PATTERNS OF CERVICAL LYMPH NODE METASTASIS AMONG LARYNGEAL CANCER PATIENTS PRESENTING AT THE KENYATTA NATIONAL HOSPITAL

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H58/69059/2013

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A Dissertation Submitted in Partial Fulfilment of the Requirements for the Award of the Degree of Master of Medicine in Otorhinolaryngology-Head & Neck Surgery (M. Med ORL-HNS) of the University of Nairobi.

STUDENT'S DECLARATION

I declare that this dissertation is my own original work and has not been presented for a Degree in any other University.

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DEDICATION

First, I would like to dedicate this dissertation project to patients in Kenya and across the World suffering from cancer of the larynx. As a doctor, I appreciate the immense opportunity provided by patients in my learning. Finally, I dedicate this work to the late Dr. Geoffrey William Griffin, the founder Director of Starehe Boys' Centre & School who picked me from obscurity and gave me an opportunity to get an Education that my family could not afford to give me. I am forever grateful for the opportunity which has brought me this far.

ACKNOWLEDGEMENTS

I would like to record my utmost appreciation to the following individuals and institution(s) for the support they have given me during my postgraduate studies and the successful completion of this dissertation.

First, I thank the Almighty God for His guidance and favour throughout the programme. Next, I would like to thank my supervisors Dr. Mugwe and Dr. Irungu for patiently guiding me through all the stages of the dissertation project journey.

I also wish to thank my wife Lydia and my children Griffin, Robert, Got Jnr and Silpah for their immense patience and support during my long absence from home as I undertook the postgraduate studies.

Next, I wish to thank my statistician Mr. Wycliffe Ayieko and Dr. Herbert Murayi, Consultant Radiologist, Kenyatta National Hospital for patiently reviewing all the CT Scans reported in this study.

Finally, I thank the Gandhi Smarak Nidhi Fund at the University of Nairobi for the generous Scholarship the fund gave me to support my postgraduate studies.

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LIST OF ABBREVIATIONS

AJCC	-	American Joint Committee on Cancer
CCL	-	Chemokine ligand
Cm	-	Centimetre
CT	-	Computed Tomography
CXCL	-	Chemokine ligand gene superfamily
DNA	-	Deoxyribonucleic acid
ENT	-	Ear, Nose and Throat
FNAC	-	Fine Needle Aspirate Cytology
ERC	-	Ethics and Research Committee
GERD	-	Gastro-oesophageal Reflux Disease
HNSCC	-	Head and Neck Squamous Cell Carcinoma
HPV	-	Human papillomavirus
KES	-	Kenya Shillings
KNH	-	Kenyatta National Hospital
MB.ChB	-	Bachelor of Medicine and Bachelor of Surgery
Mm	-	Millimetre
M. Med	-	Master of Medicine
MMP-9	-	Matrix metalloproteinase -9
MRI	-	Magnetic Resonance Imaging
N0	-	Negative neck node status
N+	-	Positive neck node status
ORL-HNS	-	Otorhinolaryngology- Head & Neck Surgery
PET	-	Positron Emission Tomography
PGS	-	Paraglottic space
RNA	-	Ribonucleic Acid
SPSS	-	Statistical Package for Social Sciences
SCC	-	Squamous Cell Carcinoma
UICC	-	International Union for Cancer Control
UoN	-	University of Nairobi
VEGF	-	Vascular Endothelial Growth Factor

ABSTRACT

Background

Regional metastasis to the cervical lymph nodes is common in laryngeal carcinoma and is one of the most important prognostic factors of the disease irrespective of the mode of treatment.

Objective

To determine the patterns of cervical lymph node metastasis among laryngeal cancer patients presenting for treatment at the Kenyatta National Hospital.

Study design

A hospital based descriptive cross-sectional study.

Study setting

Kenyatta National Hospital ENT and radiology departments.

Study population

All patients with histologically confirmed laryngeal carcinoma at the hospital not yet on any treatment.

Study duration

The study was undertaken over a period of 9 months between October 2018 to June 2019.

Methodology

The study involved 79 patients with cancer of the larynx confirmed on histology who were examined for presence and patterns of cervical lymphadenopathy. Data on their direct laryngoscopy examination findings was also collected. Each patient's primary and nodal disease stage was confirmed by a contrast-enhanced CT scan of the neck reported by the same Consultant Radiologist.

Results

Trans-glottic cancer patients were 81.0%, 10.1% supraglottic and 8.9% glottic. 53.2% presented with T4 primary disease, 38.0% T3, 2.5% T2 and 6.3% T1 disease respectively. 45.6% had N0 neck node disease while 54.4% had N+ neck node disease. T4 primary cancer and poorly differentiated histology were significantly associated with N+ neck node status, P=0.001 and 0.010 respectively. Glottic primary cancer was significantly associated with N0 neck node status P=0.003.

Analysis

Data was analysed using SPSS version 22 and the Chi-squared and Fisher's exact tests were used to test for association with a $P<0.05$ being statistically significant.

Conclusion

The majority of laryngeal cancer patients at the KNH present with trans-glottic cancer at stage T4 primary disease. Both the T4 primary disease and advanced histologic grade of differentiation are significantly associated with presence of cervical lymph node metastasis.

CHAPTER ONE: BACKGROUND

1.1 Introduction

Cancer of the larynx is one of the commonest head and neck cancers in Kenya and globally [1]. Kenya currently does not have a reliable National cancer registry and data on cancer is very scanty. Where available, the data is mostly hospital-based. Onyango and colleagues, [2, 3] reported a prevalence of 39% of laryngeal cancer among patients with head and neck cancer while Sandabe et al [4] reported a prevalence of 20% of all head and neck cancers. It is predominantly a disease of the elderly male in their 7^{th} decade of life with a male to female ratio varying from 5.2 :1 to 24: 1 [2,4,5,6,7]. In the USA, the American Cancer Society estimates that in 2017; 13,360 new cases of laryngeal cancer were diagnosed of which 10,570 were male; with 2990 males and 720 females dying from it respectively [1]. Among patients with head and neck cancer, lymph node metastasis is one of the most important prognostic factors. In patients with histologically proven head and neck cancer, including cancer of the larynx, the presence of an ipsilateral metastatic node reduces the 5-year survival rate by 50%, whereas the presence of bilateral metastatic nodes reduces the 5-year survival further to 25% [8].

Metastatic cervical nodes from head and neck carcinomas are usually site-specific with respect to the location of the primary tumour. Assessment of the pattern of distribution of metastatic cervical nodes in patients with carcinomas of unknown primary may provide a clue to the site of the primary tumour. In addition, metastatic nodes in an unexpected site indicates that the primary tumour may be biologically more aggressive [9]. The Kenyatta National Hospital is a National Teaching & Referral Hospital which serves Kenya and the wider East and Central Africa. It is also the only public cancer treatment centre in Kenya. About 100 patients with histologically confirmed cancer of the larynx are seen annually at the hospital. The hospital routinely uses clinical examination and contrast enhanced CT scans of the neck for staging of primary laryngeal carcinoma and cervical lymph node metastasis. This study seeks to investigate and document the pre-treatment clinical and CT cervical nodal staging of laryngeal carcinoma patients at the hospital.

1.2 Surgical Anatomy of the Larynx

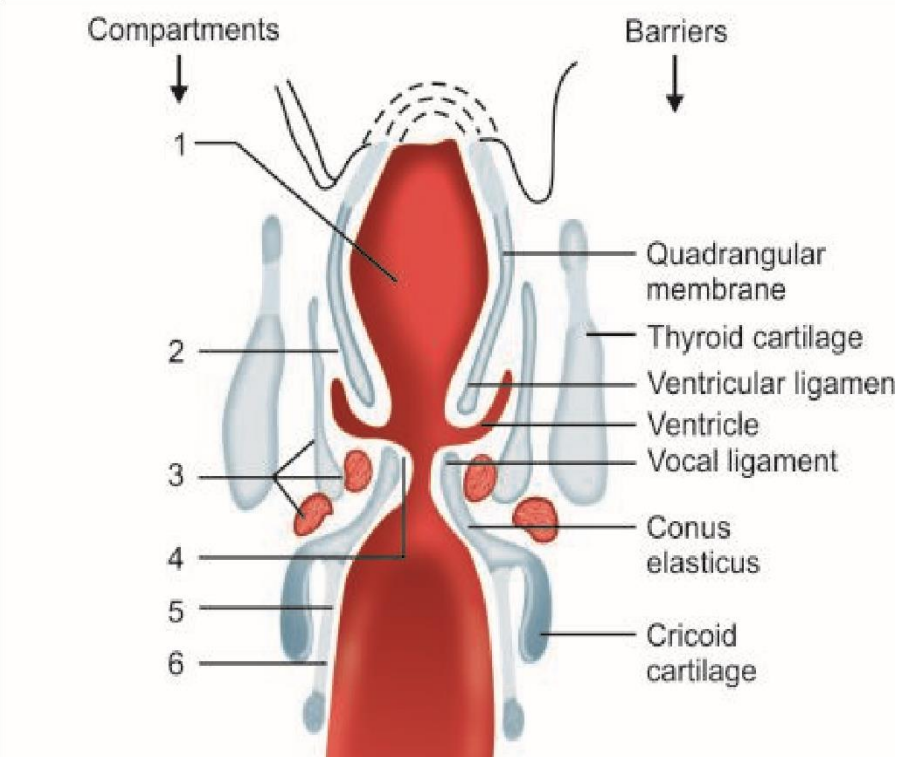

Figure 1: Coronal view of the larynx

Coronal view of the larynx demonstrating the natural barriers to spread of laryngeal tumors along with spaces through which tumors can spread. 1–supraglottis, 2–portion of the pre-epiglottic space continuous with the PGS, 3–PGS, 4–Reinke's space, 5–Subglottis, 6–cricoid area [11]

The larynx develops from the respiratory and digestive tracts between the 6^{th} and 12^{th} weeks of intrauterine life [10].

