

**Clinico pathological features and treatment outcomes in parotid malignancies**

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**CLINICO PATHOLOGICAL FEATURES AND TREATMENT OUTCOMES IN  
PAROTID MALIGNANCIES**

**By**

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**A Dissertation/Thesis Submitted in (Partial) Fulfillment of the Requirement for the  
Degree of Master of Medicine (Clinical Oncology) of**

**Muhimbili University of Health and Allied Sciences  
October, 2017**

**CERTIFICATION**

The undersigned certifies that she has read and hereby recommended for acceptance by Muhimbili University of Health and Allied Sciences a dissertation entitled: “**Clinico pathological features and treatment outcomes in parotid malignancies**” in (partial) 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

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Date

**DECLARATION AND COPYRIGHT**

I, **Aleesha Adatia**, 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.

**Signature**..... **Date**.....

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## **DEDICATION**

His Highness Prince Karim Aga Khan for his 60<sup>th</sup> Diamond Jubilee anniversary and for his numerous blessings and motivation.

All my family members, special dedication to my mother Narmin Adatia and my husband Alim Kassam.

## **ABSTRACT**

### **Background**

Neoplasms that arise in the salivary glands are relatively rare, yet they represent a wide variety of both benign and malignant histologic subtypes. Salivary gland neoplasms most commonly appear in the sixth decade of life.

The salivary glands are divided into 2 groups: the major salivary glands and the minor salivary glands. The major salivary glands consist of the following 3 pairs of glands: the parotid glands, the submandibular glands, and the sublingual glands. The minor salivary glands comprise 600-1000 small glands distributed throughout the upper aero digestive tract.

Among salivary gland neoplasms, 80% arise in the parotid glands, 10-15% arises in the submandibular glands, and the remainder arises in the sublingual and minor salivary glands. Tumors of the salivary glands form one of the most heterogeneous groups of oncological pathology. They constitute a substantial proportion of all tumors of the oro-facial region. Head and neck tumors represent approximately 5% of human neoplasms, and out of these, salivary gland neoplasms constitute 10%.

### **Objective**

To evaluate clinicopathological features and treatment outcomes of parotid gland malignancies in patients who attended Ocean Road Cancer Institute (ORCI) from 2009-2016.

### **Methodology**

A Retrospective study design was employed among all patients who had been diagnosed and confirmed histologically with malignant Parotid tumor referred to and treated at ORCI from January 2009-December 2016.

Analysis of this retrospective study determined the sociodemographic factors, clinicopathological features, treatment outcomes of surgery, radiotherapy, chemotherapy and assessment of 2 years overall survival of parotid malignancies from January 2009 to December 2014.

In this study, the retrospective secondary data was extracted from the patient medical files and data was collected in the data collection form. The study was conducted at ORCI in Dar es Salaam.

## **Results**

Out of 94 patients with histologically confirmed parotid gland malignancy, more males were affected compared to females with the ratio of 1.18:1 and the mean SD age of patients was 51.9 years. Adenocarcinoma was the most common malignant tumor n=37 (40%) followed by squamous cell carcinoma n=18 (19.1%) and the left parotid gland being the most affected site. 44 cases (46.8%) had pathological grading, grade IV accounting for majority of the grades (27.3%). Stage IV was presented the most n=72 (76.5%) and 8.5% presented with metastasis at diagnosis. 31% of patients were subjected to surgery while 69.1% were deemed to be unfit for surgery due to advanced disease. Radiotherapy was received by n=82 (95.2%) with 13 patients (14%) subjected to curative intent and 69 patients (86%) subjected to palliative intent. 2 year overall survival for the curative cohort from 2009-2014 is 23% and 11% for the palliative arm. The 2 year overall survival of parotid gland malignancy treated at ORCI is 12%.

## **Conclusion**

Clinico-pathological presentation of parotid gland malignancy seen in this study differs from other studies probably due to geographical variations. More males are affected than women, especially in the middle ages. Adenocarcinoma was the most frequent histology. Two years Overall survival from 2009 to 2014 was 12%. Late stage presentation was seen as a problem that needs to be addressed in order to maximize the effectiveness of the treatment, and improve the overall survival. Treatment modalities need to be standardized across health facilities in Tanzania.

Key words: Parotid Tumor, ORCI.



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**ABBREVIATIONS**

AIDS	Acquired Immune Deficiency Syndrome
CBC	Complete Blood Count
CCRT	Concurrent Chemo-Radiotherapy
DSS	Disease-Specific Survival
EBRT	External Beam Radiotherapy
ECOG	Eastern Cooperative Oncology Group
FX	Fractions
HIV	Human Immunodeficiency Virus
LINAC	Linear accelerator
MUHAS	Muhimbili University of Health and Allied Sciences
MNH	Muhimbili National Hospital
ORCI	Ocean Road Cancer Institute
RECIST	Response Evaluation Criteria in Solid Tumors
RT	Radiotherapy
SCC	Squamous Cell Carcinoma
SPSS	Statistical Package for Social Sciences
SGT's	Salivary Gland Tumors
W.H.O	World Health Organization

## **DEFINITION OF TERMS**

1. Parotid Gland Tumor: Neoplasm that arise from the Parotid Gland.
2. Radiotherapy is therapy using ionizing radiation to treat cancer so as to control or kill malignant cells.
3. Chemo radiation (CTRRT): Is the form of treatment in combination of both chemotherapy and radiotherapy so as to improve/control of the disease.
4. Complete response is defined as the disappearance of gross lesion for 1 month after the completion of radiotherapy and the absence of any viable tumor cells in the biopsies.
5. Partial response is defined as a greater than 50% reduction of tumor size for 1 month after completion of radiotherapy and absence of new lesions.
6. Stable disease is defined as the presence of gross tumor and less than 50% reduction of tumor size.
7. Progressive disease is defined as the appearance of new lesion during therapy or a greater than 25% increase in size of local tumor (an absolute increase of at least 5mm) or a persistent lesion which occurred within 3months after the radiotherapy.
8. Recurrent disease is the tumor occurring after complete remission.
9. Curative/Radical Intent, the aim is to decrease the number of tumor cells to a level that achieves permanent local tumor control.
10. Palliative Intent, the aim is to decrease symptoms of the malignant disease

## CHAPTER ONE

### 1.0 INTRODUCTION

The parotid glands are the largest salivary glands in humans and are frequently involved in disease processes. Approximately 25% of parotid masses are nonneoplastic; the remaining 75% are neoplastic.

Nonneoplastic causes of parotid enlargement include cysts, parotitis, lymph epithelial lesions associated with acute immune-deficiency syndrome(AIDS), collagen vascular diseases, and benign hypertrophy. Tumors of the salivary glands form one of the most heterogeneous groups of oncological pathology<sup>1</sup>. They constitute a substantial proportion of all tumors of the orofacial region<sup>2-5</sup>. Head and neck tumors represent approximately 5% of human neoplasms, and out of these, salivary gland neoplasms constitute 10%.<sup>4,6</sup>

Most tumors of the parotid (approximately 90%) originate in the superficial lobe. Superficial parotid lobectomy is the minimum operation performed in this situation. This procedure is appropriate for malignancies confined to the superficial lobe, those that are low grade, those less than 4 cm in greatest diameter, tumors without local invasion, and those without evidence of regional node involvement.

Salivary glands tumors (SGTs) are uncommon neoplasms that pose a diagnostic challenge due to their complex histopathological features.<sup>7</sup> Moreover, SGTs exhibit considerable variation with regard to clinical aspects, biology and clinical behavior.<sup>8,9,10</sup> Most patients with salivary gland neoplasms present with a slowly enlarging painless mass. A discrete mass in an otherwise normal-appearing gland is the norm for parotid gland neoplasms. Parotid neoplasms most commonly occur in the tail of the gland. The majority of patients with benign salivary gland tumors are aged between 40 and 59 years.<sup>11,12,13,14</sup>

However, malignant salivary gland tumors most often tend to occur in patients above 50 years of age with males more frequently affected than females.<sup>15,16,17</sup>



There have been reports suggesting a difference in the pattern of occurrence of these tumors in Africans compared to Europeans.<sup>18</sup>

The mean age of patients with salivary gland tumors from Africa has been reported to be lower compared to that reported in Europe and America.<sup>19</sup>

Similarly, regarding malignant salivary gland tumors, while European and American reports show the mucoepidermoid carcinoma to occur with the highest relative frequency, African and Asian studies have reported adenoid cystic carcinoma to be commonest<sup>16-20</sup> salivary gland tumors. SGTs represent 3 to 6% of all tumors of the head and neck region, with an annual incidence throughout the world ranging from 0.05 to 2 cases per 100,000 individuals.

Epidemiological data reveal different frequencies of SGTs in distinct ethnic groups and geographic locations, which makes it difficult to establish global estimates. Although studies provide valuable knowledge, some data are contradictory. Local records are a useful strategy for the analysis of the distribution and particular features of SGTs in a specific population and the establishment of appropriate treatment.<sup>21-27</sup>

### **Anatomy**

The paired parotid glands are formed as epithelial invaginations into the embryological mesoderm and first appear at approximately 6 weeks gestation. The glands are roughly pyramidal in shape, with the main body overlying the masseter muscle.

The two parotid glands are major salivary glands wrapped around the mandibular ramus in humans. The largest of the salivary glands, they secrete saliva to facilitate mastication and swallowing, and amylase to begin the digestion of starches. It is the serous type of gland which secretes the ptyalin. It enters the oral cavity via the parotid duct or Stensen duct. The glands are located posterior to the mandibular ramus and anterior to the mastoid process of the temporal bone.

The gland is divided into a superficial and deep portion by the facial nerve, which passes through the gland. While not truly anatomically discrete, these "lobes" are important surgically, as neoplasms involving the deep lobe require sometimes significant manipulation of the facial nerve to allow excision. The superficial lobe is the larger of the two and thereby the location of the majority of parotid tumors.

Numerous lymph nodes also are present within the parotid gland itself, subsequently draining to preauricular, infra-auricular, and deep upper jugular nodes.<sup>28</sup>

Many types of parotid malignancies exist, most arising from the epithelial elements of the gland.<sup>29,30,31,32</sup> Classification of these tumors can be quite confusing. In addition, malignancy may develop in the secretory element of the gland or malignancy arising elsewhere may first be noticed as a metastasis to the gland.

### **Mucoepidermoid carcinoma**

Mucoepidermoid carcinoma is the most common malignant tumor of the parotid gland, accounting for 30% of parotid malignancies.<sup>33</sup> Three cell types are found in varying proportions: mucous, intermediate, and epidermoid cells. Limited local invasiveness and low metastatic potential characterize this tumor, particularly when cytologically low-grade. If metastatic, it is most likely to metastasize to regional nodal basins rather than to distant locations.

For patients with low-grade tumors without nodal or distant metastasis, 5-year survival is 75-95%, whereas patients with high-grade tumors with lymph node metastasis at the time of diagnosis have a 5-year survival of only 5%. Overall 10-year survival is 50%.

### **Adenoid cystic carcinoma**

The adenoid cystic carcinoma is characterized by its unpredictable behavior and propensity to spread along nerves. It possesses a highly invasive quality but may remain quiescent for a long time. This tumor has the highest incidence of distant metastasis, occurring in 30-50% of patients.

