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Assessing The Survival And Functional Outcomes Of Patients With Supraglottic Squamous Cell Carcinoma

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ABSTRACT:

The objective of this project is to report oncologic and functional outcomes for a cohort of patients with supraglottic squamous cell carcinoma (SSCC) treated in a multidisciplinary setting including the use of transoral laser microsurgery (TLM). A retrospective observational study at Yale New Haven Hospital, academic teaching hospital was performed. A total of 56 patients without evidence of distant metastasis at presentation treated for SSCC between January 1, 2003 and December 31, 2007 were identified. The main outcome measures include overall survival (OS), locoregional and distant recurrence, and the incidence of tracheostomy and gastrostomy tube requirement.

Of the 56 patients, 22 (39%) were treated with TLM, 23 (41%) with definitive radiation (XRT) based therapy, and 11 (20%) with total laryngectomy (TL). Chronic tracheostomy requirement for the TLM, XRT, and TL groups was 0% (0/21), 35% (7/20) and 100% (11/11). Long term gastrostomy tube (PEG) use for the TLM, XRT, and TL groups was 15% (3/20), 36% (4/11) and 50% (5/10) respectively. Two year OS for TLM, TL, and XRT were 86% (18/21), 80% (8/10), and 52% (12/23) respectively. Controlling for age, stage, and treatment on multivariate analysis, younger age and treatment with either TL or TLM were significantly associated with improved survival.

In conclusion, transoral laser microsurgery, especially when employed in a multimodal approach including adjuvant chemoradiotherapy, offers acceptable oncologic results and good functional outcomes.

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Contents

INTRODUCTION

Supraglottic squamous cell carcinoma is a challenging disease affecting the parts of the human body involved in how a person interacts in the world. There has been considerable advancement in the available treatment options for supraglottic SCCA over the past decades. Currently, the goal of treatment is to optimize the chance of cure while minimizing the impact of therapy on a person's quality of life. This paper will discuss and investigate the current state of treatment for supraglottic cancer.

EPIDEMIOLOGY:

Cancer of the head and neck most commonly affects regions of the aerodigestive tract. Head and neck cancer comprises primary malignancies located in anatomically related regions including the oral cavity, oropharynx, nasopharynx, larynx, and hypopharynx. When taken in conglomerate, head and neck cancer has the sixth greatest incidence worldwide, with approximately 600,000 new cases annually. [1] More than 40,000 new cases of head and neck cancer in the United States are diagnosed annually. Men are two to three times more likely to be diagnosed with HNSCC than women and the median age of diagnosis is 60 years old. However, recent observations suggest that the number of new cases in young adults may be increasing. [2] Tumor types consist predominantly of

squamous cell carcinoma involving the upper aerodigestive tract and account for greater than 90%, of head and neck cancers. [1] Because of the overwhelming majority of squamous cell cancer, it will be the focus of discussion.

RISK FACTORS:

The major risk factors for head and neck squamous cell carcinoma include exposure to tobacco, particularly through smoking, and alcohol. Together smoking and alcohol consumption demonstrate a synergistic effect on the risk of developing HNSCC since both smoking and alcohol consumption directly traumatize mucosal surfaces. [1] Furthermore, exposure to tobacco smoke and alcohol increases the burden of carcinogenic compounds presented to the epithelial tissues. Smoking confers a dose related risk with duration of use more important that intensity. [2] Alcohol is less important as an independent carcinogenic agent except with profound use. However, alcohol exposure exacerbates the complex carcinogenic effects of tobacco. Enzymatic systems important in detoxifying carcinogens exhibit polymorphisms that add to the genetic propensity for mutagenesis. [2]

In addition to toxic exposure from tobacco and alcohol, infection with certain viruses has been described to cause HNSCC. Of particular interest, human papilloma virus (HPV) increases the risk of developing HNSCC. [1] Most

implicated are HPV variants 16 and 18. [2] These variants encode oncogenes E6 and E7. The tumor-suppressor gene p53 is downregulated by E6 while E7 suppresses pRB. [2] HPV-related tumors are primarily located in the oropharynx and behave as a unique malignancy when compared to tumors caused by exposure to tobacco and alcohol. [1] As this discussion will focus on supraglottic carcinoma, it is beyond the scope of this paper to address HPV in its entirety.

EMBRYOLOGY:

The larynx is an elegant structure designed to allow phonation and help establish safe deglutition. Embryologic development subdivides the larynx into the supraglottis, glottis, and subglottis. The embryologic origin of the laryngeal subsites are important with regards to vascular and lymphatic anatomy as well as epithelial cellular structure. These differences affect the clinical behavior of tumors presenting in each subsite.

The supraglottis originates from the buccopharyngeal primordium of the third and fourth branchial arches. [1] The supraglottis contains the suprahyoid and infrahyoid epiglottis, aryepiglottic folds, arytenoids, and ventricular bands; also known as the false cords. The embryologic development leads to arterial supply from the superior laryngeal arteries with accompanying bilateral lymphatic drainage. [1] Drainage, then, follows the superior laryngeal arteries to the carotid

sheath and further to the deep cervical chain in neck levels II and III. [3] The epithelium is composed of pseudostratified columnar cells in all areas except the lateral aryepiglottic folds and lateral epiglottis which are stratified squamous cells. Lymphatic vessels are quite superficial in the supraglottis, and with bilateral drainage, the risk of bilateral nodal metastasis at presentation is more likely. For this reason, supraglottic malignancies tend to present at a more advance stage.[1]

The glottis and subglottis are formed from the tracheobronchial premordium of the sixth branchial arch and involves and fusion of the lateral furrows. [1] The glottis contains the true vocal cords and associated anterior and posterior commissures. The arterial supply designated by this embryologic development is the inferior laryngeal arteries with associated lymphatic drainage. The lateral union of the furrows creates a unilateral arterial supply and drainage of the glottis and subglottis. Drainage of lymph follows the inferior laryngeal arteries to the prelaryngeal and pretracheal lymph nodes in neck level VI and further to the deep cervical chain in level IV. [3] The epithelium in this territory is made up of stratified squamous cells with three layers of lamina propria. This leads to a deeper level of lymph drainage meaning that a tumor must invade more deeply before entering the lymphatic system. [1] This decreases the incidence of nodal metastasis at presentation and, due to the unilateral drainage pattern, tends to be unilateral unless the T stage is more advanced. [4]

ANATOMY:

The laryngeal superstructure includes one paired arytenoid cartilage and three unpaired cartilages: the epiglottis, thyroid cartilage, and cricoid cartilage. The superior borders of the larynx include the superior surface of the epiglottis as well as the superior edge of the aryepiglottic folds. The lingual surface of the suprahyoid epiglottis and the hyoepiglottic ligament make up the anterosuperior border. Anterior borders of the larynx are the thyrohyoid membrane in the supraglottis, the thyroid cartilage in the glottis, and the cricothyroid membrane and the anterior arch of the cricoid cartilage in the subglottis. The inferior edge is designated by a horizontal plane through the inferior edge of the cricoid cartilage. The aryepiglottic folds, arytenoid cartilages, interarytenoid space, and the posterior surface of the subglottic region comprise the posterior and lateral borders of the larynx. Image 1 demonstrates the basic laryngeal structure. [1]

From an oncologic perspective, the most important anatomic details of the larynx are barriers to tumor spread and pathways that permit further tumor growth. Barriers to tumor progression within the larynx include the cartilaginous and ligamentous structures. The conus elasticus, a thick fibroelastic structure in the glottic/subglottic region also prevents spread as does the cricothyroid membrane.[1] The anterior commissure of the vocal cords also seems to be a barrier to glottic tumor spread. Two main spaces are recognized as pathways

allowing spread of tumors within the larynx- the pre-epiglottic space and the paraglottic space (Image 2). [1]

Due to fenestrations in the epiglottic cartilage, the pre-epiglottic space (Image 2), which contains only fat and areolar tissue, can be invaded by tumor. [5] The pre-epiglottic space is bounded superiorly by the hyoid bone, the hyoepiglottic ligament, and the valleculae of the hypopharynx. The thyroid cartilage and the thyrohyoid membrane form the anterior border with the epiglottic cartilage and thyroepiglottic ligment make up the posterior border. Laterally and inferiorly the pre-epiglottic space communicates with the paraglottic space. [6] Lymphatic vessels drain the paraglottic space bilaterally to neck zone II and III. [3]

The paraglottic space (Image 2) is prognostically important because progression of tumor into this potential space allows for spread to all three regions of the larynx, creating a transglottic neoplasm. [1] The space lies lateral to the true and false cords. Superiorly it is in continuity with the pre-epiglottic space. The medial borders are the quadragular membrane, an elastic supporting structure of the supraglottis, the conus elasticus, and the laryngeal ventricles. Laterally, the thyroid cartilage and the pyriform sinus of the hypopharynx create borders. The space progresses inferiorly to the cricothyroid membrane. Glottic and supraglottic lesions are stages T3 if they involve the paraglottic space. [4]

