A Descriptive Study of Patient Profiles, Clinicopathological Characteristics, and Treatment Outcomes of Patients with Oral Tongue Squamous Cell Carcinoma Treated with Glossectomy at the University of Washington Medical Center

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Abstract

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Chair of Supervisory Committee:

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Oral and Maxillofacial Surgery

Background: Oral Squamous Cell Carcinoma (OSCC) is a life-threating condition accounting for 90% of all cancers in the oral cavity (with the majority of cases affecting the tongue). Early and loco-regionally oral tongue squamous cell carcinoma (OTSCC) is treated with surgical resection (glossectomy) with or without neck dissection and postoperative adjuvant therapy.

Aim: To describe patient demographics, clinical and histopathological characteristics, survival, and other post-surgical outcomes in patients with OTSCC treated with glossectomy through the

department of Otolaryngology-Head & Neck Surgery (OTO-HNS) at University of Washington Medical Center (UWMC) within our study time period.

Materials and Methods: A retrospective chart review was performed utilizing Leaf, a self-service tool provided through the Institute of Translational Health Sciences (University of Washington, Seattle, WA). Electronic medical records of eligible patients were analyzed for demographic, clinical, histopathological, and surgical variables. Patients were eligible for inclusion if treated with glossectomy, hemiglossectomy, or subtotal glossectomy at UWMC between January 1st, 2016 and December 31st, 2019. Patients were excluded if OTSCC involved other anatomic sites, if surgery required composite resection, or if surgery was performed to treat recurrent OTSCC. Additional information related to risk factors, presenting signs and symptoms, clinical and pathologic staging, and treatment outcomes were analyzed for a random subset of 30 patients.

Results: Sixty patients with OTSCC met inclusion criteria. OTSCC was more common in men (58.3%; N=35) with mean age at 61.4 years (26 to 95 years). The great majority of patients were white (91.7%). Subset analysis found 60% of patients to be smokers with 73% having history of alcohol use. In 80% of these cases OTSCC involved the lateral border of the tongue with 53% involving left side. Clinical stage varied with 40% of patients with stage I disease (N=12), 20% stage II, 30% stage III, and 10% stage IV. Nearly 77% of patients were treated with partial glossectomy (N = 23), 3 with hemiglossectomy, and 4 with subtotal glossectomy. Approximately 50% of tumors were high grade (N = 15) with 43% low grade. Two specimens were negative for SCC on histopathologic analysis (6.7%). Twenty-three percent of specimens (N = 7) had positive resection margins. Neck dissection was performed in 63.3% of cases (N = 19) which identified positive lymph nodes in 36.7% of patients (N = 11). Perineural and lymphovascular invasion

were common with 9 instances of each. Five patients (16.7%) were diagnosed with recurrent OTSCC (2 local and 3 locoregional) with 26.7% (N = 8) deceased during the same time frame. Survival rates in the entire cohort were similar at 21.7% (N = 13 out of 60). Five-year Kaplan-Meier overall survival probability for all patients was 0.42.

Conclusions: The presence of prognostic factors for OTSCC like advanced clinical stage, high pathologic grade, greater depth of invasion, and presence lymph node metastasis, perineural invasion, and lymphovascular invasion has a negative impact on survival outcomes in patients who have undergone surgical treatment for OTSCC. These factors were common in patients who experienced recurrence and experienced death during our study follow-up period. Survival was greater in patients with earlier stage tumors highlighting the importance of early detection of OTSCC.

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DEDICATION

To the apple of my eye, my sweet little son Christopher who has made my life so beautiful and magical.

To the love of my life, my husband Joe, whose constant love, endless support and encouragement has helped me achieve my dreams. Chris and Joe, you made this possible, this is for you.

To my Mumma and Dadda, you made me who I am today. I am so fortunate to be your daughter.

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CHAPTER 1. BACKGROUND AND SIGNIFICANCE

Oral Squamous Cell Carcinoma (OSCC) accounts for approximately 90% of oral cancers and is the eighth most common cancer world-wide. OSCC is a severe and often life-threatening condition with a 5-year survival rate of less than 60%.[1] The tongue is the most common oral site in the oral cavity to be affected by OSCC. [1] According to the latest estimates by SEER, squamous cell carcinoma of the tongue represents 0.9% of all new cancer cases in the U.S. each year; however, incidence is relatively rare when compared to other cancers with OSCC representing the 19th most common cancer in the US.[1]

The tongue itself is divided into 2 anatomic parts, the anterior tongue or "oral" tongue, which is defined as the moveable portion of the tongue, and the base of the tongue. Our study focused on treatment of oral tongue squamous cell carcinoma (OTSCC). The oral tongue is the most common anatomic site of OSCC accounting for approximately one quarter of all oral cavity carcinomas and two-thirds of all OSCCs involving the tongue.[2,3,4] Squamous cell carcinoma affecting the base of the tongue are predominantly HPV-associated oropharyngeal squamous cell carcinomas (OPSCC) which have different epidemiology and pathophysiology than OSCC, and as such, were not considered in our study.

OTSCC has a less favorable prognosis when compared to cancers of the mouth.[5,6] OTSCCs are characterized by early infiltration into the underlying tongue musculature and have high risk for regional metastasis, including early lymphatic metastases.[7,8] Prognosis is further impacted by high risk for recurrence and the potential to develop drug resistance both of which create major therapeutic challenges.[9,10]

1.1 EPIDEMIOLOGY

According to the most recent estimates based on age-adjusted data from 2014-2018 cases by SEER, the rate of new cases of tongue cancer was 3.6 per 100,000 men and women per year.[1] Tongue cancer has a higher incidence rate in males (5.4 per 100,000) than women (2 per 100,000).[1] The death rate is 0.7 per 100,000 persons per year which is also higher in men (1.0 per 100,000) compared to women (0.4 per 100,000).[1] An estimated 17,960 new cases of tongue cancer will be diagnosed in the United States in 2021 with 2,870 expected deaths.[1]

1.2 SURVIVAL

Five-year relative survival (RS) rates for OTSCC vary significantly based on the extent of the disease. Early-stage tumors (clinical staging of T1-T2N0), in which cancer is localized to the tongue, have an 82% five-year RS compared to 69% when cancer has spread to regional lymph nodes.[1] RS is only 41% when cancer has metastasized to distant sites.[1] SEER reports a five-year RS of 68.1% when considering all clinical stages[1]

1.3 DETECTION

Early studies report poorer survival in OTSCC when compared to other oral anatomic sites and a higher likelihood of failure post-surgery.[2,7,8] These observations are thought to be related less to inherent tumor biology and more to anatomic factors such as the proximity of the tumor to the bone and the density of regional lymphatics.[2,6] In contrast, the tongue is more accessible than other anatomic sites in the oral cavity raising the potential for earlier detection.[2,11]

Kim et al. reported improved RS for OTSCC over the past two decades despite greater incidence of OTSCC during the same time period. They postulated that this could be due to early detection, but no definitive conclusion was possible in their study.[12]

1.4 RISK FACTORS

Consumption of tobacco and alcohol are well known risk factors in OTSCC.[13,14,15,16] Smoking has been directly linked to approximately 92% of oral cavity tumors in men and 61% in women and is also associated with high risk of developing a second primary cancer.[17,18] Risk increases with the frequency and number of cigarettes smoked per day.[2,18,19] Alcohol contains congeners and carcinogens and exhibits a synergistic effect on cancer risk when combined with tobacco resulting in approximately 10-fold risk for OSCC. [14,15,17, 20] Both tobacco and alcohol are also associated with a poor prognosis in oral cancer.[21] Other lesser known, but important, risk factors include betel use, radiation exposure, immunocompromised states, chronic irritation, trauma, poor oral hygiene, and genetic factors. [22] Human papillomavirus (HPV) infection is a well-established etiologic factor in base of tongue cancers, and others OPSCCs, but not in cancers affecting the oral cavity.[23]

1.5 OTSCC TREATMENT

The treatment of OTSCC has always been a major therapeutic challenge and surgery plays a vital role in achieving locoregional disease control. The primary goal of surgery is to remove the tumor with adequate tissue margins. [6,9,24] Surgical resection may be performed with or without adjuvant radiation, chemotherapy, or immunotherapy with adjuvant therapies utilized to decrease risk for cancer recurrence when micrometastasis is suspected. In these cases adjuvant therapy increases likelihood of survival and the probability of cure in early-stage disease.[9] Loco-regionally advanced disease has a poorer prognosis and less than half of patients have a chance of complete cure.[9] A multimodal diagnostic and therapeutic workup is essential. In both early and advanced disease multimodal diagnostic and therapeutic workups are essential. Ultimately, treatment decisions are based on the relative stage of the disease, tumor differentiation, the

tumor's depth of invasion (DOI), the extent of lymph node involvement, the presence or absence of perineural invasion (PNI) and/or lymphovascular invasion (LVI), and the presence or absence of positive margins on surgical resection.[9]

Staging of OTSCC is based on the American Joint Committee on Cancer (AJCC) Staging manual (Appendix A-C) which helps to predict survival and guides management of the primary tumor. Stage of the disease at initial diagnosis is the most important factor affecting the outcome of patients with OTSCC and staging is essential in treatment planning. [25,26,27,28] Stage I or II ("early-stage") disease is generally defined by a relatively small tumor without lymph node involvement. Early-stage disease is amenable to surgical resection alone resulting in higher survival rates and better post-surgical outcomes due to the extensive scope of the surgeries. Stage III and IV ("advanced-stage") OTSCCs are generally larger tumors which may invade adjacent/underlying structures and/or cancers metastasizing to regional lymph nodes or distant anatomic sites.[29] Patients with clinical or radiographic evidence of cervical metastasis may require more radical procedures depending on the number and size of affected lymph nodes.[24,30] DOI of the primary tumor has also been shown to be a key risk factor for lymph node metastasis impacting surgical planning and decisions related to adjuvant therapy.[31,32,33,34]

ADJUVANT THERAPY

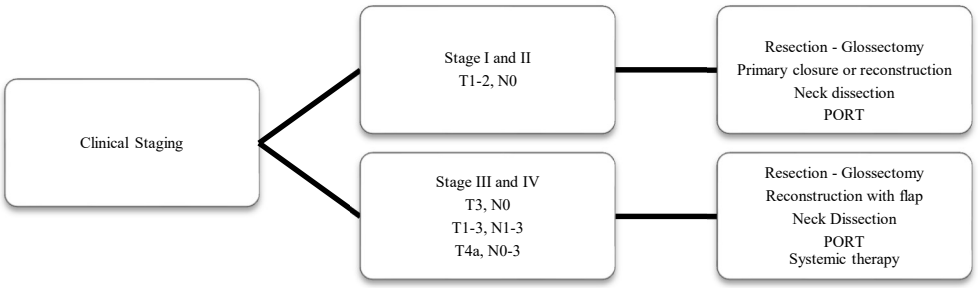
Several published studies have shown an improvement in survival with adjuvant therapies for patients with local and regional metastasis. [2,6,35,36,37,38] Presence of nodal metastasis and the presence of positive margins on surgical resection predict lower survival and higher likelihood of local recurrence.[34] Post-operative radiation therapy (PORT) improves locoregional control in patients with locally advanced OTSCC. Treatment for both stage III and IV disease involves surgery and adjuvant radiation therapy targeting the tumor bed and regional lymph nodes.[34]

PORT is also becoming increasingly common in the treatment of stage II OTSCC, specifically in cases with positive surgical margins, the potential for positive lymph nodes, and/or perineural invasion.[35]

1.6 TREATMENT PLANNING

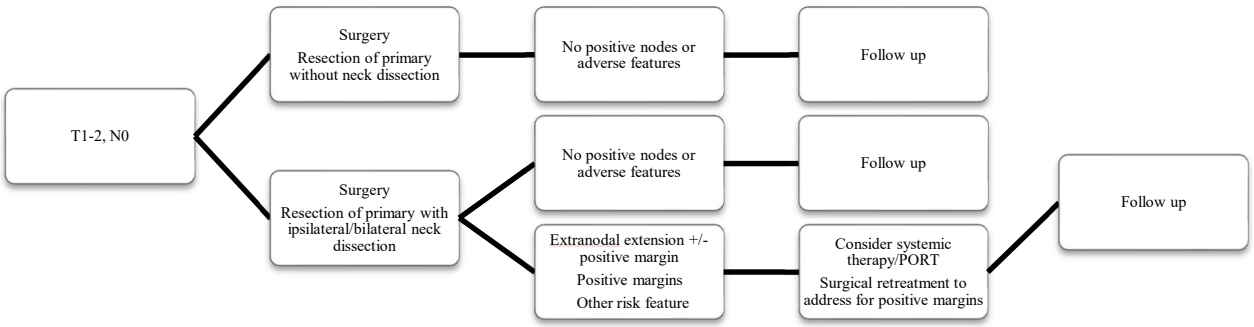
Evidence-based and consensus-driven guidelines for the management of oral cavity cancer have been developed through the National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology for Head and Neck Cancers and are updated frequently.[39] The NCCN guidelines are a comprehensive, sequential treatment algorithm used in clinical decision making in 97% of cancers in the United States. The guidelines are used to improve preventive, diagnostic preventive, diagnostic, therapeutic, and supportive services for all patients to achieve optimal treatment outcomes.[39] The guidelines are organized in flowcharts to provide guidance at all stages of clinical decision-making. A representative algorithm for OTSCC adapted from the current NCCN guidelines can be seen in **Figure 1**, **Figure 2** and **Figure 3.**[39]

