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Stage T4B head and neck cancer survival outcome comparisons based on treatment modality: is surgery a viable treatment option?

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SCHOOL OF MEDICINE

Thesis

**STAGE T4B HEAD AND NECK CANCER SURVIVAL OUTCOME
COMPARISONS BASED ON TREATMENT MODALITY: IS SURGERY A
VIABLE TREATMENT OPTION?**

by

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ABSTRACT

Importance: Advanced stage head and neck cancers are often deemed unresectable due to the aggressive nature of the cancer. In evaluating survival patterns of patients with stage IVb tumors, it is valuable to determine whether patients who undergo oncological surgery have favorable outcomes in order to deem surgery as a viable treatment option and demonstrate that these patients can survive with adequate treatment.

Objective: To determine whether patients with stage IVb cancers who undergo oncological surgery have favorable survival outcomes.

Materials and Methods: Of 320 cases reviewed of patients treated for head and neck cancer at Boston Medical Center between June 2009 and October 2014, 18 patients with stage IVb tumors were identified. Information regarding date of initial diagnosis, date and type of treatment, and date of death were extrapolated from medical records. Mean survival rates were calculated to compare survival outcomes of those who received and those who did not receive surgical intervention.

Results: The mean survival rate for patients who underwent surgical intervention was found to be 29.5 months while those who did not receive surgical intervention had a

mean survival of 20.83 months.

Conclusion: Cancers of the head and neck are associated with poor prognoses and are often deemed unresectable. Patients should be offered definitive treatment despite recommended palliative treatment, as, with adequate treatment, favorable survival outcomes are attainable.

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LIST OF ABBREVIATIONS

AJCC.....	American Joint Committee on Cancer
ECOG.....	Eastern Cooperative Oncology Group
HNC.....	Head and Neck Cancer
NCCN.....	National Comprehensive Cancer Network
NCDB.....	National Cancer Data Base
SCC.....	Squamous Cell Carcinoma
UADT.....	Upper Aerodigestive Tract

INTRODUCTION

Cancer is among one of the top leading causes of death in the United States, projected to contribute to 589,430 deaths in the U.S in 2015 (SEER). Mortality rates vary by staging and locations, with later stages having poorer prognoses in comparison to cancers discovered in earlier stages. Head and neck cancer (HNC) accounts for 3% of all malignancies in the United States and 10% on a global scale (SEER). With the incidence in males is 3.5 times more than females, it is the eighth most common cancer in women, fifth in men, affecting approximately 634,000 men and 227,000 women annually. In 2014, 40,100 people were diagnosed with head and neck cancer with 11,800 reported deaths, with a rising incidence in people below age 40 in the United States from 3% to 6% between 1973 and 1993 (Brockstein, 2003). Laryngeal, oral cavity, and pharyngeal cancers are reportedly more common in African Americans, while the highest incidence of nasopharyngeal cancers are Asian (SEER; Cancer, 2014; Brockstein, 2003).

Being such a prevalent disease in today's world, there is great interest in determining the most effective treatment modalities in hopes of improving the outcomes of those diagnosed with cancer. In this study, case reports were reviewed from patients diagnosed with stage T4b head and neck cancers to compare survival outcomes of those that underwent surgical intervention and those that did not. This analysis will provide information regarding the efficacy and viability of surgical

intervention as a treatment method for advanced stage head and neck cancers that are otherwise treated with less aggressive approaches for palliation.

Squamous Cell Carcinomas versus Nasopharyngeal Cancers

Over 95% of head and neck cancers (HNC) are squamous cell carcinomas (SCC), which originate in the epithelium of the mucosal lining in the upper aerodigestive tract (UADT), with the remaining cancers identified as nasopharyngeal cancers, which have distinct etiologies from SCC's. The three types of nasopharyngeal carcinomas categorized histologically by the World Health Organization are Type I, keratinizing squamous cell carcinoma, type II, non-keratinizing differentiated carcinoma, and Type III, undifferentiated carcinomas. Nasopharyngeal carcinomas have associations with Epstein-Barr Virus (EBV) (Bernier, 2011).

Locations/staging:

Cancer stages are typically assigned using TNM (tumor, node, metastasis) notation, which categorizes tumors with respect to the size (T), regional lymph node involvement (N), and presence or extent of metastasis (M). These aspects are identified and the tumor is categorized as stage I, II, III, or IV with subdivisions a-c (Greene, 2002).

Staging for SCC's among the various regions in the head and neck are relatively similar, while nasopharyngeal cancers have distinct staging from SCC's. The typical staging designations for SCC's are as follows:

TX – Primary tumor cannot be assessed

T0 -- No evidence of primary tumor

Tis – Carcinoma is in situ

T1 – Tumor is < or equal to 2cm

T2 – Tumor is > 2cm and < 4cm

T3—Tumor is > 4cm

T4 – Tumor invades adjacent structures

T4a- surgically resectable

T4b- surgically unresectable

NX – Regional lymph nodes cannot be assessed

N0—No regional nodes metastasis

N1— Metastasis is in a single ipsilateral lymph node, equal to or < 3cm

N2— Metastasis in a single ipsilateral lymph node, tumor > 3cm but <6cm, or metastasis in bilateral or contralateral lymph nodes <6cm

N2a – metastasis in single ipsilateral node; tumor >3cm but <6cm

N2b – Metastasis in multiple ipsilateral, <6cm

N2c – metastasis in bilateral or contralateral lymph nodes, < 6cm

N3—Metastasis in lymph node > 6cm

MX—Distant metastasis cannot be assessed

M0—No distant metastasis.

M1 – Distant metastasis.

Stage Grouping:

Stage 0	Tis	N0	M0
Stage 1	T1	N0	M0
Stage II	T2	N0	M0
Stage III	T3	N0	M0
	T1	N1	M0
	T2	N1	M0
	T3	N1	M0
Stage IVA	T4a	N0	M0
	T4a	N1	M0
	T1	N2	M0
	T2	N2	M0
	T3	N2	M0
	T4a	N2	M0
Stage IVB	T4b	Any N	M0
	Any T	N3	M0

Stage IVC Any T Any N M1

(Deschler, 2008)

Staging varies by location and is important to identify, as it dictates the course of treatment and is highly indicative of a patients' prognosis (Greene, 2002). With head and neck cancers, early stage patient demonstrate a 60-95% chance of cure with local treatment and those with advanced stage cancer have greater than a 50% risk of recurrence or metastasis after treatment (Brockstein, 2003).