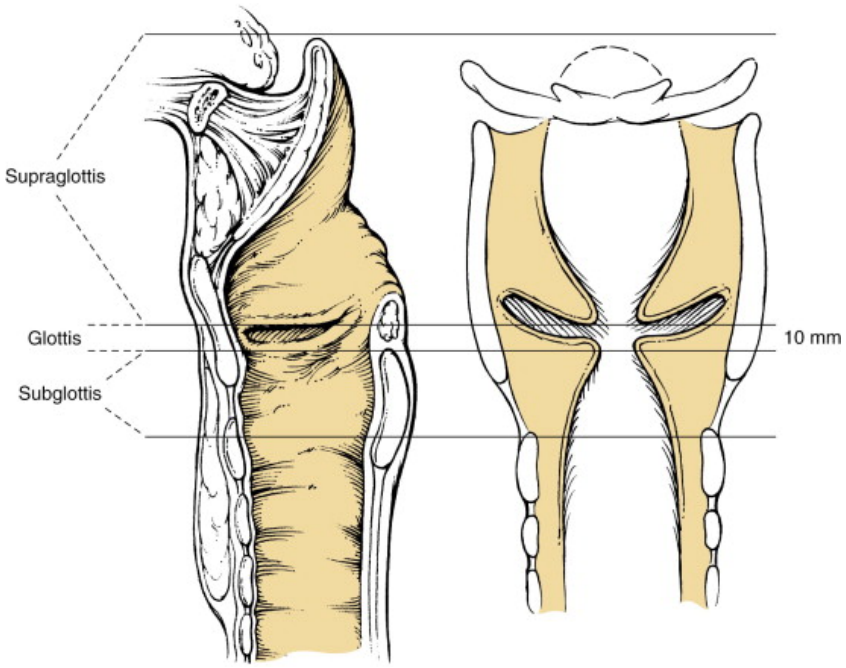

Image 1: Anatomy of the laryngeal sites.
Image from Cummings - Head and Neck surgery [1]

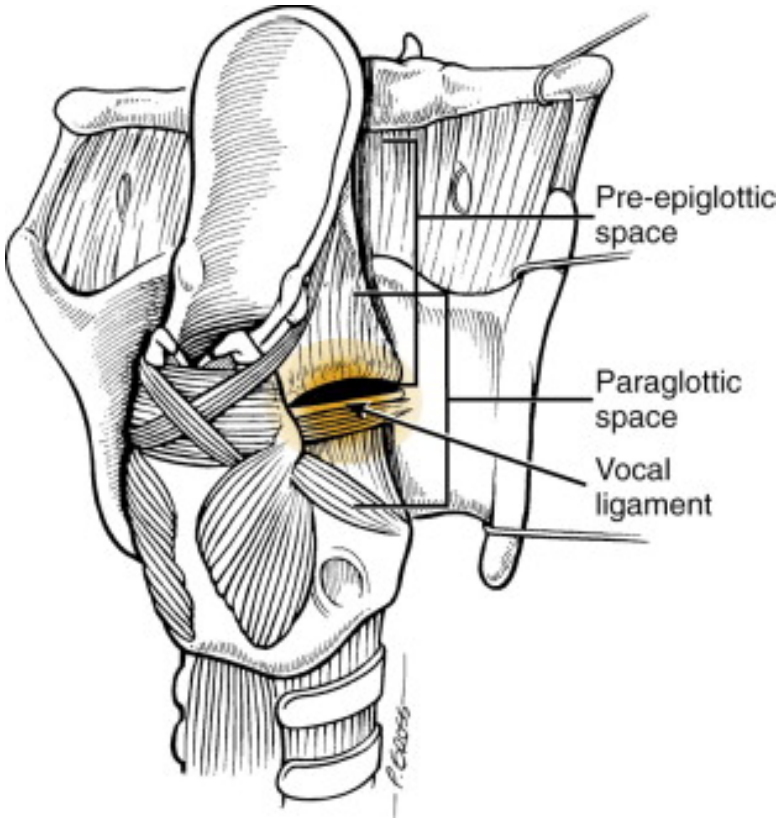

Image 2: Anatomy of the pre-epiglottic and paraglottic spaces
Image from Cummings - Head and Neck surgery [1]

STAGING:

Staging follows the tenants of the TNM staging system to describe the extent and severity of a tumor. Tumor characteristics including size and invasion generate the T stage. Presence and laterality of nodal involvement provide N staging. The M stage refers to presence of metastatic disease. By design, the overall stage of disease provides prognostic relevance. Each characteristic is important in isolation, however, nodal spread and metastasis are particularly prognostic. TNM staging can carry two important prefixes - clinical or pathologic TNM staging. Clinical examination and radiographic reveals a clinical (cTNM) stage. Biopsy of post-operative histopathology reveals a tumor's pathologic (pTNM) stage. A discussion of supraglottic staging with regards to prognosis will be discussed in a different section.

In addition to TNM staging, the American Joint Commission on Cancer (AJCC) created a classification that weighs T, N, and M status to produce a stage I-IVc. [4] AJCC staging offers a more simplified classification scheme that includes the prognostic relevance of nodal disease and metastasis. The staging system demonstrates the prognostic significance of metastasis - any M1 tumor is automatically classified as stage IV. [4] The AJCC staging also demonstrates the importance of nodal involvement as a tumor with any nodal involvement is at

least stage III while more advanced nodal disease such as bilaterality upstages the tumor to stage IVa. [4]

T STAGE:

The T stage in laryngeal cancer depends on the subsite involved. Since the focus of this paper is on supraglottic cancer, only supraglottic T staging will be described. The T stage is categorized based on sites of invasion, vocal cord fixation, cartilaginous invasion, and extra-laryngeal involvement. T1 lesions are localized to a single subsite of the supraglottis with retained vocal cord function. Invasion of more than one supraglottic subsite, glottic involvement, or spread to local mucosal surfaces of the valleculae, base of tongue, or pyriform sinus advance the stage to T2. [4] Normal vocal cord function without fixation must be present in T2 lesions. Vocal cord fixation automatically upstages a tumor to T3. [4] Invasion of the pre-epiglottic space, paraglottic space, post cricoid region, or minimal invasion into the inner cortex of the thyroid cartilage begets a T3 lesion as well. [4] T4 lesions are further subdivided into T4a and T4b. Invasion past the inner cortex of the thyroid cartilage or invasion of extra-laryngeal structures deliniate a T4a lesion. [1] Extra-laryngeal structures include the trachea, esophagus, thyroid tissue, or soft tissues of the neck such as the strap muscles or deep muscles of the tongue. A T4b lesion invades deeply to the prevertebral

space, the mediastium, or encases the carotid artery. [4] The utility of T staging for therapeutic planning and prognosis will be discussed in a different section.

N STAGE:

All laryngeal tumors bear the same N classification system. Presence, size, and laterality of nodal involvement generate the N stage. The designation Nx is used when nodal involvement has yet to be or cannot be investigated. An N0 tumor does not involve any lymph nodes. It is relatively common for a cN0 lesion to be upstaged after neck dissection once histopathology has revealed occult nodal involvement. Nodal involvement of 3 cm or less in a single node ipsilateral to the tumor is classified as N1. [4] The N2 categorization includes nodes less than 6cm in greatest dimension and is broken down into N2a, N2b, and N2c. Nodes must remain ipsilateral to the tumor. A single node greater than 3 cm but less than 6cm is designated N2a. [4] Multiple ipsilateral nodes less than 6 cm classifies as N2b. [4] Bilateral or contralateral nodal involvement less than 6 cm is categorized as N2c. [4] Once a node is greater than 6 cm in greatest dimension, it is classified as an N3 node. [4]

M STAGE:

Of all the classifications in the TNM staging system, M stage is most binary. Patients without metastatic workup at said to have stage Mx disease. The absence of distant metastasis classifies as M0. The presence of any distant metastasis is termed M1. [4] The M1 status of a patient is the most foreboding classification system as it represents a tumor that has evolved to be able to invade the vascular system and invade at a distant site. Numerous oncogenic and mutagenic derangements must have occurred to allow this. [1]

ADDITIONAL PROGNOSTIC MARKERS

In addition to AJCC staging criteria and other clinical factors that are used to risk stratify patients and guide treatment, prognostic biologic factors, such as individual protein expression, mRNA expression patterns, and a few epigenetic biomarkers have been reported which can independently correlate with outcomes in laryngeal cancer. The mutational landscape of head and neck squamous cell cancers was recently reported following whole exome sequencing. Although novel mutations were identified, no correlation of mutational patterns with prognosis was performed. In addition, it appears that different subsites of head and neck cancers may have different mutational trends. [7] Identifying mutational patterns that carry independent prognostic significance within a subsite would

help guide future assessment of treatment outcomes and hopefully enable more individualized treatment approaches. For this reason, a major goal in head and neck cancer continues to be to identify biologic markers that help to prognosticate outcomes and can guide treatment. [8]

After a review of the literature, the following genes were determined to be important and interesting targets for investigation: p53, Bcl-2, Ki67, $p16^{ink4}$, BNIP3, TGM2, CD24, and Notch 1. These candidate genes are involved in multiple pathways implicated in carcinogenesis or are shown to be associated with poorer prognosis in laryngeal squamous cell carcinoma. As an apoptotic protein, p53 is a commonly mutated gene in solid tumors and is overexpressed in the majority of head and neck cancer. However, results are inconsistent on p53's prognostic relevance. [9] Bcl-2 is a key regulator of cell death and survival that is commonly expressed in laryngeal cancer with inconsistent prognostic correlation. [9] Ki67 is a protein involved in cell proliferation and is used to estimate the proliferative rate of tumors. Again, there is disagreement on the utility of Ki67 as a prognosticator – some previous studies have shown expression to predict poorer prognosis while others have not shown any correlation. [9] As a cell cycle regulator, $p16^{ink4}$ has been implicated in poorer prognosis in patients with cancer of the larynx. Its expression has also been shown to be anatomical location specific with predominance in the supraglottic and tonsillar regions. [9]