Three histologic types have been identified: cribose, tubular, and solid. The solid form has the worst prognosis; the cribose pattern possesses the most benign behavior and best prognosis. Overall 5-year survival is 35%, and 10-year survival is approximately 20%. Others include Malignant Mixed, Acinic Carcinoma, primary Squamous cell carcinoma, Sebaceous Carcinoma and Lymphoma.

## 1.1 Literature Review

Generally, therapy for parotid malignancy is complete surgical resection followed, when indicated, by radiation therapy.<sup>33</sup> Conservative excisions are plagued by a high rate of local recurrence. The extent of resection is based on tumor histology, tumor size and location, invasion of local structures, and the status of regional nodal basins.

According to NCCN guidelines 2.2017<sup>[35]</sup> the treatment paradigm is superficial parotidectomy for smaller parotid malignancies and total parotidectomy is indicated when the tumor invades into or adjacent to deep lobe. Total parotidectomy attempts to spare cranial nerve VII (Facial nerve). Facial nerve should be sacrificed if it is invaded or patient presents with facial palsy.

Indications for adjuvant RT (radiotherapy) typically include positive margins, invasion outside of salivary gland, positive nodes and high grade histology.

Treatment volume: Treat parotid bed only for low grade cancers with indications for local irradiation but no lymph node involvement. Treat parotid bed and ipsilateral neck for high grade cancers, recurrent cancers, or lymph node metastases.

Radiation dose to high risk: Tumor bed - 60 Gy at 2 Gy/fraction (fx) or 63 Gy at 1.8 Gy/fx.  
Positive margins - 66-70 Gy. Neck (undissected) - 50-54 Gy. Neck (dissected) - 60-63 Gy.

Low to intermediate risk: 44-50Gy at 2Gy to 54-63Gy/fx at 1.6/1.8Gy/fx.

Postoperative RT: The preferred interval between resection and postoperative RT to be less than or equal to 6 weeks.

High risk: 60-66Gy at 2Gy/fx in 6-7 weeks and low to intermediate risk 44-50Gy at 2Gy to 54-63Gy/fx at 1.6/1.8Gy/fx.

According to a study done by Masanja et al<sup>34</sup>, Salivary gland tumors constituted 6.3% of all oral-facial tumors and tumor like lesions. Among the salivary gland tumors, 54% were benign and 46% malignant, which occurred in 80 males and 53 females. Pleomorphic adenoma was the commonest occurring tumor (44.4%) and among malignant tumors adenoid cystic carcinoma occurred in 54.3% followed by mucoepidermoid carcinoma (22.9%) and adenocarcinoma (11.4%).

The parotid gland was the commonest site of occurrence followed by the palate. At initial stages the only complaint from the patients was essentially a slowly growing painless swelling. Treatment modality was mainly surgical in both benign and malignant tumors, however, for malignant tumors radiotherapy alone or in combination with surgery was sometimes employed.

The study concluded that on average salivary gland tumors occurred at a relatively younger age compared to that reported in Western countries. Contrary to reports from Europe and America, adenoid cystic carcinoma was the most frequently occurring malignant salivary gland tumor. Late presentation was seen as a problem that needs to be addressed in order to maximize the effectiveness of treatment.<sup>35</sup>

Clinical-Pathological Features of Parotid Malignancy around the globe and nearby countries:

A study done in Kenya by Hill et al<sup>36</sup>, over the period 1992 to 1999, 135 major primary salivary gland neoplasms were examined. Amongst 103 parotid tumors, 46% were pleomorphic adenomas and 19% were monomorphic adenomas. Consistent with other studies from sub-Saharan Africa, the Warthin's tumor was rare. The commonest malignant tumor was the mucoepidermoid carcinoma comprising 14% of specimens. The commonest tumor was the pleomorphic adenoma (78%) and the commonest malignant tumor was the mucoepidermoid carcinoma(9%).

The study concluded that compared with other African studies, these figures are similar although in Kenya there is a predominance of monomorphic adenomas. Compared with

Western studies there is an increased ratio of malignant to benign tumors and Warthin's tumors are much less common in Africa.<sup>36</sup>

Socio-demographic factors and clinical-pathological features associated with parotid malignancy:

In a study in Uganda by Edda AM Vuhahula<sup>37</sup> showed otherwise, during the span of 10 years, 268 cases of salivary gland tumors were diagnosed. Of these, 113 (42.2%) were males, 148 (55.2%) females. Thirty four percent of tumors originated from the parotid, 33.2% from the submandibular and 32.8% from minor salivary glands. There were a total of 125 (46.6%) malignant tumors. The mean age of patients with malignant lesions (43.1 years; SD=16.75; median=44.00 years).No Whartin's tumor was encountered. The malignant tumors were dominated by adenoid cystic carcinoma (28.8%) followed by mucoepidermoid carcinoma (21.6%).

It was concluded that the pattern of distribution of salivary gland tumors in black African population seems to differ from that of Western series in that; females are more affected than males, ii) there is a low proportion of tumors from the parotid gland and high proportion of tumors from the submandibular and minor salivary glands, iii) the parotid and minor salivary gland tumors have more probability of being malignant than those tumors from the submandibular gland iv) the newly categorized pathological entities are common and v) Whartin's tumor is extremely rare in black African population.<sup>37</sup>

There are several treatment related factors influencing survival of parotid gland malignancy major determinants being histology and clinical stage. Other poor prognostic factors include high pathological grade, neural involvement, locally advanced disease, advanced age, associated pain, regional lymph node metastasis and distant metastasis.<sup>39,40,41.</sup>

A univariate analysis by Dominik Stodulski et al proved that the biggest influence on treatment results had the following factors: invasion of the parapharyngeal space and facial nerve paresis—nearly by ten times worsening the prognosis.<sup>42</sup>

Multivariate analysis by Dominik Stodulski et al revealed the correlation between neoplastic infiltration of the anatomical structures and treatment outcome. The independent factors that had significant influence on 5-year disease free survival were infiltration of the mandible, facial nerve, and skin. Infiltration of the mandible increased the treatment failure by 4.13 times. Infiltration of the facial nerve and skin worsened the prognosis by 2.38 and 2.04 times, respectively.

**Treatment outcomes:**

Generally, therapy for parotid malignancy is complete surgical resection followed, when indicated by radiation therapy. Radiation therapy is rarely the definitive treatment modality of parotid gland neoplasms, being used alone usually for tumors that are considered nonresectable. The use of radiation in T1 and T2 parotid gland tumors found a 5-year disease free survival increased from 70% to 92% with postoperative radiotherapy. Newer techniques have been found to be beneficial for postoperative radiation. These include intensity modulated radiation therapy (IMRT), gamma-knife stereotactic radiosurgery and brachytherapy. These have been shown to have good local control and minimal radiation to the normal tissues. However, none of these radiation modalities are available in Tanzania. The use of conventional radiotherapy with cobalt<sup>60</sup> has not been shown to improve overall survival but has shown to have severe toxicities. Parotid gland malignancy responds poorly to chemotherapy. However adjuvant chemotherapy is only indicated for palliation.

A study by Kim et al, of 126 patients treated for primary parotid cancer found the following disease-specific survival rates for the various tumor stages (mean follow-up period 29.7 months)

Stage I (97%)

Stage II (81%)

Stage III (56%)

Stage IV (15%)

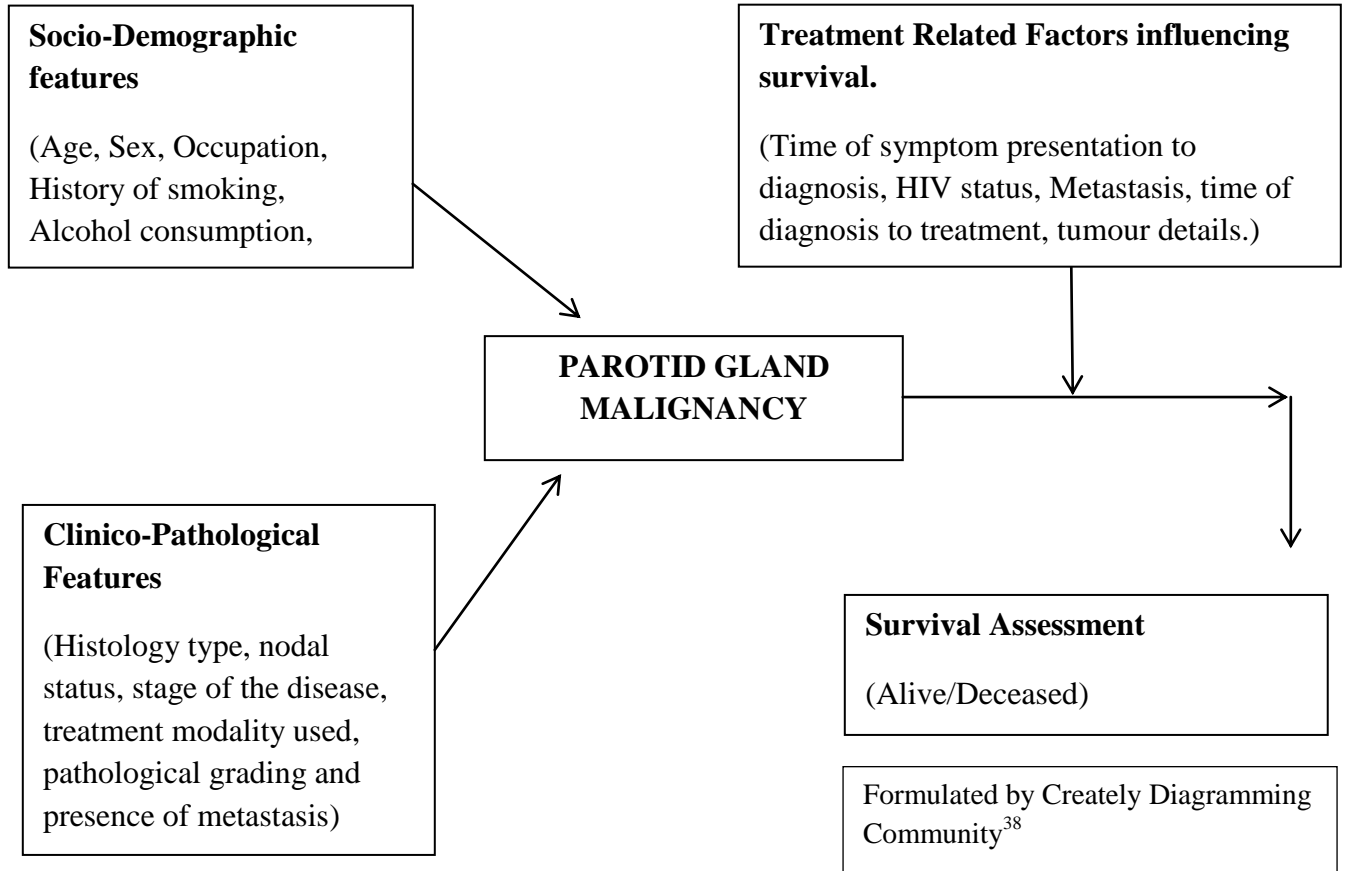
Patients in the study underwent superficial, total, or radical parotidectomy, with 57 also undergoing postoperative radiotherapy. Fifteen patients (12%) experienced disease recurrence.<sup>43</sup>

In Tanzania, histopathologic diagnosis is often unavailable at the time of initial surgery, and grading usually cannot be performed with frozen-section analysis. However, frozen sections that can be done has been found have an accuracy of 92.3%, sensitivity of 62.5%, and specificity of 100%. Thus, histologic information is typically not available before surgery. However, histopathologic diagnosis and grade should be considered because they may affect the decision regarding further surgery, elective neck dissection, or adjuvant radiation therapy.