The pattern of spread of laryngeal cancers is determined either by the anatomic barriers that hinder the spread of cancer or the soft tissue pathways within the larynx that permit the spread of the cancer within or without the larynx [11].

The lymphatic drainage of the different anatomic sites of the larynx varies according to their embryologic origin. A clear understanding of the embryology of the larynx improves

the appreciation of the risk and patterns of metastasis to the regional lymph nodes based on the site of origin of the primary cancer of the larynx.

The larynx is divided into three main anatomical sites: the supraglottis, the glottis and the subglottis. Each of these sites is further subdivided into subsites from where laryngeal cancer can arise with unique patterns of spread.

1.2.1 The Supraglottis

The supraglottis of the larynx extends from the tip of the epiglottis superiorly to a horizontal plane through the lateral margin of the ventricle at its junction with the true vocal cords.

The subsites of the supraglottis include: the laryngeal surface of the epiglottis, lingual surface of the epiglottis, the false vocal cords, the arytenoids, aryepiglottic folds, the saccule as well as the lateral and superior surfaces of the ventricle [11].

Embryologically, the supraglottis forms from the buccopharyngeal primordium of the 3rd and 4th branchial arches. The supraglottic lymphatic drainage follows the superior laryngeal arteries through the thyroarytenoid membrane towards the carotid sheath and drains into the lymph nodes at levels II and III.

In its development, the supraglottis is formed without a midline union and as such it has a bilateral lymphatic drainage [12]. Patients with supraglottic cancer are more likely to have bilateral cervical lymph node metastasis.

1.2.2 The Glottis and Subglottis

The subsites of the glottis include: the true vocal cords, the ventricle, the anterior and posterior commissures. The inferior boundary of the glottis is a horizontal plane about 10mm inferior to the apex of the laryngeal ventricle.

The subglottis extends from the inferior limit of the glottis to the inferior border of the cricoid cartilage.

Embryologically, the glottis and subglottis are derived from the tracheobronchial primordium of the 6th branchial arch and are formed by the union of lateral furrows on either side of the primordium which fuse in the midline. Consequently, the lymphatics of the glottis and subglottis tend to drain unilaterally [12].

The lymphatics of the glottis and subglottis follow the inferior laryngeal arteries and drain into the pre-laryngeal and pre-tracheal lymph nodes in level VI. Vocal cords also have sparse lymphatics and thus cancers which originate in the glottis must invade very deeply to have a risk of regional metastasis.

1.3 Implications of Anatomy on Cancer Spread

Advanced laryngeal cancer may involve multiple anatomic subsites but the disease progression is predictable based on the presence of natural barriers and pathways which may prevent or facilitate the spread of the cancer.

Some of the natural barriers which limit the spread of laryngeal cancer include: the thyroid and cricoid cartilages, the hyoepiglottic ligament, the conus elasticus, the quadrangular membrane, the thyrohyoid membrane and the cricothyroid membrane [12].

There are also natural pathways within the larynx that facilitate the spread of laryngeal cancer within and without the larynx. The thyroepiglottic ligament and the anterior commissure provide minimal if any resistance to tumour spread thus allowing cancers of the anterior commissure to invade the thyroid cartilage due to a deficiency of the thyroid perichondrium at the insertion of the anterior commissure.

The pre-epiglottic and paraglottic spaces provide pathways of spread of laryngeal cancer within the laryngeal framework. Cancers that involve the infrahyoid epiglottis will almost always invade the pre-epiglottic space. Laterally, the pre-epiglottic space is continuous

with the paraglottic space on either side providing a pathway for cancer to spread submucosally to involve the glottis and subglottis. Spread of cancer through the pre-epiglottic space also predisposes to cancer spread into the soft tissues of the neck via the superior laryngeal neurovasculature.

The paraglottic space binds the laryngeal ventricles bilaterally and its medial limit is the quadrangular membrane, the ventricles and the conus elasticus. Laterally, the paraglottic space is bound by the thyroid cartilages and the piriform sinus mucosa. Invasion of laryngeal cancer into the paraglottic space can lead to the spread of the cancer into the extra-laryngeal soft tissue and the thyroid gland by penetrating through the cricothyroid membrane [11,12].

Save for some little variations; the lymph fluid is drained along relatively predictable and constant lymph vessels into certain lymph node groups. This forms the basis for dividing lymph nodes in the head and neck region into groups. In the year 2000, the American head and neck society committee neck dissection issued a classification which has aided and improved assessment of lymph nodes by regions and improved the nomenclature of selective neck dissection as summarized in table 1 [13].

Table 1: American head and neck society (2000) classification of neck nodes

Level	Lymph node group	Boundaries of the neck levels
I A	submental	between the anterior bellies of the digastric muscle
I B	submandibular	between the boundaries of the anterior belly of the digastric muscle, the stylohypoid muscle and the mandible
II	upper jugular	includes nodes located around the upper third of the internal jugular vein and spinal accessory nerve. This extends from the skull base above to the inferior border of hyoid bone below. The anterior boundary is the stylohyoid muscle, and the posterior boundary is the posterior border of sternomastoid muscle
II A		anterior to the vertical plane defined by thespinal accessory nerve
II B		posterior to the vertical plane defined by the spinal accessory nerve
III	middle jugular	includes nodes located around the middle third of the internal jugular vein extending from the inferior border of the hyoid bone above to the inferior border of cricoid cartilage below. The anterior (medial) boundary is the lateral border of the sternohyoid muscle, and the posterior (lateral) boundary is the posterior border of sternocleidomastoid muscle
IV	lower jugular	includes nodes located around the lower third of internal jugular vein extending from the inferior border of the cricoid cartilage above to the clavicle below
V	posterior triangle	includes nodes located along the lower half of the spinal accessory nerve and the transverse cervical artery. The supraclavicular nodes are also included in the posterior triangle group. The superior boundary of this level is the apex formed by convergence of sternomastoid and trapezius muscles
V A		above a horizontal plane marking the inferior border of the anterior cricoid
V B		below a horizontal plane marking the inferior border of the anterior cricoid
VI	anterior compartiment	includes pre and paratracheal nodes, precricoid (Delphian node), and the perithyroidal nodes including the nodes along the recurrent laryngeal nerves. The superior boundary is the hyoid bone, the inferior boundary is the suprasternal notch. The lateral boundaries are the common carotid arteries.

1.4 Carcinogenesis and Histopathology of Primary Cancer of the Larynx

Of all head and neck malignancies including the larynx, more than 90% are squamous cell carcinomas [14]. The four most common risk factors for the development of cancer of the larynx are: cigarette smoking, alcohol ingestion, the human papillomavirus (HPV) infection and GERD [14,15]. Irrespective of the factor predisposing to squamous carcinogenesis of the larynx, the process involves progressive accumulation of a large series of genetic abnormalities in the genes which regulate cell cycle progression, mitogenic and differentiative signaling pathways, angiogenesis and cell death. This mutagenic process is referred to as multistep carcinogenesis. A body of evidence for mutational progression in the development of squamous cell carcinomas of the head and neck was first derived from cytogenetic studies. These studies demonstrated a pattern of non-random clonal losses; duplications; and rearrangement of chromosome segments in head and neck tumours [15,16].

Based on the degree of keratinization, histopathologists classify squamous cell carcinomas as well differentiated (over 75% keratinization), moderately differentiated (25-75% keratinization) and poorly differentiated (less than 25% keratinization) [17]. Studies have shown that the degree of differentiation of primary cancer of the larynx may correlate with its propensity to develop cervical lymph node metastasis [18].

1.5 Theoretical Basis of Tumour Metastasis to the Lymph Node

Lymphangiogenesis is a multistep process in lymphogenic metastasis whose exact molecular mechanics remains unclear. However, it is known that different lymphangiogenetic cytokines of squamous cell carcinomas especially VEGF-C and D which are mostly expressed in the area of tumour invasion front do stimulate the genesis of lymphatic vessels in different ways [19]. It has been demonstrated that increased expression of these cytokines is associated with a high density of lymphatic vessels and lymphogenic metastasis [20]. Tumour induced lymphangiogenesis is thus considered a crucial step in lymphogenic metastasis.

The lymphatic endothelium also plays a crucial role beyond just being the limit of a lymphatic vessel. This endothelium forms an interactive surface for tumour cells. The endothelium and tumour cells demonstrate a wide variety of phenotypic changes with expression of different receptors for example CLEVER – I mannose receptor and the LYVE-1. These receptors play a crucial role in tumour cell adhesion process at the lymphatic endothelium as well as migration of the tumour cells into the lymphatic system.

It can be postulated that if the lymphangiogenic characteristics of the lymphatic endothelium were to be inhibited, there would be a significant reduction in the lymphatic tumour metastatic rate.

The interactions of the tumour cells with the tumour induced lymphatic endothelia lead to the secretion of different chemokines and formation of a variety of receptors on the tumour cell surfaces as a decisive step in the migration of tumour cells into the lymphatic vessels.

Some of the chemokines like CXCL1, CXCL2 and CCL20 have been demonstrated in tongue cancer-induced lymphatic endothelia [21]. Tumour cells also change their phenotypic characteristics in the process of lymphogenic metastasis and disconnect from their united structure and follow chemotactic gradients in the tissue in the direction of lymphatic vessels. Dislodged tumour cells then produce proteolytic enzymes such as MMP-9 for local tumour invasion, as well as expressing specific adhesion molecules [22].