Head and neck cancers are divided into six regions: oral cavity, pharynx, larynx, nasal cavity and paranasal sinuses, and salivary glands. Tumors of the thyroid region are categorized as head and neck cancers but are examined separately due to their distinct etiology (Greene, 2002). Each region is described below:

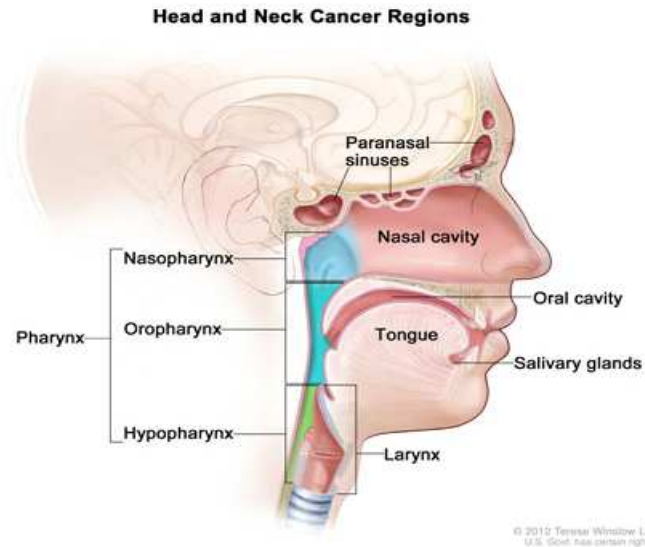


Figure 1: Head and Neck Cancer Regions (Figure downloaded from National Cancer Institute).

Oral Cavity (and lips)

The oral cavity, the most common site for squamous cell cancers, includes the lips, anterior tongue, floor of the mouth, mandible, gums, lining of the cheeks and lips, and the hard palate (Brockstein, 2003). Of these subregions, SCC's are most commonly found in the tongue. Due to their proximity to structures in the neck, tumors of the floor of the mouth spread easily throughout the head and neck regions (Brockstein, 2003).

Pharynx

The pharynx is divided into three subregions: the nasopharynx, the upper region, the oropharynx, where the oral cavity ends at the junction of the hard and soft palates, and the hypopharynx. Pharyngeal cancers also include cancers of the base of tongue, and soft palate. While tumors of the anterior tongue are the most common in the oral cavity region, base of tongue tumors are less common yet are typically found at later stages due to its location. The oropharynx allows airflow from the nose into the upper airway and closes off the oropharynx from the nasopharynx, preventing regurgitation of food and liquids into the nasal cavity. As aforementioned, nasopharyngeal cancers have distinct etiologies from squamous cell carcinomas. The oropharynx includes the base of the tongue and tonsils as well. Metastasis into the lymph nodes is common in tumors of the oropharynx. The last region of the pharynx is the hypopharynx, which connects the oropharynx with the esophagus. Hypopharyngeal tumors typically present in the late stages; by nature they are aggressive tumors that are discovered after metastases (Brockstein, 2003).

Larynx:

The larynx, more commonly known as the voice box, is located below the pharynx. This region includes the vocal cords and the epiglottis, which protects the

airway from food aspiration. This region is separated into subsites: supraglottis, glottis, and subglottis . Due to the involvement of the glottis in speech, these cancers are found before metastases. Cancers of the subglottis are the least common cancer subsite of the larynx. Subglottic cancers have high mortality rates as they are often found in the late stages (Brockstein, 2003).

Nasal Cavity

The nasal cavity is the hollow space inside the nose while the paranasal sinuses are the hollow spaces in the bones of the head surrounding the nose (Brockstein, 2003).

Salivary Glands:

The salivary glands consist of the parotid, submandibular, and sublingual glands (Brockstein, 2003).

Survival Rates

Staging varies by location and is important to identify, as it dictates the course of treatment and is highly indicative of a patients' prognosis (Greene, 2002). With head and neck cancers, early stage patient demonstrate a 60-95% chance of cure with local treatment and those with advanced stage cancer have greater than a 50% risk of recurrence or metastasis after treatment (Brockstein, 2003).

As aforementioned, cancers in each region are distinct from one another; this difference can be observed by evaluation of the survival rates. Survival curves can display either observed survival, which expresses the percentage of patients alive after a certain interval of time, or relative survival, the percentage of patients that are alive after an interval of time relative to people without cancer. The American Joint Committee on Cancer provides survival analyses as such through evaluation of reported cases using the National Cancer Data Base, NCDB from various years.

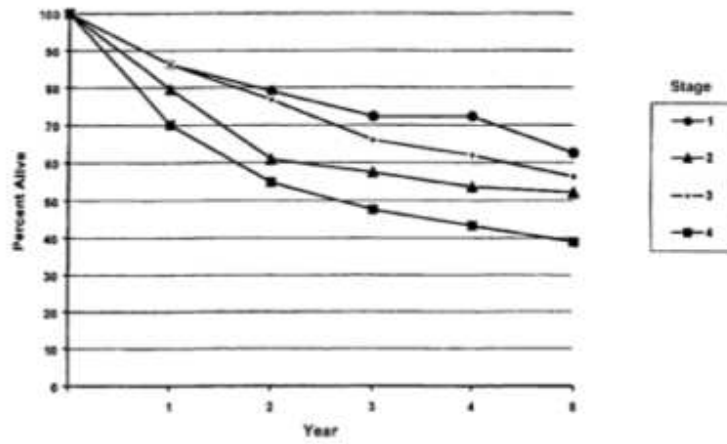
The AJCC relative survival curve for oral cavity expresses a 68.1% five-year survival rate for those with stage one cancers of the oral cavity, while stage 4 cancers are significantly less at 26.5% from data collected from the NCDB in 1985 to 1991 (Greene, 2002). An identical analysis run using data from 1998-1999 boast survival rates of 71.5% for stage one cancers and 31.9% for stage 4 (Edge & Compton, 2010). These differences between the older and newer reports, while marginal, show promise that advancement in medical technologies are bettering patients chances of survival.

The differences among regions of the head and neck are distinct from one another, however, there are regional differences among the subsites within the pharynx; this can be visualized in the survival curves in Figures 2-4 which show relative survival rates calculated by the AJCC using data from the NCDB from 1985-1991.