The remaining candidate genes represent emerging players in head and neck cancer. BNIP3 and TGM2 are target genes associated with action of the transcription factor hypoxia-inducible factor-1 (HIF-1a). [10] BNIP3 is normally upregulated by hypoxia and, as a member of the BCL-2 family, induces apoptosis. BNIP3 has been shown to be silenced in tumor cells causing a failure of apoptosis and association with poorer survival and chemoresistance. TGM2 has been shown to enhance survival in hypoxic cells. Increased expression of TGM2 has been associated with drug resistance in cancer and worse survival. CD24 has been studied in a variety of cancers but has recently been described in laryngeal cancer. [11] Down-regulation inhibits proliferation and induces apoptosis while increased expression increased tumor growth and propensity for metastasis. In a recent study, CD24 expression was shown to be associated with tumor invasiveness and metastasis with high levels of expression associated with tumor progression. [12] Notch1 is a transmembrane signaling protein whose function in contextually related to the cells that it is found in. In a recent study using exome sequencing, Notch1 was shown to acts as a tumor suppressor in head and neck SCC. [13]

SUPRAGLOTTIC CANCER:

While it is convenient to discuss HNSCC as a single entity, it is becoming increasingly clear that each anatomical site is distinct with regards to diagnosis,

natural history, and clinical response to treatment. Furthermore, even subsites (Image 1) appear to represent clinically discrete diseases. Supraglottic tumors have different behavior and prognosis than glottic and transglottic cancers. [14] Additionally, treatment options for supraglottic squamous cell carcinoma have been evolving for the last two decades with an emphasis on functional organ preservation. [8] Supraglottic SCC should be considered a distinct clinical entity. For this reason, the remainder of the discussion will focus on the supraglottis.

Supraglottic squamous cell carcinoma comprises 30-40% of larynx cancers and has unique risk for and patterns of regional metastatic spread and local extension compared to other larynx sub-sites. [1] Patterns of metastatic spread and extension are primarily due to embryologic characteristics previously discussed including superficially penetrating lymph vessels, bilateral drainage pattern, and proximity to the preepiglottic and paraglottic spaces. These factors increased the likelihood that tumors had nodal involvement at the time of diagnosis. [15] Furthermore, bilateral nodal involvement, more common to supraglottic tumors, involves a more advanced T stage and overall AJCC stage at time of diagnosis in many cases.

MODALITIES OF TREATMENT

There has been considerable advancement in the available treatment options for supraglottic SCCA over the past decades. Historically, a total laryngectomy dominated treatment of supraglottic tumors. [16] Over the last three decades, treatment options have been evolving and have increasingly consisted of organ preserving strategies. [8] Definitive radiotherapy and chemoradiotherapy treatment protocols as well as an emphasis on surgical techniques allowing partial laryngectomy have decreased the use of total laryngectomy (TL) in early stage tumors and raised questions about it's employment even in more advanced stages. The idea of non-operative treatment versus operative management of supraglottic lesions has given way to utilization of a multimodal approach.

TOTAL LARYNGECTOMY

In 1873, Billroth of Vienna performed the first total laryngectomy for laryngeal cancer. [1] This patient was deceased within 7 months. A patient of Bottini of Turin who received a total laryngectomy in 1875 lived for 10 years. [1] With much advancement in anesthesiology, antibiotics, and surgical skill, the total laryngectomy became, and still is considered the gold standard treatment for supraglottic lesions.

The operative basics involve tracheostomy and a large apron incision allowing access to the midline neck structures. The operation includes disruption of the hyoid bone and resection inferiorly to include from the epiglottis to below the cricoid. Ultimately, a stoma is created and bilateral neck dissection in performed either concurrently or in a staged fashion. [1]

Indications of total laryngectomy include cartilaginous invasion of the tumor and extra-laryngeal spread. [4] Further evidence of advanced disease including subglottic extension, bilateral arytenoid joint involvement, and hypopharyngeal involvement typically indicates need for total laryngectomy. [4] In particular patients, were the risk of aspiration is high or will be detrimental due to underlying pulmonary disease may also lead to consideration of total laryngectomy. In addition, salvage total laryngectomy may be necessary after failure of chemotherapeutic or radiation therapy. Local recurrence and need for completion laryngectomy after partial laryngectomy can also occur. [1]

Complete evaluation of the fitness of the patient prior to the decision to proceed with any treatment, especially total laryngectomy, is essential. Smee et al. investigated the importance of fitness for surgery in prognostic evaluation of a patient with supraglottic carcinoma. [17] He recapitulated what Piccirillo et al, Sjogren et al, and Paleri et al had demonstrated previously; that comorbidities

significantly affect survival. [17-20] Smee et al. went on to describe this in general as 'fitness for surgery'. [17]

With the current range of organ preservation paradigms, it is particularly important however difficult to decide when total laryngectomy is appropriate. Principles of individualized and personalized therapy which involve the patient and their family intimately in the decision-making process will lead to better patient satisfaction. To achieve this, discourse on the complete range of treatments available and appropriate for each patient's lesion and comorbidities must be started early and ensure patient understanding. The other options for treatment of supraglottic disease will be discussed below.

OPEN SUPRAGLOTTIC LARYNGECTOMY

Total laryngectomy, although gold standard treatment for supraglottic malignancies, involves considerable changes in quality of life. In particular, the loss of voice and difficulty with swallowing can be exceedingly challenging for patients. Techniques of organ preservation have been evolving in an attempt to mitigate the disruptive end-results of total laryngectomy. Billroth first performed a hemilaryngectomy for malignancy in 1874 and techniques for partial laryngeal surgery have evolved significantly. [1] Open supraglottic laryngectomy, popularized first by Bocca in Europe and then Som, Ogura, and Kirchner in the

United States, is still used at some centers. [21] Benefits of the open supraglottic laryngectomy include preservation of vocal cord function and lower rates of tracheotomy dependence. However, the laryngeal framework and supporting musculature is violated as part of the approach creating swallowing difficulties. Open partial laryngectomy operations have decreased with an increase in trans-oral laser microsurgical techniques. [22] Merits of an endoscopic approach will be discussed in the next section.

ENDOSCOPIC LASER SUPRAGLOTTIC LARYNGECTOMY

Endoscopic use of the CO_2 laser by Strong and Jako in 1972 lead to the establishment of transoral laser microsurgery (TLM) techniques for supraglottic laryngectomy. [23] A transoral approach eliminates the disruption of musculature involved in swallowing and maintains the laryngeal cartilagenous suprastructure. The transoral approach has gained popularity due to advancements in technology that have improved exposure and visualization. The advent of laser dissection to remove tumors in a tailor made fashion while avoiding disruption of the laryngeal framework has helped to reinforce this surgical technique. Additionally, instant coagulation of tissue surfaces with the laser allows for piecemeal dissection of a tumor as opposed to the standard oncologic en-bloc resection. [24] Piecemeal dissection helps to tailor-make resection and increases the likelihood of a clean margin result.

The unique feature of true supraglottic lesions in that they do not involved the cricoarytenoid structures. These structures are the basic functional units of the larynx and allow for vibration of the vocal cords. Supraglottic laryngectomy, whether open or endoscopic, attempts to preserve the functional unit of the cricoarytenoids. Criticism of transoral laser microsurgery tends to surround the issue of recurrence. Numerous institutional outcomes studies have shown that recurrence lead to worse outcomes. [25] Radiation and chemotherapy regimens are used as primary treatment as well as in a multimodal fashion to treat the disease and decrease the chance of locoregional recurrence. [26] A discussion of primary radiation and chemotherapy and its utility in a multimodal approach to supraglottic carcinoma will follow.

IMPLICATIONS OF OPERATIVE MANAGEMENT

As with any significant operation, complications exist and can be considerable. Early complications include those common to all surgical intervention including risks of anesthesia, intraoperative bleeding, inability for complete resection, postoperative infection, and wound dehiscence. [27] Hematoma formation can be of particular issue due to potential for airway compression and compromise. Additionally, space-occupying hematoma can stress suture lines and compromise pharyngeal repairs. Pharyngocutaneous fistula formation can occur and is especially a risk in patients with poor nutritional status.

Total laryngectomy leads to an impressive change in how an individual lives their life. A laryngectomized patient will never again breath from their nose or mouth. As such, olfaction will no longer occur leading to profound changes in taste. Furthermore, they will have to undergo extensive therapy to learn to safely swallow in order to prevent aspiration. Phonation will require either an electrolarynx, specialized speaking valve, or tracheoesophageal puncture. With speech therapy, they will be able to develop esophageal speech that, in some cases, is intelligible. In many cases, nutritional support with a percutaneous esophagogastrectomy tube will be required and, at times, lifelong.