The management of patients with OTSCC is complex and involves a multidisciplinary team of specialists and supportive care services with members from head and neck surgery, pathology, medical oncology, radiation oncology, plastic and reconstructive surgery, specialty nursing, dentistry and dental specialties, physical medicine and rehabilitation, clinical nutrition, clinical social work, and diagnostic and interventional radiology. Additional adjunctive services may also be required through neurosurgery, ophthalmology, psychiatry, addiction services, audiology, palliative care and speech and swallowing therapy.[28]



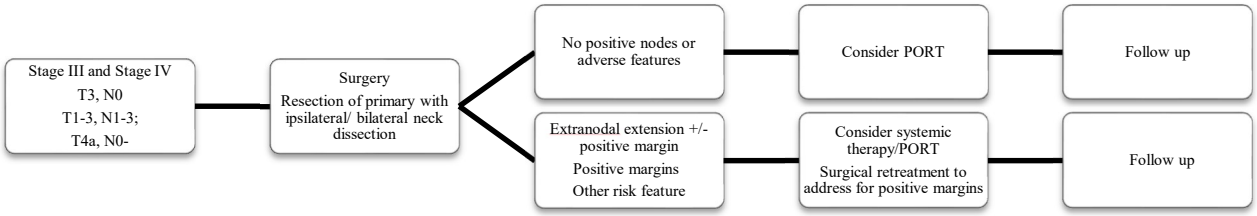
T = Tumor size; N = Lymph node involvement; PORT = Post-operative radiation

Figure 1. Treatment Algorithm for OTSCC Based on 2021 NCCN Guidelines



T = Tumor size; N = Lymph node involvement; PORT = Post-operative radiation

Figure 2. Treatment Algorithm for Early-Stage OTSCC Based on 2021 NCCN Guidelines

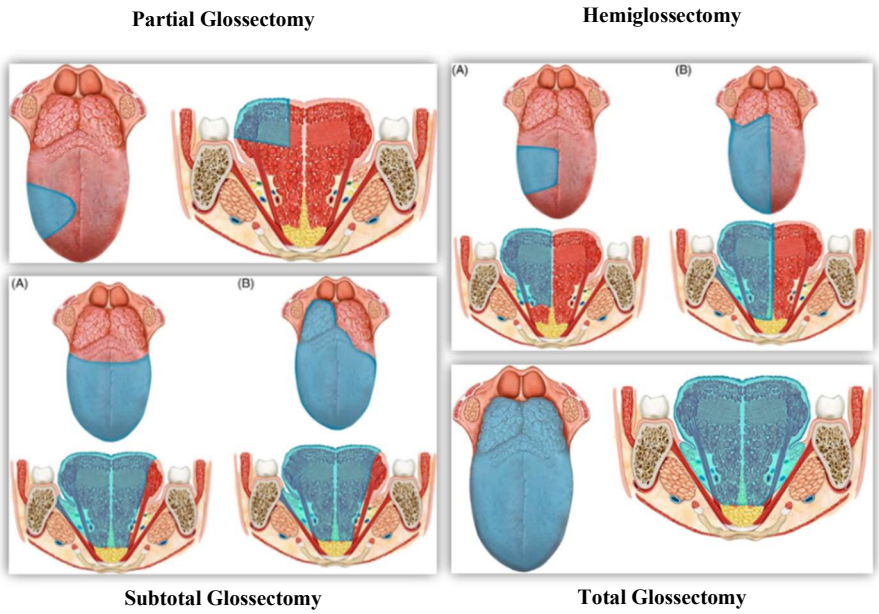


T = Tumor size; N = Lymph node involvement; PORT = Post-operative radiation

Figure 3. Treatment Algorithm for Advanced-Stage OTSCC Based on 2021 NCCN Guidelines

1.7 SURGICAL MANAGEMENT

Surgical excision is classified as partial glossectomy, hemiglossectomy, subtotal glossectomy, or total glossectomy based on the anatomical extent of the tumor**. (Figure 4)**



Ansarin M, Bruschini R, Navach V, et al. Classification of GLOSSECTOMIES: Proposal for tongue cancer resections. Head Neck. 2019;41(3):821-827. doi:10.1002/hed.25466

Figure 4. Types Of Glossectomy

Most early-stage tumors are treated with a partial glossectomy.[35,36] Partial glossectomy involves excision of the lesion and adjacent normal mucosa, submucosa, and the intrinsic muscles up to the surface of the extrinsic muscles with appropriate safety margins, which are defined as 1.5 cm.[40] Partial glossectomy is usually indicated in the treatment of lesions involving the submucosa and superficially infiltrating the intrinsic muscles of the tongue while sparing the extrinsic muscles. It is also the treatment of choice when DOI is less than 10 mm.[40] If the primary tumor is stage I, the conservative surgical treatment allows for good preservation of function. [40,41,42]

Hemiglossectomy is indicated in lesions infiltrating the intrinsic muscles with minimal invasion of extrinsic musculature or when DOI is greater than 10 mm but confined within the ipsilateral tongue.[40] Hemiglossectomy involves surgical excision of the mucosa, submucosa, intrinsic and extrinsic muscles ipsilateral to the lesion. As in partial glossectomy, the mucosa is resected up to healthy tissue with margins of at least 1.5 cm. Hemiglossectomy is a more complex procedure that necessitates ligation of the lingual artery and en bloc removal of the lingual and hypoglossal nerves in the primary tumor. Treatment is often combined with removal of cervical lymph nodes. The ipsilateral tongue is preserved along with the tip of the tongue if possible. This allows for better preservation of function and mobility of the tongue after reconstruction of the defect.[40] Subtotal or total glossectomies are required when tumors extend beyond the anterior tongue, though it is noted that not all such cases are amenable to surgical intervention. Subtotal glossectomy involves preservation of the base of the tongue, posterior hyoglossus muscle, and hypoglossal and lingual nerves from the less involved side.[40] Total glossectomy involves removal of the entire tongue.

Total glossectomy is indicated in patients with advanced or recurrent disease involving the oral tongue and the base of the tongue.[40] Reconstruction of surgical defects is challenging and surgeries are associated with functional morbidities affecting oral intake, speech, and swallowing. Subtotal and total glossectomy are generally associated with poor long-term functional outcomes.[9,36]

Functionally, the mobile tongue serves critical functions in articulation, mastication, deglutition, and taste. Surgical defects from glossectomy mainly affect swallowing and speech articulation. Patients often report alterations in word articulation with distortion in individual speech sounds ("phenomes"), challenges in forming a food bolus prior to swallowing ("bolus preparation deficit"), delay in initial swallowing, and oral remnants of food after swallowing.[43] Surgical reconstruction is used to help restore form and function with reconstruction of the defect dependent on the size and location of the tumor. For smaller defects resulting from T1 or limited T2 lesions, primary closure with or without skin grafting may be appropriate.[35] Larger defects may require free tissue transfer for reconstruction, which includes radial forearm or anterolateral thigh flaps.[35,40] Functional outcomes are affected by the extent of tongue resection, type of reconstruction, motility of residual tongue, and adjuvant radiotherapy.[43]

The presence of clinically positive lymph nodes is the most important prognostic factor for survival in patients with OTSCC[28] and 5-year survival decreases by half when regional metastasis has occurred.[25] Neck dissection is generally performed in patients with clinical evidence of cervical node metastasis with the extent of dissection determined by nonsurgical examination (e.g., neck palpation) and imaging studies (e.g., CT, MRI, ultrasound-guided fine needle aspiration, PET-CT).[44] For early-stage tumors negative for clinically positive nodes (cN0), some investigators favor elective neck dissection (END) due to concerns for occult nodal

disease that is not appreciable on clinical examination.[44,45,46,47,48] Occult metastasis is a significant feature in early OTSCC and concern is strengthened by the fact that locoregional recurrence is the primary sign of treatment failure in patients treated with local surgery alone.[44,49,50,48]

1.8 PROGNOSTIC FACTORS

Treatment outcomes in OTSCC are influenced by factors related to the patient, tumor, and treatment received.[51] Patient factors include patient age, gender, race, and history of tobacco and/or alcohol consumption. Tumor factors include size, TNM stage, histologic grade, depth of invasion, lymph node involvement, PNI and LNI. Treatment-related factors include adequate surgical margins during resection and the use of adjuvant therapy.[51]

A retrospective study in Italy completed by Carta and colleagues evaluated treatment outcomes and prognostic factors in 80 patients with OTSCC treated with compartmental glossectomy and primary flap reconstruction. The study concluded that lymphovascular invasion, advanced-stage disease, and lymph node involvement were reliable predictors of survival. Overall survival (OS) in the cohort was 66.8% versus 73.2% disease specific survival (DSS) and 62.6% relapse free survival. Patients not treated with adjuvant therapy were more likely to have recurrence and were less likely to be alive at 5 years post-operatively.[6] A similar study in the United States by Ganly et al. evaluated 164 patients with early-stage (pathologic T1-T2N0) OTSCC treated with partial glossectomy and ipsilateral elective neck dissection without PORT. They concluded that patients in the cohort had greater than expected rate of neck failure than expected in early-stage disease. Contralateral recurrence was present in nearly 40% of recurrence cases suggesting the possibility of occult metastasis. Tumor thickness was shown to be a significant predictor of recurrence with treatment failure occurring predominantly in patients with primary tumors greater than 4 mm

thick.[35] Thickness was also found to be a prognostic factor by Rajhi et al. in a retrospective study completed in Saudi Arabia evaluating 85 patients with early-stage (T1-2N0) OTSCC treated primarily with surgery and adjuvant therapy if indicated. Tumor thickness and distance from the resection margin are significant prognostic factors for both local tumor control and OS. Univariate analysis for DSS for patients with tumor thickness (TT) of ≤10 mm (P=0.0002) and distance from resection margin (DFRM) of >5 mm (P = 0.005) showed survival advantage. On multivariate analysis, the effect of TT of ≤10 mm remained the same.(P = 0.001). A higher RFS was observed with TT of 10 mm (P = 0.0002), DFRM of >5 mm (P = 0.0002) and DFRM of >10 mm (P = 0.007). Higher RFS was also found for TT ≤10 mm (P=0.01) and DFRM >5 mm (P = 0.01) on multivariate analysis. Neck node recurrence was associated with poor prognosis and low survival rate.[36]

The relative success of multimodal therapy versus monotherapy has also been repeatedly reported in literature. A retrospective study completed in Turkey by Aksu and colleagues evaluated a cohort of 80 patients with OTSCC. In their study 61 patients were treated with combined surgery and radiation therapy and 19 patients with inoperable tumors were treated with radiation alone. The authors reported 5-year OS of 42% and loco-regional disease-free survival of 46%. The 5-year OS was much lower in the radiation only group (16% versus 49% in the combined therapy group, p <0.0002). The 5-year disease-specific survival rate was 23% in the radiation group while in the surgery it was 49%; the difference was statistically significant (P = 0.02). They concluded that combined treatment improves overall and disease-free survival in patients with stage II, III and IVA OTSCC.[37] A retrospective study in Canada by Gorsky et al. examined disease survival in patients with OTSCC and OPSCC of the tongue base treated with surgery alone, radiotherapy alone, or a combined approach. They reported the mean OS as 3

years and 5 months, with a 5-year OS of 40%. Patients with stage 1 tumors had DSS of more than 80%. The 5-year survival of patients with OTSCC was 43% and cancer of the base of the tongue was 27%. They concluded that patients presenting with advanced-stage disease or tumors involving the base of the tongue had a poorer prognosis. OTSCC was more likely to be symptomatic and the authors hypothesized that this contributed to earlier diagnosis in OTSCC vs. base of tongue OPSCC.[2]

1.9 PURPOSE AND SIGNIFICANCE OF THE STUDY

The purpose of this study was to analyze and describe patient demographics, clinical and histopathological characteristics, post-surgical outcomes, and survival in patients with OTSCC treated with glossectomy through the department of Otolaryngology-Head & Neck Surgery (OTO-HNS) at University of Washington Medical Center-Montlake Campus (UWMC) between January 1st, 2016 and December 31st, 2019. Similar studies throughout the world have reported institutional experiences in the treatment of patients with OTSCC.[2,6, 31,36, 37] Post-surgical analysis of OTSCC patients treated primarily with surgery may help to identify subgroups at greater risk for negative post-operative outcomes. Our study also aims to analyze the potential effects of tumor-related prognostic factors (e.g., tumor size, tumor grade, depth of invasion, margin status) on recurrence and survival outcomes. Finally, our study will compare treatment provided at our institution with established NCCN guidelines to determine overall adherence and factors influencing alternative therapy, if applicable.