1.5.1 Tumour Invasion of Lymph Nodes and Nodal Transformation

After the tumour cells bind with lymphatic endothelia and enter the vascular lumen; the tumour cells are drained via an afferent lymph vessel into the sentinel lymph node. These tumour cells initially form small foci of 2-3mm as micrometastases in the marginal sinus of the node [22]. The micrometastases are initially located far from the hilum and at this stage may only be identified by immunohistochemistry or molecular genetic studies. With growth of the metastasis, the internal architecture and the blood supply of the lymph node change because of formation of new blood vessels around the metastatic region.

Concurrently, growth of the affected node occurs. Even at this early stage; the changes in the node may be detected by ultrasound examination with doppler sonography [22].

By the time the whole lymph node is affected by tumour cells and its size increases up to 20mm, the hilum of the node is no longer identifiable, and at this size areas of necrosis in the node can be clearly detected by ultrasonography [25]. Lymph node capsule may still be preserved at this stage. Further growth of tumour cells within the node progressively leads to infiltration of the capsule with extracapsular seeding of tumour cells. It is estimated that extracapsular seeding of tumour cells occurs in about 70% of lymph nodes larger than 3 cm in diameter. While in nodes less than 3cm, it can be found in approximately 40% of cases [24]. Coatesworth AP, et al. [23]; in a prospective histologic examination of 96 neck dissection specimens of patients with clinical N0 neck demonstrated occult lymph node metastases in 30.2% of the specimens. Among the patients with occult cervical modal metastasis, 63.2% had extracapsular metastasis. This observation reveals that about 19% of all patients with clinically N0 neck could actually have occult nodal metastasis with extra-capsular spread.

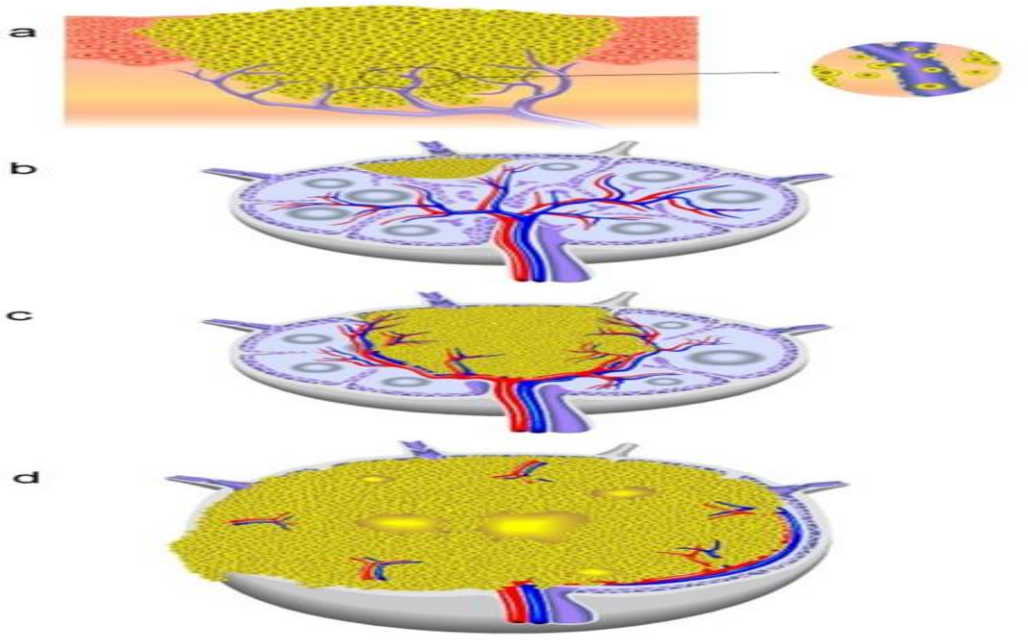

Figure 2: Progression of tumour metastasis in a lymph node

a. Tumour-induced angiogenesis, b. Development of micrometastases, c. Enlarged lymph node metastases, d. Extracapsular spread [22]

1.6 Clinical Presentation of Cancer of the Larynx

The symptom complex associated with cancer of the larynx depends upon the location and extent of the primary tumour. Persistent hoarseness of voice may be the initial complaint in glottic cancer, later symptoms may include dysphagia, referred otalgia, chronic cough, haemoptysis and stridor.

Supraglottic cancers are often discovered later and may present with airway obstruction or palpable metastatic lymph nodes. Primary subglottic cancers are rare and the affected patients typically present with stridor and or complaints of dyspnoea on exertion.

1.7 Diagnosis and Staging of Cancer of the Larynx

The tumour node metastasis (TNM) staging of the American Joint Committee on Cancer (AJCC) and the International Union for Cancer Control (UICC) is the most widely used to stage cancer of the larynx [26]. The complete staging of the primary tumour as well as regional and distant metastasis is achieved by clinical examination and imaging. The initial assessment of the primary tumour is based upon a combination of inspection, palpation, indirect mirror examination and direct endoscopy. An examination under anaesthesia is best performed to characterize the extent of tumour, to look for synchronous primary tumours and to obtain biopsies for tissue diagnosis.

Imaging studies are useful to augment the physical examination and evaluation particularly in assessing the degree of local invasion of the paraglottic space, pre-epiglottic space and pyriform sinuses as well as involvement of regional lymph nodes and presence of distant metastases or second primary malignancies [27]. The most common distant metastatic sites are the lungs, liver and bone while the most common sites for second primary malignancies are in the head and neck region, followed by the lungs and oesophagus [27].

1.8 Staging of Cervical Lymph Nodes in Cancer of the Larynx

Every effort should be made to accurately evaluate and stage regional lymph nodes as they bear a great prognostic significance. While performing a pre-therapeutic evaluation for lymph node metastasis, clinical palpation remains the basic method applied [27]. Palpation

criteria to consider a node metastatic include: a firm to hard consistency of the lymph node, size more than 10mm and fixation to underlying structures [27].

The sensitivity of exclusive inspection and palpation in detecting cervical lymph nodes ranges from 60% - 70% [27]. Application of CT scanning and MR Imaging is complementary with sensitivity ranging from 65%-88% in literature [28].

Globally, the most significant procedure currently used to detect lymph node metastasis is B mode ultrasonography combined with ultrasound guided node aspiration cytology [28]. Based on a comparative meta-analysis, this modality has a sensitivity of 80% and a specificity of 98% and is superior to both CT scanning and MR imaging [28]. However, this technique is time consuming and suffers from wide inter-operator variability making its clinical use difficult. To forestall the difficulties associated with ultrasonography and ultrasound guided FNAC, CT scanning and MRI are more commonly used in pre-treatment staging of nodal disease.

1.8.1 CT Scanning in Staging of Metastatic Lymph Nodes

Contrast-enhanced CT scanning of the neck has found wide and practical use in the radiological staging of both the primary cancer of the larynx and metastasis to regional cervical lymph nodes and even distant metastasis. CT scanning eliminates inter-operator variability which affects Ultrasound guided FNAC.

Contrast enhanced CT scans allow for characterization of the cervical nodes in detail. The CT scan criteria used to define a node as metastatic include: nodes with central necrosis regardless of size in the absence of clinical infection, heterogeneous density of the node, aggregation of lymph nodes, evidence of extra capsular spread as shown by irregular borders, presence of contrast material surrounding the node. Size criterion may vary from 10-15mm. Computed tomography has improved the accuracy of diagnosis of cervical metastasis. It has limitations of being expensive and has hazards of radiation exposure [28].

Pathologic or metastatic lymphadenopathy is radiologically defined as a node greater than 10 mm in its transverse diameter or one that contains central necrosis [28,29]. Central nodal necrosis has been variously proven to be the most accurate marker of metastatic lymphadenopathy with up to 100% sensitivity and specificity on CT and ultrasound examination when compared against histological examination of the lymph nodes [30,31,32].

Ahsan et al. [33] observed that as high as 60% of laryngeal carcinoma patients have cervical lymph node metastasis at presentation. Kirchner et al. [34] found the incidence of nodal metastasis at presentation to be 42.8%, however, it is safer to predict that these rates are even an understatement of the problem given the high rates of occult nodal metastases that are observed in head and neck squamous cell carcinomas. When analysing incidence of nodal metastasis by tumour subsite, Ahsan et al. [33] observed the highest incidence of 72% among supraglottic cancers. An incidence of 30% was observed in glottic cancers, while subglottic cancer had 0% nodal metastasis at presentation. This finding was comparable to the observations by Kirchner et al. [34] who reported 65% nodal involvement for supraglottic cancers, 25 % for glottic cancers and 0% for subglottic carcinoma. The supraglottis being a midline structure, appears to be anatomically designed to have a wider lymphatic network that may explain this preponderance to lymphadenopathy in this region.

Studies have also documented that the incidence of lymph node metastasis in cancer of the larynx also varies by the lymph node level. Level II and III cervical nodes are the main lymphatic drainage station for the supraglottic larynx; therefore, these nodes are more commonly involved than other lymph node groups, especially in occult node metastasis. Nevertheless, in clinically palpable neck disease, all the 5 cervical node levels may be involved [35]. In their study, Ahsan et al. [33] reported Level II nodal involvement in 53% of their patients. This was followed by level III at 25% and level IV at 6.67%. Level V nodes were only involved in 3% of patients, and where Level V nodes were involved, this was part of multiple level nodal metastasis and all patients who had multilevel nodal involvement had supraglottic carcinoma. Level I group of nodes tend to be spared in laryngeal carcinoma metastasis with Ahsan et al [33] reporting 0% isolated Level I nodal metastasis. However, there seems to be very few studies that have looked at this parameter to help make definitive conclusion.