Organ preserving operative techniques are designed to mitigate the detrimental effects of a total laryngectomy. Similar complications do arise even with the best organ preserving operation. Temporary tracheostomy creation may be required during the operation and in cases of tracheal stenosis unrelieved by dilation in the postoperative setting. Swallow function is affected, albeit to a lesser extent than in total laryngectomy, and can require nutritional support with a surgical feeding tube. [28]

Patients must be counseled on the risks, benefits, and changes that will affect their quality of life prior to undergoing any operation to treat their supraglottic lesion. Laccourreye (2012) described that some patients desire cure, no matter

the means to achieve it. [29] Others may emphasize quality of life after diagnosis and treatment of their disease. Treatment options must be tailor-made to the individual patient's goals and objectives of life after diagnosis with a supraglottic malignancy. [29]

CHEMORADIOTHERAPY

The emphasis of organ preservation in supraglottic carcinoma led to the investigation of non-operative radiation and chemotherapy-based regimens. When first employed as definitive treatment strategies for supraglottic carcinoma, radiation and chemotherapy based protocols touted similar oncologic and survival outcomes with vastly improved organ preservation. [30] Enhanced organ preservation, thus, implied better voice quality, swallowing function, and lower tracheostomy rates. [31] Additionally, another major advantage of chemoradiotherapy is preservation of surgery as an option for salvage in the setting of recurrent disease. The use of chemoradiotherapy as part of the treatment for supraglottic neoplasms has evolved greatly over the last twenty to thirty years. The current understanding of its utility will be evaluated while discussing multimodal therapy.

Supraglottic lesions follow the same treatment principles of glottic neoplasms with the exception that the neck is always treated with radiation due to the higher

risk of occult nodal disease. Radiation is delivered in multi-dose fractionations up to 70 Gy to the laryngeal site. [1] The neck is treated bilaterally in supraglottic disease. A neck dissection may also be considered in definitive chemoradiation for supraglottic carcinoma. The dosing schedule is rigorous and missed fractions have been shown to lead to worse outcomes. [32] Therefore, a patient's ability to comply must be evaluated before radiation therapy is instituted.

Chemotherapeutic approaches continue to progress as the biology and genetics of supraglottic squamous cell carcinogenesis is understood. As a part of the armamentarium, chemotherapy acts to improve the tissue's sensitivity to radiation. Although never used in isolation for supraglottic malignancies, chemotherapy – particularly cisplatin-based therapy, is used either concomitantly with radiation therapy or as induction for definitive radiation-based treatment. [1] In addition to its use as part of primarily nonoperative treatment, induction chemotherapy can be used in a neoadjuvant approach to operative management of supraglottic lesions. Finally, chemotherapy or chemoradiotherapy is often employed in the adjuvant setting to operative management. [33]

Chemoradiotherapy requires assessment of the entire clinical picture of a patient as systemic treatment can exacerbate other pathologies. It must also be recognized that all treatments carry to possibility of significant mobility and mortality. While surgical management is often criticized as disfiguring and can

profoundly alter a patient's quality of life, radiation and chemotherapeutic treatment strategies have major impacts on an individual's wellbeing.

Side effects of radiotherapy depend on the size of the field requiring treatment. Early-stage, small lesions confer minimal complications from radiotherapy. As the field of treatment grows, complications and side effects become more considerable. Skin erythema, hoarseness, and dysphagia predominate the self-limiting adverse radiation effects. [1] Hypothyroidism may occur due to the proximity of thyroid tissue to laryngeal structures. Mucositis and xerositis are particularly irritating complications for patients and can last indefinitely. Radioprotecting medications such as amifostine help to prevent and limit these adverse effects. [1] Arytenoid edema and even necrosis are rarer but more serious complications. Laryngeal edema and mucositis can increase risks of aspiration and ultimate respiratory compromise. Odynophagia and dysphagia can lead to swallowing difficulty and, in some cases, necessitate the use of percutaneous esophagogastrectomy (PEG) tube placement for nutritional support. Radiation also leads to significant neck fibrosis that can be uncomfortable to the patient and complicate operative management in the case of salvage surgery. [1]

Numerous investigations into biologic agents targeting supraglottic squamous cell carcinomas have introduced the possibility of increased refinement and

individualization of treatment based on a tumor's genetic milieu. It is beyond the scope of this thesis to discuss these agents. However, an individualized approach to oncologic treatment of supraglottic lesions is a major goal and will considerably change the treatment of many head and neck neoplasms.

MULTIMODAL THERAPY

Currently, the major focus of treatment is to optimize the chance of cure while maximizing postoperative laryngeal function and minimizing complications. Multimodality therapy has become well established in effective treatment of the disease. While total laryngectomy remains the gold standard oncologic option, respect for quality-of-life issues surrounding treatment of supraglottic carcinoma has pushed the field to think differently about approaching a patient with the disease. Functional larynx preservation can be achieved surgically or non-surgically. [31] Non-surgical modalities include primary radiation with or without concurrent chemotherapy. Surgical options include using open or endoscopic techniques often followed by adjuvant radiation or chemoradiation. Less aggressive surgery has been combined with adjuvant radiation or chemoradiation in a multi-modality approach to optimize survival in the face of improved post-treatment laryngeal function. [34] The role of organ-preserving transoral surgery is not well defined in the overall multimodal treatment of supraglottic SCCA.

The advent of chemoradiation therapy as well as the amplification of operative techniques at organ preservation has increased the multidisciplinary approach to supraglottic cancer. A patient's healthcare team should include a medical oncologist, radiation oncologist, head and neck surgeon, oromaxillofacial surgeon, radiologist, as well as speech and swallow therapist and nutritional specialist. The multidisciplinary approach has lead to improvements in patient satisfaction, outcomes, and research collaboration.

THE CHALLENGE OF INSTITUTIONAL STUDIES

As has been described, many therapeutic approaches exist for the treatment of supraglottic carcinoma. Organ-preserving therapy, in the form of chemoradiation, has become popular in the United States. Organ-preserving surgical techniques are available for treatment of early supraglottic carcinoma and appropriately selected advanced stages. NCCN guidelines do not specify what is the preferred method of treatment except for specific advanced cases. [4] Anecdotally, preferences of practice vary with region within the United States. Furthermore, international practice patterns are even more dramatically different judging by that the majority of literature on endoscopic and robotic resection emerges from Europe. Groome et al (2003) compared management of supraglottic neoplasms in Ontario, Canada with a comparable cohort from the SEER Database. [35] They

identified profound differences in management practices, however, there were limited differences in outcomes. Shah et al (1997) accrued data on over 16,000 patients with squamous cell laryngeal cancer and observed diversity in the management of the disease across the US. [11] Differences in management existed even between site and stage.

The differences in management strategy are demonstrated by the innumerable single institutional reviews emerging into the literature. These reports attempt to describe what they believe to be the choice management strategy for supraglottic lesions. Implicit in reports on a single management strategy is an inherent selection-bias of patients appropriate to receive the treatment of interest.

STATEMENT OF PURPOSE AND HYPOTHESIS

RETROSPECTIVE REVIEW:

Outcomes when transoral laser microsurgery (TLM) is part of a multimodality approach are not well defined. Current guidelines for early and late stage disease include the use of TLM, open partial laryngectomy, radiation, chemotherapy, and total laryngectomy. [4] Current NCCN Head and Neck Cancer Guidelines for early stage supraglottic carcinoma (T1-2, N0; selected T3) is endoscopic resection +/- neck dissection, open partial supraglottic laryngectomy +/- neck dissection, or definitive radiation. [4] Advanced stage disease requires an increasingly multimodal approach with the possibility of total laryngectomy. [4] What stands out in the guidelines is the absence of consensus on the optimal treatment option. Therapeutic choice, therefore, becomes a factor of institutional trends and physician training. An individualized approach to treatment of supraglottic carcinoma is essential but challenging due to the numerous different therapeutic modalities available. Currently, attempts in the literature to evaluate larynx-preserving surgical approaches to supraglottic carcinoma tend to compare a highly selected patient group receiving the treatment of interest to previously published data. Furthermore, conclusions of many studies commonly use the phrase “in a select group of cases” when weighing in on the utility of newer techniques. This terminology leaves much open to interpretation. What is

absent from published data, to our knowledge, is a comparison of a comprehensive cohort of patients receiving all modern treatments for supraglottic cancer. Overall, the guidelines reflect a lack of consensus regarding optimal treatment and there is considerable treatment variation between centers. Although several series in the literature report functional and oncologic outcomes for selected patients with supraglottic squamous cell carcinoma treated with TLM there are no complete patient cohorts reporting outcomes with TLM as part of a multidisciplinary approach including the use of TLM, radiation, chemotherapy, and total laryngectomy.

The purpose of this observational study is to report on the oncologic and functional outcomes in a complete cohort of patients without selection based on stage or treatment type. The goal is to demonstrate how treatment of the disease, as a whole, has been approached at this institution.

SEER VS. INSTITUTIONAL REVIEW:

Innumerable institutional studies have investigated oncologic outcomes of the various treatment options for supraglottic neoplasms. Many of these studies involve a specific treatment and, thus, patient population properly selected for that treatment. This introduces a selection bias implicit in the institutional studies. Abstracting all institutional studies in the United States with a comparable SEER

cohort will allow direct visual comparison of the national trends in the disease with reports emanating from single institutions. The purpose is to illuminate the difference between specific study outcomes and national trends in oncologic outcomes.

HYPOTHESES:

1. Oncologic outcomes will vary based on treatment with transoral laser microsurgery, total laryngectomy, or definitive radiation based therapy.