The challenges faced for parotid gland malignancy are numerous, some identified such as late stage presentation of patients, advanced ages, immunocompromised states, neuronal involvement, few hospitals to manage parotid gland malignancies, few surgical-oncologists, lack of newer techniques for radiation and targeted chemotherapies and to emphasize on the inadequate knowledge of parotid gland malignancies and treatment modalities. All these factors determine the treatment modality, prognosis and outcome, overall survival, sociodemographic features affecting Tanzanian residents and there is very little knowledge on clinicopathological aspects of parotid gland malignancies diagnosed at a tertiary health center and this study can compare the findings with epidemiological data from different geographic locations.



## 1.2 Conceptual Framework



All Parotid Gland Malignancies were retrieved retrospectively from medical records to evaluate the clinicopathological features and treatment outcomes. Associated factors were all taken into consideration which formulated the outcome measure of the study. Missing of important data was managed by calling the patient and the next of kin on the given cell numbers. If data was still incomplete, it was excluded from the study and was compensated by increasing the number of files assessed.

### **1.3 Problem Statement**

Salivary glands diseases are conditions that are frequently seen at Muhimbili National Hospital (MNH) Oral and Maxillofacial department and referred to ORCI for further management. Patients with salivary gland tumors usually present with a variety of clinical features including dry mouth, facial nerve palsy, swelling and/or ulceration resulting in impaired function and disfigurement which are symptoms for numerous head and neck cancers.

Although there are different salivary gland diseases, patients that present with salivary gland tumors; parotid gland malignancy is the most common. These tumors when left without intervention for a long time have the capacity to increase in size and cause pain and disfigurement resulting in increased morbidity and incapacitation of the patient. Progression of the disease in the oral cavity may result into invasion of the structures of head and neck, secondary metastasis, difficulty breathing and impaired feeding which increases patients' suffering, decrease the quality of life and a high mortality rate from the malignancy itself.

In Tanzania patients usually present very late, with advanced swellings or ulcers of the mouth with a variation of biopsy features with very little knowledge on the most common histopathological type. With several related factors such as exposure of occupational carcinogens, traditional healers seeking behaviors, HIV status, smoking and alcohol consumption in Tanzania the burden of disease is increasing. Diagnosis of salivary glands diseases is highly challenging and requires biopsy as the definitive investigation which cannot be accomplished at hospitals with no biopsy taking skills/laboratory services. And currently little is known on the occurrence and clinico-pathologic presentation of parotidglands malignancies and its management at Ocean Road Cancer Institute, therefore, there was a dire need to study the clinical and pathologic characteristics and treatment outcomes of the Parotid gland malignancies in Tanzania.

#### **1.4 Rationale of the study**

Parotid gland malignancies are rare neoplasms that generate interest due to their histopathological diversity and clinical behavior. The aim of the present study is to investigate clinic-pathological aspects parotid gland malignancies diagnosed at ORCI and compare the findings with epidemiological data from different geographic locations. Cases of parotid gland malignancy in the head and neck region at ORCI in the period between 2009 and 2016 were reviewed.

Patient gender, age, parotid anatomical location site (left/right), histological type, date of diagnosis to treatment were recorded. Availability of complete information about these aspects was considered the data collection form.

I am expecting that after this study more knowledge on Parotid gland tumors will expand. Findings of this study have provided a baseline data for the clinico-pathological features of the parotid gland tumors and survival outcomes are known in consideration with treatment outcomes and sociodemographic features which contribute to the patient's quality of life.

#### **1.5 Research Question**

What are the clinic pathological features and treatment outcomes of parotid gland malignancies in patients attending Ocean Road Cancer Institute from 2009-2016.

## **1.6 Objectives**

### **1.6 1 Broad Objective**

To assess clinic pathological features and treatment outcomes of parotid gland malignancies in patients attending Ocean Road Cancer Institute from 2009-2016.

### **1.6.2 Specific Objectives**

1. To assess the socio-demographic characteristics of patients with parotid gland malignancies attending the ORCI
2. To describe clinico-pathological features in patients with parotid malignancies attending ORCI.
3. To assess treatment related factors influencing survival of patients with parotid malignancies attending ORCI.
4. To assess the 2 year overall survival of parotid malignancies in patients attending ORCI.

## CHAPTER TWO

### 2.0 MATERIALS AND METHODS

#### 2.1 Study design

This was a retrospective study designed to evaluate the clinico-pathological features and treatment outcomes among patient treated at ORCI.

Secondary data was obtained from the patient's medical records.

#### 2.2 Study population

Participants in this study comprised of all patients who attended for treatment at the ORCI during the study period.

##### 2.2.1 Inclusion Criteria

All patients with Parotid Gland Malignancies with confirmed histopathological evidence attending the ORCI from 2009 to 2016.

##### 2.2.2 Exclusion Criteria

All histologically confirmed minor salivary gland malignancies and submandibular and sublingual glands attending the ORCI.

Incomplete information resulting from medical records and follow up of patients.

#### 2.3 Sample size

The sample size of the study was calculated using the formula;

$$n = \frac{z^2 p (100 - P)}{\epsilon^2}$$

Where:

n = Minimum sample size designed,

z = the point on standard normal deviation corresponding to 95% Confidence

Interval which is 1.96,

$p$  = The prevalence of Parotid Gland Malignancies according to the study done by Massanja et al 6.3%<sup>20</sup>

$\epsilon$  = Margin of error set at 5%

$$n = \frac{(1.96)^2 \times 6.3 \times (100 - 6.3)}{(5)^2}$$

$$n = 91$$

For adjusting non response; where cross-sectional study done couple of years on parotid malignancies; response was 95%. For follow up study respond rate may decrease to 90%.

$$\text{Then; } N = n/R \quad 91/0.90 = 101$$

The number of patients to be recruited was 101.

Sample size calculation was included to reflect the power and validity of the study. Since this was a retrospective study, the sample size was used for sample recruitment purposes.

All individuals from 2009 up to 2016 were included in the study and the sample size obtained was 94.

5 patients were excluded from the study; 2 were self-referral outside the country, 2 refused treatment and 1 did not receive treatment due to financial constraints.

## 2.4 Study area

The study was conducted at Ocean Road Cancer Institute (ORCI), which is the only hospital at the country treating cancer patients. It is located along the Indian Ocean in Dar es Salaam, Tanzania. The facility is one of the oldest health institutions in Tanzania founded in 1895 by the German colonial government.

The institute works in partnership with the Tanzania community so as to create and maintain an integrated, accessible, and affordable cancer health care system with quality service to improve health and well-being. ORCI offers numerous patient services including laboratory services, diagnostic imaging, chemotherapy, radiotherapy, palliative care services, cervical cancer screening, and an HIV/AIDS care and treatment clinic.

Also ORCI offers teaching programs for undergraduate and postgraduate medical students as well as other health care workers, further more ORCI runs research projects in various aspects of cancer.

The hospital has two cobalt 60 machines, one conventional simulator, one remote loading high dose rate brachytherapy unit, two X-ray machine, two ultrasound machine and well equipped laboratory where complete blood counts investigations, comprehensive chemistry panel investigation are carried.

All salivary gland malignancies patients are brought to ORCI are treated with radiotherapy and most of them are brought in advanced stage. In 2006 up to 2014 the institute received a total number of 37244 for all cancer patients while the number of salivary gland malignancy patients attended ORCI were 161 according to the ORCI data.

The ORCI has a standard protocol which is used in the management of parotid gland malignancies. This protocol is well familiar with all physicians and residents practising at ORCI. The protocol for salivary gland malignancy has two respective arms, Curative intent and Palliative Intent last reviewed in 2014.

#### Curative Intent:

Investigations required:

EUA for trismus/painful or inaccessible lesion

CT scan -to visualize facial canal in facial nerve involvement

Definitive Treatment of Parotid Neoplasm:

Primary Tumor:

Superficial parotidectomy is the minimal surgical procedure.

CN VII is spared if there is clearly identifiable plane between it and the tumor .

Facial nerve is resected if encased, nerve graft is considered.

Total parotidectomy is required for deep lobe involvement or compromised deep margin.

Lateral trasorrhaphy if CN VII is sacrificed or post-operative weakness is anticipated.

Skin defect is reconstructed by loco-regional/free flap.

Neck:

Surgery-depending on the extent of involvement and likelihood of post-operative radiotherapy:

Indications for post-operative radiotherapy

Large primary - T4 or T3 with soft tissue infiltration

High grade tumors

Extensive soft tissue and bony invasion

Extra nodal extension or multiple nodal involvement

Lympho-vascular and perineural invasion

Close or positive margins of excision

Metastatic Disease

Solitary/localized lung metastasis from adenoid cystic carcinoma may be evaluated for resection.

Post-operative radiotherapy for the primary/nodal disease:

Dose: 60-66Gy/30-33 fr/5-6 weeks using reducing fields. The site of residual disease, positive cut margins may be taken to higher doses.

Palliative Intent:

Indications for Palliative Radiotherapy:

Not fit for surgery.

Poor Karnofsky Performance Score <40.

Advanced disease.

## **2.5 Data management**

Data collection

Data was obtained from the patient's files.



## **2.6 Variables**

Dependents: Fate of patient: Alive/Deceased

Independents: Sex, age, Smoking, occupation, education, marital status, Alcohol consumption, Exposure to any carcinogens, HIV status, CD4 level, Received Chemotherapy, Received combined therapy.

Secondary characteristics data: data summarized in categorical and descriptive methods.

Outcome variables (treatment outcome and survival) were measured from the time of diagnosis which was the time of histopathological evidence of parotid gland malignancy from the biopsy report to time of death which was documented on the files and for the loss of follow up and deaths at home; the respective family was contacted and reconfirmed by a death certificate. Missing of important data were managed by calling the patient and next of kin on the given cell phone numbers. Failure of obtaining complete data was omitted from the study by the primary investigator as completion of data is essential for data analysis. Loss to follow-up of the patients was managed by excluding from the study and was compensated by analyzing more files which had complete data.

## **2.7 Investigation tool reliability and validity issues**

The tool was piloted and any gaps identified were refined. Reliability of data extracted from the registers were assured by checking outliers of recorded values, unit of measurements and prescribed dosage based on treatment recommended standards and guidelines. In case of doubt for laboratory test results; counterchecking action was made by comparing inpatient records and laboratory records. Other attributes were assessed that comply with reliability included date of input information, the profession of a person who filled the register and where possible the methods and device used to capture the test results. This signified that if the collected data is current, collected by a professional person in the area of the study topic and recommended methods and devices of measurements were used then collected information is considered reliable. All records extracted were evaluated for it validity i.e. were they useful and relevant in achieving the study objectives.

## **2.8 Data Quality control**

The data obtained was coded, edited and cleaned before any statistical analysis was carried out on the data. Additional internal documentations such as variable and value labels were added and any necessary additional variables were created through algebraic or logical expressions. Data capture sheet was pre-tested to improve consistency. Data was double checked while entering to control for errors.