Nasopharyngeal cancers boast the highest five-year survival rates with stage one cancers calculated at 62.5% and 38.9% for patients with stage four cancers

(Figure 2). The relative survival rate has shown improvement over time as the AJCC analyses from 1998-1999 data expresses a 71.5% five-year survival rate for stage one nasopharyngeal carcinomas and 38.4% for stage four cancers (Edge & Compton, 2010). The combined AJCC stage for SCC's of the pharynx from data collected from 1998-1999 express five-year survival rates for stage one cancers at 35.6% and 19.4% for stage four (Edge & Compton, 2010).

Stage one oropharyngeal cancers have a 57.3% survival rate for stage one patients and 29.6% for stage four (Figure 3), while, the worst prognoses of the pharyngeal regions are shown for hypopharyngeal cancers with stage one cancers exhibiting a 40.7% survival rate and stage four 19.9% (Figure 4). The later collected data from 1998-1999 shows improvement in survival for oropharyngeal cancers to 72.6% for stage one, and 32.4% for stage four, while hypopharyngeal cancers have also displayed improvement with a 53% and 24.4% five-year survival rate for stage one and stage four hypopharyngeal cancers, respectively (Edge & Compton, 2010).



RELATIVE SURVIVAL BY STAGE	1	2	3	4	5	95% Cis*	CASES
1	86.2	79.0	72.3	72.3	62.5	50.5 – 74.5	104
2	79.6	60.9	57.4	53.6	52.1	39.9 – 64.3	96
3	86.2	76.7	65.9	61.9	56.3	48.1 – 64.4	205
4	70.1	54.8	47.6	43.3	38.9	34.6 – 43.3	669

Figure 2: AICC five-year relative survival for squamous cell carcinoma of the nasopharynx (Figure taken from Greene, 2002).

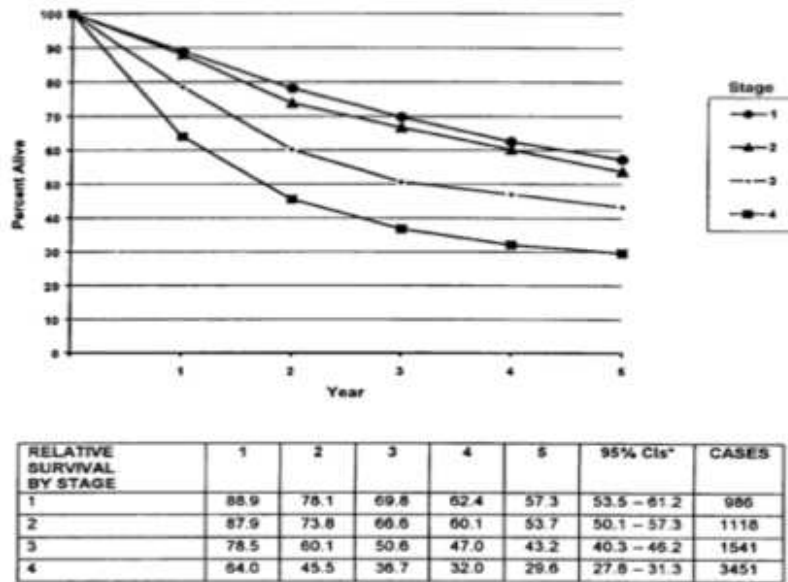
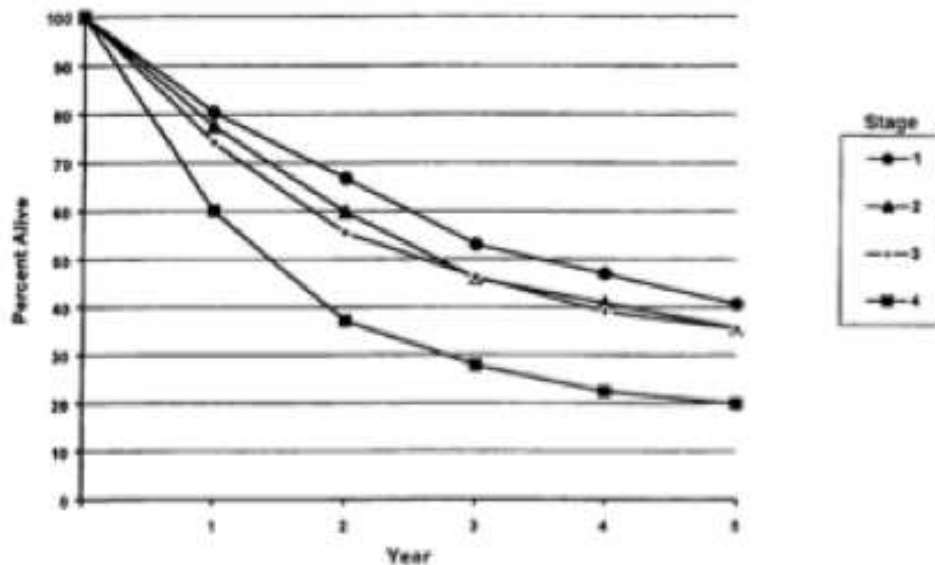


Figure 3: AJCC five-year relative survival for squamous cell carcinoma of the oropharynx (Figure taken from Greene, 2002).



RELATIVE SURVIVAL BY STAGE	1	2	3	4	5	95% Cis*	CASES
1	80.3	66.7	53.0	47.0	40.7	31.4 - 47.4	304
2	77.5	59.8	46.0	40.9	35.6	29.6 - 41.6	350
3	74.1	55.5	46.3	39.0	35.5	31.1 - 39.8	620
4	60.1	37.1	27.9	22.4	19.9	17.7 - 22.0	1688

Figure 4: AJCC five-year relative survival for squamous cell carcinoma of the hypopharynx (Figure taken from Greene, 2002).

The plotted survival curve for laryngeal cancers exhibit a 79.9% survival rate for stage 1 cancers, and 36.7% for stage 4, significantly greater than the survival rates observed in pharyngeal cancers based on data from 1985-1991 (Greene, 2002). Later data analyses from 1998-1999 express a relative survival rate of 84.3% and 35.5% for stage one and stage four laryngeal carcinomas, respectively (Edge & Compton, 2010).

The calculated AJCC five-year relative survival rates for the nasal cavity show a 60.4% survival rate for stage one cancers and 31.1% for patients with stage 4 cancers (Greene, 2002).

The five-year survival shows marked differences between stage one and stage four rates at 85.8% and 31.9% respectively in the salivary glands (Greene, 2002).

Figure 5 superimposes each subsite for comparison of survival rate by region. Survival rates vary by region, with lip cancers having the greatest survival rate after time of initial diagnoses, and hypopharyngeal cancers showing the shortest long-term survival after diagnoses.