In a separate study in Italy, Luka et al. [36] showed that levels II and III nodes are the most commonly involved in laryngeal cancer metastasis. They documented an incidence of 82%

and 41% respectively for Levels II and III nodes. This compared with the observations in the study by Ahsan and Kirchner. The T-stage of the primary laryngeal carcinoma at presentation has an important correlation to the nodal status of the disease. Wenyue, JI, et al [37], observed that about 6% of their laryngeal cancer patients presented at T1, 31% at T2, 38% at T3 and 25% at T4 disease. Luca et al. [36] further documented that about 40% of all supraglottic cancers will show locoregional metastasis at presentation. They also observed that the frequency of metastasis for T1 supraglottic cancers ranged between 6 to 25%, T2 cancers at 30-70% with that of T3 cancers being at 65-80%. Despite huge advancements in staging procedures, occult cervical metastasis in supraglottic cancers is still at 20%. Glottic tumours show a comparatively lower lymph node metastatic rate which may be attributed to the lower lymphatic density in this region. Anatomically, the highest density of lymph collectors of the larynx is found in the triangle formed by the epiglottis, the false vocal folds and the aryepiglottic fold [38].

Mobility of the vocal folds also bears a significant correlation to the incidence of lymph node metastasis in glottic cancers. It is postulated that mobile vocal folds represent a dynamic barrier to lymphatic drainage [38], however, increased impairment of vocal fold mobility as in T2 and T3 glottic cancers leads to unhindered flow of lymph into the locoregional nodes. Nevertheless, there is no study which has been conducted to evaluate the correlation between vocal fold mobility or fixity with regional lymphatic metastatic rate, thus the anatomic postulations are yet to be put to test. In their study, Ahsan et al. [33] observed that the metastatic rate according to the T stage of the disease shows an increase in the frequency of lymph node metastasis in tandem with the advancing T stage of the primary tumour. They observed the metastatic rate of T1 cancer to be 14.3%; T2 to be 41.2%; T3 at 81.8% and 100% for T4 cancers. Therefore, extra-laryngeal growth of the primary cancer is a major predictor of metastatic activity.

A few retrospective studies have been done to determine the association between the histologic type and grade of differentiation of laryngeal cancer with the tendency to develop lymph node metastasis. Kowlasky, Ozdek and Resnick et al, in several retrospective studies [39,40,41] found some association. Kowlasky, for example

demonstrated an Odds ratio of 4 showing that grade 3 laryngeal cancers (poorly differentiated) were four times more likely to manifest with cervical nodal metastasis which is both clinically detectable and occult than grade 1 cancer. However, the observation was not statistically significant. These studies were all retrospective based on neck dissection specimens from clinically N0 necks because of the technical difficulty with accurate pre-treatment lymph node staging.

CHAPTER THREE: STUDY JUSTIFICATION

This study generated crucial data on the pre- treatment regional lymph node staging of the laryngeal cancer patients seen at our hospital which is crucial in selecting appropriate treatment modality. This was also be the first study in Kenya which has attempted to exclusively examine the prevalence and patterns of regional lymph node involvement in laryngeal cancer patients in the Kenyan population based on the contrast enhanced CT scan of the neck which is the most widely used modality for radiological staging of this disease in Kenya. The information from this study will be useful to doctors when counselling these patients on treatment options and prognosis. Currently, there is little information on the correlation between the histologic type and grade of primary laryngeal cancer and lymph node metastasis and this study has documented such a correlation generating useful data when counselling patients with the various types of laryngeal cancer.

3.1 Research Question

What are the patterns of cervical lymph node metastasis among laryngeal cancer patients presenting for treatment at the Kenyatta National Hospital?

3.2 Aims and Objectives

3.2.1 Broad Objective

To determine the patterns of cervical lymph node metastasis among laryngeal cancer patients presenting for treatment at the Kenyatta National Hospital.

3.2.2 Specific Objectives

(i) To determine the distribution of sub-sites of the larynx from which primary cancer of the larynx arise among patients at the KNH.

(ii) To determine the correlation between the sub-site(s) of origin of primary laryngeal cancer and level(s) of metastatic cervical nodes involved on CT scan.

(iii) To determine the correlation between the histological type and grade of the primary cancer of the larynx with the metastatic cervical nodes detected on CT scan.

CHAPTER FOUR: STUDY METHODOLOGY

4.1 Study Design

A hospital based descriptive cross-sectional study.

4.2 Study Setting

The study was done at the KNH ENT department clinic, ward, theatre and the radiology unit. The KNH is a tertiary referral and teaching hospital which receives patients from Kenya and the wider East and Central Africa and the only public cancer treatment centre in Kenya.

4.3 Study Population

All patients with histologically confirmed laryngeal carcinoma seen at the Kenyatta National Hospital during the study period.

4.4 Sampling Method

Consecutive sampling of all patients with laryngeal carcinoma confirmed on histology who were fully evaluated for treatment at the hospital and gave a written consent to participate. The patients were recruited from the ENT department of the hospital.

4.5 Sample Size Calculation

According to KNH data from hospital records, an estimated number of 100 [42] fully evaluated laryngeal cancer patients are seen annually ready for treatment. Therefore, out of this population a representative sample was derived, and the sample size calculation was obtained using the formula for finite population [43].

$$n' = \frac{NZ^2P(1-P)}{d^2(N-1)+Z^2P(1-P)}$$

Where:

n' = sample size with finite population correction,

N = size of the target population = 100,

Z = Z statistic for 95% level of confidence = 1.96,

P = Prevalence of cervical node metastases in laryngeal cancer patients=60% derived from a study by Ahsan et al in Bangladesh [29]

d = margin of error = 5%

n'= 79, the minimum number of patients required

4.6 Participant Recruitment

4.6.1 Inclusion Criteria

The following patients qualified to be included in the study:

(i) Patients with laryngeal carcinoma confirmed on histology who have gave a written consent to participate.

(ii) Patients who had been evaluated by either direct and/ or indirect laryngoscopy for clinical staging of the primary cancer of the larynx.

(iii) Patients who had a contrast enhanced CT scan of the neck taken within 6 weeks for radiological staging of both the primary cancer and the cervical lymph nodes.

(iv) Both adults and children who met the inclusion criteria were included.

4.6.2 Exclusion Criteria

The following patients were considered not to qualify and were excluded from the study:

(i) Patients who did not have a histological confirmation of laryngeal carcinoma.

(ii) Patients who had undergone any form of treatment whether curative or palliative for the disease.

(iii) Patients who declined to give a written consent.

4.7 Recruitment and Consenting Procedure

The principal investigator looked for patients with suspected laryngeal cancer who had been booked for elective direct laryngoscopy and biopsy, called them and performed the direct laryngoscopy examination and laryngeal biopsy for them and documented the findings. More patients were recruited from those undergoing emergency direct laryngoscopy and biopsy from the accident and emergency department. The consent for direct laryngoscopy was done in the normal manner by following the KNH consenting protocols for all surgical procedures. After the direct laryngoscopy and biopsy, patients'

histology results were obtained and reviewed. Those that had a diagnosis of cancer of the larynx on histology became eligible and were recruited into the study. The purpose of this study was explained to the eligible patients and those willing to participate were taken through the general information and consent form specific for this study and those who signed the consent form were recruited into the study when they met the inclusion criteria. Patients referred from other hospitals with a diagnosis of cancer of the larynx on histology were also eligible to participate in the study and were recruited once they signed the consent form.

4.8 Data Collection Procedure

Upon recruitment, the principal investigator performed and documented a complete ENT examination including for cervical lymph nodes. The patients were then sent to the KNH radiology department for a pre-and post-contrast CT scan of the neck. The principal investigator then collected the CT scan images of the patients and read and interpreted them with the help of a Consultant Radiologist from the KNH radiology department and documented these findings on the data sheet. This was repeated until the desired number of patients were evaluated. For those who came with a contrast enhanced neck CT scan from outside the KNH, the principal investigator examined the patient and read the CT scan images afresh and the final CT scan report was that by the Consultant radiologist at the KNH. The procedure described is the standard procedure of evaluating all patients with suspected laryngeal carcinoma from presentation to diagnosis thus the principal investigator collected all the data as part of routine clinical care of these patients.

4.9 Data Quality Control

Quality control was a continuous process for reliable and valid findings of the study. The principal investigator did the patient selection, history taking and clinical examination for all the patients. The data collection tool was pre-tested for completeness, missing information and validity of responses. The principal investigator performed clinical ENT examination on all patients. For direct and/ or indirect laryngoscopy examinations, the principal investigator provided for each patient a standard reporting form with anatomical diagrams to be marked by all persons who perform the examination for uniformity of

clinical staging of the primary tumour. All the CT scans were initially reported by the principal investigator and reviewed by one consultant radiologist whose professional judgment was final.

4.10 Data Management

All data retrieved from completed questionnaires was coded in a database using Microsoft Excel to maintain confidentiality. The data was compiled, and cross checked for errors and corrected as per the questionnaires. The questionnaires have been kept in a lockable cabinet with access restricted to the investigator and supervisors; they will be destroyed within two years of publication of the findings in a scientific journal.