## **2.9 Data analysis**

Analysis plan for each objective:

Objective 1: Socio-demographic characteristics of patients with parotid gland malignancies who attended ORCI: Descriptive analysis was made and data is presented on tables and bar charts. The results presented include sex, age, occupation, education, marital status, smoking and alcohol consumption

Objective 2: Clinico-pathological features in patients with parotid malignancies who attended ORCI

Clinico-pathological features including pleomorphic adenomas, monomorphic adenomas and other histological subtypes were assessed and comparison was made between age and sex. Descriptive results from this analysis are presented in tables and figures.

Objective 3: Treatment related factors influencing survival of patients with parotid malignancies who attended ORCI: The treatment related factors which may influence survival of patients included time of diagnosis, time of initiation of therapy, type of treatment modality received, clinical and pathological staging, presence of metastasis and the treatment intent whether curative or palliative. Descriptive analysis was conducted for these variables and results are presented on tables and bar charts.

Objective 4: Assessment of survival of parotid malignancies in patients who attended ORCI: Here survival assessment was the fate of patient; Alive/Deceased. Chi-square analysis was done to assess demographic and behavioral risk factors. The risk factors will include sex, age,

occupation, education, marital status, smoking, alcohol consumption, Exposure to any carcinogens, HIV status, CD4 level, Received Chemotherapy, Received combined therapy. Because of smallness of the sample size no logistic regression analysis was conducted.

Data entry and analysis was processed using Statistical Package for Social Sciences {SPSS} Computer Software version 21.0. Social demographic and Clinical factors were analyzed by using frequency and percentage as well as mean and standard deviation. The univariate, bivariate and multivariate analysis were performed and determination of the association between dependent and independent variables were performed. An association was regarded as statistical significance if the p-value was less than the significance level of 0.05 i.e.  $p < 0.05$ .

#### **2.10 Ethical clearance and Ethical consideration:**

The protocol was submitted for ethical clearance to MUHAS Research and Publications Committee. The permission to do the study at ORCI was sought from the Institution of Ethical Review Board and Executive Director of ORCI. The Hospital Administration was well informed about the purpose of the study and that information provided from the patient's files will be confidential. To ensure confidentiality patients names were not included in the data collection form. The files were returned to medical records department after data extraction from the files.

#### **2.11 Study limitations and mitigation measures**

1. Missing of important data as the files were used, this was managed by calling the patient and next of kin on the given cell phone numbers.
2. Failure of obtaining complete data was omitted from the study by the primary investigator as completion of data is essential for data analysis.
3. Loss to follow-up of the patients, this was managed by excluding from the study and was compensated by analyzing more files which have complete data.

Proposal development: Funds were partly used as allowances for facilitator and two research assistants training for two days so as to perform work as per requirement. Also A4 papers,

pens, pencils and folders will be required for the development of checklist; as well as for printing checklists and data collection forms.

Data collection, entry and analysis: Some amount of fund was used as allowances for principle investigator and two research assistants to collect data and to enter data, payment to the statistician for data analysis. Other expenses included transport and also communication and installation of SPSS computer software program (version 21.0.) in the computer for data entry and data analysis.

Compilation, report writing and dissemination: A comprehensive report is prepared and is being disseminated to Muhimbili University of Health and Allied Sciences, and the Department of Clinical Oncology, ORCI.

This is a self-sponsored study with no interest of conflict.

## **2.12 Dissemination Plan**

The results obtained from this study will be part of partial fulfillment of the Masters of Medicine in Clinical Oncology, and will be presented to Muhimbili University of Health and Allied Sciences. Moreover; the hospital authority will have access to use the result and the study in a proper way whenever deemed necessary to do so. The results may also be presented in scientific meetings and published in local and international journals.

## CHAPTER THREE

### 3.0 RESULTS

#### 3.1 The socio-demographic characteristics of patients with parotid gland malignancies

##### Demographic background.

A total of 94 (male =51 and female =43), with a male to female ratio of 1.18:1 reported with parotid gland carcinoma were involved in this study. An overall mean (SD) age of the patients was 51.9(16.6) years. Age range was from 21-83 years.

The mean (SD) of male and female was 58.1(13.9) and 44.5(16.7) years and the mean age difference between male and female was significant ( $p<0.0001$ ).

**Table 1** shows that more than half (54.3%) of the patients were male and 51% were aged 50-75 years and 69.2% of the study population were either peasants or into small scale businesses.

Eight (8.5%) patients had history of smoking and the same number of patients had history of alcohol consumption. Only one patient reported history of tobacco smoking and there were 0 numbers of cases with report of being exposed to carcinogens.

**Table 1: Demographic background of the patients with Parotid gland malignancy. N=94**

<b>Factors</b>	<b>Frequency n=94</b>	<b>Percentage</b>
<b>Sex</b>		
Male	51	54.3
Female	43	45.7
<b>Age group</b>		
0-24	7	7.4
25-49	31	33
50-75	48	51.1
>75	8	8.5
<b>Occupation</b>		
Peasant	34	36.2
Business	31	33
Employed	12	12.8
Student	5	5.3
Retired	6	6.4
Housewife	6	6.4
<b>History of Smoking</b>		
Yes	8	8.5
No	86	91.4
<b>History of Alcohol Consumption</b>		
Yes	8	8.5
No	86	91.4
<b>Exposure to any carcinogens</b>		
Yes	0	0
No	94	100

### 3.2 To describe clinico-pathological features in patients with parotid malignancies attending ORCI

There has been a variation in the reported histology of malignant salivary gland tumors.

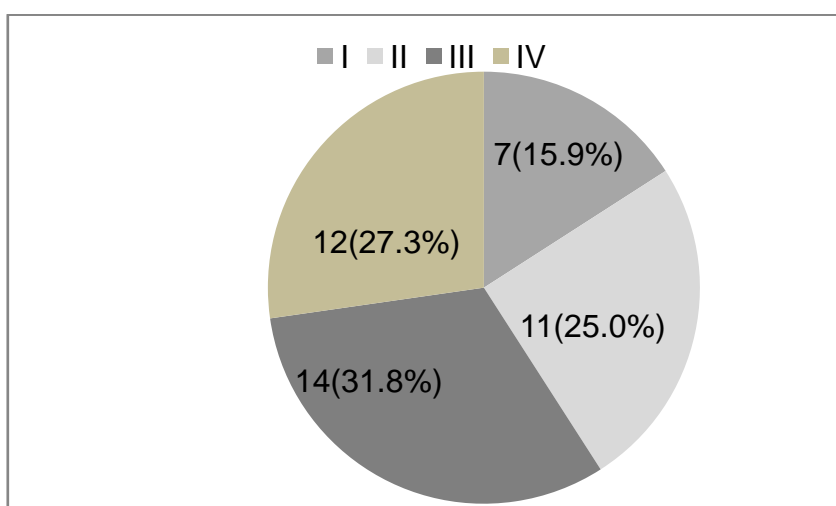
In the present study adenocarcinoma was the commonest malignant tumor that accounted for 40% of all parotid gland malignancies followed by mucoepidermoid carcinoma, squamous cell carcinoma, adenocystic carcinoma with acini cell carcinoma being the rarest.

Most common site was noted to on the Left side accounting for 48 (52.7%).

**Table 2: Histology of malignancy of parotid gland by site.**

<b>Histology of malignancy</b>	<b>Right,n=46 (%)</b>	<b>Left, n=48 (%)</b>	<b>Total, n=94 (%)</b>
Adenocarcinoma	18(45)	19(47.5)	37 (40)
Mucoepidermoid Carcinoma	7(15.2)	12(25.0)	19(20.2)
Squamous cell carcinoma	9(19.6)	9(18.8)	18(19.1)
Adenoid Cystic carcinoma	10(62.5)	6(37.5)	16(17.5)
Pleomorphic Adeno Carcinoma	1(2.2)	1(2.1)	2(2.1)
Acinic cell carcinoma	1(2.2)	1(2.1)	2(2.1)

Pathological grading was done for 44(46.8%) patients, while the remaining histology reports were not graded/ assessed. **Figure 1** shows the pathological grading of parotid gland malignancy:



**Figure 1: Pathological grading (n=44)**

Grade IV accounted for the most common grading (poorly differentiated) followed by grade III with 27.3%, grade II with 25% and grade I (well differentiated) with 15.9% respectively.

#### **Stage and Nodal disease**

Majority of the patients 72 (76.5%) presented with a stage IV disease (T4a,T4b), followed by Stage III with 7 (7.4%), Stage II with 4 (4.2%) and a few number that were unstaged pre-operatively or post operatively accounted for 11 (11.7%)

65.9% of the patient presented with nodal disease at the time of diagnosis 62(65.9%) whereas 33 cases (35%) nodal status could be assessed. 8 (8.5%) presented with metastatic disease at the time of diagnosis.



**Table 3: Stage of the disease of the patients. N=94.**

<b>Stage</b>	<b>Frequency</b>	<b>Percentage (%)</b>
Stage 1	0	0
Stage 2	4	4.2
Stage 3	7	7.4
Stage 4	72	76.5
Unstaged	11	11.7
<b>Total</b>	<b>94</b>	<b>100%</b>

### **3.3 To assess treatment related factors influencing survival of patients with parotid malignancies attending ORCI**

The assessment of treatment related factors that may or may have not influenced the treatment outcome was assessed by several sub variables such as,

- a. Time of symptom to diagnosis
- b. Time of diagnosis to initiation of treatment (either surgery or radiotherapy)
- c. HIV status
- d. Stage, disease extension site and presence of Metastasis at time of diagnosis
- e. Tumor Operable/ Non operable
- f. Type of surgery
- g. Treatment received
- h. Treatment Interrupted or not

#### **Time of symptom to diagnosis and Time of diagnosis to initiation of treatment**

The time of symptoms presentation to diagnosis ranged from 1 month to 12 years. While time of diagnosis to treatment initiation ranged from 14 days to 10 months. Mean time of treatment initiation was within 30 days of diagnosis.

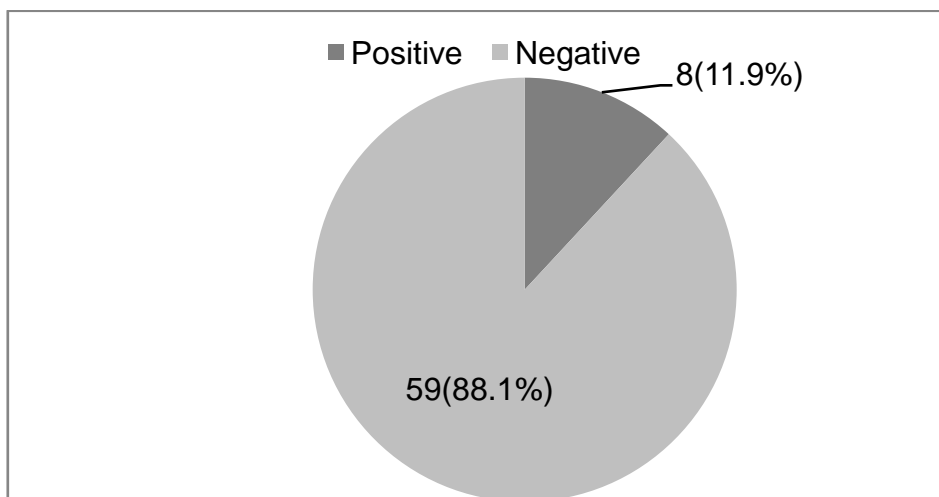
### HIV Status

Out of 94 patients, 67(71.3%) the HIV status was checked. **Figure 2** shows the HIV status.