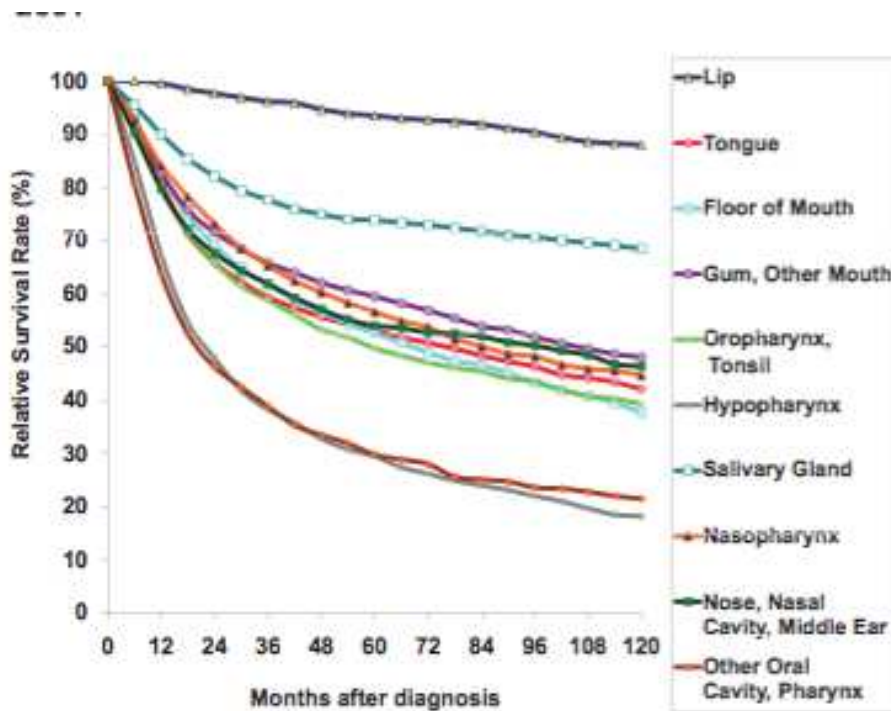


Figure 5: Relative Survival Rate of Head and Neck Cancer patients divided by subsite, reported between 1988 and 2001 using SEER data (Figure taken from SEER).

Causes/Risk Factors:

Cancer is a result of uncontrolled cell growth; these malignant transformations can be caused by a variety of factors. The loss of chromosomal region 9p21 is the most common cause. This mutation inactivates p16, a gene vital to cell cycle regulation. In 50% of cancers, a mutation in the p53 gene is involved (Brockstein, 2003).

While cancer can often be attributed to random genetic mutations, several risk factors have also been identified as causal for head and neck cancer. With over 50 carcinogens found in tobacco such as polycyclic aromatic hydrocarbons, nitrosamines, and aromatic amines, unsurprisingly, it is among one of the strongest contributors to head and neck cancer (Cancer, 2014). The strongest correlation has been found between tobacco and alcohol use and head and neck cancer with 75% being attributable to use of these substances (Alcohol, 2007). As the two habits are strongly associated with each other, a study was conducted to analyze the habits of exclusive tobacco or alcohol users. With tobacco use, a relationship between the two demonstrate a dose-response relationship was found, corresponding to frequency and duration, while exclusive alcohol users were only found to have

increased risk for head and neck cancer if they drank five or more drinks per day (Alcohol, 2007). An association has also been shown with tobacco use and laryngeal cancers in particular and alcohol use with both pharyngeal and laryngeal cancers (Alcohol, 2007).

Over 5% of patients who continue to smoke experience second primary malignancies, SPM's, or new cancers originated in other sites of the body after initial cancer, which can be attributed to the carcinogens taking their toll on other regions of the body. SPM's typically present in other head and neck regions, or the lungs and esophagus (Brockstein, 2003). The risk of SPM has been found to show correlation with age as well as extent of tobacco usage (Brockstein, 2003).

Human papilloma virus, or HPV, a DNA virus, results in high-risk infections for malignant transformations as it encodes two major oncogenes (E6 and E7) involved in cell cycle regulation, inactivating p53 and resulting in the promotion of cell proliferation and growth. HPV has been associated with increased risk for HNC's as 35% of those with HNC have HPV; this association is particularly seen between HPV and oropharyngeal cancers (Ernster et al., 2011). Similarly, Epstein-Barr virus, EBV, has been strongly associated with nasopharyngeal carcinomas. In addition, poor diet and oral hygiene has been linked to head and neck cancer, including poor dentition, lack of toothbrush use, and not having dental check-ups (Guha et al., 2007). This observation is validated by the observable higher incidences of head and neck cancers among persons of lower socioeconomic status due to lack of education on proper oral hygiene and availability of resources to

obtain proper dentition. Two-thirds of malignancies are reported from developing countries where there are high consumption rates of tobacco and alcohol, and poor diet (Bernier, 2011).

Diagnosis Techniques:

Signs and symptoms of head and neck cancer range from facial pain, earaches, headaches, throat pain, diplopia, and hearing deficits, to nasal obstructions. These symptoms are typically subtle and can easily be missed by both the patient and a medical examiner; with early stage tumors often being asymptomatic, diagnoses are often not made until the cancer has progressed to a later stage (Brockstein, 2003). With diagnoses of cancer, it is also crucial to determine the staging as this indicates course of treatment. With thorough physical examination, the cancer can be assessed pending confirmation through histological testing. If a tumor in the oral cavity or oropharyngeal cavity is evident during examination, fine needle aspiration (FNA) can be used to confirm a diagnosis, while other unknown primary malignancies can be revealed with use of a panendoscopy with random biopsies of other HNC regions (Brockstein, 2003).

Often endoscopic procedures are employed to better visualize the tumorous growth; laryngoscopy, pharyngoscopy, nasopharyngoscopy, depending on the area of interest. Several other region-specific tests can be employed to diagnose cancer;

in the case of laryngeal cancer, often barium swallow tests are a useful diagnosis tool.

Imaging tools such as ultrasound, magnetic resonance imaging (MRI), computed tomography (CT) scans, and positron emission tomography (PET) scans, are effective in confirming differential diagnoses as they can provide information about extent of the cancers invasion to adjacent structures and lymph node involvement. These tools are employed based on the area of interest.