2. Functional outcomes after transoral laser microsurgery is superior to both total laryngectomy and definitive chemoradiotherapy.

3. Multimodality therapy in the form of adjuvant chemoradiation therapy is associated with improved survival.

4. Survival reported in institutional studies will vary significantly from population based outcomes.

MATERIALS AND METHODS

All portions of the retrospective review, systematic review of the literature, and SEER database analysis including, but not limited to: record review, database generation, and statistical analysis were conducted by the researcher responsible for this dissertation.

RETROSPECTIVE REVIEW:

Study Subjects

The Yale University Institutional Review Board approved this study prior to data compilation and analysis. Patients evaluated with supraglottic SCCA at Yale New Haven Hospital over a 5 year period between January 1, 2003 and December 31, 2007 were retrospectively identified. Patients records were queried using ICD-9 codes for glottis (161.0), supraglottis (161.1), subglottis (161.2), laryngeal cartilage (161.3), and aryepiglottic fold (148.2). Codes for all larynx subsites were reviewed to ensure inclusion of patients that may have been miscoded. CPT codes for open supraglottic laryngectomy (31367, 31368), horizontal/laterovertical/anterovertical/antero-latero-vertical hemilaryngectomy (31370, 31375, 31380, 31382), epiglottidectomy (31420), unlisted procedure of the larynx (31599), and total laryngectomy (31365, 31360) were also searched. Patients with pathologically confirmed supraglottic squamous cell carcinoma

were included. The Yale Cancer Center Tumor Registry, a comprehensive registry of all cancer patients diagnosed, treated, or seen at Yale New Haven Hospital, was used as an additional check that all patients treated for supraglottic squamous cell caricinoma had been captured. Patients with distant metastasis present at the time of diagnosis were excluded from analysis.

A total of 60 patients were identified. One patient did not have complete staging information and was excluded. Three patients treated with open supraglottic laryngectomy were excluded from survival and function analysis due to the small sample size in this treatment group. The remaining 56 patients were included for analysis. Patients were evaluated in a multidisciplinary fashion in the setting of a tumor board.

Study Variables

Clinical, pathological, functional, and survival data was collected from the medical records and entered into an Excel spreadsheet. Demographic data included: gender, age at diagnosis, smoking/alcohol use, and race. Pathologic and clinical data included tumor histology, location, TNM stage, AJCC stage, and margin status. Treatment data collected included total laryngectomy (TL), transoral laser microsurgery (TLM), and radiation therapy including radiation with or without chemotherapy either in the definitive or adjuvant setting. Post-treatment

functional outcome collected included incidence of PEG during treatment, PEG requirement after treatment, tracheostomy, and complications during treatment.

Statistical Analysis

Differences between treatment modalities and functional outcomes were measured with Chi-squared analysis. Kaplan-Meier analysis was performed to establish overall survival outcomes. Further assessment of survival differences between groups was done with Logrank and Cox regression analysis. Disease-specific survival could not be acceptably analyzed given the available data. Statistics were performed using SPSS, Kaplan-Meier curves were generated using R.

SEER VS. INSTITUTIONAL REVIEW:

A systematic review on supraglottic squamous cell carcinoma survival outcomes was performed. The databases queried included: Medline, Embase, Scopus, and Web of Science. After a preliminary search of the literature, a MeSH analysis was generated to further refine search terms to enhance capture within the topic. A total of 687 articles were discovered. Only United States publications were of interest to increase the comparability between the reports and SEER outcomes. 385 international papers were excluded. A total of 43 publications included reports supraglottic squamous cell carcinoma. The many excluded publications reported on glottic cancer, biomarker analysis, or were review articles without reported institutional outcomes. Of the remaining 43 publications, 18 articles reported data on survival statistics based on treatment modality for T1-T4 disease (Table 1). From the data reported in these publications, survival statistics were back-calculated to produce descriptive survival statistics for each treatment modality investigated and for each stage represented. No one single publication reported confidence intervals. Therefore, confidence intervals were calculated using the formula 1.96 x SQRT (proportion x (1 - proportion / n)) where proportion equals the reported or back-calculated survival. The Survival Epidemiology and End Results (SEER) database for the National Cancer Institute was query for all patients with supraglottic squamous cell carcinoma between 1988-2004 was obtained. The proprietary SEER

database manipulator was used to generate 2- and 5-year overall survival (OS) and disease specific survival (DSS). Graphic representations of SEER derived survival statistics compared to institutionally reported survival were created using Graphpad Prism 6 and Apple Numbers.

Author	Pub Date	Author	Pub Date
Ganly, I et al[1]	2009	Mendenhall, W. et al[11]	1990
Agrawal, A et al[2]	2007	Lee, K et al[12]	1990
Grant, D et al[3]	2007	Chan et al[13]	2001
Sessions D, et al[4]	2005	Chiu et al[14]	2004
Alpert, T et al[5]	2004	Devineni et al[15]	1991
Hinerman, R. et al[6]	2002	Hicks et al[16]	1999
Nakfoor, B et al[7]	1998	Nguyen-Ten et al[17]	2001
Myers, E and Alvi, A[8]	1996	Shimm et al[18]	1989
Mendenhall, W et al[9]	1996	Spector et al[19]	1995
Weber, P et al[10]	1994		

Table 1: Selected Institutional Reports
Articles selected from a systematic review of the literature that included survival statistics for each stage of disease. References in order of appearance:
39,34,22,47,36,40,45,44,42,49,43,41,37,38,26,15,46,30,48

RESULTS

RETROSPECTIVE REVIEW:

Of the 56 patients eligible for analysis 22 (39%) were treated with TLM , 23 (41%) with XRT/CRT, and 11 (20%) with TL. Neck dissection was performed in 17/22 (77%) of patients treated with TLM and 10/11 (91%) of patients treated with TL. Adjuvant XRT or CRT was used in 82% of patients treated with TLM and in 82% of those treated with TL. All patients treated with XRT/CRT received standard fractionation and dosage. Average follow-up for all patients was 45 months. There was no significant difference in follow-up between treatment groups.

Patient age, gender, race, T stage and AJCC stage were not associated with 5 year overall survival (OS) (table 2). Among tumor and patient characteristics only treatment modality was statistically associated with OS ($p = 0.009$), confirming our first hypothesis. Smoking status approached significance ($p = 0.087$). There was not a significant difference in the distribution of stage between treatment groups ($p = 0.454$). Five patients with pathologically T3 disease were treated with TL; 3 had large transglottic tumors or post-cricoid involvement, 1 was downstaged to T3 after being clinically staged T4, and 1 patient was unable to complete treatment with CRT due to renal failure and was subsequently treatment was converted to TL (table 3).

Variable	No. of patients (%)	5yr Overall survival	P value
Mean age	62 (39-80)	-	-
Sex			NS
Male	41 (73)	14/31 (40%)	
Female	15 (27)	5/13 (38%)	
Ethnicity			NS
White	46 (82)	15/41 (37%)	
Black	7 (13)	3/5 (60%)	
Other	3 (5)	1/2 (50%)	
Risk Factors			NS
Tobacco	53 (95)	16/45 (36%)	
EtOH History	39 (70)	15/33 (45%)	
Tumor T Stage			NS
Early	28 (50)	8/24 (33%)	
Advanced	28 (50)	11/24 (46%)	
AJCC Stage			NS
I	5 (9)	1/4 (25%)	
II	6 (11)	1/5 (20%)	
III	15 (27)	5/13 (38%)	
IV	30 (54)	13/27 (48%)	
Therapeutic			**0.009**
TL +/- XRT	11 (20)	8/18 (44%)	
TLM +/- XRT	22 (39)	7/9 (78%)	
XRT/CRT	23 (41)	5/22 (23%)	

Table 2: Characteristics of patients and tumors
There was no significant differences found between treatment groups or AJCC Stage. Five year overall survival was only significantly different based on therapeutic modality.

Patient	Therapeutic Modality	Complication	Resolution
1	TLM	Neck hematoma	Surgical evacuation
2	TL	Wound Dehiscence	Revision
3	XRT-based	AKI	Medical management

Table 3. Major acute treatment complications
Available documentation in the retrospective review identified three patients who had major complications in the acute postoperative setting.

Local recurrence for TLM, TL, and XRT/CRT was 1/20 (5%), 0/11 (0%), and 1/11 (9%) (Table 4). Chronic gastrostomy tube use for TLM, TL, and XRT/CRT was 3/20 (15%), 4/11 (36%) and 5/10 (50%). Chronic tracheostomy for TLM, TL, and XRT/CRT was 0/21 (0%), 11/11 (100%), and 7/20 (35%) (Table 5). Two year overall survival for TLM, TL, and XRT/CRT was 86% (18/21), 80% (8/10) and 52% (12/23). Kaplan-Meier survival curves by treatment modality are shown in Figure 1. There was a significant difference in overall survival between treatment groups based on Log Rank analysis (p = 0.009), supporting hypotheris 1. No significant difference was found between AJCC stages (p = 0.471).

	Local	Regional	Distant Metastasis
Transoral Laser Microsurgery	1/20 (5%)	5/20 (25%)	3/20 (25%)
Total Laryngectomy	0/11 (0%)	0/11 (0%)	1/11 (9%)
XRT-based Therapy	1/11 (9%)	1/11 (9%)	3/12 (25%)

Table 4. Incidence of locoregional recurrence[a] and distant metastasis[b] in patients with adequate follow-up data
The distribution of post-treatment outcomes are presented here.