All patients were screened for HIV at time of presenting symptoms (at Muhimbili National Hospital) and before treatment initiation (at Ocean Road Cancer Institute).

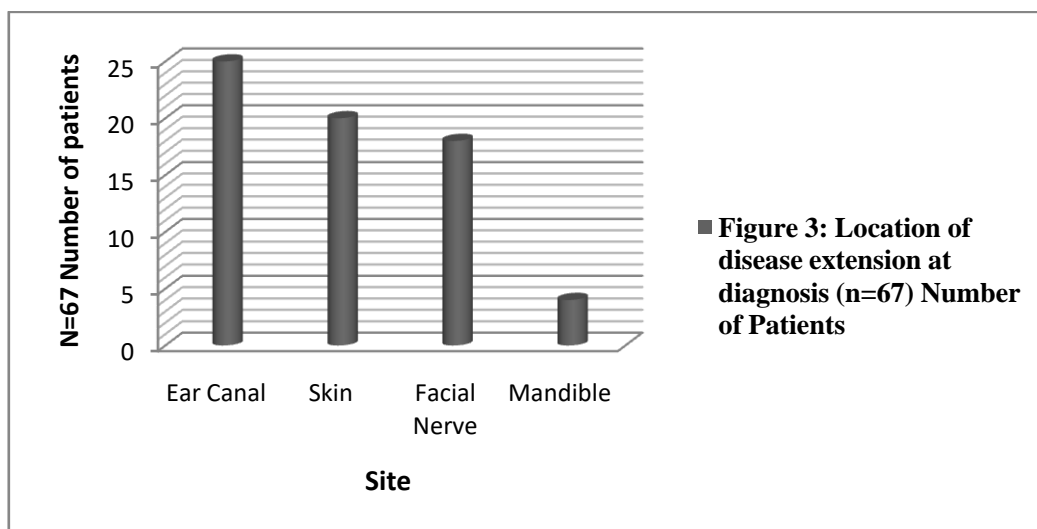
The proportion of patients who were HIV positive was 11.9% and all were on ARV medications. CD4 counts were not known for all patients, however known CD4 counts ranged from 129-250 cells. Viral load was not assessed for any of the positive patients. All patients HIV positive disease had no opportunistic infections at the time of diagnosis and treatment cycles and all patients had known disease before diagnosis of parotid gland malignancy. 19 ((20.2%) of the cases HIV was not checked.

**Figure 2: HIV status of the patients (n=67)**



**Locally advanced disease involvement site and presence of metastasis at time of diagnosis.**

**Figure 3: Location of disease extension at diagnosis (n=67)**



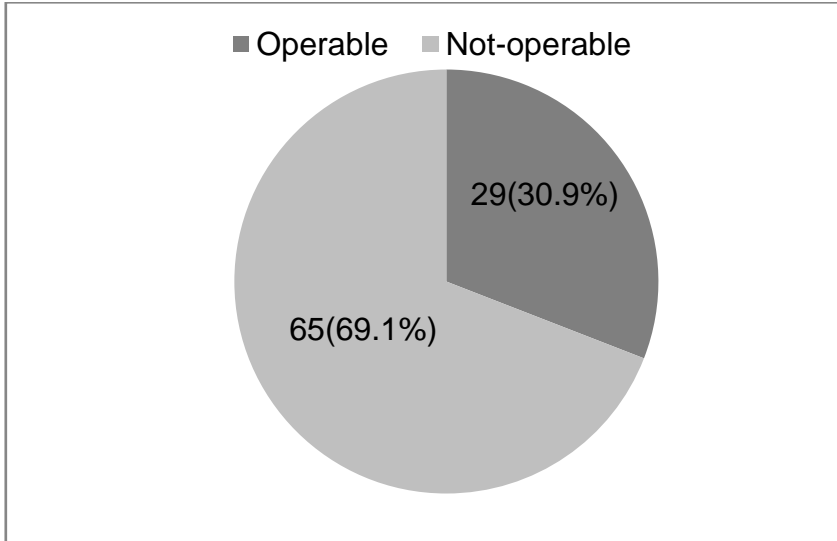
The most common site of disease extension was noted in the ear canal accounting for 32%, followed by skin with 30%, facial nerve involvement 29% and mandible with 9.5% 8 (8.5%) presented with metastatic disease at the time of diagnosis, out of which, all (100%) had pulmonary metastasis.

**Tumor: Operable/Non-Operable at time of diagnosis.**

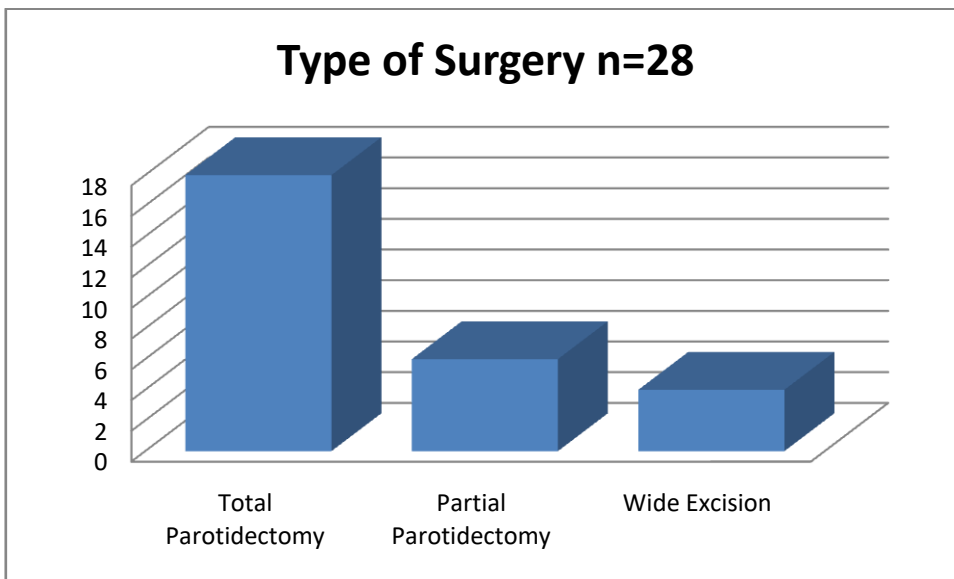
Standard of care for Parotid gland malignancy is primarily surgery, while in this study only 31% of patients were subjected to surgery while majority of the patients 69.1% had unresectable disease after being assessed thoroughly by the surgeons.

Information on lymph node resection was available for only five patients out of 29 who were operated, remaining 24 patients the information was either not documented/lymph node resection was not performed.

Results for surgical margin was recorded for 5 (17%) and not assessed for the remaining 23 (79%).

**Figure 4: Surgical evaluation; Tumor operable/ non- operable n=94**

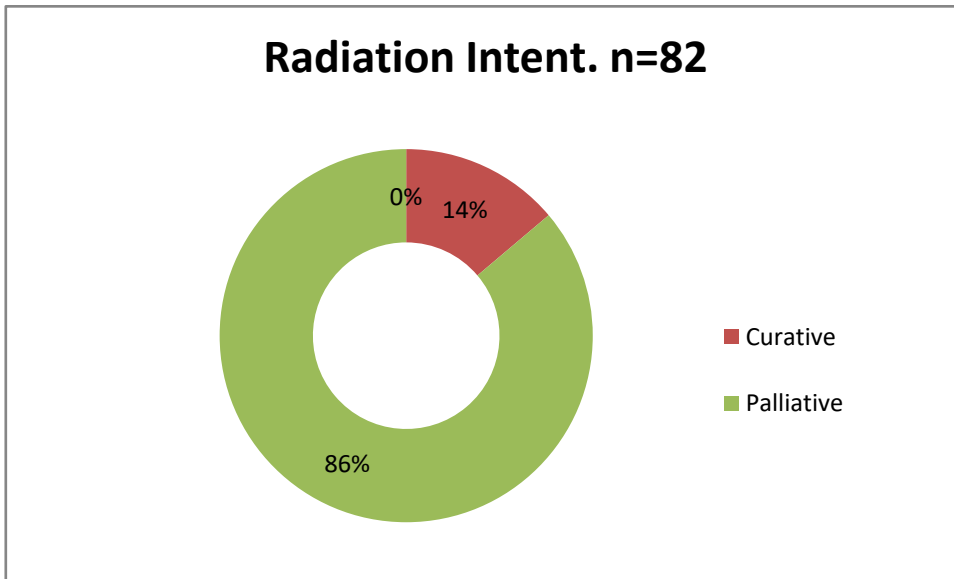
The ones who underwent surgery, below Figure 5 summarizes' the type of surgeries performed.

**Figure 5: Type of surgery performed**

### Treatment Received

Eighty two (95.2%) patients received radiation, whether the intent was curative or palliative (See definition) 13 patients (14%) received curative intent with the dose ranging from 60-66Gy. 69 patients (86%) received palliative dose which ranged from 50Gy to 20Gy. Curative dosages were given as 44Gy to tumor bed and 20Gy after cone down), 5 patients received 20Gy for symptomatic management which was pain and bleeding, and the remaining 88 (93.6%) received 30Gy in 10 fractions for 3 weeks. (3Gy daily- palliative dose). The indications for curative vs palliative was based according to the treatment protocols of ORCI (See pages 16-17)

All patients were treated with Cobalt 60.

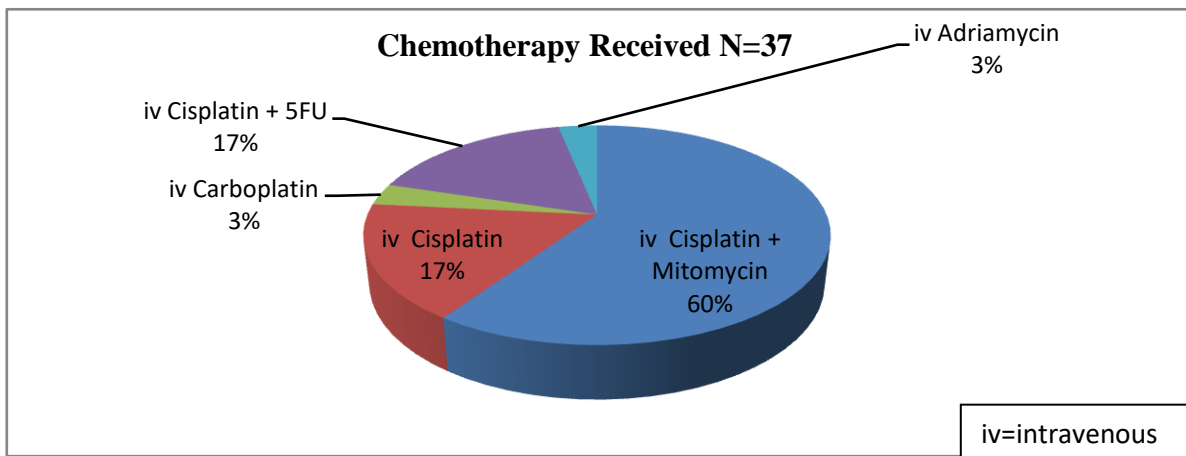


**Figure 6: Intent of radiotherapy received**

Figure 6: summarizes the radiotherapy intent of parotid gland tumors that were managed at ORCI

The figure below (**Figure 7**) shows that more than half (54.1%) of these patients received IV Cisplatin + IV Mitomycin. About 62% (n=23) of those who received chemotherapy completed the treatment. Forty eight (53.1%) patients received combined therapy (surgery radiotherapy and chemotherapy). The following were therapies received by patients who received chemoradiation 26(56.3%), surgery and radiation alone 20(41.6%). These chemotherapy regimens were mostly used for palliative purposes.