1.10 RESEARCH AIMS

1. Characterize patients with OTSCC treated with glossectomy according to:
    - Patient demographics (gender, age, race, date of death)

- Modifiable risk factors for OTSCC (smoking, tobacco chewing, alcohol history)
- Tumor characteristics at time of glossectomy (anatomic subsite, clinical TNM stage, tumor grade, tumor size, DOI, positive nodes, positive margins at time of surgical resection, number of nodes examined, PNI, LVI, pathologic TNM stage)
- Post-surgical treatment outcomes (flap failure, pain, paresthesia, speech difficulties, recurrence, and death)
- Five-year survival analysis

2. Compare treatment modalities used with current NCCN guidelines based on TNM stage.[39]
3. Compare institutional experiences at our center with other published literature.

1.11 RESEARCH QUESTIONS

1. How do the demographic characteristics of patients treated with glossectomy at UWMC compare to the demographics of patients treated at other institutions in published literature?
2. What range of cancer stages were treated with glossectomy in our cohort?
3. Was TNM stage associated with treatment outcome in this population?
4. What range of tumor grades were treated with glossectomy in our cohort?
5. Was histologic grade associated with treatment outcome in this population?
6. What are the success rates of glossectomy in this population (with success defined by recurrence rate and overall survival)?

CHAPTER 2. MATERIALS AND METHODS

2.1 STUDY DESIGN

A retrospective chart review was performed to evaluate the medical records of patients treated with glossectomy for oral tongue squamous cell carcinoma (OTSCC) through the Department of Otolaryngology-Head and Neck Surgery (OTO-HNS) at University of Washington Medical Center, (UWMC) Seattle, WA, USA between January 1st, 2016 and December 31st, 2019. Leaf, a self-service tool provided through the Institute of Translational Health Sciences (University of Washington, Seattle, WA), was used to query electronic health records to identify patients diagnosed with malignant neoplasm of anterior two-thirds of the tongue, part unspecified (ICD10:C02.3) **or** who had a diagnosis of other and unspecified parts of tongue (ICD10:C02.0-C02.9) **and** were evaluated by OTO-HNS, admitted to UWMC, and treated with glossectomy between January 1, 2016 and December 31, 2019. Leaf generated a cohort of eligible study subjects identified by name and medical record numbers (MRNs) and electronic medical records (EMRs) were reviewed via Epic Hyperspace (Verona, WI). Institutional Review Board approval was provided by the Human Subjects Division at the University of Washington.

2.2 INCLUSION AND EXCLUSION CRITERIA

Patients were eligible for inclusion in the cohort if they had biopsy confirmation of oral squamous cell carcinoma (OSCC) of the tongue and were treated with glossectomy through OTO-HNS at UWMC-Montlake between January 1st, 2016 and December 31st, 2019. Potential subjects were excluded if they were less than 18 years of age at the time of surgery; had a diagnosis of OSCC involving the base of the tongue, floor of mouth, oropharynx, or mandible; were treated with glossectomy with composite resection (as this involves en bloc resection of

primary tumor, cervical nodes, and a portion of the mandible if tumor lies close to bone); or had a history of past surgical resection with recurrent OSCC.

2.3 SURGICAL METHODS

All patients analyzed in this study were admitted to UWMC-Montlake for surgical treatment of OTSCC. Glossectomy was performed in an operating room setting and patients were followed according to standard procedures during their post-operative inpatient hospitalization and after discharge from UWMC. Pre-surgical evaluation included history and physical examination, incisional biopsy, imaging (CT, MRI, PET-CT) and clinical staging according to the 7th and 8th edition of AJCC/UICC/TNM Classification.[52,53] Physical examination and radiographic studies were reviewed by a multidisciplinary Head & Neck tumor board which included head and neck surgeons, reconstructive surgeons, dental surgeons, radiation oncologists, medical oncologists, neuroradiologists and pathologists. Tumor board discussions helped to determine the type of glossectomy performed, indications for neck dissection, and strategies for surgical reconstruction of the tongue.

Surgical procedures were classified into partial glossectomy, hemiglossectomy, subtotal or total glossectomy based on the extent of tissue removed. Surgical defects were repaired with primary closure or reconstructed with microvascular free flaps. Partial glossectomy usually involved primary closure without the need for reconstruction. If partial glossectomy required reconstruction with a flap, a radial forearm free flap (RFFF), anterolateral free flap (ALT), or alloplastic graft (AlloDerm®) were used. Defects resulting from hemiglossectomy were reconstructed using RFFFs, ALTs, or submental flaps. Subtotal glossectomy defects were reconstructed either with ALT, rectus abdominis free flaps, or pectoralis major myocutaneous flaps.

Surgical treatment was planned and performed according to the National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines. Tumors were classified with clinical TNM staging (cTNM) preoperatively and pathological TNM staging (pTNM) post-operatively. Outpatient follow-up included post-operative assessment at 1 week, 1 month, 3 months, 6 months, 12 months, and 24 months post-discharge with minor variations based on course of healing. Data related to post-operative outcomes were obtained through September 30th, 2021. Post-operative evaluations were completed based on NCCN guidelines with additional follow-up completed at the discretion of the surgical team.

2.4 DATA COLLECTION AND SECURITY

Referral notes, clinical chart notes, preoperative and postoperative histopathology reports, and follow-up notes were reviewed in subject EMRs to collect demographic, pre-operative, and post-operative data. Demographic data, date of death (where applicable), date of initial OTO-HNS evaluation, and date of last follow-up visit were collected for the entire cohort (N = 60) while information related to risk factors, presenting signs and symptoms, clinical and pathologic staging, and treatment outcomes were analyzed for a random subset of 30 patients. **Figure 5** depicts the process of cohort discovery and methodology for data collection. A list of data variables is included in **Appendix A**.

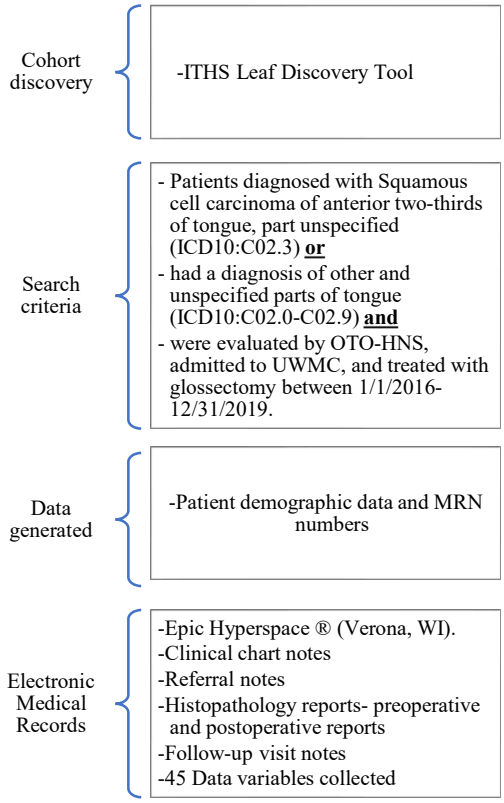


Figure 5. Process of Cohort Discovery and Data Collection

Data was deidentified by assigning a unique identification number to each patient before transporting to Microsoft Excel (Microsoft, Seattle WA USA). The identification key was stored separately from the Excel table. Data security was maintained in accordance with University of Washington Human Subject Divisions guidance for data security protections. Only deidentified data was used for statistical analysis.

2.5 STATISTICAL ANALYSIS

Descriptive statistics for each data variable were calculated for each case including the percentage, mean and standard of deviation and median range. Analysis of descriptive variables was performed using Microsoft Excel. Kaplan-Meier Survival Analysis of entire patient cohort (N = 60) was completed using the R statistical software package. Comprehensive analysis of

other post-operative variables was limited to a random subset of 30 subjects due to the complexity obtaining post-surgical outcome data. The relatively small size of our study cohort provided insufficient power for determining statistically significant differences in post-surgical outcomes, therefore no statistical impact was lost by performing a subgroup analysis.

CHAPTER 3. RESULTS

One-hundred thirty-one patients were treated with glossectomy through Otolaryngology-Head and Neck Surgery (OTO-HNS) at University of Washington Medical Center-Montlake (UWMC) during our study time frame. Sixty patients met inclusion criteria while 71 potential subjects were excluded. **Figure 6** depicts the process for patient selection.

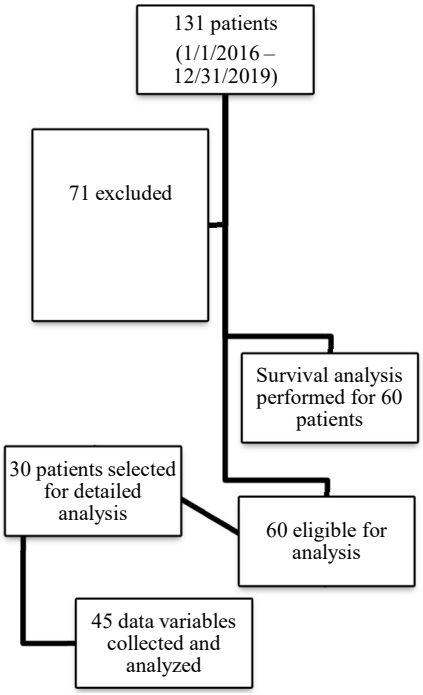


Figure 6. Flow Diagram of Patient Selection

3.1 PATIENT CHARACTERISTICS

DEMOGRAPHIC VARIABLES

Within our cohort oral tongue squamous cell carcinoma (OTSCC) was more common in men (58.3%; N = 35 of 60) than in women (41.6%; N=25 of 60). Mean age at diagnosis was 61.4 years with range from 26 to 95 years. The majority of the patients were diagnosed in the 7th decade (33.3%) followed by the 6th decade (26.6%). The age distribution is available in **Table 1**.

The mean age among males was 59.6 years (26 to 88) and the mean age among females was 63.8 years (38 to 95). Racial demographics are summarized in **Table 2.**

Table 1. Age Distribution (N=60)

Age	N	%
20-29	1	1.6 %
30-39	1	1.6 %
40-49	8	13.3 %
50-59	16	26.6%
60-69	20	33.3%
70-79	7	10.0 %
80-89	5	8.3%
90-99	2	3.3%

Table 2. Patient Demographics - Race (N=60)

	N	%
Race		
White	55	91.6 %
Black or African American	1	1.6 %
Native Hawaiian or Other Pacific Islander	1	1.6 %
Unavailable or Unknown	1	1.6 %
Asian	2	3.3 %
Hispanic	0	0 %
Native Alaskan/American Indian	0	0 %

SUBGROUP ANALYSIS (N = 30)

DEMOGRAPHIC VARIABLES

Subgroup analysis was performed for 30 random patients in the cohort. Demographic characteristics of the subgroup are included in **Table 3.** Within the subgroup 34% were diagnosed with OTSCC in the 7th decade with an additional 30% diagnosed in the 6th decade.

Table 3. Patient Characteristics (N = 30)

	N	%
Gender		
Male	20	66.7%
Female	10	33.3%
Mean Age (SD)	59.3(12.2)	
Median Age (SD)	60(13.7)	
Race		
White	27	90.0%
Black or African American	1	3.3%
Native Hawaiian or Other Pacific Islander	1	3.3%
Unavailable or Unknown	1	3.3%
Asian	0	0.0%
Hispanic	0	0.0%

MODIFIABLE RISK FACTORS FOR OTSCC (TOBACCO AND ALCOHOL CONSUMPTION)

Sixty percent of patients (N = 18) had a history of smoking while 73.3% (N = 22) had history of alcohol consumption. Only 1 patient (1.67%) used chewing tobacco. Information regarding smoking, alcohol, and chewing tobacco use was not available for 10% of the cohort.

CLINICAL PRESENTATION

The most common anatomic subsite for oral tongue squamous cell carcinoma (OTSCC) was the lateral border of the oral tongue (80%), followed by the ventral (16.7%), and dorsal surfaces (3.3%). Two-thirds of the lesions that involved the lateral surface of the tongue occurred on the

left-side of the body (N = 16 of 24). Anatomic subsites are detailed in **Table 4**. Clinical signs and symptoms at time of diagnosis are summarized in **Table 5.**

Table 4. Anatomic Subsites in OTSCC Cases (N = 30)

Primary Site of Tumor	N	%
Tongue Tip	0	0.0 %
Lateral Border	24	80.0 %
Left	16	
Right	8	
Dorsal Surface	1	3.3 %
Ventral Surface	5	16.6 %
Left	3	
Right	2	

LESION IDENTIFICATION

Lesion duration ranged from 2 to 12 months prior to OTSCC diagnosis. The majority of patients (N = 17) sought treatment within 6 months. Four patients reported a duration of "several months" but were not aware of an exact duration. Details related to lesion duration are summarized in

Table 6.

