SURVIVAL IN LARYNGEAL CANCER AND ITS PREDICTORS AT OCEAN ROAD CANCER INSTITUTE FROM 2008-2012

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SURVIVAL IN LARYNGEAL CANCER AND ITS PREDICTORS AT OCEAN ROAD CANCER INSTITUTE FROM 2008-2012

By

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A Dissertation Submitted in (Partial) Fulfillment of the Requirements for the Degree of Master of Medicine (Clinical Oncology)

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CERTIFICATION

The undersigned certifies that she has read and hereby recommends for acceptance by Muhimbili University of Health and Allied Sciences a dissertation entitled ***Survival in laryngeal cancer and its predictors at Ocean Road Cancer Institute from 2008-2012*** in fulfillment of the requirements for the degree of Master of Medicine (Clinical Oncology) of Muhimbili University of Health and Allied Sciences.

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Dr. Nazima Dharsee

(Supervisor)

_____

Date

DECLARATION
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I**, Emmanuel Lugina Lugina**, declare that this **dissertation** is my own original work and that it has not been presented and will not be presented to any other University for a similar or any other degree award.

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To my Lecturers and Professors, thanks for the incredible knowledge you shared with me.

To my employer, thank you for granting me permission to pursue this course.

To my family, a very deep and heartfelt appreciation for their devoted and unconditional support.

DEDICATION

Every challenging work needs self effort as well as guidance of elders especially those who are very close to our heart. My humble effort I dedicate to

My beloved and sweet late mother Prof. Helen Igobeko Lugina

My dear father Maxmillian Lugina

ABSTRACT

Background: In Tanzania cancer of larynx is second in occurrence after sinonasal cancer among the HNSCC. There is no information in Tanzania about survival of laryngeal cancer patients after treatment as well as factors associated with survival.

Purpose: The objective of this study was to determine the 5 years overall survival rate and factors associated with survival of laryngeal cancer patients treated at Ocean Road Cancer Institute from 2008 -2012.

Material and Methods: This was retrospective study done at ORCI by reviewing records of 82 laryngeal cancer patients treated at ORCI from 2008 and 2012.All patients were followed up for 5 years. A structured questionnaire was used to extract information about characteristics of the patients and survival. For patients who were no longer attending follow up clinic a phone call was made to next of kin to the patient to inquire about the status of the patient.

Five years overall survival (OS) was estimated by using the Kaplan–Meier method. Log–rank statistics was employed to identify significant prognostic factors for overall survival. Multivariate analysis was done by using Cox Proportional Hazard statistics. Association between categorical covariates was determined by using Chi-Square test and association between continuous variables determined by independent sample t-test.

Results: The five years overall survival rate was 29 % and median survival time was 23 months. The main independent predictors of OS for the whole cohort in univariate analysis were T stage, presence of neck nodes, site of the tumor, level of hemoglobin and blood transfusion. High radiotherapy dose was associated with higher OS among patients treated with palliative intention. Presence of dyspnea at presentation, low performance status and N stage had borderline statistically significant association with OS. The effect of the presence of distant metastases (M stage) on survival could not be evaluated in our analysis due to the small number of patients with M1 stage. Only site of the tumor was statistically significant in multivariate analysis.

Conclusion: The OS of laryngeal cancer patients is relatively lower in this study compared to those in developed countries. Early laryngeal cancer stages, glottis tumors, high hemoglobin, absence of blood transfusion prior to radiotherapy and high radiotherapy doses were associated with higher OS.

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LIST OF ABBREVIATIONS

AJCC	American Joint Committee on Cancer
BED	Biologically effective dose
CRT	Concomitant Chemo-radiotherapy
CSS	Cancer specific survival
CI	Confidence Interval
DFS	Disease Free Survival
DNA	Deoxyribonucleic Acid
ECE	Extra-capsular Extension
EBV	Epstein-Bar Virus
EQD_2	Equivalent total dose in 2 Gy fractions
Gy	Grays
HR	Hazard Ratio
IMRT	Intensity Modulated Radiotherapy
LRC	Local-Regional recurrence free survival
NCCN	National Comprehensive Cancer Network
NPL	Neutrophil to Lymphocyte ratio
OS	Overall survival
ORCI	Ocean Road Cancer Institute
OTT	Overall treatment time
KPS	Karnofsky Performance Scale
RT	Radiation Therapy
SRT	Surgery followed With Radiotherapy
HNSCC	Head and neck cancers are squamous cell carcinoma
HPV	Human Papiloma Virus
RTOG	Radiation Therapy Oncology Group

CHAPTER ONE

1. INTRODUCTION

1.1 Background

Worldwide laryngeal cancer accounts for nearly 1% of all malignancies and approximately 22% of head and neck tumors (1). The incidence of the laryngeal cancer varies widely in different countries. Several recent studies have shown suggested that the incidence of laryngeal cancer and other smoking-related cancers are declining in North America(2) and Western Europe. One factor in this decline may be decreased exposure to carcinogens, specifically tobacco. It has been hypothesized that this declining incidence may reflect achievement in antismoking effort (3). However in the developing countries, the incidence of laryngeal cancer is on the increase. The reason for this is unknown but may not be unconnected to frequent exposure to inhalational irritants at workplaces, homes as well as malnutrition (4).

There is a geographical difference in the occurrence of Laryngeal cancer among the HNSCC. Laryngeal cancer is the most common HNSCC in Nairobi (5). In Mwanza laryngeal cancer is third in occurrence among head and neck cancers after oral cavity cancer and pharyngeal cancer (6). At Muhimbili National Hospital in Dar es salaam the cancer of larynx (20.4%) is second in occurrence after sinonasal cancer (27.4%) among the HNSCC (7). The mean age at diagnosis of laryngeal cancer was 64 years (8). Laryngeal cancer tends to be diagnosed at an earlier age in developing countries as compared to developed countries.

All published studies indicate a pronounced male predominance among laryngeal cancer patients. Men are affected 4-5 times more often than women. The distribution of laryngeal cancer by site is as follows: 30% to 35% in the supraglottic region, 60% to 65% in the glottic region and 5% in the subglottic region (3).

The Larynx is divided anatomically into the supraglottis, glottis, and subglottis. The supraglottis consists of the epiglottis, false vocal cords, ventricles, aryepiglottic folds, and

arytenoids; the arytenoids are cartilages that articulate on the cricoid. The glottis includes the true vocal cords and the anterior commissure. The subglottis is 2 cm long and extends from 5 mm below the free edge of the true vocal cords to the lower margin of cricoid cartilage (9). To facilitate communication, lymph nodes of Head and Neck are organized into levels. Level I include the submental and submandibular areas; levels II-IV include the internal jugular vein lymph nodes; level V includes the posterior triangle (9).

The supraglottic region has a rich capillary lymphatic plexus and initially drains to level II and then III and IV lymph nodes .There is essentially no capillary lymphatic of the glottis region. Lymphatic spread from cancer at the glottis only occurs if tumor extends to supraglottic or subglottic areas. The subglottic area has relatively few capillary lymphatics and spread is primarily to the pre-tracheal (delphian) nodes and the level IV nodes (9). More than 50% of patients with supraglottic primary present with spread to regional lymph nodes because of abundant lymphatic network that crosses the midline. Thus, supraglottic cancer is often advanced at diagnosis. In contrast, lymphatic drainage of the glottis is sparse and early stage primaries rarely spread to regional lymph nodes. Because hoarseness is an early symptom, most glottic cancer is early stage at diagnosis (10).

These cancers are strongly associated with certain environmental and lifestyle risk factors like tobacco and alcohol consumption. More recently a new disease has emerged related to several strains of Human Papiloma Virus (HPV 16,18) (11). Olsen et al. showed that the risk of laryngeal cancer was highest in people with little or no vocational training and without a higher school education (12).

A retrospective study which investigated symptoms of laryngeal cancer in Finland, found that hoarseness was more commonly associated with glottic and subglottic tumors, although it was the most frequent symptom also in supraglottic disease. Supraglottic tumors caused a markedly higher occurrence of sore throat, dysphagia, globus, otalgia and haemoptysis. Dyspnoea was most common in patients with subglottic tumors. About 10% of patients having a supra- or subglottic lesion presented with a neck mass detected by the patient (13).

In a retrospective study done in Nigeria the duration of illness at presentation ranged from 2 to 15 months, with a mean of 7.3 ± 3.8 months. Hoarseness and difficulty with breathing were the most common symptoms, and 91.8% of patients presented with acute upper airway obstruction necessitating emergency tracheostomy (4). In a study done in Finland the median duration of the symptoms was 4.2 months and this was not significantly affected by tumor site. The symptom duration was significantly longer in stage III–IV cases (median 4.7 months) than in stages I–II (median 3.8 months) (13). In Retrospective analysis of the clinical efficacy of concurrent weekly cisplatinum – radiotherapy for patients with laryngeal carcinoma in Egypt the gap between initial complaint and diagnosis was 6-12 months (14).

The 2010 AJCC staging classification (seventh edition) for laryngeal primary tumors is determined by number of subsites involved, vocal cord mobility and presence of metastases (15).
Squamous cell carcinoma (98%) is the most common histological finding. Other rare histology include the verrucous carcinoma (1.2%) and pseudosarcoma (0.3%) (3).

The Overall 5-year relative survival rate in studies done in Denmark for patients with laryngeal cancers is 77% (16) and in Egypt is about 45 %(14). In these studies they found that the factors affecting survival in laryngeal cancers were age, duration of symptoms, duration of treatment waiting time, overall treatment waiting time, duration of treatment interruption, pretreatment hemoglobin level, stage, pretreatment platelet count, pretreatment neutrophil to lymphocyte ratio, treatment modality and radiation dose. Few studies have been done in Africa on laryngeal cancer survival. In Tanzania, no study has been done to date on laryngeal cancer survival. Therefore the aim of this study was to determine the factors that are associated with survival in patients laryngeal cancer treated at Ocean Road Cancer Institute in Tanzania.

1.2 Literature Review

1.2.1 Evolution of the management of laryngeal cancer

Total laryngectomy was popular during since the twentieth century. Despite its efficacy as an oncologic procedure, complete loss of the larynx, is a devastating event that results in

obvious significant diminution of quality of life for many individuals because of loss of speech. (17).

Despite the effectiveness of total laryngectomy, it became apparent that in many cases of the earlier stages of laryngeal cancer, removal of the entire larynx was not necessary for cure.

The basis for conservation surgery is that most otherwise healthy patients can adapt to loss of significant portions of the larynx while maintaining the functions of deglutition, breathing and speech. It has been shown that when partial laryngectomies are performed on well selected lesions the long-term survival rates are compatible with that of total laryngectomy for the same lesion.

The employment of non-surgical modalities has gone through three phases; radiation alone as an alternative to surgery, neoadjuvant radiation to selected patients who were likely to respond to subsequent therapeutic radiation therapy, and finally CRT either alone or in conjunction with salvage surgery.

Radiation alone

In the period from the 1940 - 1980, radiation therapy was often employed as an alternative to, and in preference to surgery as the initial treatment of both early and advanced laryngeal cancer (17). Results of treatment of early laryngeal cancer were, and still are, considered by many surgeons and radiation oncologists to be comparable to those obtained with surgery.

Neoadjuvant chemotherapy – the ‘‘VA Protocol’’

In 1991, the VA Laryngeal Cancer Study Group study ushered the era of organ preservation therapy (18). This study effectively demonstrated the efficacy of induction chemotherapy and radiation therapy in the treatment of advanced laryngeal cancer. Patients in the first arm of the study were treated initially by total laryngectomy. Patients in the second arm were treated initially with neoadjuvant chemotherapy followed by radiation therapy. Patients who did not respond to chemotherapy or who failed radiation therapy were treated with total laryngectomy. In this study, approximately two-thirds (64%) of all

non-surgically treated patients retained their larynges and their 5-year survival was equivalent to that of patients treated by initial total laryngectomy.

In 2003, the important phase III study RTOG 91-11 was published (19).Three arms were compared in this study. The first was radiation alone. The second was radiation with cisplatin. The third arm was induction cisplatin and fluorouracil for two cycles. If there was no response, salvage total laryngectomy was performed. If there was a partial or complete response, one additional cycle of cisplatin and fluorouracil was given, followed by definitive radiation therapy. The induction arm of this study showed similar overall survival as patients who underwent total laryngectomy in the VA larynx preservation study. Overall survival was similar for all three arms. Locoregional control was superior in the concurrent chemo radiation arm, but morbidity was also increased. Additionally, the highest rate of organ preservation (84%) was in the concomitant chemo radiation arm compared to the radiation monotherapy group (67%) and the induction chemotherapy group (72%). This study (RTOG 91-11) has effectively established that concurrent chemotherapy and radiation is the superior, non-surgical, larynx preserving strategy.

Chemo-radiation

Clearly, the results from the 1991 VA Laryngeal Cancer Study Group and RTOG 91-11 provide evidence that organ preservation treatment is an option for the appropriately selected patient with advanced laryngeal cancer.

1.2.2 Treatment Overview of Laryngeal Cancer

The choice of treatment modality depends on tumor stage, performance status, co-morbidity and functional outcome. Treatment of patients with laryngeal cancer is divided into two categories: tumors of the glottis and tumors of supraglottis. Tumors of subglottis are so uncommon.