4.11 Data Analysis

Data analysis has been done using SPSS version 22. Descriptive statistics were calculated to summarize characteristics of the sample of patients presenting to KNH with laryngeal cancer. Three continuous variables were collected, namely age, number of pack years of smoking and nodal diameter. The mean and standard deviation was calculated for age and nodal diameter and the median number of pack years of cigarette smoking presented along with its range. The remaining variables were collected as categorical data. For these, data frequencies and proportions were calculated and presented in form of tables of frequency distributions, and figures. The incidence of cervical lymph node metastasis was determined by calculating the proportion of laryngeal cancer patients in the sample with confirmed metastatic node involvement on CT scan of the neck. Frequencies and percentage showing Nodal (N) staging of cancer of larynx were calculated. Chi square test was used to determine the association between the primary tumour subsite and level(s) of cervical nodes involved, and separately the association between the histologic grade of cancer and radiological N stage of the disease. All statistical significance will be based on P-value < 0.05. For small numbers, the Fisher's exact test was used to calculate the associations with a p value of <0.05 being statistically significant.

4.12 Results Dissemination

Results of this study will be disseminated to the Head of Department of Otorhinolaryngology, Head and Neck Surgery at KNH and to the overall Head of Specialized Surgical services at KNH. Copies will also be availed to the UoN Department of Surgery and the College of Health Sciences library. An online copy will also be availed on the university online repository. A manuscript will be prepared and submitted for publication in an academic journal for wider dissemination.

4.13 Ethical Considerations

This study commenced after approval and authorization from the department of surgery of the UoN, the UoN-KNH ERC and the KNH administration. The study was approved by the UoN-KNH ERC and granted approval number **P445/06/2018.**

Each patient received a pre-consent counselling on the disease and the study after which an informed consent was obtained.

With a signed informed consent, the patient was enrolled into the study.

Parents/ guardians were not be coerced to enrol the patients into the study. Non-participation did not affect such a patient's care in the hospital. Patients who opted out of the study at any time did not suffer any negative consequences.

Participation in this study did not attract any extra cost to the medical care of the participants.

Patient's hospital file number was not shown on the data collection sheet. However, to facilitate easy tracing and capture of missed information during data collection, a unique study number was allocated to each participant by the principal investigator and this number was coded to hospital file numbers. The code was known only to the Principal investigator.

The data sheet was kept safely with the researcher and confidentiality maintained throughout. Electronic data file generated was encrypted with a password only availed to the principal investigator. Any hard copy research data has been kept in a safe locked

cabinet only accessed by the principal investigator and the supervisors. The collected data will be destroyed after completion of this study.

There was no conflict of interest on the part of the principal investigator and the institutions involved in the study. The results and conclusions of the study will be shared with the medical fraternity.

CHAPTER FIVE: RESULTS

The main objective of the study was to determine the pattern of cervical lymph node metastasis among laryngeal cancer patients presenting for treatment at the Kenyatta National Hospital.

5.1 Demographic Characteristics of Study Patients

Table 2: Age and sex distribution of the patients

	Frequency	**Percentage**
Age		
31-40	1	1.3
41-50	11	13.9
51-60	17	21.5
61-70	36	45.6
71-80	8	10.1
81-90	6	7.6
Total	**79**	**100.0**
Sex		
Male	78	98.7
Female	1	1.3
Total	**79**	**100.0**

A majority of patients seen were male at 98.7% with females accounting for 1.3%. Most of the patients were in the 7^{th} decade of life accounting for 45.6%.

5.2 Examination and Imaging Findings

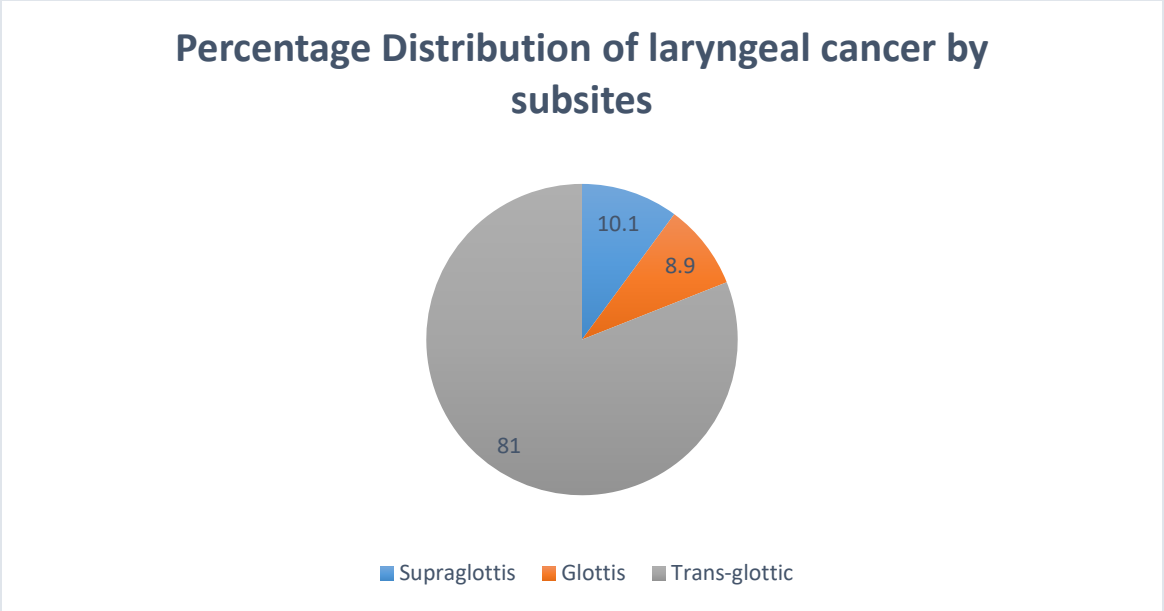

Figure 3: Percentage distribution of laryngeal cancer by subsites

Multiple subsite involvement was predominant with both clinically and radiologically trans-glottic cancers accounting for 81.0% of all the patients. Isolated supraglottic cancer accounted for 10.1% and isolated glottic cancer was at 8.9%. There was no isolated subglottic primary cancer.

5.2.1 Nodal Staging of Laryngeal Cancer Patients

Table 3: Overall clinical and radiological nodal stage of the patients

Stage	Frequency	Percent
N0	36	45.6
N1	9	11.4
N2a	5	6.3
N2b	8	10.1
N2c	13	16.5
N3	8	10.1
Total	**79**	**100.0**

Overall, 36 patients had no cervical nodes detected either on clinical examination or on CT scan, thus, patients with N0 nodal status accounted for 45.6% of the patients. 43 patients had cervical nodes detected either clinically or on imaging, thus, patients with N+ nodal status accounted for 54.4%.

Association between laryngeal subsite of primary cancer and the cervical nodal status

Table 4: Association of laryngeal subsite of primary cancer and the cervical nodal status

Subsite	N+	N0	Total	p-value
Supraglottic	6 (14.0)	2 (5.6)	8 (10.1)	0.280
Glottic	0 (0.0)	7 (19.4)	7 (8.9)	**0.003**
Clinical Transglottic	33 (76.7)	27 (75.0)	60 (75.9)	0.857
Transglottic with subglottic extension	4 (9.3)	0 (0.0)	4 (5.1)	0.121

All the patients with the glottis as the origin of their primary cancer had an N0 neck with none having an N+ neck node status, and the difference observed in this subsite was statistically significant, P=0.003.

76.7% of all the patients with an N+ neck had clinically trans-glottic laryngeal cancer while 75.0% of all patients with N0 neck also had a clinically trans-glottic cancer and the difference in this group was statistically insignificant, P= 0.857.

All patients who had a subglottic extension of the primary cancer were observed to have an N+ neck nodal status with none having an N0 neck node status, however, this observation was statistically insignificant with P=0.121.

Patients with isolated supraglottic origin of the primary cancer accounted for 14.0% of the N+ neck node status and 5.6% of the N0 neck node status. The difference in nodal status

observed with respect to the supra-glottic primary cancer was however statistically insignificant, P= 0.280.

Association between the subsite of primary cancer and level of detected cervical nodes

Table 5: Subsite of primary cancer versus the level of cervical nodes detected

Cervical node group(s) & Cancer subsites	**II**	**II, III**	**II, III, IV**	**III**	**III, IV**	**IV**	**Total**	**p-value**
Supraglottic	4	0	1	1	0	0	6	0.179
Clinical Transglottic	4	9	5	10	2	3	33	0.067
Radiological Transglottic	2	1	1	0	0	0	4	0.688
Total for node groups	10	10	7	11	2	3	43	-
Percentage	**23.3**	**23.3**	**16.3**	**25.6**	**4.6**	**6.9**	**100.0**	**0.204**

For Patients with N+ cervical nodal status, all the nodes were detected at levels II, III, and IV. On testing for the association between the subsite of origin of the primary cancer of the larynx and the predilection to any specific levels of cervical nodal groups, the differences noted were not statistically significant, P values were recorded at 0.179, 0.067 and 0.688 for supraglottic as well as clinical and radiological trans-glottic cancers respectively. Overall P value for the combination of patterns of nodal level distribution was 0.204 indicating that any differences in this observation to be statistically insignificant. In this study there was no involvement of level I, V, or VI cervical nodes detected.

Table 6: Association between laryngeal primary site and laterality of neck nodes

Subsite of primary cancer	Ipsilateral (%)	Bilateral (%)	Total	p-value
Supraglottic	4	2	6	0.699
Clinical Transglottic	17	16	33	0.728
Radiological Transglottic	2	2	4	1.000
Total	**23(53.5)**	**20(46.5)**	**43(100)**	

Among patients studied with N+ neck node status, 53.5% had ipsilateral lymphadenopathy while 46.5% had bilateral cervical lymphadenopathy. 0% had contralateral cervical lymphadenopathy. There was no significant association between the subsite of primary laryngeal cancer to either a predilection to ipsilateral or bilateral cervical lymphadenopathy. However, the finding that as high as 46.5% of patents who had N+ neck nodes status had bilateral cervical lymphadenopathy is clinically significant in the care of these patients.