The imaging tool used for diagnostic is contingent upon the location of the tumor. Due to its abilities to detect soft tissue subtleties, MRI is a preferred imaging tool for cancers of the nasopharynx, paranasal sinuses, salivary glands, and oropharynx. CT scans are preferred due to the associated cost and times for imaging and are used for bony protrusions such as the mandible, while PET scans are beneficial in determining extent of regional lymph node involvement (Brockstein, 2003).

Molecular testing is used as means to identify specific genes, proteins, and molecular aspects of the tumor; this is beneficial in creating a personalized therapy approach to target the identified markers (Bernier, 2011).

Treatment/standards of care:

A patients' prognosis and treatment approach is highly contingent on the staging of the cancer when it is discovered as well as the location. Several therapies

are employed in treatment of head and neck cancers: radiation therapy, surgery, chemotherapy, and targeted therapy; often multiple modalities are used to ensure there will not be recurrence. (Brockstein, 2003).

Surgeries range from total removal of regions such as seen in tonsillectomies and laryngectomies, which target the primary tumor sites for successful resection. However, in the case of cancers that have metastasized with evidence of lymph node involvement, procedures such as neck dissections are performed in which lymph nodes and diseased vasculature are excised (Brockstein, 2003).

Early stage head and neck cancers, stage I and stage II, specifically, can be cured 60-95% of the time with surgery or radiation (Brockstein, 2003). Different modalities are employed as the standard of treatment depending on the region. Surgical intervention is favored, particularly in early stage cancers, however the resultant disfigurements must be taken into account as they could lead to difficulty with daily functions such as eating, swallowing, and speaking. This modality is also favored due to the issue with patient compliance that becomes relevant with continuous radiation therapy treatments in terms of compliance with treatment schedule, and post-treatment care. Other than nasopharyngeal cancers, surgical resection is the standard of treatment for the typical patient that presents with early stage HNC (Brockstein, 2003).

Advance stage cancers are curable in a meager 30-40% of reported cases, and unfortunately, two thirds of those diagnosed with HNC are diagnosed at advanced stages (Brockstein, 2003). Nonmetastatic stage IV HNC's are deemed

curable in contrast to metastatic or recurrent advanced HNC. Patients with metastatic disease or locoregionally recurrent diseases are generally treated for palliation with concomitant chemotherapy and radiation therapy being the standard of care (Brockstein, 2003).

Treatment modalities, while largely based on the staging of the cancer at time of diagnosis, must consider the region. As aforementioned, head and neck cancers pose an additional complexity when assessing viable treatment options as vital functions such as breathing, speaking, and swallowing can be compromised. With cancers of the oral cavity, radiotherapy is not the recommended standard of treatment due to the proximity to the mandible and maxilla as it can result in osteoradionecrosis, death of the bone, of these structures, which could lead to further complications (Brockstein, 2003). Laryngeal cancers pose the issue of speech quality after treatment; while voice quality is reported to be better long-term when patients are treated with radiotherapy rather than surgery, chance of recurrence is greater (Brockstein, 2003).

T4b – What defines resectability?

Stage 4 cancer defines the most aggressive stage of cancer, staged as such due to the size of the tumor, excessive nodal involvement, or distant metastasis. In 2002, the American Joint Committee on Cancer (AJCC) redefined T4 and divided it into subgroups a and b. T4b is defined as the more aggressive form, having a poorer

prognosis and higher rate of unresectability than T4a. This assignment is made based on imaging to evaluate the level of infiltration of the cancer. The criteria for T4b categorization is as follows: vascular encasement and invasion in surrounding vessels such as the carotid artery and jugular vein, prevertebral space invasion, specifically fixation of the tumor to prevertebral musculature, and mediastinal invasion, which refers to infiltration of the supra-aortic vessels, aortic arch, and mediastinal fat (Yousem, 2006). T4a is designated the moderately advanced cancer, and T4b the very advanced local disease. Head and neck cancers are difficult to assess as T4a versus T4b as resectability is contingent upon many factors that are unique to each case.

METHODS

In seeking to compare the outcomes of patients with advanced stage head and neck cancers based on treatment modality (surgery and chemoradiation, chemoradiation, no treatment), medical records for patients diagnosed with head and neck cancer at Boston Medical Center between June 2009 and October 2011 were screened. Of the 320 cases reviewed, 18 patients with stage IVb tumors were identified. These charts were reviewed up through October 2014 in order to determine three-year survival. From these records, date of initial diagnosis, diagnosis, treatment types and dates, and date of death were extrapolated. Mean survival rates were calculated to compare survival outcomes of those who received and those who did not receive surgical intervention by averaging the total number of months between diagnoses and death of patients in both groups. Survival curves were then created using graphing software GraphPad Prism, Version 6.0f by inputting the patient survival rates into a chart.

RESULTS

Upon the screening of patients diagnosed with head and neck cancer between June 2009 and October 2011, eighteen patients of the 320 cases were found to have stage IVb tumors. Of the 18 patients, 3 were female and 15 were males. While the number of patients included in this study is small, this distribution among males and females reflects the trends of head and neck cancer, as men reportedly have 3.5 times the incidence as women (Brockstein, 2003). The mean age of diagnoses was 56.61 with the youngest patient of twenty-eight years and the oldest seventy-four. The mean age for females at time of diagnosis was 54.67 years, and 57 years for the males. Cancer of the oral cavity and lips were most common in this cohort with 10 patients presenting with tumors in this region. Pharyngeal cancers were identified in 6 patients, 4 of which were in the oropharynx, and 2 in the nasopharynx, and the remaining two patients had cancers in the nasal cavity (paranasal sinus) and salivary glands (parotid gland). Ten patients were identified as Caucasian, one Hispanic, one Asian, and two patients did not identify their race.

Table 1: Demographics of patients included in this study.

N = 18
Males = 15
Females = 3
Age Range = 28-74
Mean Age at Dx = 56.61
Caucasian: 10
Black/African American: 4
Asian: 1
Hispanic: 1
Race not Identified: 2
Subsites:
• Mandible (oral cavity): 1
• Nasopharynx (pharynx): 2
• Base of Tongue (pharynx): 4
• Parotid Glands (salivary glands): 1
• Oropharynx(pharynx): 4
• Lip and Oral (oral cavity): 3
• Hard Palate(oral cavity): 2
• Paranasal Sinus (nasal cavity): 1

Of the eighteen patients, 12 were treated with surgery followed by chemoradiation therapy, and 4 were treated with only chemoradiation therapy and 2 opted out of treatment and were put in hospice care. The types of surgeries performed included neck dissection, tracheostomy, alveoplasty, total laryngectomy, parotidectomy, tonsillectomy, multiple tooth extraction, sphenoidectomy, ethmoidectomy, and often many involved facial reconstruction and skin grafts. Tables 2 and 3 delineate the survival rates of the patients included in the study with and without surgical intervention respectively, while Table 3 provides comparison of survival rates based on stage, location, and treatment modality.