For patients with carcinoma in situ of the larynx, the recommended treatment options include endoscopic removal (i.e. stripping and laser) or RT (20). For early stage glottic and supraglottic cancer, surgery (partial laryngectomy) or RT have similar effectiveness (21). There has not been a true comparative study between these two modalities, and it is highly unlikely that a prospective trial will be performed.

Resectable, advanced staged glottic and supraglottic primaries are usually managed with a combined modality approach. If treated with primary surgery, then total laryngectomy is usually indicated, although selected cases can be managed with conservative surgical techniques that preserve the vocal function. If total laryngectomy is indicated but laryngeal preservation is desired, concurrent systemic CRT is recommended (22). When using systemic CRT, high dose cisplatin is preferred (at 100mg/m² on day 1,22 and 43) (23). Definitive RT (without chemotherapy) is an option for patients with advanced laryngeal cancer who are medically unfit or refuse chemotherapy. For patients with T4a tumors who decline surgery the options are either concurrent CRT or induction chemotherapy with additional management based on response (19) (23).

Follow up examination in many of these patients may need to be supplemented with serial endoscopy of high resolution, advanced radiological imaging study techniques because of edema, fibrosis and scarring that may occur on laryngeal tissue and neck after high dose RT.

1.2.3 Survival of Laryngeal Cancer

Numerous studies have shown that OS rate of laryngeal cancer is higher in developed world than in developing world there are very few laryngeal cancer survival studies in developing world.

A retrospective study done in Denmark showed that the 5 years overall survival among patients with glottic cancer was 71% (16). Another retrospective study by Khoueir et al. in Spain among patients with T3 and T4 who were treated by total laryngectomy +/- radiation/chemotherapy it was found out that the 5 years OS was 57.5% (8). This relatively lower OS rate may be due to nature of study population which comprised only patients with advanced disease only. More or less similar findings were found in Germany by Ramroth et al. where it was found that 5 years OS was 66% (24). In retrospective analysis of the clinical efficacy of concurrent weekly cisplatinum – radiotherapy for patients with laryngeal carcinoma in Egypt which is semi developed country the five years OS were was 45% (14).

1.2.4 Predictors of laryngeal cancer survival

Various factors have been associated with overall survival of laryngeal cancer in the literature.

Age has been shown to be an important predictor of treatment outcome in laryngeal cancer. In a retrospective study by Reizenstein et al. in Sweden to assess how age affect treatment outcome of laryngeal cancer it was concluded that OS was worst among oldest although a significant proportion were cured (25). Several other studies have supported this finding although it is not known for sure whether this is due tendency to avoid radical treatment in the elderly patients or poor tolerance of elderly patients to radical treatment. In a retrospective study by Eldeeb et al. age was shown not to be associated with overall survival after treatment of early laryngeal cancer (26).

It is unknown whether there are survival disparities between men and women with laryngeal cancer and there are very few published data on this issue. Some data suggest that men have worse outcomes (27) and others suggest that there is no difference in treatment outcome with regard to sex (16)(26) .

Little information is known on role of cancer risk factors like cigarette smoking, alcohol drinking, socioeconomic status and diet on survival of laryngeal cancer. In a study by Boffeta et al. (27) it was shown that poor socioeconomic status and heavy cigarette smoking were associated with poor survival while diet and alcohol consuming were not associated with poor survival.

The symptomatology of laryngeal cancer is well known with hoarseness of voice being the commonest symptom in supraglottic and glottic laryngeal cancer but there is little information on the impact of symptomatology on outcome of treatment of laryngeal cancer. In a study by Pukander et al. in Finland it was shown that multiple symptoms, presence of dyspnea, globus, neck mass or haemoptysis indicated a significantly poorer prognosis (13).

Numerous instruments have been developed to assess the health status of patients. Different instruments may focus on particular aspect of health status that includes physical, functional and overall performance parameters. Some indices assess the overall functional

status, such as Karnofsky Performance Status Scale (KPS). The KPS, for example, is a rating scale used to quantify patients' functional capacity for work and daily activities of self care. Factors that influence ratings are the degree to which symptoms hinder work activities and amount of assistance needed in self care. In a study by Yucel et al. it was found that good performance status of patients with laryngeal cancer was statistically significantly associated with better survival (28).

Treatment delay has also been shown to influence survival of laryngeal cancer after treatment. Treatment delays can be broken down in two stages. The first stage spans from onset of symptoms to when histological diagnosis is made when the patient reaches specialized care. This stage is influenced both by the patient who denies symptoms as well as delay in primary care. The second stage is the treatment waiting time after histological diagnosis. Although the time spent in the first stage is usually longer, being responsible for the advanced stage of disease, delays in starting treatment may also bring about a worse outcome (29).The disproportion between increased demand and availability of radiotherapy treatment leads to an increase in the waiting times in developing countries like Tanzania where in developed countries the increase in waiting time is attributed to adoption of sophisticated radiotherapy machines which require more pretreatment evaluation.

Few studies have looked into the association between of duration of symptoms and survival of laryngeal cancer. Hansen O et al. assessed the relationship between the duration of symptoms before the start of radiotherapy and treatment outcome in stage I – III glottis cancer. They found that the median delay from onset of symptoms to the start of treatment was 4.4 months. The recurrence-free survival was significantly poorer for patients with duration of symptoms longer than the median value compared with patients with a shorter duration of symptoms (16). A study done by Pukander et al.(13) had different results by showing that the duration of symptoms was not associated with overall survival although there was a statistically significant association between duration of symptoms and stage of laryngeal cancer at presentation. One of setback of using duration of symptoms as a prognosticator of survival is the recall bias by the patients about the time of onset of illness.

Various studies have shown conflicting results regarding the effect of treatment waiting time on survival of laryngeal cancer. Eldeeb et al. have showed that the mean delay to start radiotherapy was 56.84 days among patients with laryngeal cancer in UK and this delay was not found to be associated with a significant survival difference (30). Leon et al. did a retrospective study on the effect of waiting time on survival of patients with head and neck cancers. The median waiting time in this study was 43 days and they concluded that waiting time to start radiotherapy did not affect survival of these patients (31). Brouha et al. in Netherlands (32) studied the outcome of 362 patients with early-stage laryngeal cancer with a median waiting time of 43 days and found no significant correlation between outcome and waiting time. Mutsoane et al. in Johannesburg have reported that the overall mean waiting time for treatment in the among laryngeal cancer patients was 98.5 days. In this study the mean waiting time was from the date when patient was first seen by the oncologist in their department to the date that treatment was started. The waiting time did not influence survival when compared with patients who were treated with radical intent (33). In another retrospective study to assess the effects of treatment waiting time on outcome of patients with early stage head and neck carcinoma receiving radical radiotherapy it was found out that treatment waiting time of more than 40 days was significantly associated with increased risk of poorer survival relative to patients treated in less than 30 days. They concluded that radiotherapy for squamous cell carcinoma of the head and neck should be started preferably within 20-30 days after evaluation by radiation oncologist (34).

Laryngeal cancer stage has been shown by various studies to an important predictor of survival in laryngeal cancer. Survival rates in the early-stage larynx cancers are higher relative to the patients with late-stage disease (28).The T stage (size of primary tumor) (28), N stage (extent of local-regional lymph nodes involvement) (27)(28) and M stage (distant metastasis) all have been shown to affect survival.

Location of tumor is also one of the predictors of OS. Given the fact that supraglottic cancers have more invasive phenotypes compared to glottic cancers; it is believed that supraglottic cancers generally have a poorer prognosis. The high incidence of lymphatic node metastases in supraglottic cancers may be one of the underlying reasons of this

deterioration. A study by Lars et al showed that glottic cancers have a better OS compared to supraglottic cancers (35)

Regarding histological grade, in general, poorly differentiated (higher grade) tumors tend to metastasize more readily then well-differentiated (lower grade) tumors and they have poor survival (35) however histological grade has limited impact on survival. Some studies have shown association between grade and survival (35) and others have not demonstrated this association (36).

Recent data have shown that inflammation is a critical component of tumor progression, and it is associated with a poor prognosis in various tumors, as an oncogenic change induces an inflammatory micro-environment that promotes the development of tumors (37). Studies have shown that a high level of neutrophils is associated with angiogenesis, which plays an important role in the growth and metastasis of malignancy. Furthermore, DNA damage and tumor metastasis suppress lymphocyte activity through the upregulation of cytokines that counteract the antitumor immune response (38).

Markers of inflammation such as the neutrophil to lymphocyte ratio (NLR) have been evaluated in various types of cancer as a prognostic indicator. The rationale of the NLR is to compare the host's inflammatory response (i.e., the neutrophils) to cancer with the host's immune response (i.e., the lymphocytes). A high NLR means an increased neutrophil count and/or a decreased lymphocyte count. High levels of neutrophil infiltration, in response to an altered balance of pro-versus anti-inflammatory cytokines, can be associated with cytotoxicity, angiostasis, and tumor regression (38). In a retrospective study done in China to investigate the association between overall survivals (OS) and the preoperative NLR in patients with advanced laryngeal squamous cell carcinoma undergoing total laryngectomy (TL) it was shown that Patients with an NLR more or equal to 2.59 showed a significantly lower OS than patients with an NLR less than 2.59 (39). NLR is easy to perform and is relatively inexpensive however its use a clinical prognosticator may be impaired by its interaction with coexisting cormobidities and various medications used.

Thrombocytosis is commonly observed in patients with solid tumors. Paraneoplastic thrombocytosis appears to involve a feedback loop, in which malignant tumors produce cytokines such as IL-6 that stimulate thrombocytosis and in turn platelets promote tumor progression. Several studies have found a link between increased platelet count and a worse prognosis in patients with lung, esophageal , gastric , colorectal , breast or gynecologic cancers (40). Numerous studies have analyzed the prognostic power of pretreatment platelet count on disease control in patients with head and neck squamous cell carcinoma (HNSCC), reaching contradictory conclusions. While some authors have found a significant relationship between a high platelet count and a decrease in overall survival (41) others showed that high or decreased platelet count compared to the normal ranges correlated with a poor prognosis (42). Finally, some authors did not find statistically significant correlation between the number of circulating platelets and outcome of treatment.

A retrospective study was done in Spain to analyze disease-specific survival according to the distribution of the platelet count in a large series of patients with head and neck squamous cell carcinoma (HNSCC). The platelet count of 250,000/µL was defined as a cut-off point with the best predictive capacity. The patients were classified into two groups: those with a high platelet count, and those with a low platelet count. On univariate analysis, there were significant differences in disease-specific survival depending on pretreatment platelet count. The 5-year specific survival rates were 74.1% and 61% for patients with a low and high platelet count, respectively (40).

As early as 1931, in an experiment with laboratory rats, Mottram demonstrated that the presence of anemia had an observable effect on the reactions of both normal tissues and transplanted tumors to ionizing radiation (43). The investigators noted that this observation “supported the clinical experience that anemic patients do not respond well to radiation” and they concluded “before treatment with radiation every endeavor should be made to bring the patient’s blood to as near normal as possible”(44).

Data suggest that most head and neck cancers contain a hypoxic cell subpopulation. Evidence comes from direct measurements of oxygen tension within tumors and also from histological and radiographic findings revealing the frequent presence of tumor necrosis in

head and neck cancers. Many investigators have found that tumor hypoxia adversely effects clinical radiotherapy outcome (i.e., local control) (45).

As stated earlier on data from the literature suggest that the outcome after curative radiotherapy for head-and-neck cancer is influenced adversely by the presence of anemia. Fein et al. have reported that pretreatment Hemoglobin level influences local control and survival in patients with T1–2 glottic cancers treated with radiotherapy. In their report, the 2-year local control rate for patients with a pretreatment Hemoglobin of less than or equal to 13 g/dl was 66% compared with 95% for patients with a pretreatment Hemoglobin level of more than 13 g/dl. Survival was similarly affected; for patients with Hemoglobin less than or equal to 13 g/dl, 2-year survival was 46% compared to 88% for patients with Hemoglobin more than 13 g/dl (46).

Tracheostomy is one of the common palliative treatment given to patients either before radiotherapy or during radiotherapy to relieve dyspnea. Some studies have shown that the need for tracheostomy is associated with poor outcome of treatment for patients with laryngeal cancer. In a retrospective study done by Tennant et al. to determine whether significant differences existed between patients who did and did not require tracheostomy before initiation of treatment it was shown that patients with advanced laryngeal cancer who require tracheostomy before radiotherapy had a lower overall survival compared to patients who did not need tracheostomy (47).

The poor survival of patients who have tracheostomy especially if it was done on emergency basis before radiotherapy is the increased rate of local failure as a result of local seeding of tumor cells during the procedure.

Overall treatment time is a very important factor determining outcome of head and neck cancers treated with radiotherapy. Overall treatment time can be prolonged when there is interruption of radiotherapy. Head and neck cancers are fast growing tumors with rapid proliferation and treatment with radiation can trigger surviving cells in the tumors to divide faster than before i.e. accelerated repopulation. The clonogen repopulation accelerates at about 28 days after initiating radiotherapy and local control is reduced by about 0.4 to 2.5 % for each day that the overall treatment time is prolonged (48).