**Figure 7: Types of chemotherapy received (n=37)**



Thirty (31.9%) out of 94 patients their treatment were interrupted; **Table 4** shows the reason for interruption whereby severe anemia, deaths and Neutropenia were the main reasons.

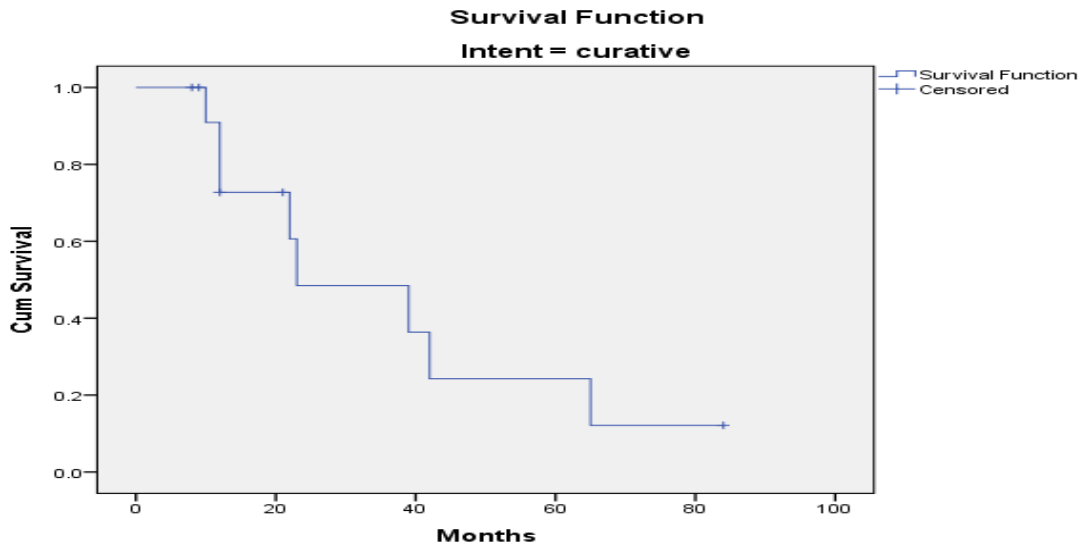
**Table 4: Cause of treatment interruption among patients**

<b>Cause</b>	<b>Frequency</b>	<b>Percentage</b>
Severe anaemia	12	40
Death	5	16.6
Neutropenia	5	16.6
Septicaemia	2	6.6
Low Karnopfsky Performance Status <50	1	3.3
Machine breakdown	1	3.3
Nausea and Vomiting	1	3.3
Patient decided not to opt for treatment	1	3.3
Severe Mucositis	1	3.3
Financial Constraints	1	3.3
<b>Total</b>	<b>30</b>	<b>100</b>

#### **3.4 To assess the overall survival of parotid malignancies in patients attending ORCI.**

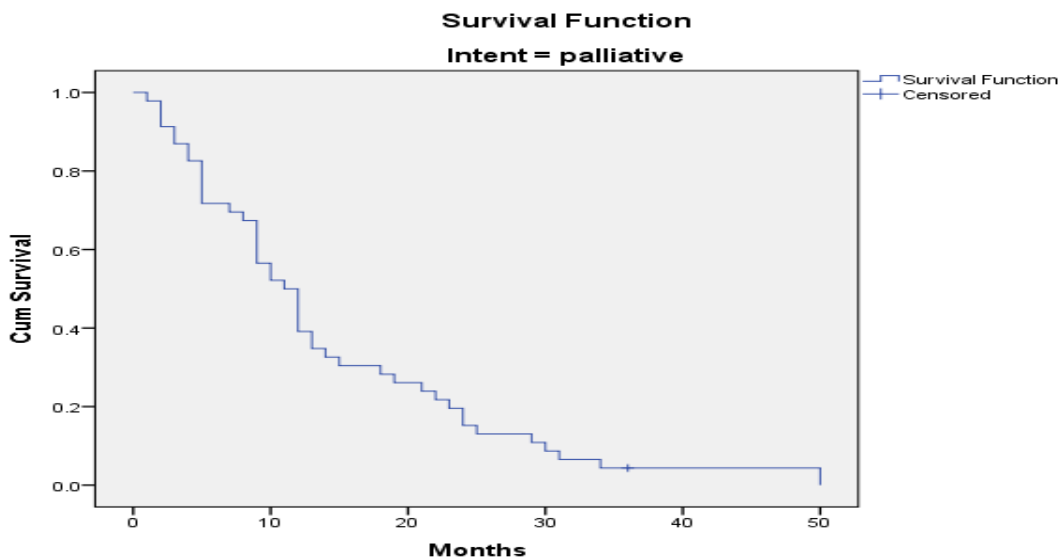
**The treatment outcome was assessed for parotid gland malignancy was overall survival, whether they are alive or dead at the end of two years, from January 2009 up to December 2014.**

**Figure 8** shows the two year overall survival of the patients (n=13) who were under the curative arm.



**Figure 8** shows the 2 year overall survival for the curative intent arm was 23%.

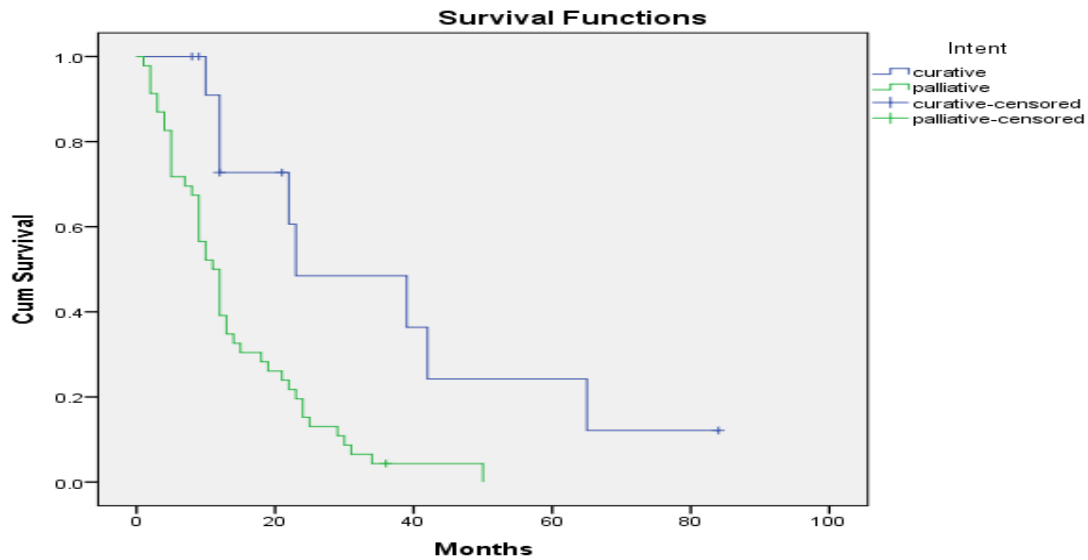
For the Palliative Intent arm (n=69), **Figure 9** shows the 2 year overall survival.



**Figure 9** shows the overall survival for the palliative cohort was 11%.



Figure 10 shows 2 year Overall survival (for curative and palliative) of parotid gland malignancies attending ORCI from 2009 up to 2014.



**Figure 10. The 2 year overall survival for both arms combines is 12%.**

The Table below (Table 5) summarizes Figure 8, Figure 9 and Figure 10.

**Table 5.**

Means and Medians for Survival Time						
Intent	Mean <sup>a</sup>					
	Estimate	Std. Error	95% Confidence Interval		Estimate	Std. Error
			Lower Bound	Upper Bound		
curative	36.424	8.074	20.599	52.250	23.000	11.651
palliative	14.174	1.708	10.825	17.522	11.000	1.272
Overall	18.354	2.323	13.801	22.907	12.000	.815

### Overall Comparisons

	Chi-Square	df	Sig.
Log Rank (Mantel-Cox)	10.149	1	.001

When both, the curative and palliative overall survival arms were compared, the curative arm survived longer compared to the palliative arm,  $p=0.001$ .

Nearly 80% ( $n=65$ ) of all deaths occurred at homes while 16(19.8%) deaths happened at the hospitals.

The cause of death was not known to three patients and the remaining cause was advanced disease 72/78(92.3%). Other causes included sepsis (3), anemia causing failure (1), Motor Traffic accidents (2) and Malaria (1)

**Figure 11: Treatment outcome by Age N=94**

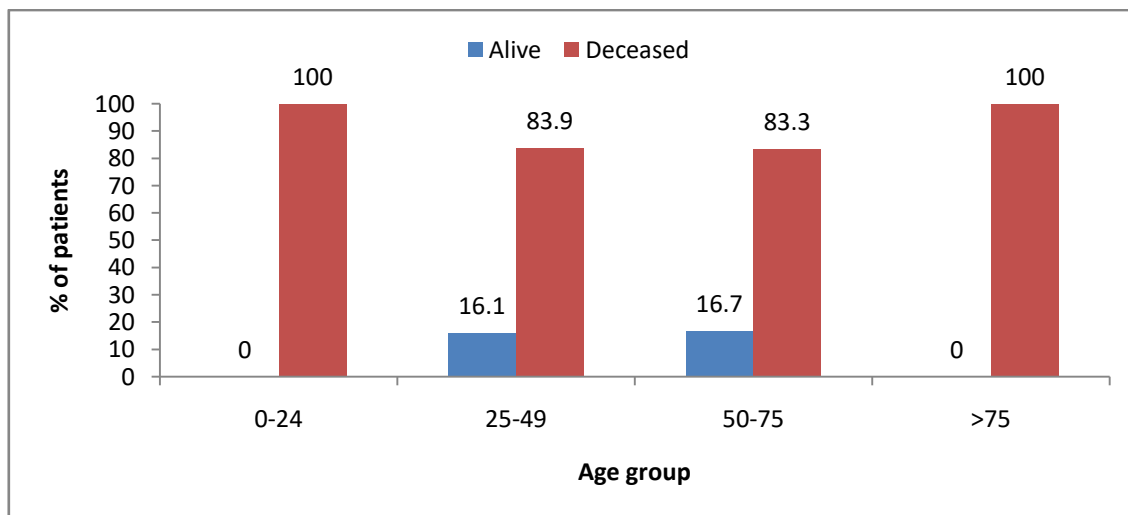


Figure 11 Indicates that all patient aged  $<25$  and those aged above 75 years had poor treatment outcomes.

Figure 12: Treatment outcomes of parotid malignancies in patients attending ORCI by gender.