Table 5. Clinical Signs and Symptoms at Time of Diagnosis (N = 30)

	N	%
Clinical Presentation		
Pain		
Yes	26	86.6%
No	4	13.3%
Numbness		
Yes	1	3.3%
No	29	96.7%
Ulceration		
Yes	11	36.7%
No	19	63.3%
Mass		
Yes	22	73.3%
No	8	26.7%

Table 6. Lesion Duration (N = 30)

Duration	Number of patients
2 months	2
3 months	7
4 months	3
5 months	3
6 months	2
7 months	1
8 months	1
10 months	1
12 months	4
unknown (“several months”)	4
unknown	2

CLINICAL STAGE

Patients were clinically staged based on primary tumor (T), regional lymph nodes (N) and distant metastasis (M) summarized in **(Figure 7)**.Sixty percent presented with early-stage clinical disease (Stage I and Stage II) and 40 percent presented with advanced or late-stage clinical disease (Stage III and Stage IV).

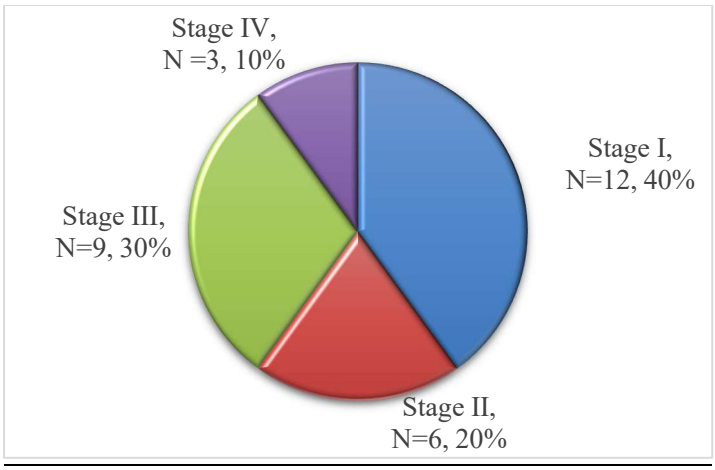


Figure 7. Clinical TNM Staging

Referring Provider

Lesions were initially identified by a variety of healthcare providers in both dentistry and medicine. Fifty-three percent of cases (N = 16) were initially detected by a dentist or dental specialist. Providers responsible for initial detection are depicted in **Figure 8**.

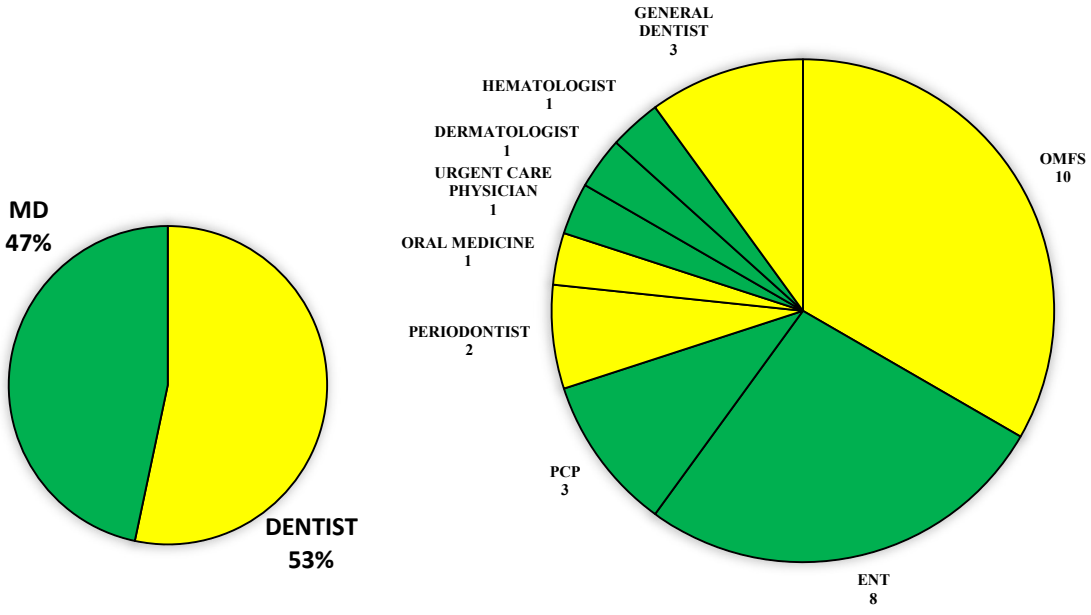


Figure 8. Referring Healthcare Providers by Specialty

3.1 SURGERY (TREATMENT)

Nearly 77% of patients were treated with partial glossectomy (N = 23), 3 with hemiglossectomy, and 4 with subtotal glossectomy. Primary closure of the surgical defect was completed in 60% of patients (N =18) with flap reconstruction in 12 patients. Surgical defects were reconstructed with free tissue transfer from radial forearm in 20% of cases (N = 6) and anterolateral thigh in 4 cases. Rectus abdominis, submental and pectoralis major myocutaneous flaps were used in 1 case each. AlloDerm® reconstruction was performed in 1 additional case. Neck dissection was completed in 19 cases.

3.2 TUMOR CHARACTERISTICS

TUMOR SIZE: The average tumor size was 2.53 cm (0.1 cm to 7.5 cm) with 76.7% of tumors (N = 23) measuring less than 4 cm at time of resection. Six of the 7 patients with tumors measuring greater than 4 cm were deceased within our study follow-up period and all 7 had advanced-stage disease. Details related to tumor size are summarized in **Table 7**.

SURGICAL MARGINS: Seven specimens (23.3%) showed SCC at the surgical margins (positive margins).

TUMOR GRADE: Histopathology characterized 30% of OTSCCs (N = 9) as well-differentiated, with 4 well-to-moderately differentiated tumors, 9 moderately differentiated, 1 poor-to-moderately differentiated, and 5 poorly differentiated tumors. Two of these resection specimens were negative for SCC on histopathologic analysis (in each case the malignant tumor had been excised in its entirety during initial biopsy). One of these 2 resected specimens was positive for high grade epithelial dysplasia while the other was negative for pathology.

Table 7. Tumor Size

Tumor Size	N	%
Tumor > 4cm	7	23.3%
Tumor ≤ 4cm	23	76.6%
Average (Range)	2.5 cm	(0.1, 7.5)

DEPTH OF INVASION: Approximately 43% of tumors had depth of invasion (DOI) greater than 10 mm (N = 13) with 15 cases less than 10 mm. DOI was unknown in 2 cases. Details are summarized in **Table 8**. The DOI for two patients was unknown. The maximum depth of invasion was 35 mm and the minimum DOI measured was 1 mm.

Table 8. Depth of Invasion

DOI	N	%
DOI > 10 mm	13	43.3%
DOI ≤ 10 mm	15	50.0%
Average Range	10.4 mm	(1, 35)

PERINEURAL INVASION: Thirty percent of cases were positive for perineural invasion (N = 9). The remaining 21 patients in subset analysis were negative.

LYMPHOVASCULAR INVASION: Thirty percent of cases were positive for lymphovascular invasion (N = 9). Nineteen patients were negative. Two cases had an indeterminate diagnosis.

LYMPH NODE INVOLVEMENT: Approximately 37% of patients had lymph node involvement (N = 11). Nineteen patients were negative for nodal metastasis.

3.3 CLINICAL VS. PATHOLOGIC STAGING

Patients treated prior to 2018 were staged with the 7th AJCC staging system and those treated after were staged with the 8th edition. Eighteen (60%) were staged according to the 8th edition while the remaining 12 were staged according to the 7th edition.

Pathologic staging resulted in 7 instances of upstaging (23.3%) and 2 instances of downstaging from clinical staging (**Table 9** & **Table 10**). Among those patients who were upstaged, 2 were upstaged from clinical stage II to pathologic stage III, 3 were upstaged from stage II to stage IV (2 to stage IVA and 1 to IVB), 2 were upstaged from stage III to stage IV (1 to IVA and 1 to IVB), and 1 from Stage IVA to IVB. Two patients were downstaged from clinical stage III to pathologic stage II.

Table 9. Clinical TNM vs Pathologic TNM

Stage	cTNM	pTNM
Stage I	12	12
Stage II	6	3
Stage III	9	7
Stage IV	3	8

Table 10. Comparison of Clinical and Pathologic T stage and N stage

T Classification	Clinical	Pathological
T1	13	12
T2	9	8
T3	6	9
T4	2	1
Nodal Status		
NX	3	9
N0	18	10
N1	6	3
N2	3	4
N3	0	4

3.4 TREATMENT OUTCOMES

FOLLOW-UP PERIOD: The average follow-up period was 17.7 months.

FLAP FAILURE: No free flap failures were identified in the cohort.

PAIN: Nearly 17% of patients reported tongue pain during post-surgical follow-up (N = 5). Two patients reported pain in the early post-operative period including 1 patient treated with left partial glossectomy who reported severe pain 2 weeks postoperatively and 1 patient who reported pain 3 weeks postoperatively and died shortly thereafter. One patient reported pain in the intermediate post-operative period, requiring pain medication 3 months post-surgery. Two patients developed pain greater than 2 years following surgery. The first reported left posterior tongue and pharyngeal pain 2.5 years post-surgery. The second developed pain 2 years post-glossectomy and was found to have cancer recurrence in the floor of the mouth. Unfortunately, this patient was lost to follow-up.

PARESTHESIA: Ten percent of patients reported paresthesia (N = 3). All patients with paresthesia had been treated with partial glossectomy. Of these, 1 reported numbness at the 9-month post-operative visit with resolution by the 18-month appointment. The second reported numbness at the 10-month visit but was lost to follow-up. The third had persistent numbness which was still present at the 24-month appointment.

SPEECH PROBLEMS: No patients reported speech problems. No speech-related data was available for 2 patients who transferred care to other facilities and were not seen for follow up at UWMC.

RECURRENCE: OTSCC recurred in 5 patients (16.7%). Two cases were local recurrences. Three were locoregional.

ADJUVANT THERAPY: Approximately 27% of patients were treated with adjuvant therapy (N = 8). Three were treated with radiation, 2 with chemotherapy and radiation (at different points in time), and 3 with chemoradiation.

3.5 SURVIVAL

Kaplan-Meier survival curve analysis was performed at 1-year intervals **Figure 9**. The survival curve estimate at a given point in time is based on the sub-sample of patients who are still being observed and the risk of dying at a specific point in time ("risk set"). The curve begins with a risk set of 60 patients with drops in the curve at each death during the follow-up period. Survival probability declined sharply within the first year post-glossectomy with 8 of 13 total deaths occurring in year 1 (survival probability = 0.86). There were 2 deaths in year 2, resulting in a survival estimate of 0.82 and 2 additional deaths in year 3 decreasing survival estimate to 0.67. There were no deaths in year 4, so the survival estimate remained consistent. A single death in year 5 decreased survival probability to 0.42 at year 5. Analysis was limited by the size of the cohort and the relatively small number of deaths during the study time period resulting in wide confidence intervals in the estimated survival curve.

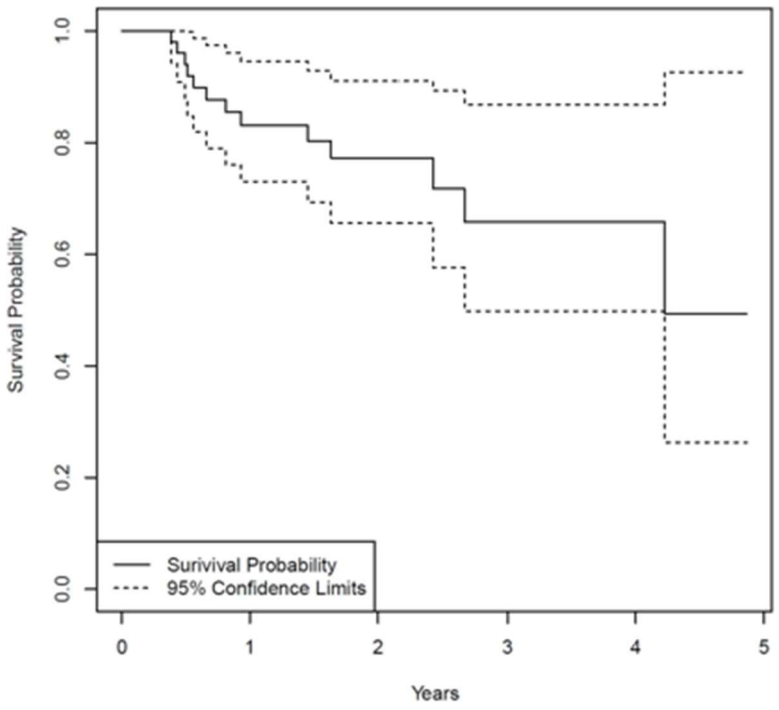


Figure 9. Kaplan Meier Survival Probability Curve

CHAPTER 4. DISCUSSION

The primary goal of our pilot study was to characterize the demographics of all patients diagnosed with oral tongue squamous cell carcinoma (OTSCC) treated with glossectomy through the department of Otolaryngology-Head and Neck Surgery (OTO-HNS) at University of Washington Medical Center Montlake Campus, (UWMC) Seattle, WA, USA between January 1st, 2016 and December 31st, 2019 and to compare these findings with reports in published literature.