In a review of literature trying to elucidate the effect overall treatment time of radiotherapy on survival in head and neck cancer it was found total days of OTT prolongation seem to be what really matters if prolongation is short (e.g., less than or equal to one week).Treatment interruption gap position and the number of missed consecutive treatment were found to have no prognostic significance, except, perhaps, in longer extensions (more than one week). The conclusion of the study was that prolongations of more than or equal to 3 days in total, irrespective of the position, should be discouraged (49). In another study done in UK it was found that there was no impact of radiotherapy treatment interruption for 1-2 days on overall survival among laryngeal cancer patients (26). A retrospective study done by Mendenhall et al. in USA intending to look at the end results after radiation therapy for T1-T2N0 glottic carcinoma it was shown that the 5-year survival rate for the overall group was 79%. Multivariate analysis of absolute survival showed that only overall treatment time significantly influenced this end point (36).

Irrespectively of the modality of primary treatment for laryngeal squamous cell carcinoma, local or loco-regional residual or recurrent tumors represent the major cause of treatment failure, emphasizing the role of loco-regional control for the patients' long-term survival. Radiotherapy doses of around 60-70 Gy have been associated with better loco-regional control and survival (50).

1.3 Problem statement

Currently there is a dearth of data on the pattern of occurrence and survival of laryngeal cancer in Tanzania. Most of the studies to assess the survival after treatment of laryngeal cancer have been done in more developed countries than Tanzania where resources are readily available.

Laryngeal cancer is highly curable cancer however in our setup the meager resources result in delay in diagnosis, delay in initiation of treatment and frequent treatment interruption, all of which could negatively impair survival.

Moreover most of our patients are of low socio-economic background and they have poor nutritional support. As a result anemia is highly prevalent in majority of patients at ORCI.

Anemia can result in impaired oxygenation of tumors and therefore decrease the therapeutic efficacy of radiation therapy which ultimately may lead poor survival.

This study aimed to assess the overall survival and predictors of overall survival of patients with laryngeal cancer at ORCI.

1.4 Rationale of the study

Findings from this study allowed us to compare our laryngeal cancer survival rates with those from other parts of the world. In addition this study looked at predictors of survival of patients with laryngeal cancer in our set up and therefore hopefully it will influence an improvement in the management of these patients.

1.5 Research Question

What is the 5 years overall survival of laryngeal cancer patients treated at ORCI and what are its predictors?

1.6.1 Null Hypothesis

There is no difference in overall survival of patients with laryngeal cancer with regard to socio-demographic characteristics, clinic-pathological factors and treatment modalities

1.6.2 Alternative Hypothesis

There is a difference in overall survival of patients with laryngeal cancer with regard to socio-demographic characteristics, clinic-pathological factors and treatment modalities.

1.7 Objectives

1.7.1 Broad Objective

The aim of this study was to determine the five years overall survival rate and factors associated with survival of patients with laryngeal cancer treated at ORCI in the period of 2008- 2012.

1.7.2 Specific Objectives

1. To determine social demographic characteristics and disease characteristics of patients with laryngeal cancer treated at ORCI in the period of 2008- 2012.

2. To determine the treatment modalities of patients with laryngeal cancer treated at ORCI in the period of 2008- 2012.

3. To determine 5 years overall survival rate of patients with laryngeal cancer treated at ORCI in the period of 2008- 2012.

4. To determine the association between socio-demographic, clinic-pathologic characteristics, treatment modalities and 5 years overall survival rate of patients with laryngeal cancer treated at ORCI in the period of 2008- 2012.

2.0 RESEARCH METHODOLOGY

2.1 Study design

The study design was a retrospective descriptive.

2.2 Study Setting

The study was conducted at ORCI which is currently the only tertiary referral hospital for treating cancer in Tanzania. The services offered include radiotherapy, chemotherapy, cancer screening, nuclear medicine, radiology, laboratory, ARV clinic and palliative care. The hospital can accommodate up to 270 inpatients. The hospital has two Cobalt-60 teletherapy units and two Cobalt-60 brachytherapy units. Approximately 4190 new cancer patients are seen at ORCI annually out of which approximately 5% have laryngeal cancer.
The storage of medical records at ORCI is both paper-based and electronic. The electronic medical storage started in 2016.The medical records that were reviewed for the purpose of this study were all paper-based. ORCI has a hospital based cancer registry. All information from medical records is usually extracted and entered in this registry.

Follow up examination after treatment of patients with laryngeal cancer is usually done every three months during the first two years, then every six months during the third to fifth year and there after annually. Follow up examination include history and physical examination and occasionally referral for laryngoscopy.

2.3 Treatment Protocol at ORCI

Radiation Therapy

Before treatment the patient has to be counseled about the treatment and side effects and informed consent is obtained. All patients treated with radical intent have to be sent for dental assessment and clearance prior to treatment.

Neck scars and the tracheostoma (if present) are wired. Patients are immobilized in a mask in supine position and neck in extension. Conventional simulation is used to delineate the part to be treated. Fields are delineated according to extent of disease. Cobalt-60 teletherapy unit is used for treatment.

The total radiation dose for T1/T2 disease is 62Gy/31 fractions to 66Gy/33 fractions and for T3/T4 disease is 70Gy/35 fractions. If patient has a tracheostomy the stoma is boosted with 20Gy in 10 fractions. During radiation therapy patients are assessed for treatment toxicity.

Glottic larynx traditional field design

For T1N0, 5 × 5-cm field size is used with the superior border at the top of the thyroid cartilage, the inferior border at the bottom of the cricoid, a 1-cm skin flash anteriorly, and a 2-cm margin posteriorly (or the anterior edge of the vertebral body)

For glottic T2N0, the field size is increased to 6 × 6 cm with the inferior border one tracheal ring below the cricoid.

For T3–4N0, the superior border is extended to 2 cm above the angle of the mandible, the posterior border behind the spinous processes, and the inferior border to include 1.5–2 cm margin on the subglottic extent of the tumor.

The lateral opposed fields are marched the low-neck anterior-posterior field.

The lateral fields are treated to 42–45 Gy , then the posterior border is moved off-cord by reducing the extended field so that posterior border now lies at the junction of the posterior third and anterior two thirds of the vertebral body, to spare the spinal cord.

Supra-glottic larynx traditional field design

For T1N0 the primary tumor and levels II–III lymph nodes are treated.

For T2–3, also low-neck is treated because of increased risk of microscopic nodal disease.

Advanced cases are treated as described above for glottic

Chemotherapy

Cisplatin 40 mg/m2 is given weekly to patients treated with radical intent. Before administration bloods are taken for Full blood count (ANC>1, hemoglobin of 10g/dl as long as not less than 7g/dl, platelets more than 50 cells/µl), urea and creatinine.

Creatinine clearance is calculated using the Cockcroft and Gault formula and if more than 60mils/min chemotherapy continues, if less than 60mils/min chemotherapy is not given.

Cockcroft and Gault formula

140-age (years) x weight (kg) x 1.23 / creatinine (mmol) for males

140-age (years) weight (kg) x 1.04 / creatinine (mmol) for female

Each patient is given pre-hydration using normal saline prior to chemotherapy. Anti emetic drugs including: 5-hydroxytryptamine-3 (5HT3) receptor antagonist, i.e. Granisetron or Ondansetron which significantly reduces acute cisplatin-induced emesis are given.

2.4 Study participants

The target population: All patients with laryngeal cancer in Tanzania.
Accessible population: All patients referred to ORCI with diagnosis of laryngeal cancer.
Study population: All patients with laryngeal cancer who fulfill the eligibility criteria.

2.4(a) Inclusion Criteria

These were age >18 years and laryngeal cancer confirmed by histopathology examination of tissue obtained via direct laryngoscopy and biopsy.

2.4(b) Exclusion Criteria

These included previous malignancy, previous radiotherapy or chemotherapy, serious co-morbidities and incomplete medical records

2.5 Endpoints

The primary end point of this study is 5 years overall survival.

Overall survival (OS) was calculated as time from end of RT to death or LFP.
LFP was defined as the failure of patient to attend two scheduled follow up clinics.
Alive was defined as status of patient being alive at last time of last scheduled follow up clinic or a status of patient being alive as confirmed by patient's next of kin via telephone.
Death was confirmed by viewing medical records or by contacting next of kin of the patient.

2.6 Sample size

The sample size for laryngeal cancer was calculated using a single proportion formula:

$$\mathbf{n = z^2 p (100- P)/ \varepsilon^2}$$

Where;

n= Minimum sample size required

z =Point on standard normal deviation corresponding to 95% Confidence Interval

∴z =1.96 (Zx of 1.96 approximated to 2)

p = Proportion of laryngeal cancer patients seen at ORCI (5%)

ε = Margin of error set at 5%

n = (2)2x5x95/ (5)2 = 76

From the formula the minimum sample size required was 76 patients. The sample size was increased to 82 to account for the loss to follow up.

2.7 Sampling method

Laryngeal cancer patients registered at ORCI from 2008- February 2012 were used in preference to other years due to the fact that this is the most recent year for study that needs five years of patient follow-up.

2.8 Data Collection

Details on patient characteristics, tumor characteristics, treatment, and the primary endpoint were extracted from medical records and used for analysis. Biologically effective dose was calculated using an alpha beta ratio of 10 so as to compare different radiotherapy regimens.

For patients who missed two consecutive scheduled follow up clinic a phone call was made to patient's next of kin asking about progress of the patient. If, during the telephone interview the patient was confirmed to have died, the next of kin was asked about the exact date of death. Patients who could not be reached or who refused to give information or whom next of kin refused to give information were considered lost to follow up.

2.9 Research Instrument

Interviewer administered structured questionnaire was used for data extraction.

2.10 Covariates

The independent variables were age, sex, education status, marital status, occupation, tobacco and alcohol consumption, performance status, stage, histological grade, location of

the tumor, histology, duration of symptoms, duration of treatment waiting time, overall treatment time, year of treatment pretreatment hemoglobin level, pretreatment NPL, pretreatment platelet count, treatment intention, type of treatment , total radiotherapy dose.
Treatment intention was either curative intention when the total radiotherapy dose was more than 60 Gy or palliative intention when the total radiotherapy dose was less than 60 Gy.
HIV status was not used as a covariate because HIV screening was not routinely done prior to the year 2012.
The dependent variable was the five years overall survival.

2.13 Data Management

The questionnaires were coded prior to data entry. The coded data was entered into the computer using SPSS on a daily basis. To reduce the possible errors made during the data entry process, Check function of SPSS including logic check, possible ranges and legal value set-up will be employed.

2.14 Data analysis

SPSS version 21 (SPSS Inc., Chicago, IL) was used for statistical analysis. Survival curves were estimated by the Kaplan-Meier method. X^2 test and Fisher's exact test were used to compare proportions. Means were compared by using independent sample t-test. To identify factors predictive of survival outcome, the covariates were analyzed by univariate analysis by using the log-rank test. Factors significant on univariate analysis were then assessed by multivariate analysis using a Cox regression model. Drop-outs were considered as censored information and a P value of less than 0.05 was considered statistically significant.

2.15 Ethical issues

Ethical clearance was sought from Ethical Clearance Board (IRB) of the Muhimbili University of Health and Allied Sciences (MUHAS). The approval to conduct the study was sought from Ocean Road Cancer Institute including the use of medical records for the extraction of the information for the study. Confidentiality was observed when extracting information from the files and even after the study period.

Each patient who met the inclusion criteria received a phone call that started with a concise informative introduction about the study and included an oral consent to take part in it, based on absolute anonymity.

When a phone call was made to the next of kin, a question was asked about the progress of the patient if the patient has missed scheduled follow up clinic and wait for the relatives to volunteer the information regarding the status of the patient. If the patient was alive, an advice to bring the patient for the scheduled follow up clinic was offered and if the patient was dead, condolences were express accordingly and the exact date of death was asked.

3. RESULTS

One hundred and thirty nine patients with squamous cell carcinoma of the larynx treated at ORCI between January 2008 and December 2012 were reviewed and 82 patients were found to be eligible for inclusion in the study. Patients who could not meet the inclusion criteria were excluded. This was done in order to achieve a minimum sample size of 76 patients. All patients had at least 5 years of follow-up.

Table 3. 1: Socio demographic characteristics of the study population (n=82)

Variable		Frequency	Percentage
Age	31-60	45	54.9
	>61	37	45.1
Sex	Male	75	91.5
	Female	7	8.5
Marital Status	Married	64	78
	Single	8	9.8
	Divorce	4	4.9
	Widow	5	6.1
	Cohabiting	1	1.2
Educational Status	None	11	13.4
	Primary School	27	32.9
	Secondary School	19	23.2
	Post Secondary School	25	30.5
Occupational Status	Peasant	43	52.4
	Civil Servant	16	19.5
	Retired	12	14.6
	Self Employed	11	13.4
Tobacco Use	Current Smoker	56	68.3
	Past Smoker	6	7.3
	Never Smoked	17	20.7
	Unknown	3	3.7
Alcohol Use	Current drinker	46	56.1
	Past drinker	12	14.6
	Never drank	21	25.6
	Unknown	3	3.7

Table 1 shows the social demographic characteristics of study population. The mean and median ages at diagnosis were 61 and 60 years with a range of 41 to 84 years. The male to female ratio was 10:1. Majority of the study participants were married (78%).The education level of the study participants was equally distributed among different categories. Majority of study participants were current smokers (68%) and current alcohol drinkers (56%).There was an association between tobacco consumption and gender whereby more male were current cigarette smokers than females by Chi-Square test (P=0.025).

