is related to advanced stage of disease at presentation. Although no consensus exists regarding ideal therapy for advanced stages of disease, treatment with the use of chemotherapy and radiation seem to offer the best possibility for a positive outcome. Survival following treatment with chemotherapy and radiation is comparable to that observed with surgery and radiation at 5 and 10 years post treatment. Detailed analysis of long-term functional outcomes are necessary to guide the treatment selection process. Future improvements in outcome will parallel the advances made in the understanding of the biology of this disease.

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Appendices

Appendix A. TNM Staging System for oropharyngeal cancer

Primary tumor (T)	
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma in situ
T1	Tumor less than or equal to 2cm in greatest dimension
T2	Tumor >2cm but <4cm in greatest dimension
T3	Tumor >4cm in greatest dimension
T4	Tumor invades through cortical bone, inferior alveolar nerve, floor of mouth, or skin of face, i.e. chin or nose
T4a	Tumor invades adjacent structures (e.g. through cortical bone, into deep (extrinsic) muscle of tongue (genioglossus, hyoglossus, palatoglossus, and styloglossus), maxillary sinus, and skin of face)
T4b	Tumor invades masticator space, pterygoid plates, or skull base and/or encases internal carotid artery

Nodal involvement (N)	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in a single ipsilateral lymph node, <3cm in greatest dimension
N2	Metastasis in a single ipsilateral lymph node, >3cm but less than or equal to 6cm in greatest dimension; or in multiple ipsilateral lymph nodes, less than or equal to 6cm in greatest dimension; or in bilateral or contralateral lymph nodes, less than or equal to 6cm in greatest dimension
N2a	Metastasis in a single ipsilateral lymph node >3cm but less than or equal to 6cm in dimension

N2b	Metastasis in multiple ipsilateral lymph nodes, less than or equal to 6cm in greatest dimension
N2c	Metastasis in bilateral or contralateral lymph nodes, less than or equal to 6cm in greatest dimension
N3	Metastasis in a lymph node >6cm in greatest dimension

Distant metastasis (M)	
MX	Distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis

AJCC stage groupings

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	• T4a, N0, M0 • T4a, N1, M0 • T1, N2, M0 • T2, N2, M0 • T3, N2, M0 • T4a, N2, M0

Stage IVB	• Any T, N3, M0 • T4b, any N, M0
Stage IVC	• Any T, any N, M

Appendix B. Baseline characteristics of the study population

Variable	N	% Percent
Gender		
Male	231	79.7
Female	59	20.3
Age Category		
<65 years	182	62.8
65+ years	108	37.2
Stage		
I	12	4.2
II	27	9.4
III	441	14.2
IV	208	72.2
Stage T		
T1	38	14.1
T2	95	35.2
T3	67	24.8
T4	70	25.9
Stage N		
N0	66	24.4
N1	44	16.3
N2	134	49.6
N3	26	9.6
Stage M		
M0	261	97.0
M1	8	3.0
Location		
Right	116	43.0
Left	124	45.9
Middle/Anterior	30	11.1
Major Treatment Modalities		
Surgery	15	5.3
Radiotherapy	94	33.5
Surgery + Radiotherapy	35	12.5
Radiotherapy + Chemotherapy	56	19.9
Surgery + Radio + Chemo	10	3.6
None/Palliative	71	25.3
Surgical Margin		
Clear	22	71.0
Close	4	12.9
Involved	5	16.1

Appendix C. 10-year overall survival probabilities by major demographic and clinical variables

Variable	N	Median Survival in months (95% C.I.)	10-year survival Probability	P-value*
Gender				**0.1125**
Male	231	15 (8.3, 21.7)	0.21	
Female	59	23 (0, 49.1)	0.31	
Age Category				**0.0000**
<65 years	182	32 (21.4, 42.6)	0.29	
65+ years	108	8 (5.1, 10.9)	0.14	
Stage				**0.0394**
I	12	40 (0, 152.8)	0.37	
II	27	32 (6.6, 57.4)	0.26	
III	441	44 (15.7, 72.3)	0.28	
IV	208	11 (7.5, 14.5)	0.23	
Stage T				**0.0000**
T1	38	94 (1.1, 186.9)	0.43	
T2	95	38 (23.1, 52.9)	0.29	
T3	67	16 (9.2, 22.8)	0.25	
T4	70	6 (2.7, 9.3)	0.10	
Stage N				
N0	66	23 (13.1, 33.0)	0.24	**0.0003**
N1	44	54 (4.9, 103.1)	0.32	
N2	134	18 (6.6, 29.4)	0.26	
N3	26	4 (2.3, 5.7)	0.10	
Stage M				**0.0002**
M0	261	23 (14.4, 31.6)	0.23	
M1	8	4 (2.2, 5.9)	0.00	
Location				**0.0014**
Right	116	20 (11.1, 28.9)	0.27	
Left	124	31 (13.7, 48.3)	0.28	
Middle/Anterior	30	7 (2.8, 11.2)	0.09	
Major Treatment Modalities				**0.0000**
Surgery	15	66 (23.1, 108.9)	0.25	
Radiotherapy	94	20 (12.5, 27.5)	0.21	
Surgery + Radiotherapy	35	118**	0.45	
Radiotherapy + Chemotherapy	56	--	0.54	
Surgery + Radio + Chemo	10	88 (0, 184.3)	0.44	
None/Palliative	71	3 (1.7, 4.3)	0.00	
Surgical Margin				**0.1543**
Clear	22	68 (0, 138.7)	0.28	
Close	4	--	0.75	
Involved	5	11 (0, 26.0)	0.20	

* Log-rank test p-value

** The standard error of the median survival time could not be estimated, and therefore, the 95% CI could not be calculated