More males were affected with the ratio of 1.18:1 and more deaths were in the male subgroup.

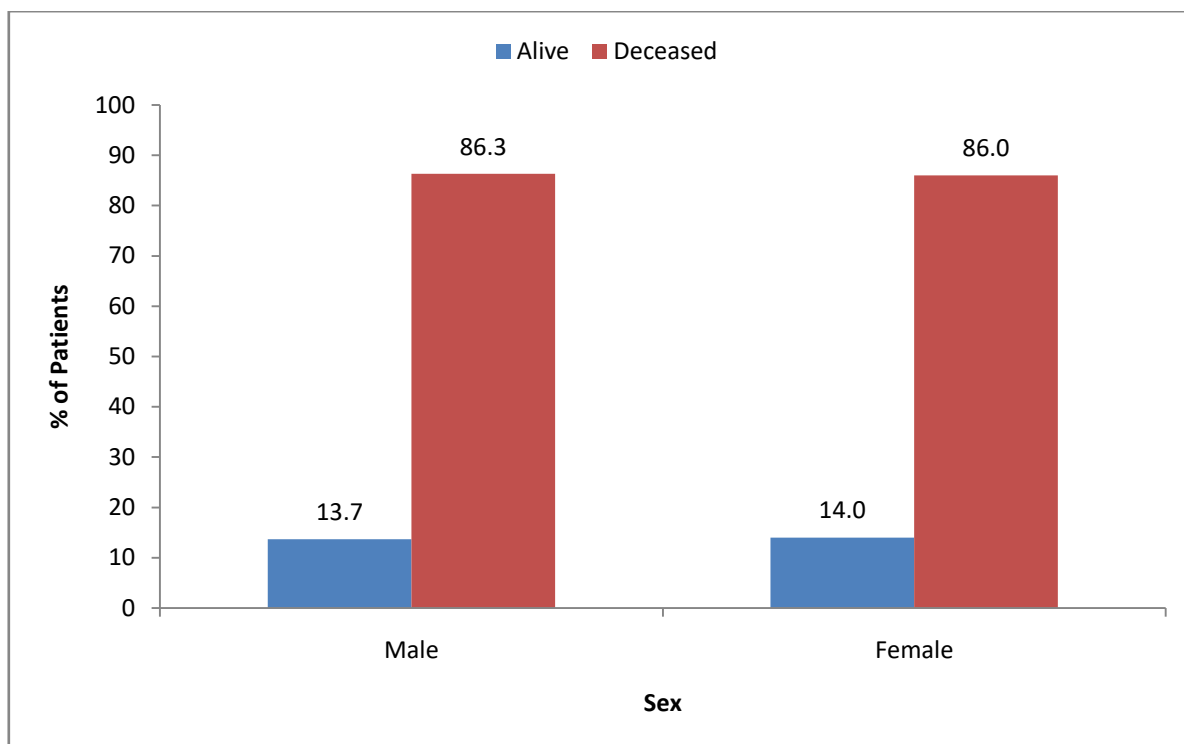


Figure 12: Treatment outcome by gender N=94.

**Table 6: Factors associated with poor (death) treatment outcomes among patients with parotid carcinoma. N=94**

<b>Factors</b>	<b>Total, N=94(%)</b>	<b>Deceased, (%)</b>	<b>Chi-square</b>	<b>P- Value</b>
<b>Sex (n=94)</b>				
Male	51(54.3)	44(86.3)	0.011	0.603
Female	43(45.7)	37(86.0)		
<b>Age group (n=94)</b>				
<50	38(40.4)	33(86.8)	0.024	0.565
50+	56(59.6)	48(85.7)		
<b>HIV status (n=68)</b>				
Positive	8(11.9)	6(75.0)	1.045	0.291
Negative	59(88.1)	52(89.7)		
<b>Pathological grading (n=44)</b>				
I-II	18(41.9)	18(100)	2.322	0.186
III-IV	25(58.1)	22(88.0)		
<b>Treatment initiation (n=83)</b>				
Timely( $\leq$ 14days)	7(8.4)	7(100)	1.292	0.32
Delayed (>14days)	76(91.6)	64(84.2)		
<b>Received surgery services</b>				
Yes	29(30.9)	24(82.8)	0.41	0.522
No	65(69.1)	57(87.7)		
<b>Received Chemotherapy</b>				
Yes	37(39.4)	31(83.8)	0.292	0.402
No	57(60.6)	50(87.7)		
<b>Received combined therapy</b>				
Yes	48(52.1)	39(81.2)	1.993	0.133
No	46(48.9)	42(91.3)		
<b>Completed treatment</b>				
Yes	23(62.2)	18(78.3)	1.365	0.243
No	14(37.8)	13(92.9)		

## CHAPTER FOUR

### 4.0 DISCUSSION

Majority of the patients who needed histopathology evidence of parotid malignancy were referred to and referred from MNH which is the only largest and affordable center in the whole country with specialized oral and maxillofacial surgery services. Others were referred from private institutions directly to ORCI for further management.

#### 4.1 Socio-demographic features

In this study it was found that generally salivary gland diseases mostly occurred in patients Between 50 to 75 years of age with the highest frequency in the 6th decade.

This could be due to the fact that most of the parotid gland malignancies affect older generation and are slow growing with no pain and therefore likely to be detected later.

A total of 94 (male =51 and female =43), with a male to female ratio of 1:1.18 were reported in this study. The mean age difference between male and female was significant ( $p < 0.0001$ ).

A few studies namely, studies by Chidzonga<sup>47</sup> in Zimbabwe and Nitin<sup>48</sup> in India had higher numbers of males compared to females. The higher number of females may be attributable to the fact that generally women have a higher tendency of reporting their medical problems earlier than men. However Al-Khateeb et al<sup>44</sup> in Jordan and Zhao et al<sup>46</sup> in India reported females having more parotid gland neoplasms compared to males.

Furthermore, according to Arotiba GT et al<sup>52</sup> from Lagos Nigeria found squamous cell carcinoma affected more males (41.2%) than females (4.7%) ( $P = 0.03$ ); parotid mucoepidermoid carcinoma affected more females (53.3%) than males (11.8%) ( $P = 0.0149$ ). Males presenting with pleomorphic adenoma were relatively younger than their female counterparts. Majority of patients with malignant tumors (83.9%) had significant local extension, regional or distant metastasis at presentation. However, a quarter of these patients with cancer defaulted the planned treatment regime because they could not afford the cost of treatment or they opted for traditional medical care.

According to the WHO and other reports<sup>53,54</sup> and in agreement with the present results, female patients are overall more affected than men, although there are some studies that report higher prevalence's in men (as above) These differences may be explained due to geographical variations of the populations. These findings also suggest a possible wide variation in the presentation of salivary gland tumors indifferent populations.

### Occupation

It has been shown that workers in a variety of industries have an increased incidence of salivary gland carcinomas. These include rubber manufacturing, exposure to metal in the plumbing industry and nickel compounds, woodworking in the automobile industry and employment in hairdressing and beauty shops. An increased risk of salivary gland cancers was reported in people living in certain Quebec counties where asbestos was mined, and the risk was inversely proportional to the distance from the mines.

In this study, none of these occupations were noted, majority being peasants and involved in small-scale business.

### Lifestyle and nutrition

No association has been found between tobacco use and alcohol consumption and salivary gland cancers in a several case/control studies.

Over the years there has been some progress in clarifying specific causes of salivary gland cancer. The best known risk factor is that of radiation exposure as evident in the increased risk in atomic bomb survivors and in patients receiving therapeutic radiation. An increased occurrence in children with leukemia's treated with multiagent chemotherapy and prophylactic cranial irradiation has also been noted<sup>55</sup>. A dose response effect for low dose irradiation has been shown with a mean latency period of tumor development of 11 years for malignant tumors and 21.5 years for benign tumors<sup>56</sup>. However, no increased risk is noted for exposure to UVB radiation.

Of potential viral etiologies, only EBV infection is implicated in the pathogenesis of salivary lymphoepithelioma-like carcinomas that are more commonly encountered in Eskimo and

Chinese rather than Western populations. However, no increased risk is documented for infections with herpes, papilloma or HIV viruses<sup>57,58</sup>. Contrary to one previous study<sup>59</sup>, it is acknowledged now that there is no increased risk of a second primary breast cancer in women who have had previous salivary gland cancer. However, there is some increased risk for the development of second primary cancers of the oropharynx, thyroid gland and lung, especially for those whose salivary gland cancers were treated with radiotherapy<sup>60</sup>. Unlike other head and neck cancers, alcohol and smoking abuse are not associated with increased risk for developing salivary gland neoplasms with the exception of a greatly increased risk and association of smoking with Warthin's tumor<sup>61,62,63</sup>. One interesting finding, unconfirmed by others, is an elevated risk of salivary gland cancer in women employed as hairdressers and those working in beauty salons<sup>64</sup>.

#### **4.2 Clinico-Pathological Features**

Among the malignant tumors, adenocarcinoma was the most commonly encountered lesion, which is in contrast to several reports that the most common malignant tumor was either adenoid cystic carcinoma or mucoepidermoid carcinoma.

There has been a variation in the reported occurrence of malignant salivary gland tumors.

While Al-Khateeb<sup>44</sup> reported that mucoepidermoid carcinoma and adenoid cystic carcinoma occurred equally as commonest malignant salivary gland tumors, Masanja et al<sup>34</sup> reported adenoid cystic carcinoma to be the commonest malignant tumor.

Hill et al<sup>36</sup> in Kenya reported mucoepidermoid tumor being the most common and Edda et al<sup>37</sup> in Uganda reported adenocystic carcinoma to be the most encountered.

In the present study adenocarcinoma was the commonest malignant tumor that accounted for 40% of all parotid gland malignancies followed by mucoepidermoid carcinoma, squamous cell carcinoma and adenocystic carcinoma with acini cell carcinoma being the rarest.

This difference in the two Tanzanian studies might be because of the geographical difference, duration of the study and study site.

Only one case of acinic cell carcinoma was seen. The rarity of this tumor and its involvement of the parotid gland are in keeping with the report of Tian et al.<sup>46</sup>

The findings of this study did not concur with other African and Western countries reports which showed a lower occurrence of adenocarcinoma in comparison to other malignant salivary gland tumors.<sup>45</sup>

Adenocarcinomas mostly presented as painful swellings but as summarized above, presentations and extension of disease varied upon individuals, most commonly being difficulty in hearing followed by ulcerations and a non-healing wound and facial asymmetry. Due to the above presenting symptoms at diagnosis, 76.5% of patients presented with stage 4 disease. This significant finding was due to several reasons such as the Tanzanian practice of seeking medical attention to traditional healers, physicians misdiagnosing and treating with antibiotics which consumes diagnosis time and also because of ignorance of symptoms (symptom presentation ranged from one month to twelve years)

Pathological grading was only performed in 46.8% of the cases and the most common grade encountered was grade 4 which is a poorly differentiated tumor which also accounts for a poor prognostic factor when considering the outcome of the patients. Due to this reason, 8.5% of the patients presented with pulmonary metastatic disease.

Prognostic indicators of parotid gland malignancy include:

Stage of the disease, histology, high grade, perineural invasion, locally advanced disease, advanced age, lymph node metastasis and distant metastasis.