4.1 GENDER

The most recent age-adjusted incidence rates published by the Surveillance, Epidemiology, and End Results (SEER) indicate a 2.7:1 male to female ratio in patients diagnosed with tongue cancer.[1] The male to female incidence ratio was substantially lower in our population with 35 males and 25 females diagnosed with OTSCC (1.4:1). Interestingly, our ratio was comparable to gender distribution in other institutional studies in the North America. Han, et al, reported a male to female ratio of 1.5:1 in a study in Los Angeles while Ganly et al. reported a ratio of 1.2:1 in a study utilizing data from New York City and Toronto.[35] All patient's in Ganly's study were patients with early-stage OTSCC, similar to our study, while Han et al. included patients with advanced-stage disease treated with total glossectomy for both oral tongue and tongue base cancer. Though the small sample size limits our ability to draw a definitive conclusion this observation suggests that earlier stage OTSCC, amenable to glossectomy, may have a less pronounced gender disparity. A study in Italy reported a ratio similar to that reported by SEER with a 3:1 male to female ratio.[6] In contrast, a study in Saudi Arabia reported greater incidence in females (0.8:1)[36] and a study in Turkey reporting a nearly equal incidence in males and females (1.05:1).[37]

4.2 AGE

In our cohort the median age at diagnosis was 60 years old (SD = 13.7). One third of patients in our study were diagnosed in the 7th decade of life (N = 20) followed closely by the 6th decade (26.6%). This finding closely approximates SEER data which reports a median age of 64 at the time of diagnosis with OTSCC most commonly diagnosed between the ages of 55-64.[1] Similar findings have been reported in both the United States and throughout the world.[6,35,36,37,54]

4.3 RACE

In the United States, the incidence rate of tongue cancer is highest in the white population (4.0 per 100,000) when compared to Asian and Pacific Islanders (2.2 per 100,000), the Hispanic population (2.2 per 100,000), Black (1.9 per 100, 000), and American Indian and Alaska Natives (1.7 per 100,000).[1]

In our cohort 92% of patients were white (N = 55) which is consistent with higher incidence of OTSCC in the white population nationally, but higher than what would be expected based on racial demographics in Washington state in which 78.5% of individuals identified as white in the 2019 United States Census.[55] Five percent of patients in our cohort were Asians or Pacific Islanders and 1.67 % were black. There were no cases of OTSCC treated with glossectomy in the Hispanic or American Indian/Alaska Native populations at our center during this time period. Racial data was unavailable for 1% of patients in out cohort. In Washington state 20.5% of residents identify as Asian and Pacific Islander, 9.9% Hispanic, 4.4% Black, and 1% American Indian/Alaskan Native.[55] The higher percentage of white patients in our cohort, when compared to the demographics in the state, may represent greater access to care. White patients may have been more likely to be treated at UWMC due to greater access to an academic medical center, closer geographic proximity to our hospital, higher likelihood of insurance coverage accepted at

UWMC, or other factors. It is also possible that white patients were more likely to meet our inclusion criteria due to smaller tumor size at diagnosis. Our inclusion criteria required treatment with glossectomy for primary tumors involving oral tongue while excluding tumors involving other anatomic sites and/or requiring composite resection. Because of this, the majority of our patients were early stage (60% stage I or stage II) which could potentially relate to access to care and earlier diagnosis of OTSCC. Unfortunately, the size of our cohort and lack of access to geographic and socioeconomic variables limits conclusions that can be drawn from this observation.

4.4 CLINICAL PRESENTATION

In our subgroup analysis, 24 of 30 cases involved the lateral border the tongue. The ventral surface of the tongue was the second most common site at 16.7%. The lateral and ventrolateral surfaces of the tongue have been consistently reported as the most common sites for OTSCC in literature. [8,56,57] Interestingly, 16 of the 24 cases involving the lateral surface of the tongue were on the left side. The posterolateral surface of the tongue consists of non-keratinized epithelium that represents a more flexible permeable surface layer and is unable to resist the infiltration of carcinogens, viruses and is more susceptible to traumatic injury.[8] Lederman postulated that the pooling of carcinogens in the high-risk sites such as the ventrolateral tongue, floor of the mouth, and soft palate complex ("gutter zones") predisposes toward development of carcinoma.[8,57,58] This theory could explain the frequency of OTSCC on the lateral border of the tongue. Laterality of the lesion may be influenced patient habits, leading to greater pooling of carcinogens on the affected side (e.g., holding a cigarette on the left/directing the stream of smoke toward the left side of the oral cavity). Only one of the patients in our cohort was

diagnosed with OTSCC involving the dorsal tongue. OTSCC of the tongue dorsum is rarely reported in literature.[8,59]

PAIN

At the time of initial examination, 26 patients in our subgroup analysis (86.67%) reported pain as a presenting symptom. Only 1 reported numbness. Tongue soreness/discomfort was reported as the most common complaint, in a retrospective study of 322 patient completed Gorsky et al., with 66.5% of patients reporting discomfort up to 6 months prior to diagnosis.[2] Pain in the tongue may arise early in the disease, in contrast to cancers of the lips and buccal mucosa, which are often asymptomatic until advanced stages when patients may develop severe pain. [60,61] The cause of pain in OSCC is multifactorial and can be caused by damage to the surface epithelium, loss of normal barrier function, exposure of nerves, invasion or chemosensitization of receptors, and secondary infection of the lesion.[62,63] In addition to these factors, pain in the tongue can be caused by movement resulting in friction against the teeth.[60] This greater propensity to frictional trauma may cause pain and/or discomfort at an earlier stage allowing for earlier identification. The early diagnosis of asymptomatic OSCC requires a high index of clinical suspicion and special attention to detect possible intraoral anatomical changes.[2]

MASS

In our subgroup analysis, 73% of patients (N = 22) presented with a tongue mass at the time of clinical examination. This percentage is much higher than incidence reported by Gorsky et al. in which only 29% of patients presented with a tongue mass.[2] In their study presence of a mass or lump was more likely in lesions involving the oral tongue versus tumors involving the tongue.[2]

ULCERATION

Classic features of advanced-stage OSCC include surface ulceration, nodularity, and fixation to underlying tissues.[60,64] Eleven patients in our subgroup analysis presented with tongue ulceration. Among these 11 patients, more than half (6 patients) had advanced-stage disease (Stage III or IV).

4.5 MODIFIABLE RISK FACTORS FOR OTSCC (TOBACCO AND ALCOHOL CONSUMPTION)

Numerous epidemiologic studies have demonstrated a relationship between tobacco use and risk of oral cancer.[13,14,15,16] Tobacco can cause epigenetic alteration of oral epithelial cells, inhibit multiple systemic immune functions, and cause oxidative stress, which likely contribute to OSCC.[13] Alcohol consumption has also been reported as a modifiable risk factor for oral cancer, though it has not been found to be an independent risk factors in all studies.[65] Studies have shown that alcohol and tobacco seem to have a synergistic effect in the etiology of OSCC. [65,66] A large case-control study conducted in Sao Paulo, Brazil examined the effects of tobacco and alcohol on oral cancer risk both independently and in combination. They study showed an independent effect of smoking on oral cancer, though the effect was lower than expected. Alcohol consumption was not independently associated with oral cancer I the study. The combined effect of smoking and alcohol remained significantly associated with oral cancer.[66] Additional studies have shown a synergistic effect of tobacco and alcohol on oral cancer risk, though the exact role in the pathogenesis of oral cancer is not fully understood [66] Ethanol increases cellular permeability, by dissolving the lipid components of epithelial cells, increasing penetration of carcinogens across the oral mucosa.[67]

In our subset analysis, 60 percent of the patients reported smoking history (N = 18) with 1 patient reporting history of tobacco-chewing. Seventy-three percent of patients in our study reported history of alcohol consumption. Variable reporting of smoking history and alcohol consumption precluded our ability to classify patients as heavy or light users. In the study by Ganly et al. 59% of patients had a tobacco habit.[35] Bachar et al. reported heavy tobacco and alcohol consumption in 60% of cases.[31]

It is noted that mucosal permeability varies in different areas of the oral cavity based on the relative degree of tissue keratinization.[67] For example, the mucosa covering the hard palate and gingivae are less permeable, thus less likely to transform compared with thin and non-keratinized epithelium covering the ventral/lateral tongue, floor of the mouth, and soft palate which are far more permeable.[65,67] A retrospective study in Scotland examined 454 patients with history of smoking and/or alcohol consumption to examine the relationship between consumption and incidence of OSCC and identified the tongue and floor of the mouth to have higher incidence when compared to other oral subsites. They reported that men generally have a greater risk than women of developing these cancers, with a ratio of 2 : 1. Since a greater proportion of the males had a smoking and drinking history they suggested that this could point to confirming the association of smoking, drinking and oral cancer.[16] Similar logic may explain the high incidence of OTSCC affecting the lateral border of the tongue in our study. Though our study was insufficiently powered to confirm a statistical relationship between OTSCC and tobacco and alcohol consumption is notable that 53.3% of patients in our subset analysis (N = 16) consumed both tobacco and alcohol.

4.6 OTSCC TREATMENT

GLOSSECTOMY

The rationale and surgical techniques for resection of cancer in the tongue have evolved over time.[40] Historically, most early and intermediate staged cancers were treated with a partial glossectomy with margins approximately 0.5 to 1 cm from the macroscopic limits of the tumor. More recently, wide resection has become more common with macroscopic tumor-free margins of 1.5 to 2 cm.[40] With advanced imaging techniques, staging, and improved knowledge of tumor behavior (e.g., tendency to spread along muscles, nerves and vasculature), surgeons are able to evaluate the individual involvement of each tongue muscle to optimize surgical removal of the tumor.[7,40,68,69] Glossectomy is critical in achieving completed tumor removal and minimizing functional impact, however, the terms used to describe the procedure (e.g., partial glossectomy, hemiglossectomy, etc.) do not have a clear classification system defining the extent of tissue resection.[40,69,70] According to Ansarin et al, the current terminologies used to describe the extent of removal are vague and lack a clear anatomical and functional definition of the procedure which leads to confusion. This difficulty limits the ability to compare surgeon experiences and affects teaching and training surgical fellows.[40] The authors proposed a new classification of surgical procedures that accounts for all surgical variables and highlights the anatomic structures involved in the procedure. This definition was used to classify the various types of glossectomy in our study (**Figure 4**).

Most early (cT1-T2N0) and intermediate staged tongue cancers are treated with partial glossectomy. A majority of patients in subset analysis (76.6%, N = 23) were treated with a partial glossectomy. Fifteen patients treated with partial glossectomy early- or intermediate-stage disease (Stage I, N = 12; Stage II, N = 3). Eight had advanced-stage disease (Stage III, N = 6;

Stage IV, N = 2). Patients in this group were diagnosed with advanced disease due to the presence of regional lymph node involvement though tumors were still amenable to partial glossectomy. Infiltrative tumors confined to the ipsilateral tongue were treated with a hemiglossectomy.[40] Three patients in our subgroup analysis were treated with hemiglossectomy in our study (Stage III, N =2; Stage IV, N = 1) Tumors extending beyond the midline or involving the contralateral side without involving the base of the tongue were treated with a subtotal glossectomy.[40,69] Four patients in our subgroup analysis were treated with subtotal glossectomy (Stage III, N = 1; Stage IV, N = 3). Massive infiltrating lesions involving the bilateral oral tongue or tongue base, are traditionally treated with a total glossectomy.[37,54,40,69] Patients requiring total glossectomy have very advanced disease and were excluded from our study to allow for better comparison among surgical groups.

In the study by Aksu et al, evaluated 61 patients with for OTSCC treated with surgery and post-operative radiation therapy (PORT). Thirty-four percent of patients in the study had Stage II disease, 18% had Stage III disease, and 48% had Stage IVA disease. The majority of patients were treated with a hemiglossectomy (77%). Partial glossectomy was completed in 21% of cases with total glossectomy in a single case.[37] Retrospective analysis by Carta et al. employed the classification system proposed by Ansarin et al.[6,40] (In their study 81 surgical procedures were completed: 80.3% were type IIIb glossectomy/compartmental hemiglossectomy, 8.6% type IVa glossectomy/subtotal glossectomy, 6.2% type IVb glossectomy/near-total glossectomy, and 4.9% type V glossectomy/total glossectomy. In their cohort 18 patients had Stage I OTSCC, 28 were Stage II, 9 Stage III, 25 Stage IVA, and 1 patient Stage IVC.[6]

RECONSTRUCTION

The choice of reconstruction following tumor excision is based on the extent of the tumor and the estimated volume of tongue to be replaced following resection.[42] The primary goal is to restore the tongue's anatomy while preserving its form and function.[42] Reconstructive options should aim to provide bulk and maintain mobility.[42] For smaller defects, treated with a partial glossectomy/wedge shaped resection, primary closure is sufficient because tongue mobility is not affected.[42,43] The majority of patients in our subset analysis (53%, N = 16) were treated with primary closure. Nearly all had small T1 and T2 tumor defects (cT1, N = 12; cT2, N = 3). Only 1 patient with cT3 was treated with primary closure after partial glossectomy.