	Chronic Tracheostomy[a]	PEG tube during treatment	PEG tube required after treatment
Transoral Laser Microsurgery	0/21 (0%)	8/21 (38%)	3/20 (15%)
Total Laryngectomy	11/11 (100%)	5/11 (46%)	4/11 (36%)
XRT-based Therapy	7/20 (35%)	11/18 (61%)	5/10 (50%)

Table 5. Functional Outcomes of patients with >3year follow-up
Functional outcomes are reported for each therapeutic modality. The incidence of chronic tracheostomy was significantly different between treatment group (P = <0.001). Otherwise, no other significant differences were found between treatment groups

In unadjusted cox regression analysis (table 6), survival was significantly different between treatment groups (p = .015), indicating a survival risk to receiving XRT-based therapy. Receiving adjuvant radiation therapy following surgery conferred a significant survival benefit (HR = 3.475, p = 0.001). This confirms our third hypothesis. Age less than fifty was significantly associated with improved survival compared to age greater than seventy (HR = 11.363, p = 0.021).

	Variable	Estimates		
		Hazard Ratio exp(B)	95% CI	P-value
Unadjusted	Treatment Modality			**0.015**
	TLM (*v. XRT-based*)	**0.478**	0.235 - 0.973	**0.043**
	TL (*v. XRT-based*)	**0.211**	0.062 - 0.720	**0.013**
	AJCC Stage			0.497
	II	2.573	0.610 - 10.855	0.198
	III	1.282	0.345 - 4.765	0.711
	IV	1.260	0.368 - 4.314	0.713
	Adjuvant Therapy	**3.475**	1.687 - 7.157	**0.001**
	Recurrence	0.558	0.236 - 1.320	0.184
	Age			**0.051**
	50-70yo	6.471	0.906 - 50.143	0.062
	>70yo	**11.363**	1.438 - 89.805	**0.021**

Table 6. Univariate Cox Regression Analysis.
In an unadjusted regression model, XRT-based therapy conferred a significant risk to survival. Receiving adjuvant therapy provided a significant survival benefit. Reference variables: XRT-based, Stage I, Age <50yo, no adjuvant Tx, no locoregional recurrence

In multivariate analysis (Table 7) , the significance of treatment remained when adjusting for AJCC stage. This significance was lost, however, when adjusting for adjuvant therapy and incidence of recurrence. When adjusting for stage of disease and patient age, XRT-based therapy carried a significant survival risk over receiving a TL (HR = 0.245, p = 0.028). Furthermore, patient age remained significant with a survival benefit in patients less than 50 years old (HR = 10.816, p = 0.032).

		Hazard Ratio	95% CI	P-value
Adjusted for: Tx, Stage, and Age	Treatment Modality			0.084
	TLM (*v. XRT-based*)	0.721	0.343 - 1.515	0.388
	TL (*v. XRT-based*)	**0.245**	0.070 - .857	**0.028**
	AJCC Stage			0.565
	Age			0.089
	50-70yo (*v. <50yo*)	6.704	0.861 - 52.211	0.069
	>70yo (*v. <50yo*)	**10.816**	1.229 - 95.163	**0.032**
Adjusted for: Tx and Age	Treatment Modality			0.078
	TLM (*v. XRT-based*)	0.681	0.329 - 1.409	0.301
	TL (*v. XRT-based*)	**0.252**	0.073 - 0.861	**0.028**
	Age			0.110
	50-70yo (*v. <50yo*)	6.041	0.780 - 46.806	0.085
	>70yo (*v. <50yo*)	**9.003**	1.085 - 74.701	**0.042**
Adjusted for: Tx and Adjuvant therapy	Treatment Modality			0.675
	TLM (*v. XRT-based*)	1.174	0.435 - 3.173	0.751
	TL (*v. XRT-based*)	0.670	0.135 - 3.339	0.626
	Adjuvant Therapy	**3.333**	1.099 - 10.106	**0.033**
	XRT	2.722	0.812 - 9.124	0.105
	CT/XRT	**4.293**	1.122 - 16.434	**0.033**

Table 7. Multivariate Cox Regression Analysis.
In an multivariate regression model, XRT-based therapy conferred a significant risk to survival only compared to TL when controlling for stage and age. Receiving adjuvant therapy provided a significant survival benefit. Reference variables: XRT-based, Stage I, Age <50yo, adjuvant Tx, no locoregional recurrence

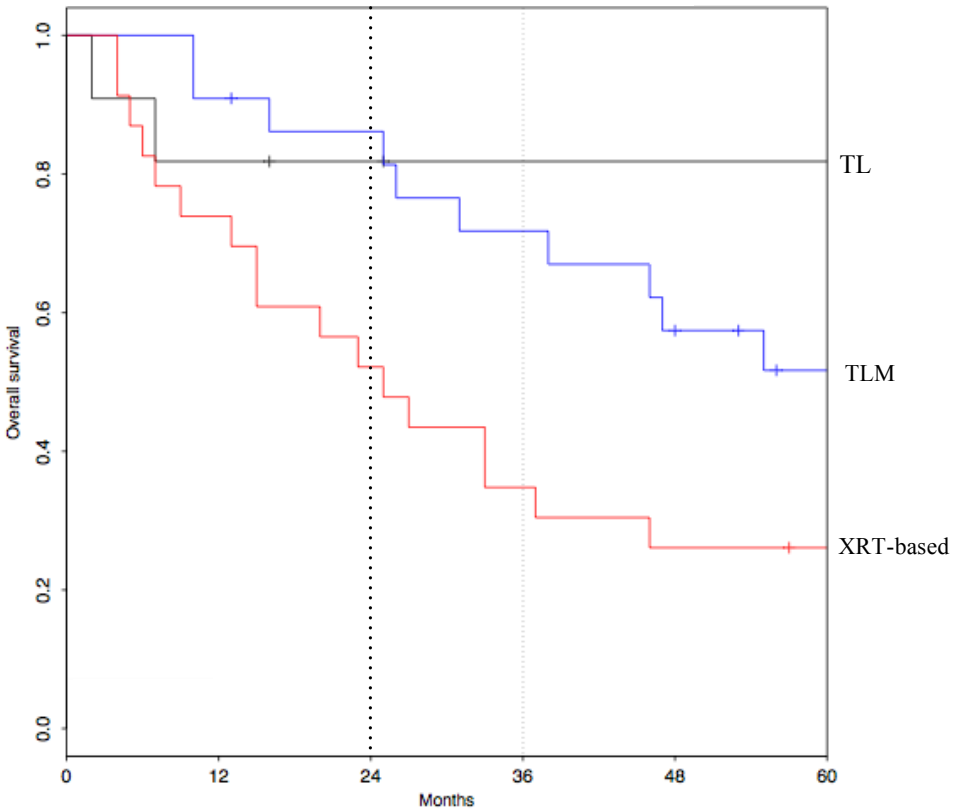

Figure 1: Kaplan-Meier Survival Curve based on Therapeutic Modality
Survival curves for each therapeutic modality are shown. A log rank analysis demonstrated significance in survival (p = 0.009)

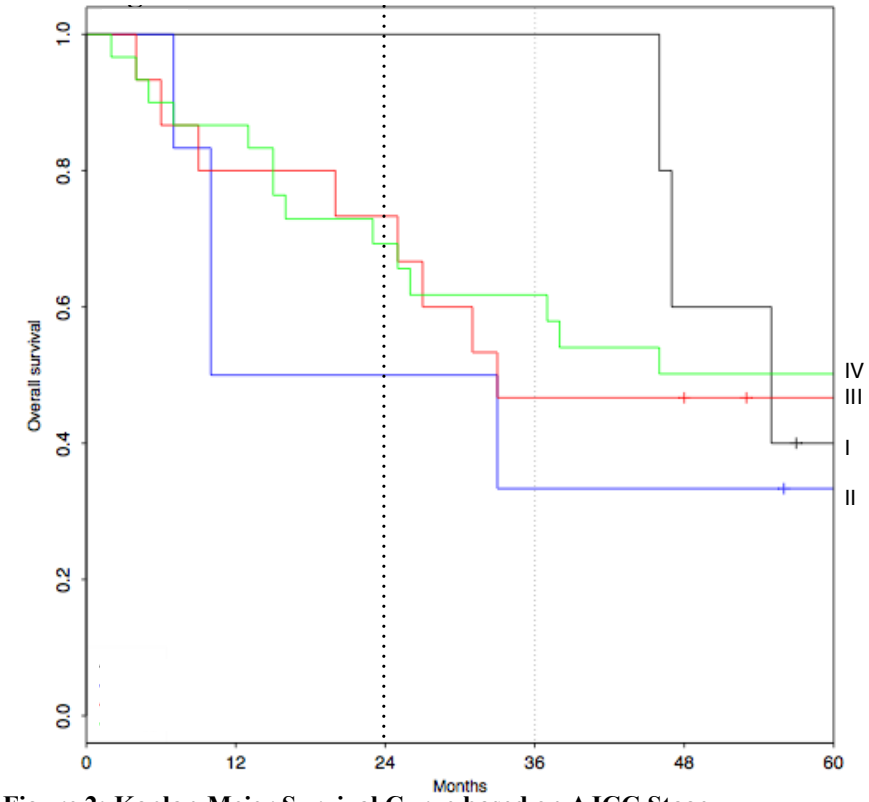

Figure 2: Kaplan-Meier Survival Curve based on AJCC Stage
Survival curves for each therapeutic modality are shown. A log rank analysis demonstrated lack of statistically significant difference in survival (p = 0.471).