Table 3. 2: Clinical– pathologic characteristics of the study population (n=82)

Variable		Frequency	Percentage
Presenting symptoms	Hoarseness of voice	74	90.2
	Dyspnea	43	52.4
	Cough	16	10.0
	Neck mass	14	19.5
	Dysphagia	8	17.1
	Sore throat	2	2.4
	Otalgia	1	1.2
	Odynophagia	1	1.2
	Aspiration	1	1.2
KPS (%)	Less than 80	40	51.2
	More than 80	42	48.8
Duration of symptoms (months)	<6	27	32.9
	7-12	28	34.1
	>13	27	32.9
Duration of waiting time (days)	<30	49	59.8
	31-60	15	18.3
	>61	18	22.0
Histological grade	1	42	51.2
	2	24	29.3
	3	16	19.5

Table 2 shows that hoarseness of voice was the commonest presenting symptom (90.2%). Around half of the study participants had a low performance status (KPS less than or equal to 80). The mean and median duration of symptoms was 14 and 12 months respectively and it ranged from 3 to 48 months. The mean and median duration of treatment waiting time were 55 and 30 days respectively and it ranged from 1 to 378 days.

Table 3. 3: Clinical– pathologic characteristics of the study population (n=82)

Variable		Frequency	Percentage
T stage	T1 & T2	20	24.4
	T3 & T4	62	75.6
N stage	N0	55	67.1
	N1	11	13.4
	N2	9	11.0
	N3	7	8.5
Neck Nodes	Positive	27	33.0
	Negative	55	67.0
M stage	M0	80	97.6
	M1	2	2.4
TNM Stage	1	16	19.5
	2	6	18.6
	3	28	32.1
	4	32	39.0
Location of tumor	Supraglottis	30	36.6
	Glottis	51	62.2
	Subglottis	1	1.2
Pretreatment Hb (g/dl)	<9	8	9.8
	>9	74	90.2
Pretreatment platelet (10^3/µL)	<319	41	50.0
	>319	41	50.0
Pretreatment NLR	<2.4	42	51.2
	>2.5	39	48.8

In Table 3 further clinical pathological characteristics are shown. The majority of the study participants (75%) had advanced T stages (T3 and T4) and 33% had positive neck nodes.

Glottis was the commonest tumor site (62%). Most of the patients (73.1%) had advanced TNM stages (stage 3 and stage 4). About 76% of patients with supraglottic cancer had nodal metastasis whereas about 37% of glottic cancer had nodal metastasis. Around 90% of supraglottic cancers were in T3 and T4 stages while only 68% of glottic cancers were in T3 and T4 stages. The mean pretreatment hemoglobin level was 11g/dl. The mean pretreatment NLR was 2.44 and mean pretreatment platelet count was 328,000 /µL.

Table 3. 4: Treatment modalities among patients with laryngeal cancer seen at ORCI

		Whole cohort (n=82)		Curative treated cohort (n=11)		Palliative treated cohort (n=71)	
Variable		**Frequency**	**%**	**Frequency**	**%**	**Frequency**	**%**
Tracheostomy	Yes	62	75.6	7	63.6	55	77.5
	No	20	24.4	4	36.4	16	22.5
Blood transfusion	Yes	6	7.3	0	0	6	8.5
	No	76	92.7	11	100	65	91.5
Initial treatment	RT	49	59.8	6	54.5	43	60.6
	CRT	33	40.2	5	45.5	28	39.4
Number RT fields	2 fields	70	85	10	90.9	60	84.5
	3 fields	1	1.2	0	0	1	1.5
	4 fields	11	13.4	1	9.1	10	14
Type of Chemotherapy (n=33)	Weekly Cisplatin	28	84.8	4	80	24	85.7
	Weekly Carboplatin	4	12.2	0	0	4	14.3
	Three weekly Cisplatin & 5-FU	1	3	1	20	0	0
Treatment interruption	<3 days	42	51.2	4	36.4	38	53.5
	>3 days	40	48.8	7	63.6	33	46.5
OTT	<30 days	42	51.2	0	0	42	59.1
	>30 days	40	48.8	11	100	29	40.9
BED (Gy)	<48	41	50.0	0	0	41	57.7
	>48	41	50.0	11	100	30	42.3

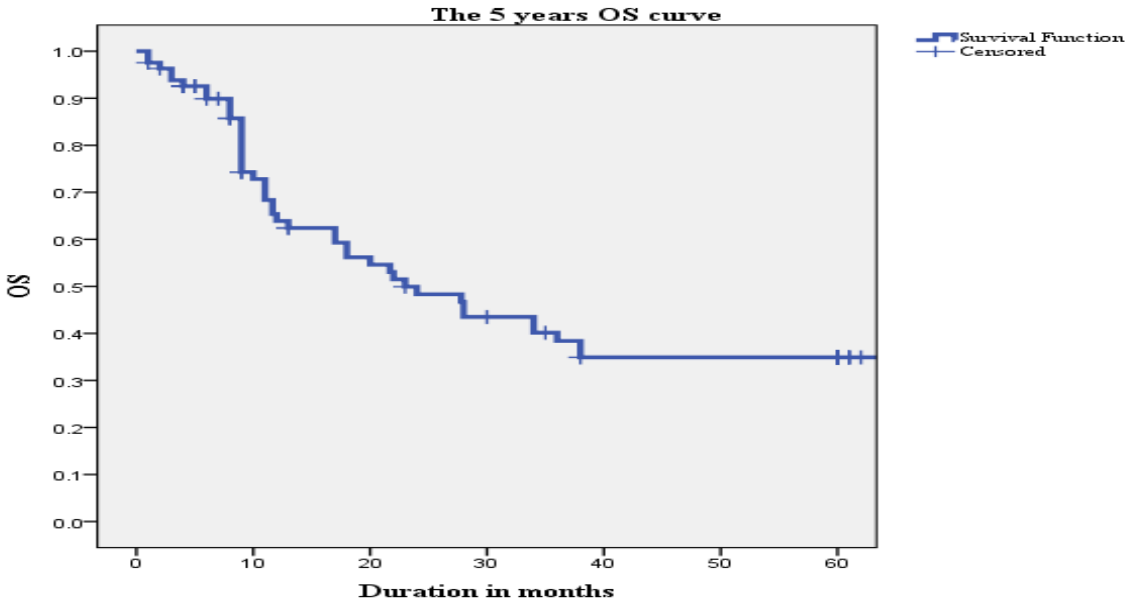
Table 4 shows that 62 patients (75%) had tracheostomy and there was no statistically significant difference in the tracheostomy rate between patients treated with curative and palliative intention according to Chi-Square test. Out of these patients who had tracheostomy most (82%) had advanced stages (T3 and T4) compared to early T stages and this was statistically significant by Chi-Square test (P=0.014). Most of the patients in the whole cohort (85%) of patients were treated by 2 radiotherapy fields. Among those who had concurrent chemo-radiotherapy as an initial therapy the commonest radio- sensitizer chemotherapy in the whole cohort was weekly cisplatin (87%).

The mean treatment time was 32 days for the whole cohort and it was 29 days for patients who were treated palliatively and 58 days for patients who were treated curatively.

The mean duration of treatment interruption was 5.4 days for patients who were treated palliatively and 20.7 days for patients who were treated curatively and the difference was statistically significant according to independent sample t-test (t(80)= -3.35, P=0.000) .

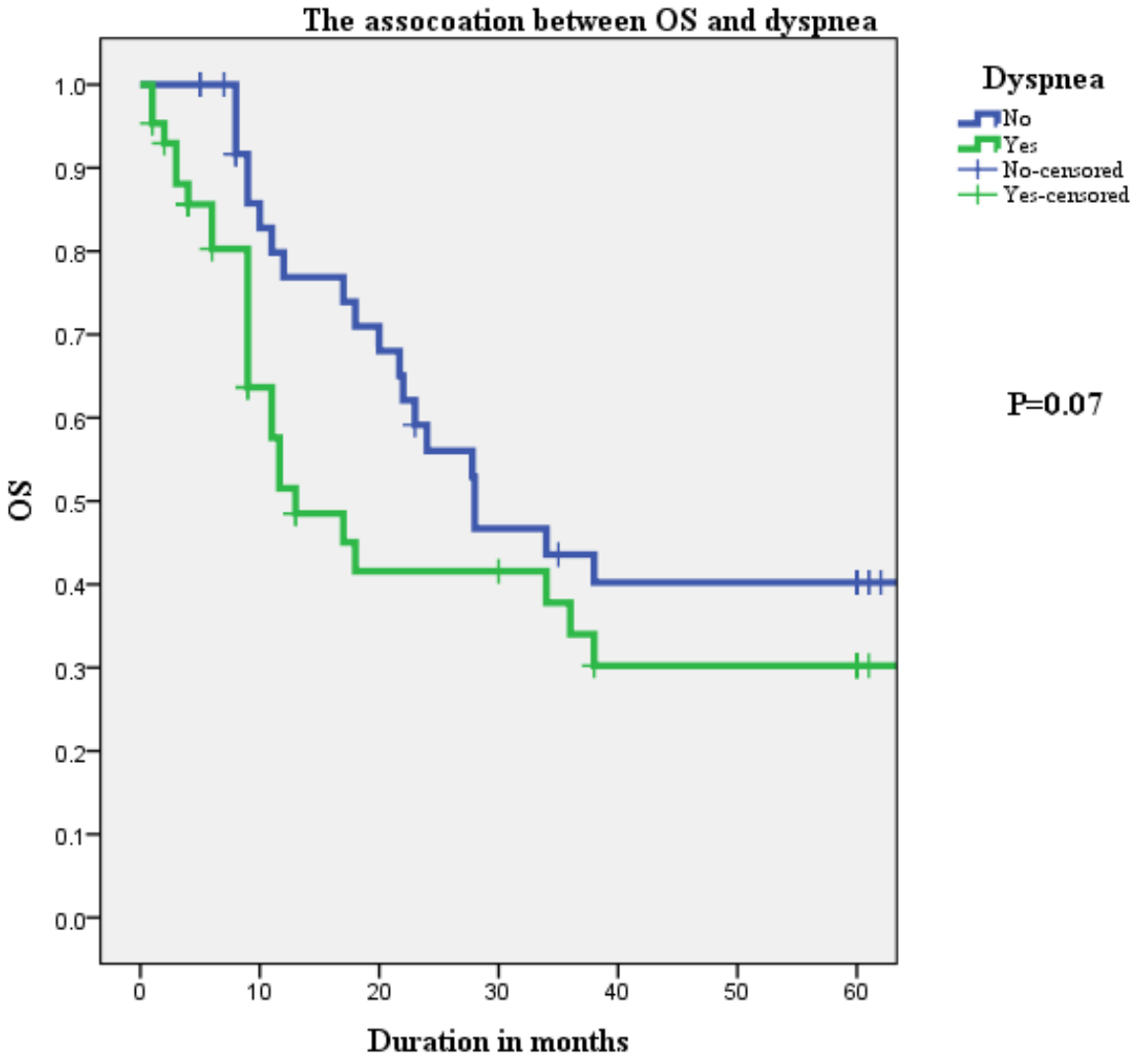
Using the alpha beta ratio of 10 the mean BED was 55 Gy for the whole cohort which corresponds to $EQD_{2\ of}$ 45.8 Gy. The mean BED for patients who were treated curatively was 81.4 Gy which corresponds to EQD_2 of 67.8 Gy and BED for patients who were treated palliatively was 51.2 Gy which corresponds to 42.7 Gy.

Figure 3. 1: Overall survival rate of the study population for whole cohort (n=82)



According to Figure 1 the 3 years OS and 5 years OS were 35% and 29% respectively for the whole cohort. The mean survival time was 34 months 95% CI (27-40) and median survival time was 23 months 5%CI (13-32) for the whole cohort. There was no difference in overall survival rates between patients who were treated with curative intention and those who were treated with palliative intention.

Figure 3. 2: The association between OS and dyspnea for the whole cohort (n=82)



In figure 2 there was a trend for poor survival for patients who had dyspnea as an initial present but the association was border line statistically significant.