Table 2: Survival outcomes of patients with surgery:

Patient #	Date of Dx	Date of Surgery	Date of Death	Survival (months)
1	9/22/10	10/28/10	3/1/11	6
2	5/10/11	6/24/11	3/26/12	10
3	5/10/10	6/14/10	Living	51
4	10/8/10	10/28/10	Living	46
5	6/18/09	3/11/10	12/2010	18
6	11/11/10	6/23/11	11/2/12	24
7	10/8/10	12/2/10	Living	46
8	2/11/11	11/8/12	Living	42
9	12/10/10	3/4/11	5/1/12	17
10	10/18/11	11/21/11	Living	33
11	10/28/11	11/17/11	Living	33
12	11/18/11	12/8/11	Living	33

Table 3: Survival outcomes of patients without surgical intervention

Patient #	Date of Dx	Date of Rx (CRT)	Date of Death	Survival (months)
1	7/8/10	8/4/10	8/8/10	1
2	3/24/11	4/26/11	6/13/2011	39
3	3/14/11	None	4/20/11	1
4	5/3/11	5/18/11	Living	39
5	4/13/11	5/26/11	Living	40
6	10/13/11	None	3/6/12	5

Table 4: Survival comparison based on treatment modality and location.

Rx Modality	Stage	Location	AJCC 5 yr survival	Survival (months)
CRT	T4b, N3, M0	Pharynx (nasopharynx)	38.4%	1
CRT	T4b, N2, M0	Pharynx (oropharynx)	26.8%	39
CRT	T4, N2, M0	Pharynx (base of tongue)	26.8%	39
CRT	T4b, N3, M0	Pharynx (nasopharynx)	26.8%	40
None	T4b, N2, M0	Pharynx (oropharynx)	32.4%	1
None	T4b, N0, M0	Oral Cavity (lip and oral)	26.5%	5
Surgery +CRT	T4b, N1, MX	Oral Cavity (mandible)	25%	6
Surgery +CRT	T4, N1, M0	Pharynx (base of tongue)	26.5%	10
Surgery +CRT	T4b, N0, M0	Salivary Glands (parotid)	38.5	51
Surgery +CRT	T4a, N2, M0	Pharynx (oropharynx)	32.4%	46
Surgery +CRT	T4b, N2, M0	Pharynx (base of tongue)	32.4	18
Surgery +CRT	T4b, N1, M0	Oral Cavity (lip and oral)	26.5	24
Surgery +CRT	T4a, N0, M0	Oral Cavity (hard palate)	32.4	46
Surgery +CRT	T4a, N2, M0	Pharynx (oropharynx)	32.4	42
Surgery +CRT	T4b, N2, M0	Pharynx (base of tongue)	26.5%	17
Surgery +CRT	T4b, N0, M0	Nasal cavity (paranasal sinus)	29.2%	33
Surgery +CRT	T4b, N2, M0	Oral cavity (hard palate)	40%	33

Surgery +CRT	T4b, N2, M0	Oral cavity (lip and oral)	26.5	33
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Nine patients, (50% of the reviewed patients) were living at the last date of data collection (October 2014). Of these 9 patients, 7 had undergone surgical intervention while the remaining two only had chemoradiation. 58.3% of patients that had undergone surgery were still living at the time of collected data while 33.33% of those that did not have surgery were living. It was found that the mean survival rate (in months) for patients who underwent surgery was 29.92 months, over 9 months longer than the mean survival rate of those who did not undergo surgery at 20.83 months after initial diagnosis. The average age at time of death was 60.3 years, 51.25 years for those who did not receive surgical intervention, and 67.6 years for those who underwent surgery.

Table 5: Outcome Demographics:

<p>Patients living at end of collection date (October 2014): 9</p> <ul style="list-style-type: none"> - Surgical treatment: 7 = 58.3% total group of patients that underwent surgery - Chemoradiation Therapy: 2 = 33.33% of patients that did not have surgery

Survival Comparison of Patients with and without Surgical Intervention

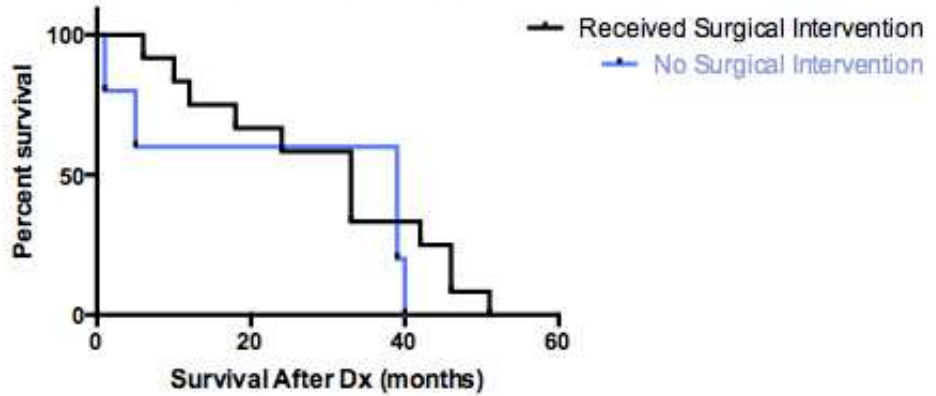


Figure 6: Survival curve – comparison of survival after time of diagnoses between patients with and without surgical intervention.

Figure 6 displays a survival curve of patients evaluated in this study. The figure was created by inputting patient survival rates into the graphing software GraphPad Prism (Version 6.0f). The resultant survival curve demonstrates the comparison between survival rates of those patients that underwent surgery and those who did not. As shown, there was a greater percentage of patients that survived beyond those who did not receive surgical intervention.

DISCUSSION

Standard treatment protocol advises against surgical intervention for T4b, advanced stage, head and neck cancers. The National Comprehensive Cancer Network (NCCN), an organization that develops practice guidelines for oncological care, delineates the standards of care and treatment protocols for all cancer subtypes. Course of treatment for advanced stage head and neck cancers mandate chemoradiation therapy as palliative treatment and advise against surgical intervention (see Figures 11-14).