SEER VS. INSTITUTIONAL REVIEW

A visual representation of institutionally reported survival statistics compared to SEER database generated survival statistics are shown in Figures 3-5. The 2- and 5-year overall survival and disease specific survival generated from the query of the SEER Database were used as zero lines on the graphic representations. The number of institutional reports included on the graphics were dependent on what statistical outcomes each publication presented.

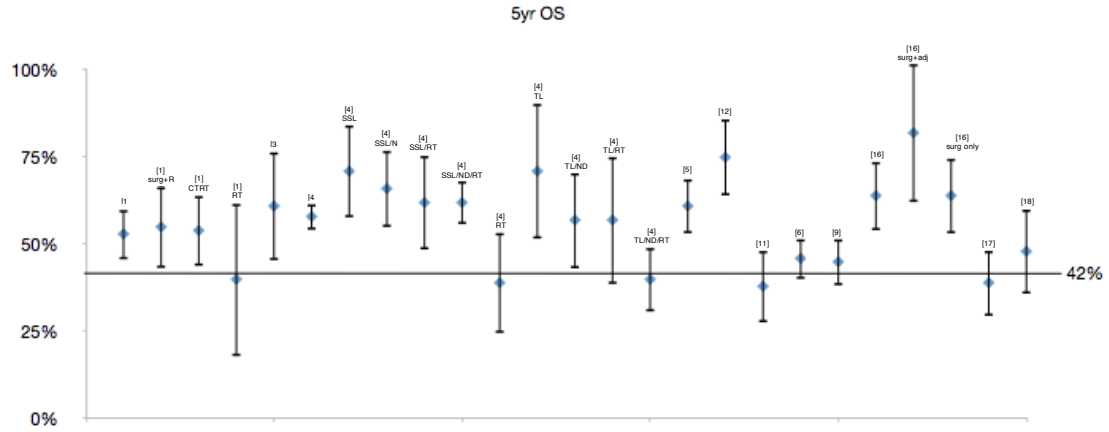

Figure 3: 5-year Overall Survival
SEER-derived 5yr OS for supraglottic cancer is 42%. Individual institutional reported 5yr OS are demonstrated with hazard ratios. Bracketed numbers reference articles shown in Table 1.
SSL = subtotal supraglottic laryngectomy, ND = neck dissection, RT = Radiation, TL = total laryngectomy

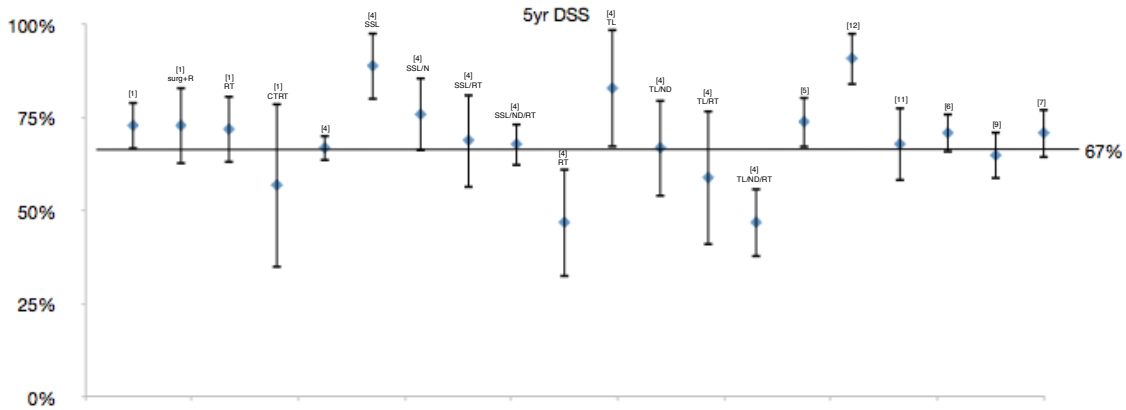

Figure 4: 5-year Disease Specific Survival
SEER-derived 5yr DSS for supraglottic cancer is 67%. Individual institutional reported 5yr DS are demonstrated with hazard ratios. Bracketed numbers reference articles shown in Table 1.
SSL = subtotal supraglottic laryngectomy, ND = neck dissection, RT = Radiation, TL = total laryngectomy

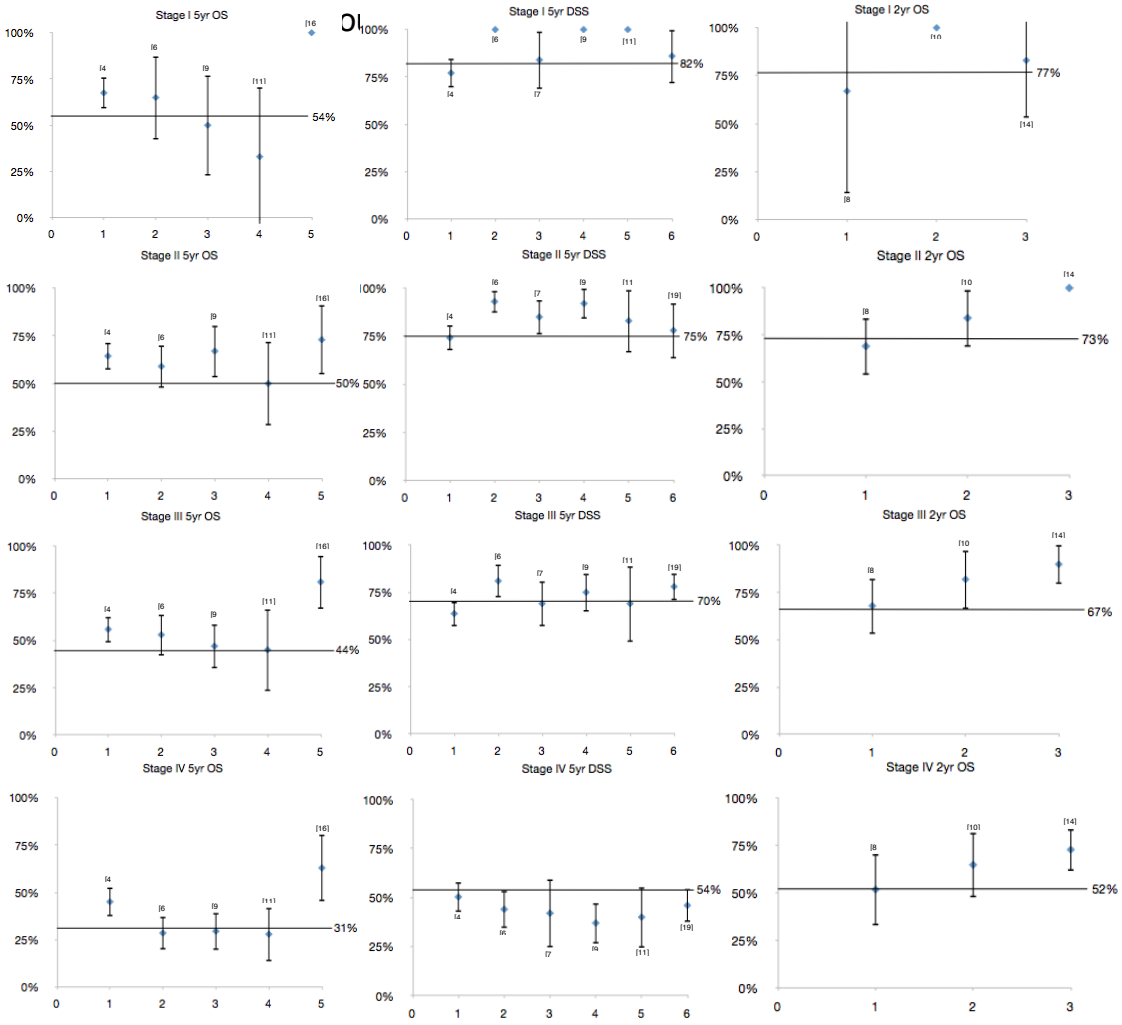

Figure 5: Survival statistics for each stage of disease
SEER-derived survival statistics for supraglottic cancer is presented along side individual institutional reported survival statistics demonstrated with hazard ratios. Bracketed numbers reference articles shown in Table 1.