Figure 3. 3: The association between OS and KPS for the whole cohort (n=82)

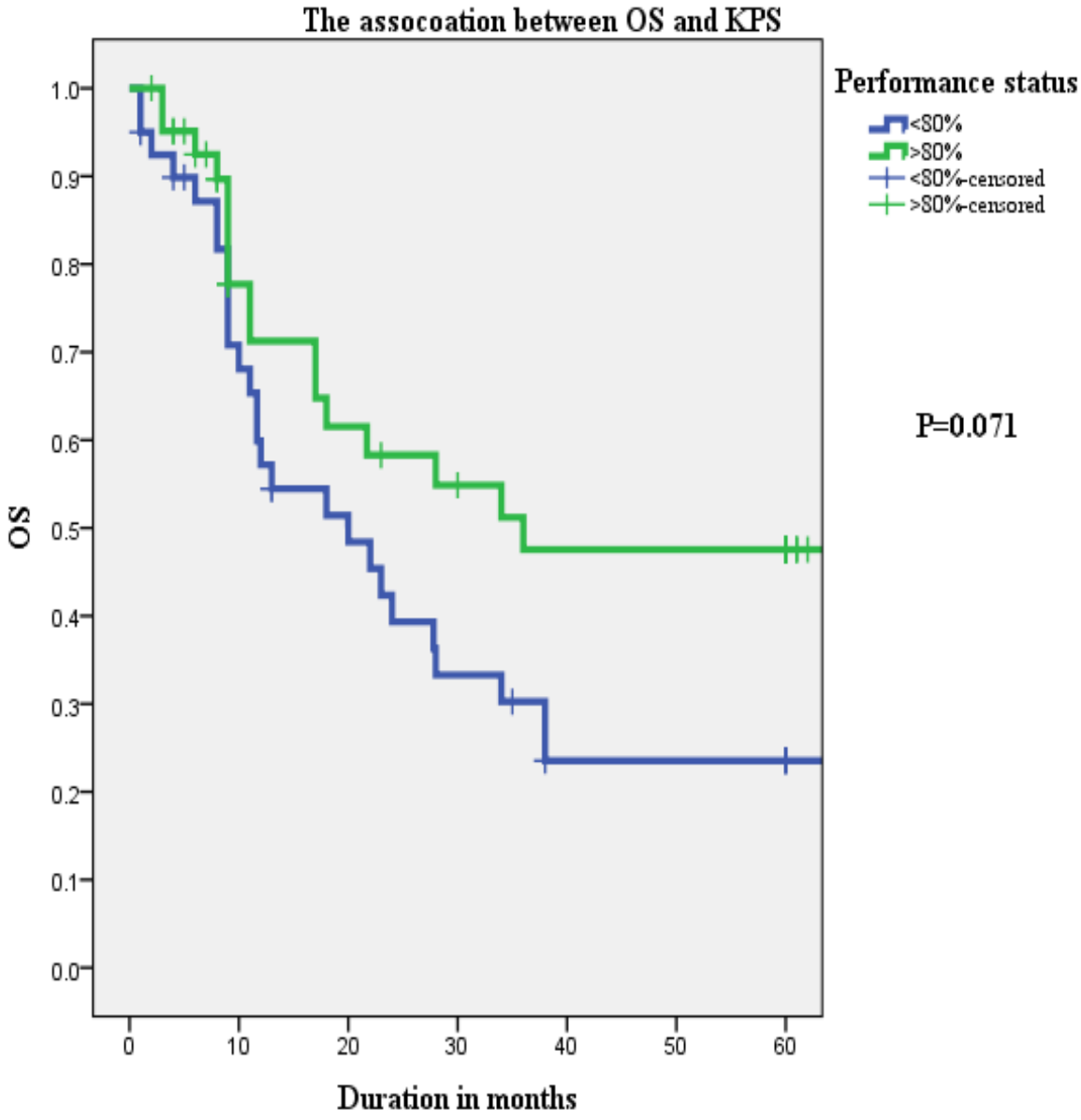


Figure 3 shows that there was a trend for patients with higher performance status to have a higher 5 years OS but the association was not statistically significant.

Figure 3. 4: The association between OS and location of tumor for the whole cohort (n=82)

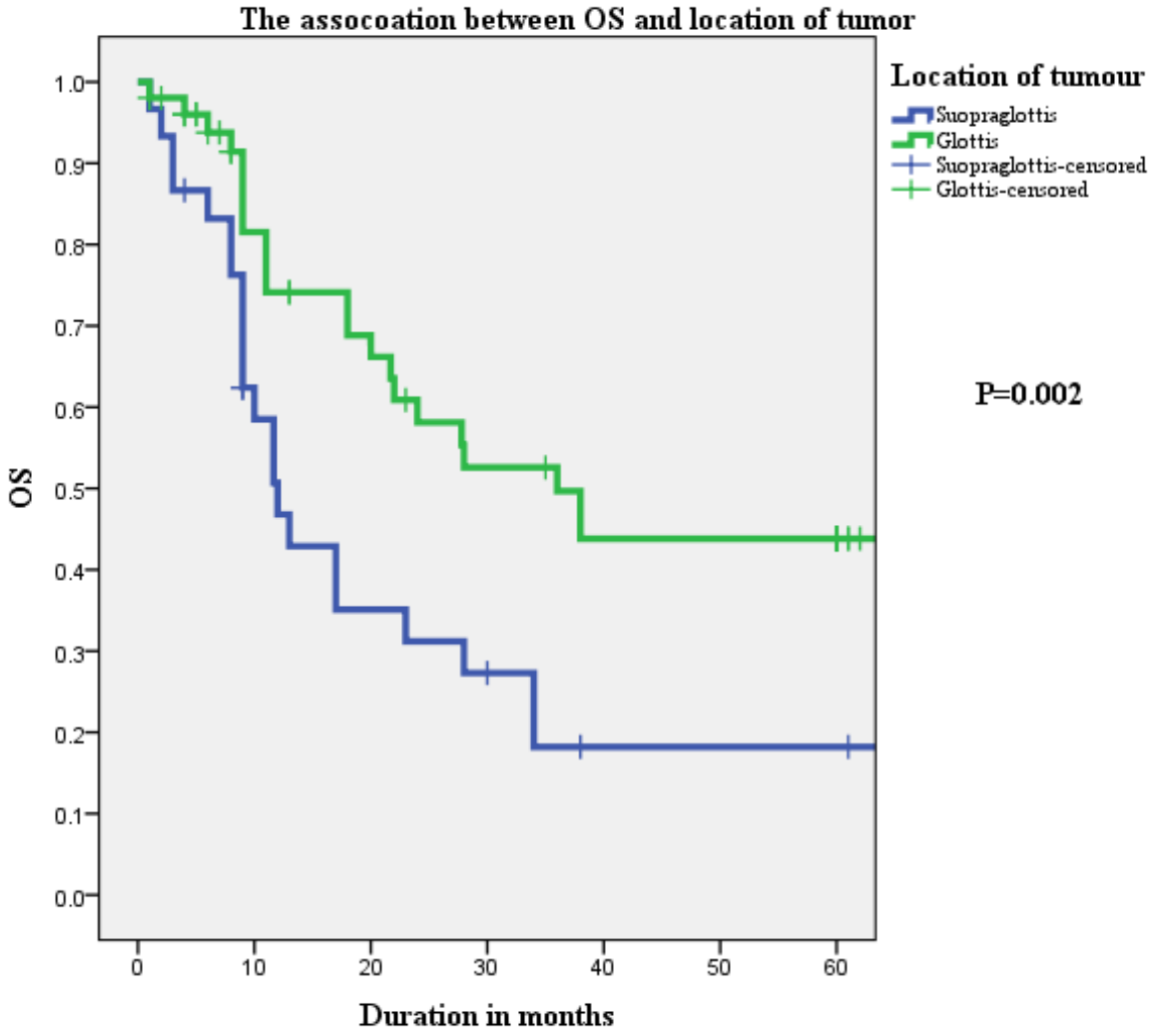
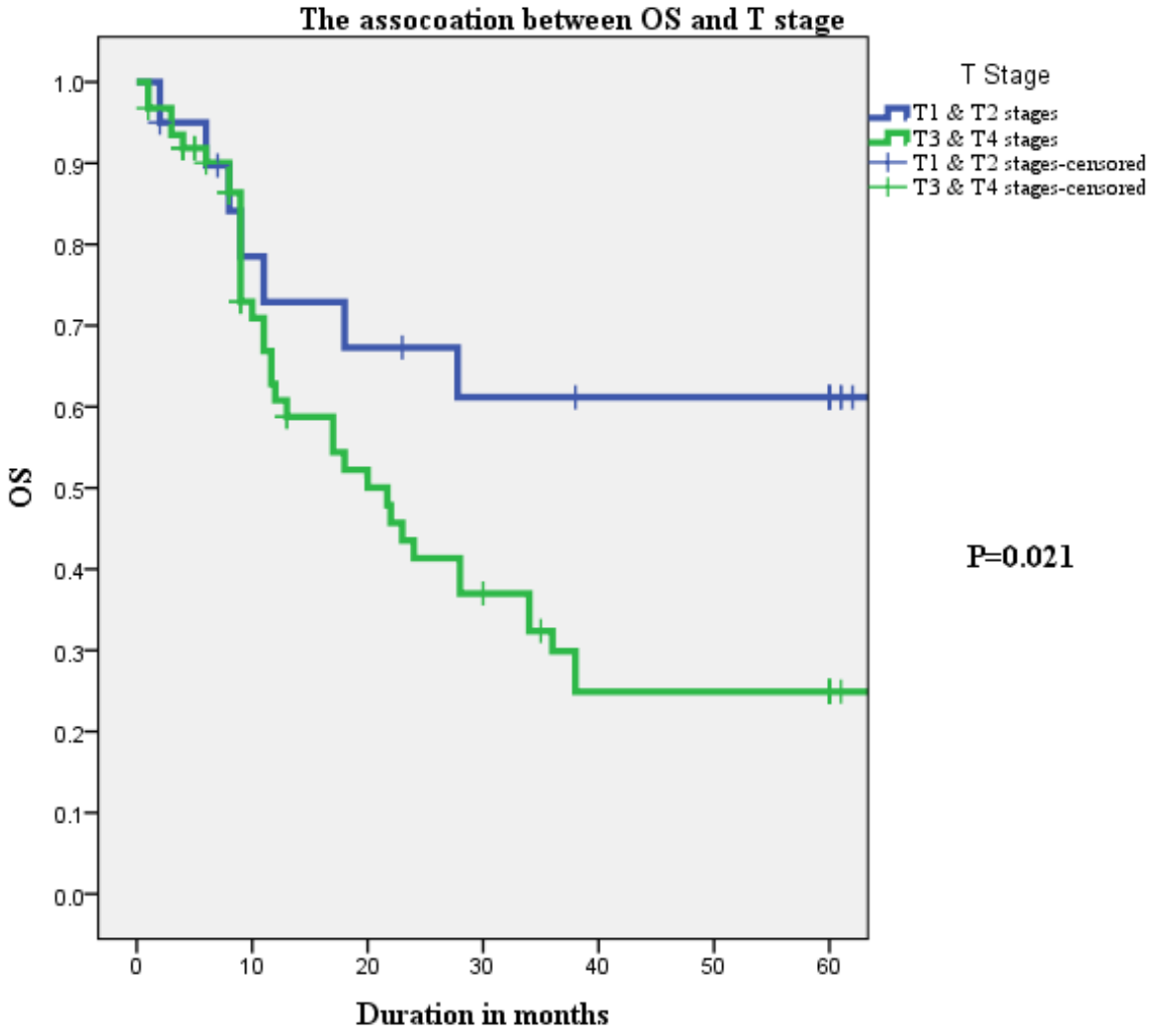


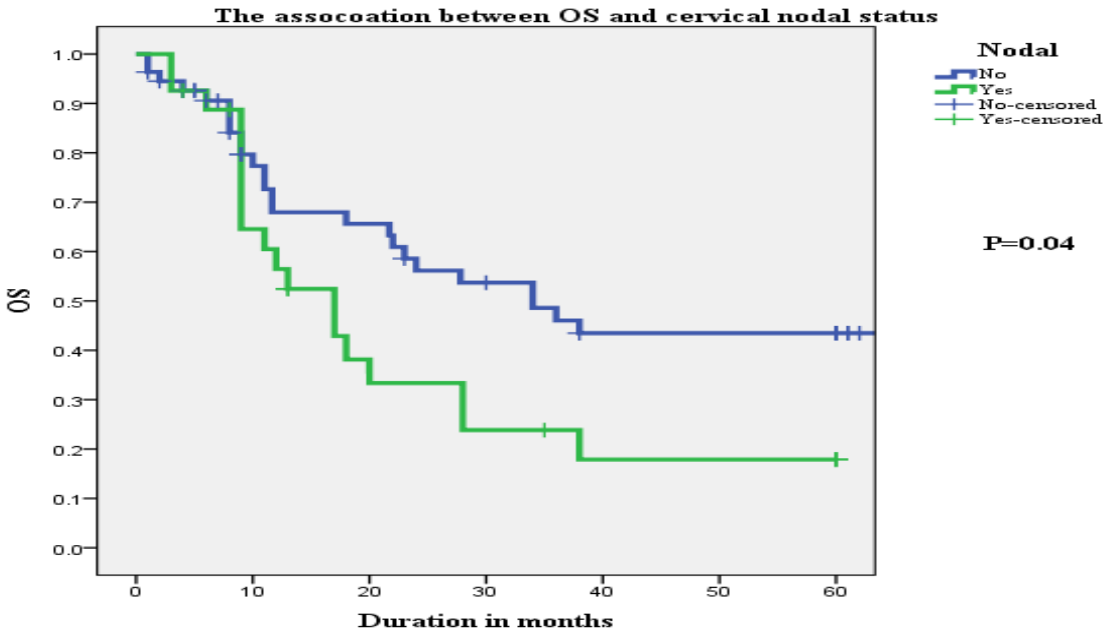
Figure 4 depicts a higher 5 years OS rate for patients who had glottic cancer than patients with supraglottic cancer. Subglottis site was excluded in the analysis because there was only one patient.

Figure 3. 5: The association between OS and T stage for the whole cohort (n =82)



According to Figure 5 patients with early T stage had a higher 5 years OS rate than patients with advanced T stages.