In a nutshell, majority of the patients in this study presented with advanced stages, higher grades, older age, perineural invasion, lymph node metastasis and with inoperable disease hence the majority received palliative radiotherapy which was mainly for symptomatic control such as bleeding and pain. Only 11 patients presented with stage II and stage III disease and zero cases for stage I.



### **4.3 Treatment related factors and Outcomes.**

#### **Operative Management**

Generally, therapy for parotid malignancy is complete surgical resection followed, when indicated, by radiation therapy. Conservative excisions are plagued by a high rate of local recurrence. The extent of resection is based on tumor histology, tumor size and location, invasion of local structures, and the status of regional nodal basins.

Most tumors of the parotid (approximately 90%) originate in the superficial lobe. Superficial parotid lobectomy is the minimum operation performed in this situation. This procedure is appropriate for malignancies confined to the superficial lobe, those that are low grade, those less than 4 cm in greatest diameter, tumors without local invasion, and those without evidence of regional node involvement.

In this study surgery was done in 31% of the patients and 69.1% had unresectable disease. The surgery that was most commonly performed was total parotidectomy with facial nerve sparing. Surgery was done in few cases because of the advanced disease, perineural invasion and large tumors which made resection difficult.

#### **Radiotherapy**

Because of the many histologic subtypes of parotid malignancies, a general statement regarding the usefulness of adjunctive therapy cannot be made.

If resectable, surgery is the primary modality of treatment for most malignant tumors of the parotid gland. General indications for postsurgical radiation therapy include tumors >4 cm in greatest diameter, tumors of high grade, tumor invasion of local structures, lymphatic invasion, neural invasion, vascular invasion, tumor present very close to a nerve that was spared, tumors originating in or extending to the deep lobe, recurrent tumors following resection, positive margins on final pathology, and regional lymph node involvement. Postoperative radiation is, thus, usually indicated for all parotid malignancies with the

exception of small low-grade tumors with no evidence of local invasion or nodal/distant spread. Radiation therapy is considered the cornerstone of adjunctive therapy.

No chemotherapy has been proven effective as single modality therapy. For certain histologic subtypes, some clinicians recommend combined modality chemotherapy and radiation. Presently, immunotherapy is in the clinical trial phase.

A recent study demonstrated that epidermal growth factor receptor (EGFR) is expressed strongly in the cell membranes of parotid mucoepidermoid carcinomas and of the lymph node metastases.<sup>49</sup> EGFR-targeting agents have potential to be used for therapy.

Although statements regarding survival are difficult to make because of the large variety of histologic types, 20% of all patients will develop distant metastases.<sup>50</sup> The presence of distant metastases heralds a poor prognosis, with a median survival of 4.3-7.3 months. In this study 8.5% of the cases had metastasis at the time of diagnosis.

#### **4.4 Survival**

A study by Kim et al found disease-specific survival rates for the various disease stages, and stage IV being 15% 5 year Overall survival.<sup>51</sup> In this study the two year overall survival was 12%. When curative arm and palliative arm were compared for a two year overall survival, the curative arm performed better with 23% compared to 11% for the palliative arm. The low overall survival may be due to a number of reasons as mentioned above and also an increased burden of cancer generally in the whole of Tanzania with more parotid gland malignancies being detected every year. With the increasing number of cases, we face a laceration and shortage of man power which compromises the quality of care given to the patients.

According to another study done by Erovic BM et al<sup>65</sup> The 5- and 10-year overall and disease-free survivals were 80.62% 69.48% and 74.37% 62.42%, respectively. Multivariable analysis showed that age greater than 60 years, advanced pN classification, histopathological grade and the presence of lymphovascular invasion significantly worsened overall and

disease-free survival. Univariable analysis revealed periparotid lymph node involvement was associated with decreased overall ( $p < 0.0001$ ) and disease-free survival ( $p < 0.0001$ ).

Furthermore, a study done by R Brayan et al <sup>66</sup>, all his patients were treated with surgery as the primary modality. Neck dissection was performed in 29% of patients, and more than half (56%) were treated with adjuvant external beam radiation therapy to a dose of 50 to 70 Gy. The disease-free survival rate and locoregional control rate at 5 years were 77% and 86%, respectively. Stage ( $P = .0017$ ), grade ( $P = .00044$ ), cervical lymph node metastasis ( $P = .03$ ), and age ( $P = .01$ ) proved to make a statistically significant contribution when describing outcome. Neither site ( $P = .5$ ), the presence of positive margins ( $P = .3$ ), nor perineural invasion ( $P = .7$ ) had a significant impact on survival.

In the western world this number maybe higher compared to this study because of several reasons such as late presentations, advanced age, few oncology and surgical units in Tanzania, the high burden of oncology cases, lack of newer treatment modalities such as IMRT and mainly lack of public knowledge on ENT screening and seeking medical attention at the soonest.

In this study, 95.2% received palliative radiation of which 31% received surgery and 53.1% of the patients received surgery followed by chemo-radiation.

Despite of all efforts made, 86% died out of which 80% died at home and only 19.8% died at a health facility. This may be due to being discharged home for palliative care. Majority of the deaths 92.3% were due to advanced disease which hindered immunity and their quality of life.

The treatment of salivary gland malignancies remains primarily surgical, although adjunctive radiotherapy may play an important role in those patients with advanced-stage disease. The benefits of combined modality therapy awaits prospective clinical trials.

## CHAPTER FIVE

### 5.0 CONCLUSION AND RECOMMENDATIONS

#### 5.1 Conclusion

Generally the clinico-pathological presentation of parotid gland malignancy seen in this study differs from other studies. Adenocarcinoma was the most frequent histology followed by mucoepidermoid carcinoma.

Patients presented for treatment at advanced stages that necessitated invasive surgery however due to several reasons malignancy was deemed un-operable.

More males were affected than females.

Majority of the patients received palliative radiotherapy.

Two year Overall survival was 12%.

#### 5.2 Recommendations

- A larger study is needed to be conducted over a longer period of time in order to have a larger sample, more histological subtype variants and importantly more time for patient follow-up in order to assess more variables.
- There should be extensive education for both community and health personnel on the presentation of salivary gland diseases, staging, importance of seeking medical attention with non-resolving symptoms, necessity of imaging modalities and treatment choices with an intention of enabling practitioners make an early diagnosis which in return leads to early management.
- Continuous education (CME) and training should be given to specialists in Medical and Clinical Oncology, Oral and Maxillofacial Surgery and Pathology so that they can be employed in regional hospitals closer to majority of people.
- Strengthening the regional hospitals and referral centers is of utmost importance and there is a need of educating and training concerned health practitioners and advocating Oncology units which can be capable of diagnosing and treating salivary gland diseases and malignancies at earliest.

- There is a need to build a multidisciplinary pool of specialists that deal with Salivary gland tumors in order to make correct, individualized treatment decisions, work hand in hand for the best outcome of the patients and build protocols which will be shared across the country in order to practice with evidence based uniform treatment methods.

## **5.2 Disposal of patients**

All patients were treated according to their diagnosis and stage.

Treatment modalities (combined modalities including surgery followed by chemo-radiation) were subjected to patients according to their disease stage, Karnofsky performance status, and prognostic factors.

For patients with locally advanced disease or metastatic disease in which surgery was not of benefit or tumor was unresectable were presented and discussed by the tumor board and then referred to Ocean Road Cancer Institute for curative/palliative management.

## **5.3 Dissemination of results**

The findings from this study are to be presented as dissertation (in partial fulfillment of Master Of Medicine in Clinical Oncology), and in scientific seminars/conferences (abstract) and scientific reports (manuscripts) submitted to an appropriate journal. Another copy of this finding will be sent to the Ministry of Health and Social Welfare as the main stakeholder of health issues in the country.

## **5.4 Strength of the study**

1. Since ORCI is the only center in Tanzania with radiotherapy services, the sample population was from several geographical locations which is a good representation of the general population of Tanzania.
2. All relevant information was available in the files.
3. There was no loss of follow up.

**5.5 Limitation of study**

1. The duration for this study was too short (as part of the MMed Program) to enable the author to assess more variables of salivary gland diseases such as treatment toxicities, acute and late side effects of chemo-radiation, emotional assessment and financial constraints that may render treatment outcome.
2. As this was a retrospective study, compilation of files and obtaining all relevant data needed for this study was time consuming and difficult.

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**APPENDICES**

**Appendix I: Data Extraction Form**

NAME (INITIALS): \_\_\_\_\_

AGE: \_\_\_\_\_

FILE NUMBER: \_\_\_\_\_

SEX:      MALE                    FEMALE

DATE:

OCCUPATION: \_\_\_\_\_

SMOKING:

YES

NUMBER OF PACK YEARS: \_\_\_\_\_

NO

ALCOHOL CONSUMPTION:

YES

TYPE:

AMOUNT:

NO

TOBACCO CONSUMPTION:

YES:

TYPE:

AMOUNT:

NO

EXPOSURE TO ANY CARCINOGENS: \_\_\_\_\_

HISTOLOGY OF MALIGNANCY: \_\_\_\_\_

DATE:

PATHOLOGICAL GRADING: \_\_\_\_\_

STAGE OF THE DISEASE: \_\_\_\_\_

PRESENCE OF DISTANT METASTASIS AT DIAGNOSIS:

STATE WHERE: \_\_\_\_\_

HIV STATUS:

POSITIVE:

RECEIVING TREATMENT: \_\_\_\_\_

WHAT TREATMENT: \_\_\_\_\_

DATE OF DIAGNOSIS: \_\_\_\_\_

CD4 COUNT AND DATES: \_\_\_\_\_

NEGATIVE

NOT CHECKED

TIME OF SYMPTOM PRESENTATION TO  
DIAGNOSIS: \_\_\_\_\_

TIME OF DIAGNOSIS TO TREATMENT  
INITIATION: \_\_\_\_\_

TUMOR DETAILS.

OPERABLE:

EXTENT OF SURGERY: \_\_\_\_\_

LYMPH NODES RESECTED: \_\_\_\_\_

STATUS OF SURGICAL MARGINS: \_\_\_\_\_

NON-OPERABLE:

STATEWHY:

\_\_\_\_\_  
\_\_\_\_\_  
\_\_\_\_\_

TYPE OF SURGERY: \_\_\_\_\_

RECEIVED RADIATION?:

DOSE: \_\_\_\_\_ GY

- PRE-OPERATIVE
- CURATIVE
- POST-OPERATIVE
- PALLIATIVE

RECEIVED CHEMOTHERAPY?:

- YES:  NO

TYPE: \_\_\_\_\_

DOSE: \_\_\_\_\_

SCHEDULE: \_\_\_\_\_

- COMPLETED TREATMENT?:  YES  NO

RECEIVED COMBINED THERAPY: (SURGERY/RADIOTHERAPY/CHEMOTHERAPY)

- YES:

DESCRIBE DETAILS OF EACH PROCEDURE

---

---

- NO:

WAS THE TREATMENT INTERRUPTED?

- YES:

STATE

WHY: \_\_\_\_\_

- NO:

FATE OF PATIENT:

ALIVE

DECEASED

MONTH AND YEAR OF DEATH: \_\_\_\_\_

CAUSE OF DEATH: \_\_\_\_\_

LOCATION OF DEATH: HOSPITAL/HOME? \_\_\_\_\_