Flaps are required or patients with wider resection and a greater volume of tissue to be replaced. Just under half of the patients in our subset analysis were treated with flap reconstruction (46.7%, N = 13).

Thin free flaps like the Radial Forearm Free Flap (RFFF) and the Anterolateral Thigh Flap (ALT) have good pliability and versatility and can restore defects approximating one-half of the total tongue volume while preserving mobility. Either can be used for partial glossectomy and hemiglossectomy defects.[42] The RFFF was the most commonly used flap in our study (20%, N = 6) followed by the ALT (13.3%, N = 4). In situations where microvascular surgery is contraindicated a pedicled flap, such as the Pectoralis Major Myocutaneous flap (PMMC) or submental artery island flap, may be the best reconstructive option.[42] Larger tongue defects caused by subtotal or total glossectomy require bulky flaps, like rectus abdominis muscle free flaps, myocutaneous ALT, or PMMC flaps.[42] In our study, 2 subtotal glossectomy defects were reconstructed with ALT flaps, 1 with a rectus abdominis free flap and 1 with a PMMC. One hemiglossectomy defect was reconstructed with a submental flap.

In the study by Carta et al, the RFFF (79.9%) and ALT (11.1%) flaps were preferred for reconstruction following partial glossectomy. Patients requiring total glossectomy were most commonly treated with Vertical rectus abdominis myocutaneous (VRAM) flaps (6.2%) or composite bony iliac crest deep circumflex iliac artery (DCIA) in 3.7% when reconstruction was associated with segmental mandibulectomy. A single case was treated with an ALT free flap.[6] The study by Han and colleagues was limited to patients treated with total glossectomy with composite resection requiring bulky flaps and bone flaps for reconstruction. Techniques in their study included VRAM flaps (40%), free fibula flaps (25%), ALT flaps (23%), RFFFs (8%), and subscapular system reconstruction (4%).[54]

NECK DISSECTION

The rich lymphatic network of the tongue facilitates metastatic spread of OTSCC and this tendency often increases with the size of the primary tumor.[2] Nodal metastasis at the time of diagnosis is the most important prognostic factor for survival and is essential information for treatment planning.[7,71,72,73] Though early-stage OTSCC can present as node-negative, the lymph nodes may still harbor occult nodal metastasis, which may be present in 20% to 50% of cases.[71,74,75,76,77] Meta-analysis conducted by Choi et al. analyzed 19 studies (N = 1567 total patients) to evaluate rate of occult lymph node metastasis in early-stage (T1-T2) OTSCC. Occult nodal metastasis was found in 24.4% of cases. Because of the relatively high likelihood of occult nodal metastasis, Elective Neck Dissection (END) is performed as part of initial management for many patients even when no clinical evidence of lymph node metastasis is present.[78]

In END, Selective Neck Dissection (SND) is utilized to sequentially remove lymph node groups, based on their risk for occult metastasis, while preserving the spinal accessory nerve, internal jugular vein and sternocleidomastoid muscle. END is a function preserving, low morbidity

option for the management of cervical lymph node disease in many patients. Radical Neck Dissection (RND) and Modified Radical Neck Dissection (MRND) are the standards when lymph nodes are positive on clinical exam (regardless of N stage). In RND or MRND one or more of the structures preserved in SND (e.g., spinal accessory nerve, internal jugular vein and sternocleidomastoid muscle) may be sacrificed along with lymph node removal.[78]

Clinical recommendations vary when the presence of lymph node metastasis is unclear. Some authors favor END while others advocate for elective radiotherapy or observation.[48,50] Neck dissection is indicated in the management of late-stage (Stage III and Stage IV) with or without nodal metastasis,[71] assuming there is occult metastasis even in a clinically negative neck. In our subset analysis, neck dissection was performed 63% of patients (N = 19), 11 of whom were confirmed to have positive lymph nodes. Clinically, 12 of the 19 patients completing neck dissection were advanced-stage (Stage III, N = 9; Stage IV, N = 3) while 7 had early-stage disease (Stage I, N = 1, Stage II, N = 6). Of the 11 with positive nodes, 36.4% were clinically negative (cN0) (Stage II, N = 3; Stage III, N = 1) and lymph node involvement was only discovered on END highlighting the potential for occult neck metastasis in early-stage tumors. Of the 11 patients with positive nodes, 3 went on to develop recurrent disease (1 local and 2 locoregional). A lower rate of occult metastasis was reported in a study by Aksu and colleagues in which 4 or 22 patients treated with neck dissection were confirmed to have occult nodal metastasis (18.2%). It is noted that 3 patients who were not treated with neck dissection develop neck recurrence. Three additional patients were diagnosed with neck recurrence who were not treated with neck dissection.[37] In the study by Al-Rajhi et al, the neck was managed by observation in 26 patients, ipsilateral MRND in 16 patients, prophylactic neck radiation in 23, and MRND followed by neck irradiation in 20 patients. Neck recurrence was observed in 35% if

patients with no neck treatment, 19% treated with MRND, 20% with MRND plus irradiation, and in 39% with radiation alone. The authors suspected occult nodal metastasis in the patients with N0 disease developing neck recurrence in the observation group.[36] All patients in Ganly et al.'s study had early-stage disease and all 164 patients were treated with neck dissection (81% supraomohyoid neck dissection, 9% MRND, 7% with bilateral neck dissection). Eighteen percent developed neck recurrence. The authors postulated the cause of neck recurrence to be either failure to remove subcentimeter occult metastases at the time of neck dissection or the presence of micrometastases. Only 2 patients with neck recurrence had confirmed micrometastases on pathologic examination. Five of 39 patients with confirmed micrometastases on neck dissection did not develop neck recurrence.[35]

4.7 TUMOR CHARACTERISTICS

TUMOR SIZE

While tumor size has been an important staging parameter, tumor diameter does not perfectly reflect total tumor volume. Discrepancies occur due to differential spread of cancer in different planes and the presence of tumor necrosis. Tumor thickness and depth of invasion (DOI) have been shown to be an important prognostic factor in head and neck cancers. [33,57,74,79] A study by Yuen and colleagues in Hong Kong evaluated 85 glossectomy specimens of OTSCC and the prognostic value of tumor size (diameter, length, thickness, width, area and volume) in the prediction of nodal metastasis, local recurrence, and overall survival (OS). In their study, tumor thickness or invasion was the only tumor-specific measurement predictive of nodal metastasis, local recurrence, or survival. Thin tumors with larger surface diameter had a higher chance of negative surgical margins and a lower risk of nodal metastasis when compared to tumors with equivalent volume but deeper DOI. The incidence of nodal metastasis increased rapidly when

tumors had deeper invasion into tongue musculature. T3 lesions with greater than 9 mm invasion were found to have 65% nodal metastasis, 26% local recurrence, and 60% 5-year actuarial disease-free survival (DFS) compared to T2 lesions with DOI between 3 mm and 9 mm which showed 50% nodal metastasis, 11% local recurrence, and 77% 5-year actuarial DFS.[7]

In our subset analysis, 76% of tumors measured less than 4 cm in size (mean = 2.5 cm; 0.1-7.5cm). Fifty percent had DOI less than 10 mm (N = 15), 43.3% had DOI greater than 10 mm, and 6.7% in which DOI was not reported (**Table 8**). Patients with tumors measuring greater than 4 cm (N = 7) were very likely to die with 6 out of 7 deceased within our study period. Each of these tumor specimens had a DOI greater than 10 mm (range: 12 to 35 cm) with the exception of 1 specimen in which DOI was not reported **(Table 11)**. The surviving individual in the large tumor group had a tumor measuring 5.5 cm in diameter but a relatively shallow DOI (13 mm) raising the possibility that DOI may have been a factor in survival. In contrast, 2 patients with early-stage disease and shallow DOI (pT1N0 with tumor size 0.3 cm and DOI 2 mm and pT2N0 with tumor size 2.8 and DOI 5mm) developed recurrent disease (1 of whom died) suggesting additional complexity. In the subset analysis as a whole, 5 of 30 patients developed recurrence, three of these patients had DOI greater than 10 mm. Unfortunately, conclusions were limited by small sample size, with insufficient power to detect statistically significant difference between groups.

Table 11. Effects of Larger Tumor Size & Depth of Invasion on Recurrence and Death

No.	Tumor diameter	DOI	Stage (Pathologic)	Type of glossectomy	Recurrence	Survival
1.	7.5 cm	25 mm	IV	Subtotal	Yes(locoregional)	Deceased
2.	5.8 cm	35 mm	IV	Subtotal	Yes(locoregional)	Deceased
3.	5.7 cm	25 mm	III	Hemiglossectomy	No	Deceased
4.	5.5 cm	13 mm	III	Partial	No	Alive
5.	4.5 cm	24 mm	III	Subtotal	No	Deceased
6.	4.1 cm	12 mm	IV	Subtotal	No	Deceased
7.	4.1 cm	Unknown	IV	Partial	No	Deceased

POSITIVE MARGINS

The aim of surgical resection of OTSCC is to achieve clear, tumor-free resection margins to minimize risk for recurrence. A positive histologic margin is defined by the presence of invasive carcinoma at the surgical margin of a resected surgical specimen.[80] Studies have consistently shown higher incidence of local recurrence in head and neck cancers in resected tumors with positive histologic margins.[7,80,81] The incidences of local recurrence in tumors with positive margins ranges from 29% to 70% compared to 4% to 38% for negative resection margins.[7,80,82,83,84]

In our subset analysis, 23% of patients had positive resection margins (N = 7) and 77%(N=23) had negative margins. Three of the 7 patients died within our follow-up period. Two patients with positive margins developed local recurrence (1 of whom died). Of the 5 with positive margins who did not develop recurrent disease, 4 were treated with adjuvant therapy.

Local recurrence may occur in patients with histologically clear resection margins due to failure in histologic detection near the margins of the tumor or the presence of “skip” micrometastasis (in which metastasis occurs beyond a seemingly clear surgical margin) .[7] Tumor implantation during surgery may also cause recurrence. "Close” histological margins may occur when tumor dimension is underestimated, when the tumor has spread along other structures, when an

unidentified second primary tumor is present, or when "tumor satellites" (group of tumor cells near the primary tumor) are present. Surgical technique and experience can also play a role.[85,80] In a study similar to ours, Yuen et al. examined 50 glossectomy specimens to evaluate local spread of OTSCC. They reported 27% incidence of local recurrence in patients with positive histologic margins. The authors recommended a minimum of 1.5 cm surgical resection margin and a maximum of 2 cm margin to avoid unnecessary removal of healthy tissue.[7] Larger surgical margins increase surgical morbidity without providing additional survival advantage.[7,40]

Perineural and Lymphovascular Invasion

Perineural invasion (PNI) and lymphovascular invasion (LVI) are commonly indicators of aggressive tumor behavior in OSCC. [51,81,86,87,88] PNI is characterized by the presence of tumor cells within the nerve sheath or perineural space and is associated with poor prognosis in OTSCC.[86,87,88,89] Because of its prognostic value the College of American Pathologists protocol requires that the presence or absence of PNI be recorded in the pathology report in oral cancer.[90] Furthermore, the NCCN guidelines classify the presence of PNI to be an indicator for adjuvant therapy.[39]

In our subset analysis, 30% of tumor specimens were positive for perineural invasion (N = 9). Among these patients, 3 developed recurrence (1 local recurrence, 1 locoregional metastasis, 1 regional metastasis). Five of these 9 patients died. In a study of 50 patients by Yuen et al., PNI was the only significant risk factor for local recurrence. Thirty percent of OTSCC patients with PNI were later diagnosed with local recurrence versus 4% in those without PNI.[7] Caponio et al. conducted a retrospective study of 200 patients treated for OTSCC to analyze the clinical and prognostic value for PNI. PNI was found in 40.5% of patients and was associated with worse disease-specific survival (Hazard ratio = 1.88, $p < 0.008$).[87]

LVI is characterized by the presence of neoplastic cells located in the wall or lumen of blood or lymphatic vessels.[51] LVI has been correlated with low survival rates and a high risk of recurrence in OTSCC.[51,91] In our subset analysis, 30% of tumor specimens were positive for LVI (N = 9). Two of the patients with LVI developed locoregional recurrence, both of whom died. In total 5 of 9 patients with LVI were deceased at the end of the study period.