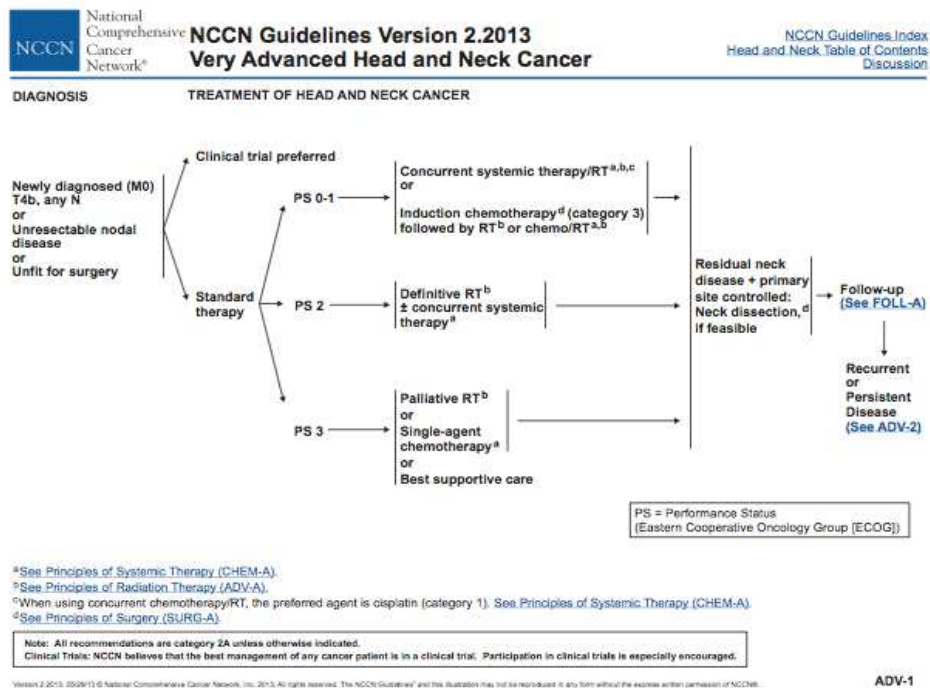
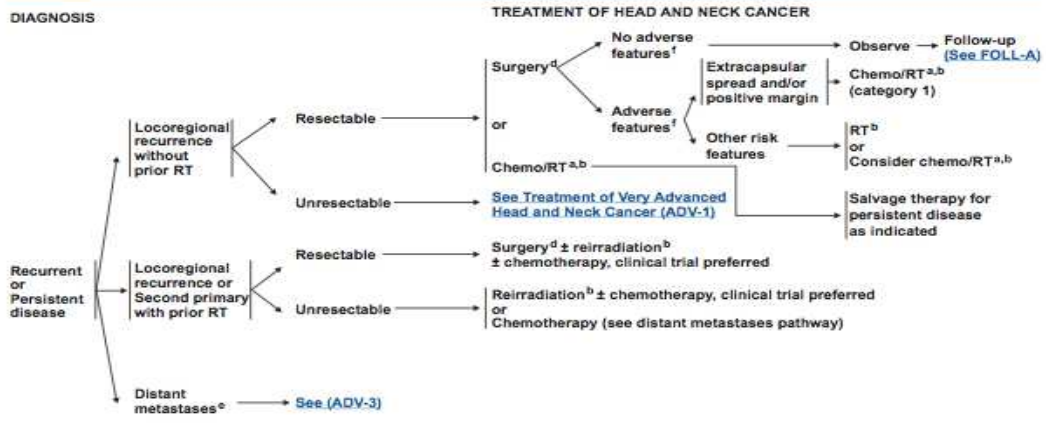


Figure 7: NCCN Treatment Guidelines Very Advanced Head and Neck Cancer – part 1 (Figure downloaded from National Comprehensive Cancer Network at www.oralcancerfoundation.org).

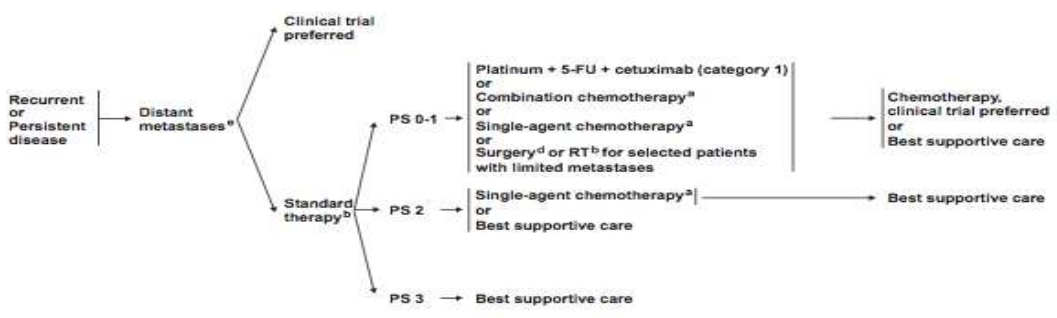


^aSee Principles of Systemic Therapy (CHEM-A).
^bSee Principles of Radiation Therapy (ADV-A).
^cSee Principles of Surgery (SURG-A).
^dConsider palliative RT as clinically indicated (eg, bone metastases). (See RAD-A).
^eAdverse features: extracapsular nodal spread, positive margins, pT3 or pT4 primary, N2 or N3 nodal disease, perineural invasion, vascular embolism (See Discussion).
 Note: All recommendations are category 2A unless otherwise indicated.
 Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

Figure 8: NCCN Treatment Guidelines Very Advanced Head and Neck Cancer – part 2 (Figure downloaded from National Comprehensive Cancer Network at www.oralcancerfoundation.org).

DIAGNOSIS

TREATMENT OF HEAD AND NECK CANCER



* See Principles of Systemic Therapy (CHEM-A).

† See Principles of Radiation Therapy (ADV-A).

‡ See Principles of Surgery (SURS-A).

§ Consider palliative RT as clinically indicated (eg, bone metastases). (See RAD-A).

PS = Performance Status (ECOG)

Note: All recommendations are category 2A unless otherwise indicated. Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

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ADV-3

Figure 9: NCCN Treatment Guidelines Very Advanced Head and Neck Cancer – part 3 (Figure downloaded from National Comprehensive Cancer Network at www.oralcancerfoundation.org).