Figure 3. 6: The association between OS and neck nodal status for the whole cohort (n=82)



In accordance to Figure 6 presence of neck nodes was associated with a lower 5 years OS rate.

Figure 3. 7: The association between OS and level of hemoglobin for the whole cohort (n=82)

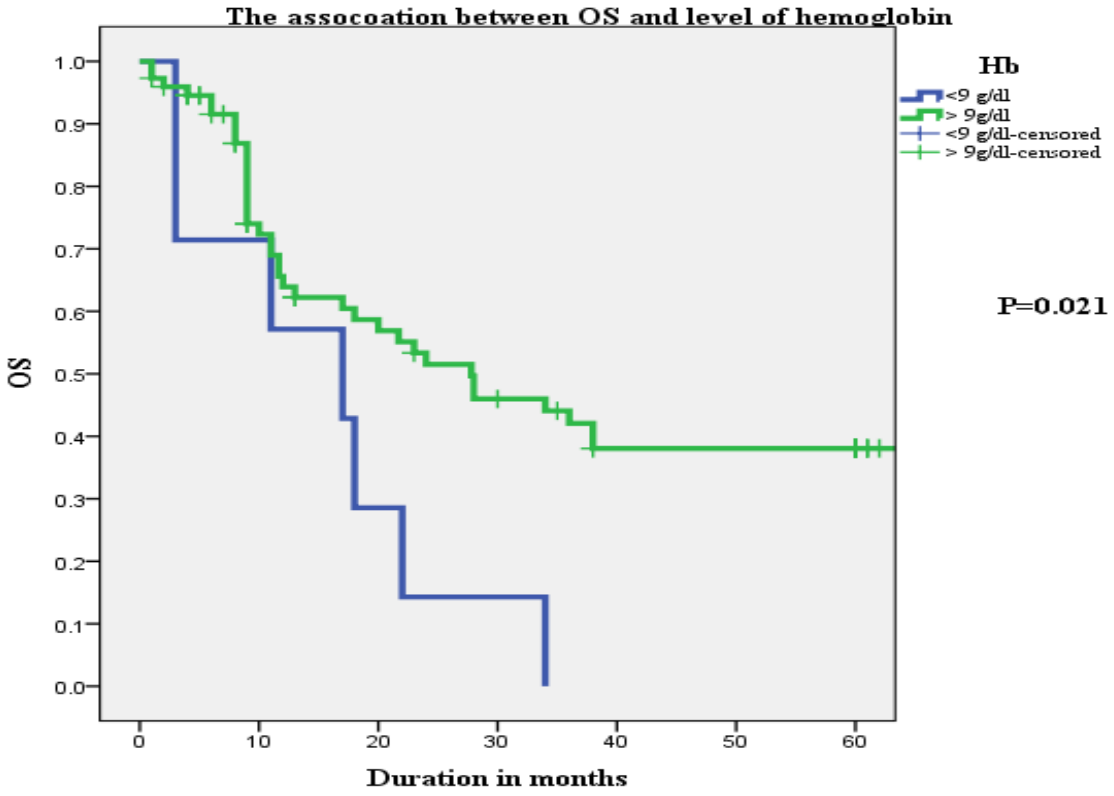


Figure 7 shows that the patients with hemoglobin less than 9 had poor 5 years OS rate compared to those with hemoglobin higher than 9.

Figure 3. 8: The association between OS and blood transfusion for the whole cohort (n=82)

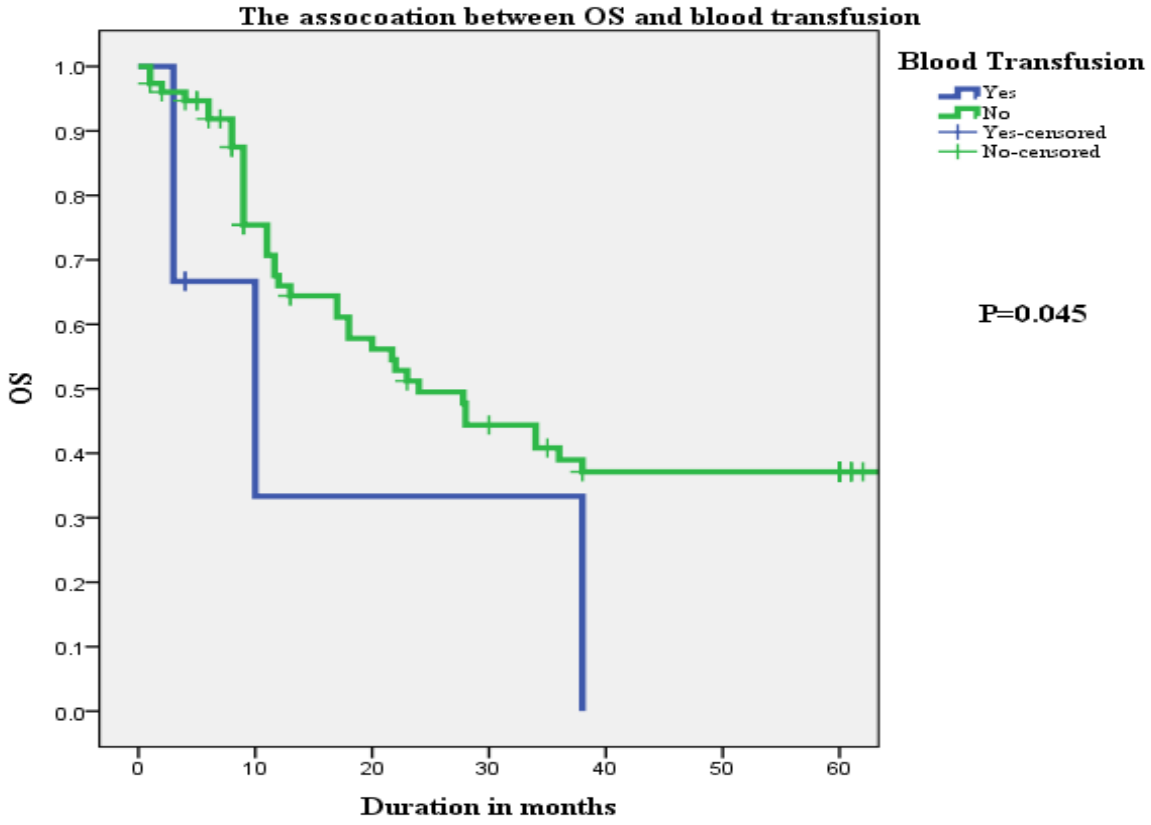


Figure 8 shows patients who had blood transfusion prior to treatment had a lower 5 years OS rate.

Figure 3. 9: The association between OS and BED among patients treated with palliative intention (n=71)

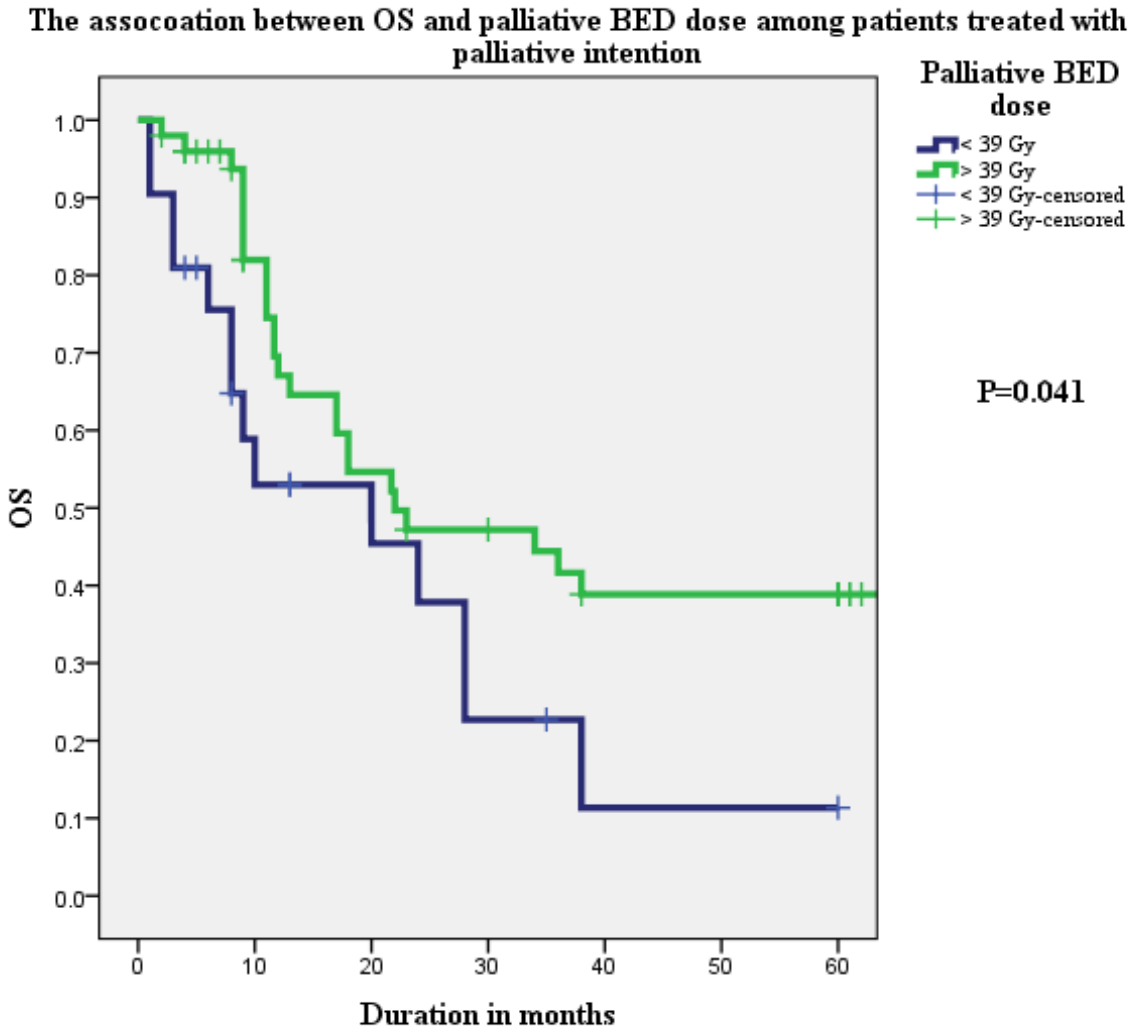


Figure 9 shows that patients who were treated with palliative BED higher than 39 Gy (EQD_2 = 32 Gy) had a higher 5 years OS.

Others covariates like age, gender, marital status, educational status, occupational status, tobacco use, alcohol use, pretreatment platelet count, pretreatment NLR ,duration of symptoms, treatment waiting time, overall treatment time duration, duration of treatment interruption ,type of initial treatment and year of diagnosis did not have a statistically significant association with 5 years OS.

Table 3. 5: Summary of univariate and multivariate analysis

Prognostic factor		N	5 years OS (%)	Univariate analysis (log rank test)	Multivariate analysis (Cox proportional hazard model)
Gender	Male	75	29	P=0.43	–
	Female	7	37		
Dyspnea	Yes	43	34	P=0.078	–
	No	39	24		
KPS	<80	40	17	P=0.071	–
	>80	42	42		
Location	Supraglottis	30	4	P=0.002	P= 0.009
	Glottis	*51*	*45*		
Hemoglobin	<9g/dl	7	0	P=0.021	P= 0.075
	>9g/dl	74	35		
BT	Yes	6	0	P=0.049	P= 0.058
	No	76	30		
T Stage	T1 &T2	20	49	P=0.021	P= 0.845
	T3 & T4	62	21		
Neck nodes	Yes	66	81	P=0.04	P= 0.107
	No	16	0		
Treatment	Radical	11	34	P=0.211	–
	Palliative	71	28		

According to Table 5 only location of the laryngeal was statistically significant in multivariate analysis.

4. DISCUSSION

In this study the mean and median ages at diagnosis were 61 and 60 years with a range of 41 to 84 years. This finding is in keeping with other studies which have shown that laryngeal cancer is a disease of elderly people. The mean age at diagnosis of laryngeal cancer in Lebanon is 64 years (8). Previous studies have shown that advanced age is associated with poor OS (24) (25) and the reason put forward for this observation was tendency to withhold radical treatment when treating elderly patients and to some extent poor tolerance of elderly people to radical therapy. In the current study there was no association between age and OS. The reason could be that in this study advanced age was not used as an excuse to withhold radical treatment of laryngeal cancer patients and indeed there was no statistical difference in the choice of treatment with regard to age even though majority of patients (62%) were treated with palliative radiotherapy only.

The male to female ration in this study was 10:1. Most previous studies have shown that there is a preponderance of laryngeal cancer among males as compared to females. This is due to different levels of exposure to the main risk factors of laryngeal cancer, as tobacco smoking and alcohol consumption (51). This study did not show any association between gender and OS. Other studies also found that there is no association between gender and survival in laryngeal cancer treatment (16).

Majority of patients in the current study were current cigarette smoker (68%) and current alcohol drinkers (56%) however the findings in the current study did not show any association between these two cancer risk factors and OS. In addition even the education status, occupational status and marital status were also not associated with OS. This is not in keeping with a study done by Boffeta et al. (27) which showed that cigarette smoking and low socioeconomic status were associated with poor survival. The reason behind this result could due to the retrospective nature of this study in which data regarding cancer risk factors is less detailed and sometimes misclassified.