Poor prognosis in patients with LVI was consistent with other studies.[7,51,88,92] Tai et al. reviewed 190 specimens in patient diagnosed with early-stage (T1-2) OTSCC and found PNI in 31.1% of patients and LVI in 21.6% of cases. Local recurrence and neck recurrence occurred in 9.5% of cases. PNI, LVI, and tumor thickness were independently predictive of occult nodal metastasis, but only PNI independently predicted neck recurrence.[92]

TUMOR GRADE

In contrast to clinical staging, which depends on clinical and radiographic findings, tumor grade is determined by degree of cellular differentiation on histologic examination.[93] Grading of OSCC is divided into 3 groups according to the degree of keratinization, nuclear pleomorphism, and mitosis rate. Tumors may be classified as well differentiated (grade 1), moderately differentiated (grade 2), or poorly differentiated (grade 3) based on differences in these cellular characteristics. According to the 8th edition of the American Joint Committee on Cancer (AJCC) staging manual, grade 1 is considered as low grade while grades 2 and 3 are high grade tumors.[93,94] Patients with grade 3 OSCC have higher risk of recurrence and lower survival rates than those with low grade tumors.[93] In a single center retrospective study by Lin et al. that analyzed histologic grade of OSCC versus survival, the authors found a strong association between high tumor grade and advanced T stage, cervical lymph node metastasis, and extranodal spread, all of which contributed to advanced-stage and likelihood of tumor recurrence.[93] A study of 380 patients by

Rodrigues et al. in Brazil, found that poorly differentiated tumors were more likely to recur than moderately or well differentiated tumors in patients treated for tongue and floor of mouth SCC. Poorly differentiated tumors were also associated with worse cancer specific survival.[95] Other studies have also made similar observations.[27, 95,96,97]

Tumor grade in our subset analysis was more likely to be high grade (50%) than low grade (43%). Thirty percent of tumors were well-differentiated (N = 9), 13.3% well-to-moderately differentiated, 30% moderately differentiated, 3.3% moderate-to-poorly differentiated, and 16.6% poorly differentiated. In 2 cases SCC was excised at the time of initial biopsy and no residual SCC was present in the graded sample. Two patients with high grade tumors experienced local or locoregional recurrence. High tumor grade was also seen in 5 of the 8 deaths in our subset (N = 30).

4.8 ADJUVANT THERAPY

Adjuvant therapy is commonly used in the treatment of OTSCC due to its aggressive nature and high risk of lymphatic involvement. Adjuvant therapy consists of post-operative radiotherapy (PORT), chemotherapy, or chemoradiation (in which chemotherapy and radiation are delivered in combination with each other). Adjuvant therapies are important adjuncts to surgical resection to achieve locoregional tumor control.[68] The NCCN guidelines recommend adjuvant therapy, particularly PORT, for patients with negative prognostic indicator namely positive resection margins, extranodal involvement, PNI and LNI.[39,68] Aksu et al. reported statistically greater DSS in patients treated with a combined treatment of surgery and PORT versus surgery alone (49% versus 23%, P = 0.02). They concluded that a combined treatment approach improves overall and disease-free survival in patients with Stage II, III and IVA oral tongue cancer.[37]

In our subset analysis, 8 patients (5 males, 3 females) were treated with adjuvant therapy. All had advanced-stage disease on pathologic staging (Stage III = 6; Stage IV = 2). Four had positive surgical margins, 5 had PNI, 4 had LVI, and 5 had positive nodes. Type of adjuvant therapy varied with 3 treated with radiotherapy, 2 with radiotherapy and chemotherapy (at different points in time), and 3 treated with chemoradiation. Unfortunately, our study was limited by an inability to gather additional details related to specific treatment protocols.

Interestingly, not every patient with NCCN indications for adjuvant therapy received it. Seven patients that had indicators for adjuvant therapy, including positive margins, PNI, LVI, and positive nodes, but were alive without evidence of recurrence at the end of our study period despite lack of adjuvant therapy. Inappropriate application of adjuvant therapy may cause adverse effects which could increase morbidity and negatively impact the patient's quality of life.[37] Because of this, the choice to defer adjuvant therapy may have been due to acceptable locoregional control with surgery alone.

4.9 TREATMENT OUTCOMES

PAIN AND PARESTHESIA

Five patients reported tongue pain during this time frame. Four of these patients went on to develop recurrent, advanced disease (3 of whom died). Pain presentation varied in these 5 patients. Three developed pain in the first 6-months post-surgery. The first, treated with left partial glossectomy, reported pain 2 weeks post-operatively which was managed with systemic medication. This patient did not return for follow-up visits. The second, treated with hemiglossectomy, reported pain 3 weeks post-operatively and died shortly thereafter. The third was treated with subtotal glossectomy and developed pain 3 months post-surgery requiring systemic pain medication. This patient had a complex post-surgical period, developed neck

recurrence and ultimately died 5-1/2 months post-surgery. Two patients developed pain several years following surgery raising concern for recurrence. The first, treated with right partial glossectomy, reported pain 2 years post-surgery and was confirmed to have recurrent disease in the ipsilateral floor of mouth. This patient was lost to follow-up and survival status is unknown. The other developed severe pain 2.5 years after completing left partial glossectomy. A laryngoscopy performed to evaluate for recurrence, but no evidence was identified on exam. MRI was advised for additional evaluation, but the patient was lost to follow-up before imaging was completed.

Three patients, all treated with partial glossectomy, reported paresthesia during post-operative follow-up. Of these, 1 reported numbness at the 9-month post-operative visit which resolved by the 18-month appointment. The second reported numbness at the 10-month post-operative visit but was lost to follow-up. The third had persistent numbness which was still present at the 24-month appointment. No patients with paresthesia developed recurrence and all were alive at the end of the study period.

SPEECH PROBLEMS

Patient motivation, a quality support system, and regular follow up with their physician and speech language pathologist are associated with improved treatment outcomes following glossectomy with free flap reconstruction. Free flap reconstruction of the tongue allows for better speech quality ("intelligible speech", improved swallowing, and higher overall quality of life after surgery.[98] Chien et al. reported 13 (89%) of 15 patients with subtotal or total glossectomy defects that were reconstructed with RFFF or ALT free flaps were able to regain intelligible speech.[99] Liao et al. reported intelligible speech in 100% of patients treated with hemiglossectomy reconstructed with free flaps (N =5).[100]

In our cohort no patients reported speech problems and there were no instances of free flap failure. Most patients in the subgroup analysis were under the care of a speech pathologist. Our results are similar to Ganly et al. who also reported no speech problems in their cohort of patients with early-stage OTSCC treated with partial glossectomy and neck dissection.[35] Detailed quality of life measures were not possible in our study due to the retrospective nature of our study design but would be very valuable in future study.

Quality of life assessments have been assessed in other studies including a study by Dzioba and colleagues evaluating 117 patients treated with partial glossectomy and reconstruction for OTSCC. Patients completed self-reported outcome measures assessing speech (Speech Handicap Index), swallowing(M.D. Anderson Dysphagia Inventory) and quality of life (European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Head and Neck Module) pre-operatively and at 1, 6, and 12 months post-operatively. Their results indicated no significant differences in swallowing function pre-operatively and 6 months post-operatively and no significant differences in speech function between baseline and 1-year. Most quality-of-life domains returned to baseline levels with 12 months, though difficulties with dry mouth and sticky saliva persisted. Pre-operative pain scores were higher than those reported at follow-up visits suggesting that pre-operative pain was related to direct effects of the tumor.[41]

4.10 RECURRENCE AND SURVIVAL

Tumor recurrence occurred in 16% of patients in our subset analysis (N = 5). Two individuals were diagnosed with local recurrence while 3 developed locoregional recurrences. Pathologic staging varied in this group (Stage I, N = 1; Stage II, N = 1; Stage III, N = 1, Stage IV, N = 2). Tumor grade was also highly varied with 1 poorly differentiated, 1 moderately differentiated, 2 well to moderately differentiated, and 1 sample confirmed to be high grade squamous dysplasia

rather than SCC. Positive nodes were present in 3 cases, PNI in 3 cases, and LVI in 2 cases. A single patient who developed recurrence had been treated with adjuvant therapy. Two of the 5 patients with recurrence died.

Our recurrence rate was relatively similar to Carta et al. who identified 22.3% in their study population (Stage I = 0.0%; Stage II, 2.5%; Stage III = 6.2%, Stage IV = 13.6%). Nodal involvement was present in 40.7% with PNI and LVI in 11.1% and 13.6% of cases, respectively. Twenty-seven percent of patients with pT3-pT4 lesions completed adjuvant therapy, while 8 patients refused adjuvant therapy despite indications for treatment.[6]

Survival analysis was completed for all patients in our cohort (N = 60 patients). Death occurred more often in women (N = 9) than men (N = 4). This finding is in contrast to statistics reported by SEER and other medical literature where death in patients with OTSCC is consistently higher in males. Age at death ranged from 42 to 93 years with a mean age of 61.9. The greatest number of deaths occurred in the 5^{th} and 7^{th} decades of life (N = 4 for both). Twelve of the 13 patients who died were white.

A recent study by Ansarin et al. analyzed age as a prognostic factor in a cohort of 577 with OTSCC.[101] They concluded that age was not a significant predictive factor for cause-specific survival (CSS) or tongue specific free survival (TSFS) in the cohort as a whole (P = 0.14 and P = 0.37 respectively); however, greater age was associated with lower survival in advanced-stage sub-groups (stages III–IV). Death was approximately twice as likely in elderly patients (above 40 years) when compared to younger patients (below 40 years) in both OS and CSS analyses (OS: HR = 2.16 95%, CI: 1.33–3.51, P = 0.001; CSS: HR = 1.76 95%, CI: 1.03–3.01, P = 0.02, respectively). All the deceased patients in our study were above the age of 40.

Of the 13 deceased patients in our full cohort, 8 were included in our subset analysis of post-surgical outcomes. Seven of these 8 individuals had advanced disease by pathologic staging criteria (Stage III, N = 2; Stage IV, N = 5) and 5 had high grade tumors. Three had positive surgical margins on resection, 5 had PNI, 5 had LVI, and 6 had positive lymph nodes. Deceased patients had a high occurrence of negative prognostic factors that have been established in other cohorts.[2,5,9,102] The lone deceased patient with early stage disease had a stage I, well-differentiated tumor with negative surgical margins, an absence of positive nodes, and no evidence of PNI or LVI.

Relative survival (RS) is an estimate of the percentage of expected survival in patients diagnosed with a specific disease (i.e., RS excludes other causes of death).[1] SEER reports a 5-year RS of 68.1% in OTSCC.[1] Cancer stage at diagnosis determines treatment options and has a strong influence on duration of survival. The earlier OTSCC is detected, the greater the 5-year RS. In OTSCC only 28.9% of cases are diagnosed at the local stage compared to 52% diagnosed in the regional stage and 16% with diagnosis after distant metastasis.[1] The 5-year RS for localized tongue cancer is 82.9%. compared to 69.4% for regional stage and 41.9% in distant metastasis.[1] Survival analysis in our study was limited by our study period and limited access to cause of death information. The OS in our study (42%) was lower than 5-year DSS, OS, and Relapse Free Survival (RFS) reported by Ganly and colleagues[35] (DSS 86%, OS 79%, RFS 70%). It is noted that Ganly et al.'s study was limited to early-stage (T1-2N0) OTSCC in which higher 5-year survival rates would be expected. A similar study of 85 patients with early-stage OTSCC by Al-Rajhiet al. reported OS of 71%, DSS of 75%, and RFS of 63%.[36] Marra and colleagues analyzed 160 patients following surgical treatment of OTSCC. Their cohort included 59.4% of patients with early-stage and 40.6% with advanced disease. The authors reported 13 instances of tumor

recurrence and 11 deaths in the first 5 years post-surgery.[9] Survival rate in our subset analysis was lower than reported by Marra et al. despite our study's smaller sample size (with 13 deaths in 30 patients despite similar instances of early and advanced-stage disease). Several other studies also reported higher 5-years survival rates including Hicks et al. (who reported 89% survival in pathologic Stage I, 95% in Stage II, 76% in Stage III, and 65% in Stage IV). [103] Carta et al. reported DSS of 73.2% and OS of 66.8% in a study analyzing surgical management of OTSCC at all pathologic stages.[6]

Five-year survival rates in other studies were more consistent with our findings. Aksu et al. reported a 5-year OS of 49% in a retrospective study of patients treated with surgery and adjuvant therapy.[37] A retrospective study by Sessions et al. of 332 patients with OTSCC treated with 5 different modalities (local resection alone, radiation alone, composite resection with neck dissection, local resection with radiation therapy, and composite resection with radiation therapy) reported OS of 57% at 5-year years with DSS of 43%. The 5-year cumulative disease-specific probability (CDSS) was 61%.[104]

Referral

Referral by a dentist or dental specialist led to diagnosis of OTSCC in 53.3% of patients in our subset analysis (N = 16) (**Figure 8**). Interestingly, Holmes and colleagues have previously reported that OSCC and OPSCC patients referred by dental providers were statistically more likely to be diagnosed at early stage than those referred by a physician or medical provider.[105] In our study, 10 of 18 early-stage tumors were referred by dentists with an equivalent number of late-stage tumors were referred by dentist and physicians. Taken together findings suggest that both dentist and physicians have similar rates of referral for diagnosis in OTSCC and that cancer stage is similar in patients referred by either group.