ECOG Performance Status

These scales and criteria are used by doctors and researchers to assess how a patient's disease is progressing, assess how the disease affects the daily living abilities of the patient, and determine appropriate treatment and prognosis. They are included here for health care professionals to access.

ECOG PERFORMANCE STATUS*	
Grade	ECOG
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair
5	Dead

* As published in Am. J. Clin. Oncol.: Oken, M.M., Creech, R.H., Tormey, D.C., Horton, J., Davis, T.E., McFadden, E.T., Carbone, P.P.: Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. Am J Clin Oncol 5:649-655, 1982.

Figure 10: Eastern Cooperative Oncology Group (ECOG) Performance Status Chart (Figure downloaded from National Palliative Care Research Center at www.npcrc.org).

Performance status, or PS, is scaled 0-5 with 0 being the most capable and unrestricted in regards to performing daily activities, 1-4 rating increasing level of disability, and 5, deceased (see Figure 10). As seen in Figures 7, 8, and 9, NCCN protocol does not include surgical intervention for advanced stage, unresectable, otherwise known as T4b, head and neck cancers.

It is proposed that surgical intervention should not be disregarded as a viable option for patients with T4b head and neck cancers. In evaluating and comparing the outcomes and survival rates of patients treated with and without surgical intervention, the collected data suggests more favorable outcomes for those that underwent surgical intervention as the mean survival rate for those that had surgical intervention was 29.92 months; 9.09 months longer than those who did not undergo surgery as treatment with the groups mean survival rate being 20.82 months. While median survival for late stage HNC is reported to be 6-9 months with a 20-30% one year survival rate, all twelve patients included in the study that underwent surgical treatment survived 6 months or longer, and ten of the twelve, 83.33%, survived a year or longer (Brockstein, 2003).

Several studies conducted at Chang Gung Memorial Hospital in Taiwan demonstrated comparable resection outcomes of T4a and T4b oral cavity squamous cell carcinomas, leading to the recommendation that the studied tumors, resectable infra-notch T4b tumors, be reclassified as T4a in the AJCC tumor staging (Liao et al., 2012). This finding suggests that T4b should not be deemed unresectable conclusively. Considering the evolving nature of medicine, we should not be

restricted to standard protocols. Guidelines are provided to direct physicians in their approaches to patient care, however they are not meant to be set rules; it should be recognized that no one tumor, patient, or circumstance is the same and treatments must be tailored to an individual. Existing literature supports this notion as surgeons attempt novel surgical techniques in order to achieve maximal resection of more aggressive cancers (Sabatini, 2009; Liao et al., 2006). Studies are looking into further substaging within T4 cancers due to the fact that different stages have different prognoses' – this effort suggests that T4b should not be looked at as an unresectable stage as each cancer is unique (Rivera et al., 2008).

An alternative staging method known as volumetric staging has been proposed which, unlike the TNM staging system that categorized with regards to size, node involvement, and level of metastases, evaluates tumors based on gross tumor volume. According to a study performed in the radiation oncology department of University Hospital of Zurich, volumetric staging proved to be a superior staging technique in terms of predicting outcome of patients with head and neck cancer (Studer & Glanzmann, 2013). With cancer staging and evaluation being such an important indicator of treatment options, the new methods of tumor evaluation suggest the TNM system is not a comprehensive staging tool and staging designation is not definitive.

There are several limitations and considerations that must be accounted for in this study. While survival rates were calculated by time of survival from date of initial diagnoses, some patients were diagnosed earlier than others analyzed in this

study, while the cut-off date for survival rate calculation was the same (October 2014). This affects the data as patients' survival rate differences may be attributable to the time of diagnoses, rather than the form of intervention.

The nature of the cancers of those patients that had not undergone surgical intervention must be taken into consideration; though a less favorable mean survival rate was demonstrated in this study, those patients may have had more aggressive and complex cancers that were truly inoperable. An additional consideration that must be accounted for is patient demographics. Those that forewent surgical intervention may have not had access to adequate healthcare resources due to social or economic factors, affecting their survival rates due to inadequate care, noncompliance with treatment regimens, and ability to afford treatments.

While the number of subjects limits this study, the purpose is to offer surgery a treatment option for patients of this aggressive-staged cancer. This proposal is not specific to any head and neck regions as several instances were evaluated in this study of patients with cancers of different sub sites and surgeries. T4b cancer is characterized as unresectable, but the data suggests that cases need to be evaluated with a case-by-case approach as surgical intervention may be a viable option for many with advanced stage head and neck cancer and may better their chances at longer-term survivals.

CONCLUSION

It is understandable for both physicians and patients to err on the side of caution when determining whether or not to move forward with surgery as a viable treatment option. As is the case with any surgical procedure, there are risks that must be considered; the operating surgeon and oncological team must work with the patient to determine the best treatment option. With head and neck cancers, risk of impairing functions vital for daily life such as breathing, speaking, and swallowing are imperative to consider, along with disfigurement; all factors contribute to a persons quality of life. The benefits must be weighed against the risks as in some cases, the difference in survival rate with versus without surgery may not be significant considering the possible complications and resultant outcomes.

While standard protocol advises against surgical intervention as means of treatment for advanced stage T4b head and neck cancers, the findings of this study suggest protocol be adjusted to consider surgery as a viable treatment option.

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CURRICULUM VITAE

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EDUCATION

Boston University School of Medicine

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RESEARCH EXPERIENCE

Boston Medical Center

Boston, MA

Research Assistant (August 2014- present)

- Worked under Otolaryngology surgeon

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Storrs, CT

Research Assistant (January 2011- July 2013)

- Studied role of hippocampus in learning and memory
- Independent Study project: investigating effect of emotional stimuli on varying hippocampal centers by analysis of immediate early genes *zif268* and *Arc*
- Duties include: behavioral training of rats, data collection and input, brain tissue analysis, paper presentations

Wilfred Laurier University

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Research Assistant (June- August 2012)

- Lab collaboration between University of Connecticut
- Duties included: Compartmental Analysis of Temporal Fluorescence In Situ Hybridization (CATFISH), cryostat use, theory and application of confocal microscope

Yale New Haven Hospital

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Research Volunteer (2009-2013)

- Data input/analysis, aiding in writing of research papers and abstracts
- Reference Presentations and Publications below

PRESENTATIONS AND PUBLICATIONS

- Co-author of “Donor Egg IVF Model to Assess Ecological Implications for ART Success” -- accepted for publication in *Journal of Assisted Reproduction and Genetics* (Aug 2014)
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Community Internist Associates

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