DISCUSSION

Since Billroth first performed a hemilaryngectomy for malignancy in 1874, techniques for partial laryngeal surgery for SSCC have evolved significantly. [50] Open supraglottic laryngectomy, popularized first by Bocca in Europe and then Som, Ogura, and Kirchner in the United States, is still used at some centers. [21] Endoscopic use of the CO_2 laser by Strong and Jako in 1972 lead to the establishment of TLM techniques for supraglottic laryngectomy. [23]

There remains controversy in the management strategy for supraglottic SCCA. The historical use of total laryngectomy as the gold standard treatment modality gave way in to primary treatment with chemoradiation to maximize laryngeal preservation, saving surgery for salvage. The initial role of chemoradiation-based therapy has been supported by landmark studies, most notably the Veteran Affairs Larynx Cancer Study[4] and the RTOG 91-11study. [51] These trials have been essential to improving larynx preservation. Overall, the application of radiation and chemotherapy at the population level for organ preservation remains associated with some controversy. [52] These and other commentaries challenge the application of the landmark VA and RTOG studies to a broad-based population. [8] The generalizability of these findings are controversial especially after a report by Hoffman, et al. observed that laryngeal cancer is the only anatomical site that has seen decreased survival in the US over the last two

decades. [8] The supraglottic subsite appears to play an important role in the observed diminished survival. Hoffman, et al. went on to show that this decrease in survival coincides with the change in treatment priorities to less aggressive primary treatment with chemoradiation rather than surgery. [8] This observation was confirmed by Zhang et al. however, this group did not find a decreased survival in patients receiving RT since 1994. [53] In a population based study, Chen & Halpern concluded that TL provides best chance of survival in patients with advanced disease. [32] Developments in surgical technique have been occurring, resulting in better functional outcomes. Chemoradiation regimens have been refined as well. However, there is a lack of consensus on what is the best practice for treating supraglottic lesions.

The treatment options for supraglottic SCCA have evolved over the last two decades. The goal of oncologic cure and functional laryngeal preservation influenced the predominant use of non-operative management with radiation and chemoradiation in the United States. Total laryngectomy and subtotal supraglottic laryngectomy via an open or endoscopic approach are also options within the modern armamentarium for supraglottic SCCA. Numerous institutional studies have been published reporting outcomes for open and transoral supraglottic laryngectomy and have been paramount is describing the feasibility and efficacy of each modality. [54] In general, these reports include series of patients selected based on tumor characteristics including stage as well as

patient characteristics including fitness for surgery, and do not report patients treated with alternate modalities. These studies commonly focus on a particular technique to report on or compare to previously published results. The benefit has been the introduction and validation of important techniques used to treat supraglottic cancer. However, many studies involved precise selection criteria based on tumor characteristics or stage of disease. Inherent to such selection processes is a level of bias introduced to statistical analysis. Furthermore, in the clinical setting the decision on what treatment to offer involves countless individual patient parameters. Study selection criteria augments the reality of clinical medicine - practicing medicine involves offering treatment options to patients where as, in the research environment, patients are selected for a certain treatment. To some degree, because of this, the role of transoral laser microsurgery in the multidisciplinary care of supraglottic squamous cell cancer remains ill defined.

The present study took an approach similar to clinical medicine - the only selection criteria was that a patient had a supraglottic squamous neoplasm. This study is the first that we are aware of which includes a complete cohort of patients with supraglottic squamous cancer treated with multiple modalities including TLM. Multiple treatment modalities were considered before a specific treatment was recommended for each patient; an intent-to-treat design. Patients of all stages were included. This study design allowed a side-by-side analysis of

all treatment types and stages without issues of dropout or crossover. Given the inclusion of many modern treatment modalities and all stages of disease, the study represents a less biased comparison in the analysis of functional and survival outcomes. The result is a reporting of our institutional approached to supraglottic cancer.

The results of the current study demonstrate a diminished survival in patients treated with XRT-based therapy when compared to TL and TLM. When controlling for both stage and age, XRT-based treatment nonetheless carries a survival risk when compared to TL. This reduced survival in the radiotherapy group may be secondary to poorer performance status or other confounding factors not captured in the available data. Poor performance status may have precluded operative management and, as Smee et al. illustrate, fitness for surgery significantly affects overall survival. [17]

Transoral laser microsurgery was superior to XRT-based treatment in direct comparison and when controlling for stage of disease. Interestingly, the significance of the difference was lost when controlling separately for age, adjuvant treatment, and recurrence. This may represent the difficult nature of this disease, but may also emphasize important factors to survival such as the use of adjuvant treatment and the impact of disease recurrence. In addition, a dramatic decrease in survival at the 5-year point was seen in both TLM and XRT-

based treatment. Interpretation of this observation becomes difficult as the sample-size is small.

In this series, the prescription of adjuvant therapy significantly improved survival when adjusting for treatment. More specifically, chemoradiation-based adjuvant therapy conferred a survival advantage in this cohort. Interestingly, when controlling for adjuvant therapy, there were no survival differences seen between treatment groups. Given the large percentage of patients getting adjuvant treatment after TL and TLM, these results reinforce the importance of a multimodal approach to supraglottic SCCA. This finding deserves further exploration to explain the importance of chemotherapy-based adjuvant treatment in the setting of surgical management of supraglottic neoplasms.

Several prognostic factors reported in the literature are reevaluated in this cohort. Age greater than 70 years old emerged as a significant survival risk in our data analysis. The importance of patient age has been reported in the literature. [47] Disease recurrence is an important prognostic factor implicated in survival outcomes. [55] Contrary to expectation, recurrence did not have a significant impact on survival in univariate or multivariate analysis, although there was a significant difference in the incidence of recurrence between treatment groups in this study. This is inconsistent with Sessions et al. who associated decreased survival with recurrence. [47] The differences in this study may be explained by the

size of this study as well as the inclusion of all treatment groups. For instance, Sessions et al. did not include patients receiving chemotherapy-based treatment in the data that lead to their conclusion associating recurrence with decreased survival. [47] Further investigation should focus on the importance of margin status and its relation to disease recurrence in the analysis of survival outcomes. Other clinical prognosticators typically described in the literature include nodal status and specific site involvement, such as the preepiglottic space and the vallecula. [56] The relatively small size of this study may be responsible for those not reaching statistical significance in our study.

Patient quality of life measures are important in the treatment of SSCC because of the significant morbidity in speech and swallow function that can occur as a result of these tumors and its treatment. Considerations of quality-of-life add to the complex nature of therapeutic decision-making. As Laccourreye et al. aptly describe in their recent study, a careful evaluation of the attitudes and opinions a patient has regarding their own survival or functional impairments is essential. [29] Multiple authors have published on advantages of post-operative function after TLM including reduced impact on swallowing, decreased length-of-stay, and shorter PEG tube and tracheostomy duration. [32] In our study, functional outcomes were comparable across treatment groups except for where differences were anticipated, such as the TL group. Although not statistically significant, the data illustrated the performance benefit of TLM compared to all

other treatments. No patients in the TLM group were chronically tracheotomy dependent. Percutaneous endoscopic gastrostomy (PEG) tube requirement in the TLM group was 15%, but lower than in both the TL and XRT groups. This study demonstrates that XRT-based treatment is not without morbidity and, on the whole, has a higher incidence of functional impairment when compared to TLM. The rates of functional outcome measures are high for each treatment modality compared to other published series, which may be due in part to comorbidity and pre-treatment health status.

The study is limited by its retrospective nature. Records were incomplete in some cases, limiting our ability to analyze post-operative function, recurrence, and cause of death. Moreover, while the size of the entire cohort is within the upper range of previously published series, subgroup sample sizes are small, making it difficult to draw conclusions between groups. A larger sample size would improve multivariate comparisons by increasing the ability to control survival analysis for multiple factors, simultaneously.

As has been previously discussed, numerous institutions have published oncologic outcomes for a variety of treatment modalities. These reports, as a whole, tend to investigate a single modality of therapy. As alluded to, such reports may introduce a degree of selection bias as patients have already been selected as appropriate candidates for the treatment of interest. We

hypothesized that this introduces outcomes that are not entirely representative of the overall nature of the disease. Figures 3-5 show the reported oncologic survival compared to national survival statistics generated by the SEER Database. As hypothesized, institutionally reported survival tends to be superior to national survival. This trend is especially consistent with reported overall survival, which is arguably more important to a patient than disease specific survival. When extrapolated by stage, institutional survival remains elevated above national statistics primarily for early stage disease. There is increased variation in survival at more advanced stage disease likely representing the difficulty treating complex lesions with more aggressively invasive components.

The graphics presented here represent a birds-eye view of survival after treating supraglottic carcinoma. There is a range of survival reported by single institutions and they tend to be superior to national survival trends. What this demonstrates is a need for emphasis on multi-institutional trials or increased utilization of population-based investigation. Taken in the context of our retrospective study in which we attempted to report with an intent-to-treat model looking at oncologic and functional outcomes of patients with supraglottic neoplasms, efforts should be made to further investigate the successes in treating the disease in a comprehensive fashion.

CONCLUSION

Today, the complexity of supraglottic cancer is further complicated by the variety of treatment options available and their application in a multimodal fashion. Since this study involved the observations of a comprehensive cohort, these results are important to the overall treatment of a patient presenting with primary supraglottic SCCA. Our study reports a comprehensive cohort of patients with SSCC treated in a multimodality fashion, including the use of TLM. Total laryngectomy performed the best in terms of survival. Amongst the organ preserving treatments, XRT-based primary therapy was associated with decreased survival risk, although selection bias would be expected with poorer performing patients being treated with XRT. The increasing expertise in microsurgical and CO_2 laser-based resection has improved upon the surgical options for functional laryngeal preservation. As reinforced by this study, transoral laser microsurgery, especially when employed in a multimodal approach including adjuvant chemoradiotherapy, offers acceptable oncologic results and good functional outcomes.

As a comprehensive approach to studying the treatment of supraglottic cancer, this study has important relevance. Future investigation into supraglottic SCCA deserves a well-designed and comprehensive prospective observation similar to this series. This study and further prospective studies will help to

improve the understanding of therapeutic decision-making and lead to better success with treating supraglottic cancer.

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