4.11 STUDY LIMITATIONS AND FUTURE DIRECTIONS

The principal limitations in our study were the studies retrospective design, small sample size, and limited post-operative follow-up period for some members of the cohort. Surgical treatments were completed between 2016 and 2019 meaning that not all patients had completed 5 years of follow-up at the time of our analysis. This required calculation of estimated 5-year survival which had large confidence intervals given the relatively small size our cohort. The small sample size of our cohort also limited the conclusions which could be drawn related to survival and post-surgical treatment outcomes as the study was underpowered to detect statistical differences between groups. Study data was restricted to information available in pathology records and notes from the department of otolaryngology head and neck surgery which limited our ability to obtain information related to adjuvant therapies and DSS. Data related to volume and frequency of tobacco and alcohol consumption was limited resulting in binary analysis for presence or absence of these risk factors.

The principal strength of this study was the availability of surgical treatment data allowing for description of surgical techniques and outcomes based on the different subsets of glossectomy and reconstructive technique. Extending the retrospective analysis to a larger number of patients treated within our center would allow for a more robust description of surgical treatment and surgical outcomes in OTSCC. This would also increase statistical power to determine association or lack of association between tumor characteristics, therapeutic interventions, and treatment outcomes. A similar study design could also be utilized at other centers to help determine local, regional, or global differences in adherence to NCCN guidelines and variations in treatment outcomes based on patient or treatment-center specific factors.

CHAPTER 5. CONCLUSION

Our analysis of patients with OTSCC treated with glossectomy through Otolaryngology-Head and Neck surgery at UWMC between January 1st, 2016 and December 31st, 2019 showed strong adherence to NCCN guidelines. Patient demographics were similar when compared to published literature, though a higher percentage of death was seen in women than would be expected from population-based data. Interestingly, subset analysis found a majority of tumors to have left-sided laterality. To our knowledge there are no studies that describe the laterality of oral tongue squamous cell carcinoma (OTSCC) and more research is warranted to determine if this finding is consistent in other study populations and if so, which factors increase risk for OTSCC in this location. Though our study was underpowered to confirm statistically significant association between clinical risk factors and specific post-surgical outcomes, death and other negative post-operative outcomes were more common in patients with negative prognostic factors reported in published literature including clinical stage, pathologic grade, depth of invasion, lymph node metastasis, perineural invasion, and lymphovascular invasion. Our study identified a higher likelihood of survival in patients with earlier stage tumors highlighting the important role that dental providers have in early detection of OTSCC.

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CHAPTER 6. APPENDIX

6.1 APPENDIX A: DATA VARIABLES

Demographic variables

- Age.
- Gender.
- Race.
- Date of death.

Clinical variables (initial evaluation with OTO-HNS)

- Pain (patient report).
- Numbness (patient report).
- Ulceration at the tumor site.
- "Mass" at tumor site.
- Lesion duration (patient or referring provider report).
- Health professional who initially detected the lesion.

Clinical variables (pre-operative)

- Anatomic region of the tongue (tip, dorsum, lateral, ventral).
- Clinical TNM staging (cTNM) (AJCC).

Consumption history*

- Smoking (yes/no).
- Chewing tobacco (yes/no).
- Alcohol (yes/no).

*Consumption classified as yes/no, rather than by frequency, duration, or total intake, due to differential reporting in patient records.

Tumor characteristics (post-operative)

- Tumor size per histology or tumor size determined clinically is the largest dimension of the tumor reported in centimeters.
- Histologic tumor grade (AJCC).
- Depth of invasion (defined as the distance from the basement membrane to the closest adjacent normal mucosa).[33,53]
- Perineural invasion (defined as neoplastic invasion of nerves and a route of metastasis).[106]
- Positive tumor margins.
- Positive nodes.
- Number of lymph nodes excised in the resection specimen.
- Pathologic TNM Stage (pTNM).

Treatment variables

- Extent of glossectomy (partial glossectomy, hemiglossectomy, subtotal glossectomy, or total).
- Neck Dissection (yes/no).
- Primary Closure (yes/no).
- Flap reconstruction (yes/no).
- Type of flap used for reconstruction (ALT, RFFF, pectoralis major myocutaneous flap, alloplastic graft, submental flap, rectus free flap).
- Neo-adjuvant therapy (radiation, chemotherapy or chemoradiation therapy).

- Adjuvant therapy (radiation, chemotherapy, or chemoradiation therapy).

Clinical outcomes (post-surgery)

- Flap failure (yes/no).
- Pain (patient report at any post-discharge follow-up evaluation).
- Paresthesia (patient report at any post-discharge follow-up evaluation).
- Speech problems (patient report at any post-discharge follow-up evaluation, defined as altered speech due to decreased tongue mobility or inability to articulate words).
- OTSCC recurrence (yes/no).
- Death.

6.2 APPENDIX B: AMERICAN JOINT COMMITTEE ON CANCER (AJCC) TNM STAGING CLASSIFICATION FOR THE ORAL CAVITY

Lip and oral cavity	7th edition	8th edition
T1	Tumor < 2cm	Tumor ≤ 2 cm, ≥ 10mm depth of invasion
T2	Tumor 2-4 cm	Tumor ≤ 2 cm, >5mm, and ≥10 mm depth of invasion or tumor > 2 cm but ≤ 4 cm and depth of invasion ≤ 10 mm
T3	Tumor > 4 cm	Tumor > 4 cm or depth of invasion>10 mm, but ≤ 20 mm
T4a	Moderately advanced local disease: (Lip) tumor invades through cortical bone or involves inferior alveolar nerve, floor of mouth, or skin of face (oral cavity) tumor involves adjacent structures such as cortical bone of maxilla or mandible, maxillary sinus or skin of face, or extrinsic muscles of tongue.	Extrinsic muscles of tongue removed, included extensive tumors with bilateral tongue involvement and /or DOI > 20 mm.
T4b	Very advanced local disease; tumor invades masticator space, pterygoid plates, skull base, and/or encases the internal carotid artery	Same
N1	Metastases to single lymph node, 3 cm or less in greatest diameter	Same, except node must be extranodal negative
N2a	Metastases to single ipsilateral node >3 cm but not >6 cm	Same, except nodes must be extranodal extension negative or single ipsilateral or node 3 cm or smaller with extranodal extension
N2b	Metastases to multiple ipsilateral nodes >3 cm but not >6 cm	Same, except nodes must be extranodal extension negative
N2c	Metastases to bilateral nodes or contralateral nodes none >6cm	Same, except nodes must be extranodal extension negative
N3	Metastases to nodes >6 cm	Subdivided into 3a: Same as N3 before, but extranodal extension negative 3b: Single ipsilateral node>3 cm in greatest dimension with extranodal extension Or multiple ipsilateral, contralateral, or bilateral nodes, any with extranodal extension Or single contralateral node 3 cm or smaller and with extranodal extension.
M0	No distant metastasis	
M1	Distant metastasis	

Edge S, Byrd DR, Compton CC, Fritz AG, Greene FL, Trotti A. AJCC Cancer Staging Handbook. Springer; 2011.
Amin MB, Edge, Stephen B., American Joint Committee on Cancer, issuing body, sponsoring body. AJCC Cancer Staging Manual. Eighth edition. Springer; 2017
Subramaniam N, Thankappan K, Anand A, Balasubramanian D, Iyer S. Implementing American Joint Committee on Cancer 8th edition for head-and-neck cancer in India: Context, feasibility, and practicality. Indian J Cancer. 2018;55(1):4-8. doi:10.4103/ijc.IJC_475_17

6.3 APPENDIX C: PROGNOSTIC STAGE GROUPS

Stage	T stage	N stage	M stage
Stage 0	Tis	N0	M0
Stage I	T1	N0	M0
Stage II	T2	N0	M0
Stage III	T1, T2	N1	M0
	T3	N0, 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

Amin MB, Edge, Stephen B., American Joint Committee on Cancer, issuing body, sponsoring body. AJCC Cancer Staging Manual. Eighth edition. Springer; 2017

6.4 APPENDIX D: AJCC PATHOLOGIC STAGING

pN category	pN Criteria
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in a single ipsilateral lymph node, 3 cm or smaller in greatest dimension and ENE(−)
N2	Metastasis in a single ipsilateral lymph node, 3 cm or smaller in greatest dimension and ENE(+); or larger than 3 cm but not larger than 6 cm in greatest dimension and ENE(−); or metastases in multiple ipsilateral lymph nodes, none larger than 6 cm in greatest dimension and ENE(−); or in bilateral or contralateral lymph node(s), none larger than 6 cm in greatest dimension and ENE(−)
N2a	Metastasis in a single ipsilateral node 3 cm or less in greatest dimension and ENE(+); or a single ipsilateral node larger than 3 cm but not larger than 6 cm in greatest dimension and ENE(−)
N2b	Metastases in multiple ipsilateral nodes, none larger than 6 cm in greatest dimension and ENE(−)
N2c	Metastases in bilateral or contralateral lymph node(s), none larger than 6 cm in greatest dimension and ENE(−)
N3	Metastasis in a lymph node larger than 6 cm in greatest dimension and ENE(−); or metastasis in a single ipsilateral node larger than 3 cm in greatest dimension and ENE(+); or multiple ipsilateral, contralateral, or bilateral nodes any size and ENE(+) in any node; or a single contralateral node of any size and ENE(+)
N3a	Metastasis in a lymph node larger than 6 cm in greatest dimension and ENE(−
N3b	Metastasis in a single ipsilateral node larger than 3 cm in greatest dimension and ENE(+); or multiple ipsilateral, contralateral, or bilateral nodes any size and ENE(+) in any node; or a single contralateral node of any size and ENE(+)

Amin MB, Edge, Stephen B., American Joint Committee on Cancer, issuing body, sponsoring body. AJCC Cancer Staging Manual. Eighth edition. Springer; 2017.

6.1 APPENDIX E: DEMOGRAPHIC CHARACTERISTICS OF PATIENTS TREATED WITH GLOSSECTOMY AT UWMC COMPARED TO DEMOGRAPHICS OF PATIENTS TREATED AT OTHER INSTITUTIONS

Our study	**Carta et al.**[6]	**Aksu et al.**[37]	**Ganly et al.**[35]	**Rajhi et al.**[36]
60 patients	80 Patients	80 Patients	164 Patients	85 Patients
M = 35; F = 25 Age range: 26-95 years	M = 59; F = 21 Age range: 27-81 years	M = 41; F = 39 Age range: 22-93 years	M = 90; F = 74 Age range: 25-82 years	M = 38; F= 47 Age range: 26-90 years
Median age: 60 years Mean age: 61.4 years	Mean age: 57.8 years	Median age: 55 years	Median age: 55 years	Median age: 60 years
Subset analysis (N = 30)				
Smoking: 60% Alcohol: 73%	Smoking: No data Alcohol: No data	Smoking: 81% Alcohol: 16%	Smoking: 59% Alcohol: 51%	Smoking: 14% Tobacco chewing: 59% Unknown: 7% Alcohol: 0%
Stage I 12 (40%) Stage II 6 (20%) Stage III 9 (30%) Stage IV 3 (10%)	Stage I 18 (22.8%) Stage II 28 (34.6%) Stage III 9 (11.1%) Stage IV 26 (32.1%)	Stage I 1 (1%) Stage II 28 (36%) Stage III 18 (23%) Stage IV 32 (40%)	Stage I 52 (32 %) Stage II 100 (61%) Stage III 12 (12%) Stage IV 0 (0%)	Stage I 1 (1%) Stage II 28 (36%) Stage III 18 (23%) Stage IV 32 (40%)
PNI: 30% LVI: 30%	PNI: 11.1 % LVI: 13.6 %	PNI: 18% LVI: No data	PNI: 13% LVI: No data	PVI: No data LVI: No data
Adjuvant therapy: 26.6%	Adjuvant therapy: 27.1%	Adjuvant therapy: 76.3%	Adjuvant therapy: 0%	Adjuvant therapy: 50.5%
5-year OS: 42% Recurrence: 16.6%	5-year OS: 66.8% Recurrence: 22.3%	5-year OS: 42% Recurrence: 10%	5-year DSS - 85.6% Recurrence: 28%	5-year OS: 42% Recurrence: 39%

PNI = Perineural invasion; LVI = Lymphovascular invasion; OS = Overall survival; DSS = Disease specific survival