5.2.2 Staging of Primary Laryngeal Cancer

Table 7: Overall Clinical and Radiological T stage of primary laryngeal cancer

	Frequency	Percent
T1	5	6.3
T2	2	2.5
T3	30	38.0
T4a	36	45.6
T4b	6	7.6
Total	**79**	**100.0**

53.2% of patients in the study presented with T4 primary laryngeal cancer. This was followed by 38.0% presenting with T3 primary cancer, 6.3% at T1 stage while T2 disease accounted for the least number of patients at 2.5%. Patients with locally advanced primary disease at levels T3 and T4 accounted for 91.2% of all patients in the study.

Association between the stage of primary laryngeal cancer and the cervical nodal status

Table 8: Association between primary stage of laryngeal cancer and neck node status

	N+	N0	Total	p-value
T1	1 (2.3)	4 (11.1)	5 (6.3)	0.110
T2	0 (0.0)	2 (5.6)	2 (2.5)	0.117
T3	12 (27.9)	18 (50.0)	30 (38.0)	**0.044**
T4	30 (69.8)	12 (33.3)	42 (53.2)	**0.001**

T4 primary laryngeal cancer accounted for 69.8% of all N+ neck disease and 33.3% of N0 neck disease. The difference observed in this group of patients was statistically significant, P= 0.001.

T3 primary laryngeal cancer accounted for 27.9% of all patients with N+ neck disease and 50.0% of all the patients with N0 neck disease. The difference observed in this group of patients was also statistically significant, P=0.044.

There was no patient with T2 primary laryngeal cancer with an N+ cervical nodal status and 5.6% of all patients with N0 cervical nodal status. However, this difference was statistically insignificant, P= 0.117.

Among patients with T1 primary laryngeal cancer, 2.3% had N+ cervical nodal status while 11.1% of them had N0 cervical nodal status. The difference in this observation was, however, statistically insignificant, P= 0.110.

Association of T stage of Primary cancer and nodal stage of the N+ neck node disease

Table 9: The T stage of primary cancer versus cervical nodal stage

T stage of primary cancer	N1 (%)	N2/N3 (%)	Total	p-value
T1	1(11.1)	0 (0)	1	0.209
T3	5(55.5)	7(20.6)	12	0.088
T4	3(33.3)	27(79.4)	30	**0.014**

Patients with T4 primary laryngeal cancer constituted 79.4% of those who presented with advanced cervical lymph node metastasis N2/N3 nodal stage and 33.3% of those with early cervical lymph node metastasis N1 nodal stage. This difference was noted to be statistically significant, P= 0.014. Advanced primary laryngeal cancer at stage T4 is significantly associated with advanced cervical lymph node metastasis of the disease.

5.3 Histology of Primary Laryngeal Cancer

Table 10: Grade of differentiation of primary cancer

Grade of cancer differentiation	Frequency	Percentage
Grade 1: Well differentiated SCC	24	30.4
Grade 2: Moderately differentiated SCC	41	51.9
Grade 3: Poorly differentiated SCC	14	17.7
Total	**79**	**100.0**

All patients in this study (100.0%) had squamous cell carcinoma of the larynx. 51.9% had moderately differentiated grade, 30.4% well differentiated and 17.7% had the poorly differentiated grade. There was no patient with grade 4 (undifferentiated) laryngeal carcinoma.

Association between grade of differentiation of primary cancer and cervical nodal status

Table 11: Association between grade of differentiation of primary cancer and nodal status

	N+	N0	Total	p-value
Grade 1: Well differentiated	14 (32.6)	10 (27.8)	24 (30.4)	0.645
Grade 2: Moderately differentiated	17 (39.5)	24 (66.7)	41 (51.9)	**0.016**
Grade 3: Poorly differentiated	12 (27.9)	2 (5.6)	14 (17.7)	**0.010**

Patients with a poorly differentiated squamous cell carcinoma of the larynx accounted for 27.9% of all the N+ cervical nodal status and 5.6% of all the N0 cervical nodal status. The difference observed in this group was statistically significant, P=0.010.

Patients with moderately differentiated squamous cell carcinoma of the larynx accounted for 39.5% of the N+ cervical nodal status and 66.7% of the N0 cervical nodal status. The difference observed in this group was also statistically significant, P=0.016.

Patients with well differentiated carcinoma of the larynx accounted for 32.6% of the N+ cervical nodal status and 27.8% of the N0 cervical nodal status. However, the difference in this group of patients was statistically insignificant, P =0.645.
There was no patient with Grade 4 (undifferentiated) laryngeal squamous cell carcinoma.

Association between grade of differentiation and nodal stage of N+ disease

Table 12: Grade of differentiation versus cervical nodal stage

Grade & Nodal stage	**N1**	**N2/N3**	**Total**	**p-value**
Grade 1: Well differentiated	1	13	14	**0.045**
Grade 2: Moderately differentiated	7	10	17	
Grade 3: Poorly differentiated	1	11	12	
Total	**9 (20.9)**	**34 (79.1)**	**43 (100.0)**	

Among the patients with N+ neck node status, 9 (20.9%) had early nodal/ regional disease N1 while 34 (79.1%) had late/ advanced nodal disease N2/ N3. Overall, when this observation was tested against the grade of differentiation of primary laryngeal carcinoma, it was statistically significant, P= 0.045. Thus, a worsening grade of histology of primary laryngeal cancer may be a significant predictor of a more advanced cervical nodal disease.

CHAPTER SIX: DISCUSSION

Cancer of the larynx is the most common head and neck cancer whose incidence ranges from 20% to 40% in various literature [2,4]. It predominantly affects the male gender with the male to female ratio also varied in available literature from 5.2 :1 to 24: 1 and the peak age is in the 7^{th} decade of life [2,4,5]. This heavy male preponderance is comparable to studies elsewhere since males tend to consume more alcohol and smoke cigarettes more than females as was found also in Kenyan surveys [6]. In the survey, 2% of women used tobacco in its various forms, whereas 1% smoked cigarettes which may explain the low prevalence of laryngeal squamous cell carcinoma in the females. Studies in other populations have shown up to 100% prevalence of laryngeal squamous cell carcinoma among males [7].

In this study, 81.0% of the patients had multisite primary laryngeal cancer being trans-glottic in origin, 10.1% had isolated supra-glottic carcinoma and 8.9% isolated glottic cancer. Overall, subglottic cancer was observed in 4 out of the 79 patients (5.06%), however, this subsite was not involved in isolation, but as part of the trans-glottic malignancies of which it constituted 6.3%. The finding differs slightly with those in the study by Sandabe et al [4] which reported the subsite distribution as 43% transglottic, 37.6% supraglottic, 9.7% glottic and 9.7% subglottic in the sub Saharan Africa population. This difference may be explained by the fact that the patients in our study presented late and thus a clear delineation of the exact subsite of origin of primary cancer was difficult.

The subsite of origin of the primary laryngeal cancer has also been postulated to have an association with the cervical nodal status of the patients. In this study, patients with isolated supraglottic carcinoma of the larynx were 10.1% while isolated glottic carcinoma patients made up 8.9% of all the patients. An overwhelming majority had laryngeal cancer of trans-glottic origin indicating that multisite involvement of the primary carcinoma is more common. Isolated cancer of the subglottic larynx was not observed.

Trans-glottic cancer of the larynx (multisite) was associated with a 76.6% detectable cervical nodal metastatic rate. This compares with the results in the studies by Ahsan [33]

and Kirchner [34] who reported 72% and 65% incidence of detectable cervical nodal metastasis respectively. Isolated carcinoma of the sub-glottis was not observed in this population, however, 4 patients out of 64 with trans-glottic laryngeal cancer had sub-glottic involvement of the primary cancer. All patients who had sub-glottic extension of the primary laryngeal cancer also had positive neck node metastasis, thus 9.3% of all N+ patients were patients with sub-glottic extension of laryngeal cancer. This finding differs with the findings by Ahsan [33] and Kirchner [34] who both reported 0% incidence of neck node metastasis in subglottic laryngeal cancer. The methodology in this study and that of both Ahsan [33] and Kirchner [34] were similar and, therefore, the difference in the findings may warrant further research involving a larger population of patients.

In this study, carcinoma of the glottis was significantly associated with lack of cervical nodal metastasis (N0 nodal status), P= 0.003. This finding significantly differs with those of Ahsan [33] who found 30% N+ neck node status and Kirchner [34] who found a 25% N+ neck node status. The methodology of this study was comparable to that by Ahsan and Kirchner [33,34] and therefore, the marked difference may be explained by racial and regional variation in the populations that may need to be investigated in a larger study.

The stage of primary laryngeal cancer (T stage) has also been postulated to be associated with presence or absence of cervical lymph node metastasis. In this study, 6.3% of patients presented with stage T1 disease, 2.5% with stage T2 disease, 38.0% stage T3 disease and 53.2% stage T4 disease. This compares with the findings of the studies by Luca et al [36] and Wenyue et al [37] especially for T1, T3 and T4 stages. However, in this study, stage T2 patients only accounted for 2.5% of the patients which was significantly much lower than the 31% -60% reported by Luca et al and Wenyue et al [36, 37], this difference may be due to a subjective definition for T2 laryngeal cancer which leads to lack of uniformity in staging.