In the current study the commonest initial symptom was the hoarseness of voice (92%). This finding is in keeping from study done by Pukander et al.(13) who showed that

hoarseness of voice was present in 87% of all patients and almost 100% of patients with glottic cancer. In this stud , dyspnea (27%) had a higher frequency than in the study done by Pukander et al. (13) in Finland where dyspnea was present in only 12% of all patients. This may be explained the fact that dyspnea is a relatively late symptom in laryngeal cancer and about 75% of patients in the current study had advanced stages compared to only 33% patients who had advanced stages in the study by Pukander et al.

Among all the initial symptoms only the presence of dyspnea showed a trend towards poor OS although the association was borderline significant (P=0.07). Pukander et al. also showed similar findings with regards to prognostic significance of dyspnea (13) although in multivariate analysis the association disappeared. Thus the independent role of the symptoms in treatment planning and evaluation of prognosis seems to be minor.

Around 50% of study population in the current study had KPS of below 80% and there was a borderline statistically significant association (P=0.07) between poor KPS and poor OS. These findings suggest that majority of patients in this study presented with advanced symptoms which impaired performance status of patients. The effect of performance status on overall survival may be related to patients' ability to resist the tumor when they have low performance status. Similar findings of the association between survival and performance status were demonstrated by Yucel et al. (28).

The mean and median duration of symptoms in the current study were 14 and 12 months respectively and it ranged from 3 to 48 months. There was no association between duration of symptoms and stage of disease at presentation. Further analysis did not show any association between duration of symptoms and OS. A study done by Pukander et al. showed there was no association between duration of symptoms and OS although there was association between duration of symptoms and stage of disease a presentation (13).
Recall bias by the patients and inaccurate recording of the symptoms are likely contributors to the lack of association between symptom duration and overall survival of laryngeal cancer. It is easy to understand that a patient presenting with an advanced tumor with prominent symptoms does not always remember the onset of the minor early symptoms. Consequently, symptom duration reported by the patient, especially in advanced cases, may be unreliable and does not indicate the real duration of the disease.

The mean and median duration of treatment waiting time were 55 and 30 days respectively and it ranged from 1 to 378 days. There was no statistical difference in treatment waiting time between patients treated with curative and palliative intention. Kaplan Meir analysis demonstrated no association between treatment waiting time and overall survival. Previous studies done in this issue have shown conflicting results. Some studies have shown that treatment waiting time longer than 60 days was associated with poor survival (52) and other studies showed that there is no association between treatment waiting time and survival (30)(32).

In the current study the lack of association between treatment waiting time and overall survival could be attributed to the heterogeneous nature of the study population in which some patients were treated with curative intent and others with palliative intent.

In the current study the majority of the study participants (75%) had advanced T stages (T3 and T4) and only 27% of study participants had enlarged neck nodes. Only 2 patients had distant metastasis. The observation that most of the patients had no palpable neck nodes and very few patients had distant metastasis could be due to inaccurate clinical staging as none of the patients had CT scans to exclude nodal or distant metastasis.

There was an association between T-stage as well as the presence of enlarged neck nodes with overall survival in this study. There was a trend of poor survival with increasing N stage but this was not statistically significant probably because of inaccuracy of N staging in this study however when N stage was re-categorized as presence or absence of cervical lymphadenopathy it showed positive association with OS. The finding of decreasing overall survival with increasing stage is in keeping with numerous previous studies. Survival analysis was not done for M stage because very few patients (2.4%) had distant metastasis.

In this study glottis was the commonest tumor site (62%). About 76% of patients with supraglottic cancer had neck nodal metastasis whereas about 37% of glottic cancer had neck nodal metastasis. Around 90% of supraglottic cancers were in T3 and T4 stages while

only 68% of glottic cancers were in T3 and T4 stages. Other studies have also shown that glottis is the most commonest site and supraglottic cancer is usually in advanced stage at diagnosis (10).

Kaplan Meir analysis in the current study demonstrated that the supraglottic cancer has poor overall survival compared to glottic cancer and multivariate analysis was also statistically significant. Similar findings were observed by Lars et al.(35).

Contrary to numerous previous studies the current study did not find a statistically significant association between NLR and overall survival of laryngeal cancer patients treated by radiotherapy. One explanation for these contradictory results could be the clinical lack heterogeneity of the study population. In this study, a higher proportion (73.1%) of patients had advanced TNM stages (stage 3 and 4), compared with other clinical studies. It is speculated that NLR, as a type of systemic inflammatory marker, may predict the prognosis by distinguishing patients with different tumor burdens. If a group of patients had a wide spectrum of tumor burdens, NLR would be an effective predictor of outcomes. In contrast, if patients enrolled in a certain study had a narrow spectrum of tumor burdens, the predictive power of the NLR would be weakened. However, this hypothesis requires further research for validation. The other explanation may be that coexisting infections which are very common among cancer patients in developing countries may be confounding factors as well. In addition, when interpreting the contradictory results in different studies, other possible reasons need to be taken into account, such as random error caused by small sample and variability of treatment in different centers.

In the current study there was no association between platelet count and 5 years overall survival. The explanation for this contradictory finding could be the limited sample size of the study. Previous studies used thousands of patients in their sample (41). The potential role of platelets in OS remains to be investigated at a broader and deeper level to verify the possible clinical significance of this finding.

There was a statistically significant association between level of hemoglobin and 5 years overall survival for the whole cohort. Patients with hemoglobin level less than 9g/dl had

poor overall survival than those with hemoglobin above 9g/dl. In addition patients with a history of blood transfusion had poor survival compared to those without history of blood transfusion possibly indicating those with blood transfusion had severe anemia which was never corrected by inadequate blood transfusion. Previous studies have shown that anemia is predictor of poor prognosis in patients treated with radiotherapy (46).

The present study showed that 62 patients (75%) needed tracheostomy before initial treatment. Out these patients who needed tracheostomy about 82% had advanced laryngeal cancer. Contrary to previous studies (47) there was no statistically significant association between the need for tracheostomy and overall survival in this study. A study done by Taha et al. in Egypt to assess the effect of preoperative and intra-operative tracheostomy in overall survival showed that preoperative tracheostomy was not associated with poor survival (53).Additional studies need to be done in our setup to assess the impact of laryngectomy prior to therapy in oncological outcomes.

According to the results of this study there was no significant association between overall survival rate and overall treatment time, duration of treatment interruption and number of radiotherapy fields. These findings could be attributed to heterogeneous nature of the study population whereby majority of the patients were treated with palliative intention (87%) and few were treated with curative intention (23%). Also in this study there was no difference between treatments by radiotherapy alone or by concurrent chemo-radiotherapy as far as overall survival is concerned. This finding contradicts previous studies (54) which demonstrated the superiority of concurrent chemo-radiotherapy in survival. Again the possible explanation for this result could be the heterogeneous study population comprising of different stages and numerous radiotherapy treatment regimens.

The mean biologically effective (BED) dose for tumor control in this study for the whole cohort was 55 Gy on the assumption that the alpha beta ration was 10. This BED of 55Gy corresponds to a total dose of 46 Gy in 2Gy daily fraction. These results shows that majority of the patients were treated with palliative intention. Studies (50) have shown that optimum radiotherapy dose of 60-70 Gy is necessary for better curative treatment and higher OS.

In this there was no difference in overall survival between patients that were treated with curative intention compared to those treated with palliative intention however among patients treated palliatively, dose higher than 32 Gy in conventional fractionation resulted in higher OS compared to lower doses. The lack of association between OS and treatment intention could be due to heterogeneous nature of the sample whereby most of patients (73.1%) had advanced TNM stages. Moreover the findings from this study reinforce the fact that higher radiotherapy doses result in higher OS even among patients treated with palliative intention.

This study did not demonstrate any effect of year of treatment on the outcome of laryngeal cancer treatment. This lack of association may be due to little change in the treatment protocol or treatment machines in the in the period from 2008 to 2012.

The 5 years overall survival rate in this study done at ORCI was 29% with median survival of 23 months. The survival rates in developing world are much lower than those in developed world. Studies done in Denmark and Spain demonstrated that the survival rate of laryngeal cancer treated by chemo-radiotherapy were 71% (16) and 66%(24). Even Egypt has a higher 5 years OS (45%)(14). Low OS in the current study could be attributed to low radiotherapy dose, advanced stages at presentation, the use of radiotherapy alone in majority of patients and coexisting anemia.

5. STUDY LIMITATIONS

This study was retrospective nature and had a limited sample size because laryngeal cancer is a relatively rare malignancy.

The major criticism of any retrospective study is that the data collected is originally not designed for a research application. Therefore, some factors responsible for the ultimate treatment outcome might be omitted in the analysis, thereby contributing to bias. Such censure correctly refers to the present study, in which the data were heterogeneous and of lesser quality according to present standards. Considering these factors, one should realize that conclusions from this study should be validated by future projects.

6. CONCLUSION

Majority of the patients had advanced stages. The Five years overall survival rate in this study was 29% with a median survival time of 23 months. The factors that were significantly associated with poor survival were supraglottis site of the laryngeal cancer, anemia, history of blood transfusion, T stage, presence of enlarged neck nodes and low total radiotherapy dose. Dyspnea at presentation, low performance status and N stage were borderline statistically significant in influencing OS.

7. RECOMMENDATIONS

1. There should be an effort to correct anemia prior to initiation of therapy.
2. Higher radiotherapy doses should be used both in curative and palliative treatment intentions.
3. Clinical examination should be supplemented with imaging investigations like CT scan to improve accuracy of staging especially N stage and M stage.
4. Thorough initial evaluation of patients as well as documentation of the findings is mandatory. Most files of the files that were reviewed had missing information regarding symptomatology, cancer risk factors, site of the cancer, and stage of the cancer, co-existing comorbid conditions, and performance status. This information is vital for selection of the best initial therapy, for cancer registry and for future researches.
5. Most of the patient files did not have contact information of both the patient and the next of kin to the patient. This contact information is important in following up of the patient. There is a need to document contact information of the patient and of at least two next of kin to the patient.

REFERENCES

1. Siegel RL, Miller KD, Jemal A. Cancer statistics. CA Cancer J Clin. 2016;66(1):7–30.
2. Hoffman HT, Porter K, Karnell LH, Cooper JS, Weber RS, Langer CJ, et al. Laryngeal cancer in the United States: changes in demographics, patterns of care, and survival. Laryngoscope. 2006;116(September):1–13.
3. Raitiola HS, Pukander JS. Changing trends in the incidence of laryngeal cancer. Acta Oncol. 1997;36(1):33–6.
4. Fasunla A, Ogundoyin O, Onakoya P, Nwaorgu O. Malignant tumors of the larynx: Clinicopathologic profile and implication for late disease presentation. Niger Med J [Internet]. 2016;57(5):280. Available from: http://www.nigeriamedj.com/text.asp?2016/57/5/280/190596
5. Onyango JF, Macharia IM. Delays in diagnosis, referral and management of head and neck cancer presenting at Kenyatta National Hospital, Nairobi. East Afr Med J. 2006;83(4):85–91.
6. Gilyoma JM, Rambau PF, Masalu N, Kayange NM, Chalya PL. Head and neck cancers : a clinico - pathological profile and management challenges in a resource - limited setting. BMC Res Notes. BioMed Central; 2015;1–9.
7. Mwansasu C, Liyombo E, Moshi N, Mpondo BCT. Pattern of head and neck cancers among patients attending muhimbili national hospital tanzania. Tanzan J Health Res. 2015;17(1).
8. Khoueir N, Matar N, Farah C, Francis E, Tabchy B, Haddad A. Survival of T4aN0 and T3N+ laryngeal cancer patients: a retrospective institutional study and systematic review. Am J Otolaryngol. Elsevier Inc.; 2015;36(6):755–62.
9. Devilta V. Cancer:Principle and Practice of Oncology. Ninth. Pine Jr J, editor. Philadelphia: Lippincott williams & wilkins, a wolters kluwer business; 2011.
10. National Comprehensive Cancer. Head and Neck Cancers Version 1.2015. 2015.
11. Kreimer AR, Clifford GM, Boyle P, Kreimer AR, Clifford GM, Boyle P, et al. Human Papillomavirus Types in Head and Neck Squamous Cell Carcinomas Worldwide : A Systematic Review Human Papillomavirus Types in Head and Neck Squamous Cell Carcinomas Worldwide : A Systematic Review. 2005;14(February):467–75.
12. Olsen J, Sabroe S. Occupational causes of laryngeal cancer. J Epidemiol Community Heal [Internet]. 1984;38(2):117–21. Available from: http://jech.bmj.com/content/38/2/117.short
13. Pukander, Hannu Raitiola J. Symptoms of Laryngeal Carcinoma and their Prognostic Significance. Acta Oncol (Madr). 2000;39(2):213–6.
14. Aboziada MA, Elyamany A. Retrospective analysis of the clinical efficacy of concurrent weekly cisplatinum – radiotherapy for patients with laryngeal carcinoma. J Solid Tumors [Internet]. 2016;7(1):1–6. Available from: http://www.sciedu.ca/journal/index.php/jst/article/view/9829
15. Greene F, editor. AJCC Cancer Staging Manual. Sixth Edit. Srpinger; 2002. 51-66 p.
16. Hansen O, Larsen S, Bastholt L, Godballe C, Jørgensen KE. Duration of symptoms:

Impact on outcome of radiotherapy in glottic cancer patients. Int J Radiat Oncol Biol Phys. 2005;61(3):789–94.
17. Genden EM, Ferlito A, Silver CE, Jacobson AS, Rene C, Werner JA, et al. Evolution of the management of laryngeal cancer. 2007;431–9.
18. Gregory T. Induction chemotherapy and plus radaiation compared with surgery plus radiation in patients with advanced laryngeal cancer. N Engl J Med [Internet]. 1991;324(24):1685–991. Available from: http://www.nejm.org/doi/pdf/10.1056/NEJM199106133242402
19. Forastiere AA, Goepfert H, Maor M, Pajak TF, Weber R, Morrison W, et al. Concurrent Chemotherapy and Radiotherapy for Organ Preservation in Advanced Laryngeal Cancer. n engl j med. 2003;34922349:2091–8.
20. Rödel RMW, Steiner W, Müller RM, Kron M, Matthias C. Endoscopic laser surgery of early glottic cancer: Involvement of the anterior commissure. Head Neck. 2009;31(5):583–92.
21. Silver CE, Beitler JJ, Shaha AR, Rinaldo A, Ferlito A. Current trends in initial management of laryngeal cancer: the declining use of open surgery. Eur Arch Otorhinolaryngol. 2009;266(9):1333–52.
22. Morrison W, Glisson B, Trotti A, Ridge JA, Ph D, Chao C, et al. Concurrent Chemotherapy and Radiotherapy for Organ Preservation in Advanced Laryngeal Cancer Arlene. New Engl J. 2003;349(22):2091–8.
23. Cooper JS, Zhang Q, Pajak TF, Forastiere AA, Jacobs J, Saxman SB, et al. Long-Term Follow-Up of the RTOG 9501/Intergroup Phase III Trial: Postoperative Concurrent Radiation Therapy and Chemotherapy in High-Risk Squamous Cell Carcinoma of the Head & Neck. Int J Radiat Oncol Biol Phys. 2012;84(5):1198–205.
24. Ramroth H, Schoeps A, Rudolph E, Dyckhoff G, Plinkert P, Lippert B, et al. Factors predicting survival after diagnosis of laryngeal cancer. Oral Oncol. Elsevier Ltd; 2011;47(12):1154–8.
25. Reizenstein JA, Bergstro SN, Lo B, Brattstro D. Original article impact of age at diagnosis on prognosis. Head Neck. 2010;32(8):1062–8.
26. Eldeeb H, Abdel-Khalk S. Does treatment interruption and baseline hemoglobin affect overall survival in early laryngeal cancer treated with radical radiotherapy? 10 years follow up. J BUON Off J Balk Union Oncol. 2014;19(1):124–9.
27. Boffeta P. Prognostic Factors and Survival of Laryngeal Cancer Patients from Turin , Italy. Am J Epidemiol. 1997;145(12):1100–5.
28. Yücel B, Eren AA, Erdifl E, Babacan NA, Altuntafl EE. Treatment results , side effects and prognostic factors Larinks kanserli hastalar › n tedavi sonuçlar ›, yan etkileri ve. J Med Updat. 2013;3(2):69–76.
29. Primdahl H, Nielsen AL, Larsen S, Andersen E, Ipsen M, Lajer C, et al. Changes from 1992 to 2002 in the pretreatment delay for patients with squamous cell carcinoma of larynx or pharynx: a Danish nationwide survey from DAHANCA. Acta Oncol. 2006;45(2):156–61.
30. Eldeeb H, Abdel-Khalk S. Does treatment interruption and baseline hemoglobin affect overall survival in early laryngeal cancer treated with radical radiotherapy? 10 years follow up. Journal of B.U.ON.: official journal of the Balkan Union of Oncology. 2014. p. 124–9.
31. León X, De Vega M, Orús C, Morán J, Vergés J, Quer M. The effect of waiting time

on local control and survival in head and neck carcinoma patients treated with radiotherapy. Radiother Oncol. 2003;66(3):277–81.
32. Brouha XDR, Op De Coul B, Terhaard CHJ, Hordijk GJ. Does waiting time for radiotherapy affect local control of T1N0M0 glottic laryngeal carcinoma? Clin Otolaryngol Allied Sci. 2000;25(3):215–8.
33. Mutsoane T. Patients treated with radical course of radiation therapy for carcinoma of the larynx at charlotte maxeke johannesburg academic hospital. University of Witwatersrand; 2014.
34. Fortin A, Bairati I, Albert M, Moore L, Allard J, Couture C. Effect of treatment delay on outcome of patients with early-stage head-and-neck carcinoma receiving radical radiotherapy. Int J Radiat Oncol Biol Phys. 2002;52(4):929–36.
35. Johansen L V, Grau C, Overgaard J. Laryngeal carcinoma--multivariate analysis of prognostic factors in 1252 consecutive patients treated with primary radiotherapy. Acta Oncol. 2003;42(7):771–8.
36. Mendenhall BWM, Amdur RJ, Morris CG, Hinerman RW. T1-T2N0 Squamous Cell Carcinoma of the Glottic Larynx Treated With Radiation Therapy. 2006;19(20):4029–36.
37. Gao F, Li X, Geng M, Ye X, Liu H, Liu Y, et al. Pretreatment Neutrophil–Lymphocyte Ratio. Medicine (Baltimore). 2015;94(11):e639.
38. Coussens LM, Werb Z. Inflammation and cancer. Nature. 2002;420(6917):860–7.
39. Fu Y, Liu W, OuYang D, Yang A, Zhang Q. Preoperative Neutrophil-to-lymphocyte Ratio Predicts Long-term Survival in Patients Undergoing Total Laryngectomy With Advanced Laryngeal Squamous Cell Carcinoma: A Single-center Retrospective Study. Medicine (Baltimore). 2016;95(6):e2689.
40. Garcı J, Camacho M, Quer M, Leo X. The prognostic value of pretreatment platelet count in patients with head and neck squamous cell carcinoma. 2016;
41. Chen YP, Zhao BC, Chen C, Shen LJ, Gao J, Mai ZY, et al. Pretreatment platelet count improves the prognostic performance of the TNM staging system and aids in planning therapeutic regimens for nasopharyngeal carcinoma: a single-institutional study of 2,626 patients. Chin J Cancer. 2015;34(1):137–46.
42. Rachidi S, Wallace K, Day T a, Alberg AJ, Li Z. Lower circulating platelet counts and antiplatelet therapy independently predict better outcomes in patients with head and neck squamous cell carcinoma. J Hematol Oncol. 2014;7(1):65.
43. Mottram J. On th e skin reactions to radium exposure and thei r avoidance in therapy; AN EXPERIMENTAL INVESTIGATION. Br J Surg. 1932;19:481–7.
44. Lee WR, Berkey B, Marcial V, Fu KK, Cooper JS, Vikram B, et al. Anemia is associated with decreased survival and increased locoregional failure in patients with locally advanced head and neck carcinoma: a secondary analysis of RTOG 85-27. Int J Radiat Oncol Biol Phys. 1998;42(5):1069–75.
45. Kumar P. Impact of Anemia in Patients With Head and Neck Cancer. Oncologist. 2000;5(90002):13–8.
46. Fein DA, Lee WR, Hanlon AL, Ridge JA, Langer CJ, Curran WJ, et al. Pretreatment Hemoglobin Level Influences Local-Control and Survival of T1-T2 Squamous-Cell Carcinomas of the Glottic Larynx. J Clin Oncol. 1995;13(8):2077–83.
47. Tennant PA, Cash E, Bumpous JM, Potts KL. Persistent tracheostomy after primary chemoradiation for advanced laryngeal or hypopharyngeal cancer. Head Neck. 2014;(November).

48. Hall EJ, Willson S. Radiologist. Seventh Ed. Philadelphia; 2012.
49. González Ferreira JA, Jaén Olasolo J, Azinovic I, Jeremic B. Effect of radiotherapy delay in overall treatment time on local control and survival in head and neck cancer: Review of the literature. Reports Pract Oncol Radiother. Wielkopolskie Centrum Onkologii; 2015;20(5):328–39.
50. Krstevska V, Crvenkova S. Altered and Conventional Fractionated Radiotherapy in Locoregional Control and Survival of Patients with Squamous Cell Carcinoma of. Croat Med J. 2006;47:42–52.
51. Ellis L, Rachet B, Birchall M, Coleman MP. Trends and inequalities in laryngeal cancer survival in men and women : Oral Oncol [Internet]. Elsevier Ltd; 2012;48(3):284–9. Available from: http://dx.doi.org/10.1016/j.oraloncology.2011.10.012
52. Murphy CT, Galloway TJ, Handorf EA, Egleston BL, Wang LS, Mehra R, et al. Survival Impact of Increasing Time to Treatment Initiation for Patients With Head and Neck Cancer in the United States. J Clin Oncol. 2015;34(2):169–78.
53. Taha MS, Sabra R, Hamdy TA, Riad MA. Impact of preoperatative tracheostomy on tracheostome recurrence and overall survival in patients undergoing laryngectomy. Egypt J Otolaryngol. 2014;30:332–6.
54. Forastiere AA, Zhang Q, Weber RS, Maor MH, Goepfert H, Pajak TF, et al. Long-term results of RTOG 91-11: A comparison of three nonsurgical treatment strategies to preserve the larynx in patients with locally advanced larynx cancer. J Clin Oncol. 2013;31(7):845–52.

APPENDICES

Appendix 1: Questionnaire

SURVIAL OF LARYNGEAL CARCINOMA AND ITS PREDICTORS AT OCEAN ROAD CANCER INSTITUTE FROM 2007-2011

1. Serial number …….....

2. Registration No……...

3. Patient Initials…….

4. Next of kin telephone number……..

5. Sex I. Male II. Female

6. Year of treatment……..

7. Age (years)…….

8. Highest level of education achieved.
   I. None
   II. Primary school
   III. Secondary
   IV. Post secondary school

9. Marital status
   I. Married
   II. Never married
   III. Divorced
   IV. Widowed
   V. Cohabiting

10. Occupation
    I. Peasant

II. ..... R
etired
III. C
ivil servant
IV. ..... S
elf employed
V. ..... U
nknown

11. Ever Smoke? I. Yes II. No

12. Ever Alcohol use? I. Yes II. No

13. Presentation
I. ..... H
oarseness of voice
II. ..... S
ore throat
III. ..... D
ysphasia
IV. ..... O
dynophagia
V. ..... A
spiration/Choking
VI. ..... N
eck Mass

14. Performance status…….

15. Duration in months from initial presentation to histological diagnosis ……

16. Date of histological diagnosis…….

17. Duration of treatment waiting time…….

18. TNM Stage……..

19. Histology…….

20. Histological differentiation I. Grade 1 II. Grade 2 III. Grade 3

21. Location of tumor I. Supraglottis II. Glottis III. Subglottis

22. Pretreatment hemoglobin level…….

23. Pretreatment platelet level…….

24. Pretreatment neutrophil to lymphocyte ratio…….

25. Blood transfusion I. Yes II. No

26. Tracheostomy I. Yes II. No

27. Treatment Intention I. Curative II. Palliative

28. Initial treatment
I. ..... R
T alone

II. ..... Concurrent CRT
III. ..... Surgery alone
IV. ..... Surgery followed by CRT
V. ..... Surgery followed by RT
VI. ..... Induction Chemo followed by CRT
VII. ..... Induction chemo followed by RT alone
VIII. ..... Chemo alone

29. Date of initial treatment……..

30. Treatment interruption in days……

31. Duration of radiation in weeks……

32. Total Dose of Radiation & Fractionation……

33. BED……..

34. Type of chemo and dose……

35. Number of chemo cycles…….

36. Date at last follow up……

37. Status at last closing date: I. Dead II. Alive III. Lost to follow up

48. Time in months from initial treatment to last follow up ……

Appendix 2: Verbal Consent Format

Consent to participate in the research.

Greetings! My name is ……...I am working on this research project with the objective of investigating the "Survival of laryngeal cancer and its predictors at ocean road cancer institute from 2008-2012"

Purpose of the study
The study aims at determining the survival of laryngeal cancer patients treated at ORCI

What Participation Involves
Researchers will review patient's medical records and interview you after you give your verbal consent.

Confidentiality
We would like to assure you that all the information you are going to answer will remain confidential and will be used for research purposes only. No one will be allowed to go through your answers except principal investigator and research assistants.

Risks
You will be asked questions about your personal and medical information. You may be embarrassed by these questions.

Rights to Withdraw and Alternatives
Taking part in this study is completely your choice. If you choose not to participate in the study or if you decide to stop participating in the study you will continue to receive all services that you would normally get from this hospital. You can stop participating in this study at any time, even if you have already given your consent. Refusal to participate or withdrawal from the study will not involve penalty or loss of any benefits to which you are otherwise entitled.

Benefits
There may be no direct benefits to you from this study. Information learned in this study may to improve the management of laryngeal cancer.

In Case of Injury
You will not be giving up any of your legal rights by signing this consent form.

Who to contact
If you ever have questions about this study, you should contact the Principal Investigator:
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