It was also observed in this study that T3 laryngeal cancer accounted for 27.9% of all patients with N+ cervical nodal status while T4 laryngeal cancer accounted for 69.8% of N+ cervical nodal status. Both T3 and T4 primary laryngeal cancer were significantly

associated with presence of cervical lymph node metastasis, P values of 0.044 and 0.001 respectively. This observation compares with those by Wenyue [35] who documented 38.0% N+ status for T3 and 25% N+ status for T4 laryngeal cancer. Nevertheless, these findings are much lower than the metastatic rates reported by Ahsan [33] at T1 14.3%, T2 41.2%, T3 81.8% and T4 100%. Attempts have also been made to establish the association between the subsite of origin of primary laryngeal cancer and the level(s) of metastatic cervical nodes. In this study, only levels II, III and IV were detected to have metastatic disease. However, when statistical test of association was done, this association between subsite of origin of laryngeal primary cancer and the levels of cervical neck node metastasis was insignificant. In spite of this, the observation is still comparable to the findings by Ahsan [33], Akhter [34] and Luca [35] who all demonstrated a predilection of levels II, III and IV cervical nodes to be the ones involved in locoregional metastasis of laryngeal cancer.

All the patients in this study (100%) had squamous cell carcinoma of the larynx. This finding is in keeping with multiple studies that have found that squamous cell carcinoma constitutes over 95% of all head and neck cancer histology including cancer of the larynx [14]. The study has also demonstrated a statistically significant association between poorly differentiated histology of the primary cancer with the presence of cervical neck node metastasis. There has also been a statistically significant association demonstrated for the moderately differentiated squamous cell carcinoma histology. Though, this study was a cross-sectional descriptive hospital-based study, its findings are comparable to those of studies by Kowlasky, Ozdek and Resnick et al, in several retrospective studies [39,40,41] who also found some association. Kowlasky for example in his study [39] demonstrated an Odds Ratio of 4 showing that grade 3 (poorly differentiated) laryngeal cancers were four times more likely to manifest with cervical nodal metastasis which is both clinically detectable as well as occult than grade 1 (well differentiated) cancer.

CHAPTER SEVEN: CONCLUSIONS

Laryngeal cancer patients presenting at the Kenyatta National Hospital predominantly have trans-glottic primary disease. A majority of these patients present with T4 primary laryngeal cancer and the advanced primary disease is significantly associated with presence of detectable cervical lymph node metastasis.

Grade 3 poorly differentiated laryngeal squamous cell carcinoma is significantly associated with presence of detectable cervical lymph node metastasis. Glottic laryngeal cancer is significantly associated with N0 neck node status.

For patients with N+ neck node status, advanced grade of differentiation of primary laryngeal cancer is associated with more advanced cervical nodal disease N2/ N3. For N+ neck node status, levels II, III and IV neck nodes were detected to be the sites of cervical metastasis, however, there is no significant association between the primary subsite of laryngeal cancer to any selected nodal level or groups of node levels.

CHAPTER EIGHT: RECOMMENDATIONS

Arising from the findings of this study, the following recommendations are suggested:

i. For laryngeal cancer patients with supraglottic and transglottic cancer and N0 neck node status, the practice of elective neck dissection involving the lateral group of cervical nodes (levels II, III and IV) remains oncologically sound as these groups of nodes appear to be the preferential sites of regional metastasis of laryngeal cancer.

ii. Elective neck dissection is not necessary for laryngeal cancer patients with glottic cancer and N0 neck node status.

iii. A systematic review of literature involving studies on glottic laryngeal cancer and cervical lymph node metastasis is necessary to generate evidence-based data on the incidence of cervical lymph node metastasis among patients with glottic laryngeal cancer.

iv. Further studies involving a larger number of patients should be done to establish the incidence of subglottic laryngeal cancer and the association between subglottic laryngeal cancer and cervical lymph node metastasis.

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APPENDICES

Appendix I: General Patient Information and Consent Form

My name is Dr. George Akuno Got, a resident doctor in ENT Head and Neck surgical unit and principal researcher in this study, which has been approved by the KNH/UON Ethical and research committee.

Background:

Studies elsewhere have shown that for patients with cancer of the larynx, spread of the cancer to the lymph nodes of the neck affect their choice of treatment and overall survival. In our hospital, we see many of these patients but we have not documented the extent to which spread of laryngeal cancer to the lymph nodes of the neck is among our patients when they come for treatment. In this study I would like to investigate this aspect of the disease by examining the necks of our patients confirmed to have cancer of the larynx and also reading their CT scans of the neck and compiling this report.

Study Procedures:

Once you consent for your participation, I will ask you questions about your age and risk factors for development of cancer of the larynx specifically smoking of cigarettes and alcohol intake. I will also document the main complaints you had at presentation to the hospital for this disease. I will proceed to examine your neck for lymph nodes and record the information in a data sheet. I will also take your CT scan of the neck and report it with the help of a Consultant Radiologist for neck lymph nodes. Finally, I will obtain your medical records and record the findings on laryngoscopy examination you underwent when laryngeal biopsy was taken and record the findings on the data collection sheet.

Voluntariness of Participation:

Participation in this study is voluntary. Once inducted in the study, you can choose to discontinue at any time.

Confidentiality:

The study will not reveal your identity and all information will be handled with utmost privacy.

Benefits:

The information we get may not be of immediate benefit to you but it will help doctors to understand further the illness and how it spreads. The findings like all scientific information will be published in scientific journal or presented in scientific conferences without divulging specific patient information.

Risks:

There are no risks or extra cost that you will incur in this study beyond that which for your routine treatment at the hospital.

Rights to Withdraw:

It is not compulsory to participate in this study. You are free to decline participation in the study and there will be no discrimination towards you. All patients will receive the same management irrespective of whether they participate in the study or not.

In case of any further queries, feel free to contact the following for clarification:

1. **Principal Investigator:**
   Dr. George Akuno Got
   0733 882 199
2. **Supervisors:**
   DR. PETER MUGWE, MB, MMED (Nbi)
   SENIOR LECTURER, DEPARTMENT OF SURGERY, UNIVERSITY OF NAIROBI
   0722 513 778
   DR. CATHERINE IRUNGU, MBChB, MMED (ENT)
   CONSULTANT ENT SURGEON, LECTURER, DEPARTMENT OF SURGERY, UNIVERSITY OF NAIROBI
   0722385710
3. **The Chairperson**,
   KNH/UON ERC,
   Kenyatta National Hospital
   Tel. No. +2542726300 Ext 44102

If you fully understand everything and are willing to participate, kindly sign the consent form provided.

Consent Form

Study number.....

I .....do herby consent to enroll self/ my child/ Mr./ Mrs./..... to be included in this study on **"PATTERN OF CERVICAL LYMPH NODE METASTASIS AMONG LARYNGEAL CANCER PATIENTS PRESENTING AT THE KENYATTA NATIONAL HOSPITAL"** as explained to me by Dr. George Got.

I also confirm that no monetary or material gains have been promised or given to me for participation in this study.

Signed..... Date.....

Signed (Doctor)..... Date.....

1. **Principal Investigator:**
   Dr. George Akuno Got
   0733 882 199
2. **Supervisors:**
   DR. PETER MUGWE, MB, MMED (Nbi)
   SENIOR LECTURER, DEPARTMENT OF SURGERY, UNIVERSITY OF NAIROBI
   0722 513 778
   DR. CATHERINE IRUNGU, MBChB, MMED (ENT)
   CONSULTANT ENT SURGEON, LECTURER, DEPARTMENT OF SURGERY, UNIVERSITY OF NAIROBI
   0722385710
3. **The Chairperson**,
   KNH/UON ERC, Kenyatta National Hospital Tel. No. +2542726300 Ext 44102

Appendix II: Kiambatisho: Maelezo ya Utafiti na Kuhusu Idhini ya Mgonjwa

Jina langu ni Daktari George Akuno Got, mtafiti mkuu kwa utafiti huu ambao unachunguza kuhusu **usambazaji wa saratani ya koromeo kwenye tezi za limfu za shingoni za wagonjwa wanaohudhuria matibabu ya saratani hiyo katika hospitali ya rufaa ya kitaifa ya Kenyatta, jijini Nairobi.**

<u>Maelezo ya taratibu ya utafiti huu</u>

Baada ya kukubali kushiriki katika utafiti huu, utaulizwa maswali kuhusu utumizi wa sigara na pombe. Pia nitakufanyia uchunguzu kwa kupapasa shingo kupata ujumbe kuhusu tezi za limfu. Hatimaye, nitaenda kusoma na kunakili picha yako ya CT Scan ya shingo. Awamu ya mwisho itakuwa kukisoma recordi yako ya matibabu hapa hospitalini na kunakili maelezo ya ugonjwa huu.

Je, kuna hatari yoyote kwa kushiriki katika utafiti huu?

Hakuna hatari yoyote itakayosababishwa na utafiti huu wala gharama yoyote zaidi watakayotozwa washiriki. Uko na uhuru wa kutoshiriki kwa utafiti huu na utashughulikiwa sawa na watakaoshiriki bila adhabu yeyote.

Ni faida gani nitakayopata kwa kushiriki?

Hakuna faida ambayo utapata kwako, iwe pesa taslimu au fidia yoyote. Lakini matokeo ya utafiti huu yatasaidia madaktari kuelewa chanzo cha saratani hii na vipi matibabu yake yanaweza kuboreshwa zaidi. Kuna uwezekano wa kuchapishwa kwa matokeo ya utafiti huu katika majarida ya kisayansi au kuwekwa kwa mikutano ya kisayansi na hata kwa gazeti ya kawaida ili kuwezesha kila mtu husika kufaidika na matokeo yoyote ile.

Kwa maelezo zaidi, unaweza kujadiliana na walio orodheshwa hapa chini:

1. **Mtafiti Mkuu:**
   Daktari George Got
   Rununu: O733 882 199

2. **Wasimamizi:**
   DR. PETER MUGWE, MB, MMED (Nbi)
   SENIOR LECTURER, DEPARTMENT OF SURGERY, UNIVERSITY OF NAIROBI
   0722 513 778

DR. CATHERINE IRUNGU, MBChB, MMED (ENT)
CONSULTANT ENT SURGEON, LECTURER, DEPARTMENT OF SURGERY, UNIVERSITY OF NAIROBI.
0722385710

3. **Mwenyekiti,**
   KNH/UON ERC,
   Hospitali ya kitaifa ya Kenyatta,
   Simu: +2542726300 Ext 44102

Kama umeridhika na mambo haya yote, na ukiwa tayari kushiriki, tafadhali weka sahihi yako kwenye fomu ya idhini.

Fomu Ya Idhini

Nambari ya utafiti .....

Mimi .....nakubali mimi/mwanangu ninayemsimamia .....kushiriki katika utafiti huu ambao nimeelezewa kikamilifu na Daktari George Got. Nathibitisha pia ya kwamba sijapewa au kuahidiwa pesa taslimu, fidia au chochote kile, kushiriki kwenye utafiti huu.

Sahihi .....

Tarehe.....

Sahihi (mtafiti).....

Tarehe.....

1. Mtafiti Mkuu:
   Daktari George Akuno Got
   Rununu: 0733 882 199

2. **Wasimamizi:**
   DR. PETER MUGWE, MB, MMED (Nbi)
   SENIOR LECTURER, DEPARTMENT OF SURGERY, UNIVERSITY OF NAIROBI
   0722 513 778

DR. CATHERINE IRUNGU, MBChB, MMED (ENT)
CONSULTANT ENT SURGEON, LECTURER, DEPARTMENT OF SURGERY, UNIVERSITY OF NAIROBI.
0722385710

3. **Mwenyekiti,**
   KNH/UON ERC,
   Hospitali ya kitaifa ya Kenyatta,
   Simu: +2542726300 Ext 44102

Appendix III: Data Collection Sheet

1. Study Number (Code)…….
2. Social-demographic data:
    a. Age (Years)……
    b. GenderM/ F…….
3. Main symptom(s) at initial presentation (Tick box)
    a. Hoarseness of voice ☐
    b. Stridor ☐
    c. Pain/ Difficult swallowing ☐
    d. Neck swelling ☐
    e. Cough ☐
    f. Others (specify)……
4. Number of pack years of cigarette smoking……
    a. Still smoking? (YES/ NO) ……
    b. If NO, duration in months since cessation……
5. Alcohol intake? YES/ NO…….
    a. If NO, duration in months since cessation……
6. A. Direct laryngoscopy findings of the primary tumor (CIRCLE INVOLVED SUBSITES)

Primary Anatomic site of tumor	**Subsites of the larynx involved**
Supraglottis	**Epiglottis, False Vocal Cords, Arytenoids**
Glottis	**True Vocal Cords, Anterior Commissure, Posterior Commissure**
Subglottis	
Transglottic	

B. Clinical T stage of the primary tumor…….

7. a. Clinical Neck Examination for lymphadenopathy by manual palpation

Level of Palpable Node(s)	**Left (number)**	**Right (Number)**	**Largest Diameter (Cm)**
I a			
I b			
II			
III			
IV			
V			
VI (paratracheal)			

b. Summary of clinical N stage of the tumor…….

8. A. Radiological evaluation of the Primary tumor by CT scan (CIRCLE THE SUBSITE)

Primary Anatomic Site	**Subsite**	**Adjacent extra-laryngeal site involved**
Supraglottis	**Epiglottis, Pre-epiglottic space, Aryepiglottic folds, laryngeal ventricles**	
Glottis	**Anterior Commissure, Posterior Commissure, Paraglottic space**	
Subglottis		

B. Radiological T stage of the tumour……

9. a. Assessment of Cervical Node status by CT scan of the neck, size criteria of a metastatic node

Level of visualized Node(s)	**Left (number)**	**Right (Number)**	**Transverse Diameter (Cm)**
I a			
I b			
II			
III			
IV			
V			
VI			

10. Assessment of Morphological criteria of nodal metastasis on CT

Level of visualized Node(s)	**Round Node (Y/N)**	**Nodal Central Necrosis (Y/N)**	**Heterogenous Contrast Enhancement (Y|N)**	**Aggregation of nodes (Y|N)**	**Perinodal contrast extravasation**
I a					
I b					
II					
III					
IV					
V					
VI					

12. Tumor Histopathology

Histology type	**Tumor Grade of Differentiation: Grade 1(well differentiated), Grade 2 (Moderately differentiated) and Grade 3 (Poorly differentiated)**
Squamous cell Carcinoma	
Others	

Appendix IV: TNM Staging For Cancer of the Larynx

Primary Tumor (T)	
TX	Primary tumor cannot be assessed
T0	No primary tumor
Tis	Carcinoma in situ
Supraglottis	
T1	Tumor limited to one subsite of the supraglottis with normal vocal cord mobility
T2	Tumor invades mucosa of more than one adjacent subsite of supraglottis or glottis or region outside the supraglottis (eg mucosa of the base of tongue, vallecula, medial wall of piriform sinus) without fixation of the larynx
T3	Tumor limited to the larynx with vocal cord fixation and/ or invades any of the following: postcricoid area, preepiglottic space, paraglottic space and/ or inner cortex of the thyroid cartilage
T4a	Moderately advanced local disease Tumor invades through the thyroid cartilage and/ or invades tissues beyond the larynx (eg trachea, soft tissues of the neck including deep extrinsic muscle of the tongue, strap muscles, thyroid or esophagus)
T4b	Very advanced local disease Tumor invades prevertebral space, encases carotid artery, or invades mediastinal structures
Glottis	
T1	Tumor limited to the vocal cord(s) (may involve anterior or posterior commissure)
T1a	Tumor limited to one vocal cord
T1b	Tumor involves both vocal cords
T2	Tumor extends to supraglottis and/ or subglottis, and/ or impaired vocal cord mobility

T3	Tumor limited to the larynx with vocal cord fixation and/ or invasion of the paraglottic space, and/ or inner cortex of the thyroid cartilage
T4a	Moderately advanced local disease Tumor invades through the outer cortex of the thyroid cartilage, and/ or invades tissues beyond the larynx (eg trachea, soft tissues of the neck including deep extrinsic muscle of the tongue, strap muscles, thyroid or esophagus)
T4b	Very advanced local disease Tumor invades prevertebral space, encases carotid artery or invades mediastinal structures
Subglottis	
T1	Tumor limited to the subglottis
T2	Tumor extends to vocal cord(s) with normal or impaired mobility
T3	Tumor limited to larynx with vocal cord fixation
T4a	Moderately advanced local disease Tumor invades through the outer cortex of the thyroid cartilage, and/ or invades tissues beyond the larynx (eg trachea, soft tissues of the neck including deep extrinsic muscle of the tongue, strap muscles, thyroid or esophagus)
T4b	Very advanced local disease Tumor invades prevertebral space, encases carotid artery, or invades mediastinal structures
Regional lymph nodes (N)*	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in a single ipsilateral lymph node, 3cm or less in the greatest dimension
N2	Metastasis in a single ipsilateral lymph node, more than 3 cm but not more than 6 cm in greatest dimension, or in multiple ipsilateral lymph

	nodes, none more than 6cm in greatest dimension, or in bilateral or contralateral lymph nodes, none more than 6 cm in greatest dimension
N2a	Metastasis in a single ipsilateral node, more than 3 cm but not more than 6 cm in greatest dimension
N2b	Metastasis in multiple ipsilateral lymph nodes, none more than 6 cm in greatest dimension
N2c	Metastasis in bilateral or contralateral lymph nodes, none more than 6 cm in greatest dimension
N3	Metastasis in a lymph node, more than 6 cm in greatest dimension
Distant Metastases	
M0	No distant metastasis
M1	Distant metastasis

Anatomic stage/ prognostic groups

Stage 0	Tis	N0	M0
Stage I	T1	N0	M0
Stage II	T2	N0	M0
Stage III	T3	N0	M0
	T1	N1	M0
	T2	N1	M0
	T3	N1	M0
Stage IVA	T4a	N0	M0
	T4a	N1	M0
	T1	N2	M0
	T3	N2	M0
	T4a	N2	M0
Stage IVB	T4b	Any N	M0
	Any T	N3	M0
Stage IVC	Any T	Any N	M1

Note: cTNM is the clinical classification, pTNM is the pathological classification

***Metastases at level VII are considered regional lymph node metastases**

Appendix V: Timeline

PERIOD	**ACTIVITY**
August 2017 –January 2018	PROPOSAL WRITING
February 2018	Proposal presentation
June 2018 to September 2018	Ethical approval
October 2018 – June 2019	Data collection
July 2019 to September 2019	**Report writing and submission**

Appendix VI: Budget

The Principal Investigator funded the budget

Budget Item	**Amount (KES)**
Research fee	2,000/=
Statistician consultation fee	30,000/=
Stationery; (a) Printing (b) Photocopying (c) Binding (d) Pens	 15,000/= 6,000/= 32000/= 1000/=
Contingency fund	20,000/=
Total	106,000/=