OUTCOMES OF PATIENTS WITH NASOPHARYNGEAL CARCINOMA TREATED WITH CHEMORADIO THERAPY A SINGLE - INSTITUTION EXPERIENCE

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DECLARATION

I declare that this dissertation is my original work and has not been submitted for the award of a degree or professional qualification in any other university

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SUPERVISOR APPROVAL

This research thesis has been submitted with my approval as university supervisor

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DEDICATION

I dedicate this dissertation to my parents for their immense support. I also dedicate this work to my loving son Adrian for being my greatest source of strength and inspiration.

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TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

ABBREVIATIONS AND ACRONYMS

AJCC	American Joint Committee on Cancer
CCRT	Concurrent Chemoradiotherapy
CN	Cranial Nerve
CT	Computed Tomography
CTC	Cancer Treatment Center
CTV	Clinical Target Volume
DFFS	Distant Failure-Free Survival
2D-EBRT	2-Dimensional External Beam Radiotherapy
3D-CRT	3-Dimensional Conformal Radiotherapy
EBNA-1	Epstein Barr Virus Nuclear Antigen 1
EBV	Epstein Barr Virus
FFS	Failure-Free Survival
5-FU	5-Fluorouracil
GLOBOCAN	Global Cancer Incidence, Mortality and Prevalence Number
GTV	Gross Tumor Volume
HDRIB	High Dose Rate Interstitial Brachytherapy
IMRT	Intensity Modulated Radiotherapy
KNH	Kenyatta National Hospital
LRFFS	Local Regional Failure-Free Survival
MRI	Magnetic Resonance Imaging
NCCN	National Comprehensive Cancer Network
NPC	Nasopharyngeal Carcinoma
OS	Overall Survival
SBRT	Stereotactic Body Radiotherapy
TNM	Tumor, Node, and Metastasis
TPF	Docetaxel, Cisplatin, 5-Fluorouracil
VCA	Viral Capsid Antigen

ABSTRACT

Background

Nasopharyngeal carcinoma is the most prevalent head and neck malignancy in Kenya and contributes to significant morbidity and mortality. Most patients present with advanced disease because there is no effective screening method. The main treatment modalities include radiation and chemotherapy administered sequentially, concurrently, and adjuvantly. Re-irradiation and salvage surgery are used in cases of residual or recurrent disease. There are no studies performed in Kenya to evaluate outcomes for nasopharyngeal carcinoma. This study aimed to evaluate the outcomes and prognostic factors for patients with nasopharyngeal carcinoma managed at Kenyatta National Hospital and compare this to studies done in NPC endemic regions.

Broad Objective: The purpose of this study was to determine the outcomes of nasopharyngeal carcinoma for patients managed with chemoradiotherapy at Kenyatta National Hospital.

Methodology: This was a retrospective cross-sectional study which evaluated patients with stages II to IVA nasopharyngeal carcinoma managed at the KNH cancer treatment center between 1st January 2015 and 30th December 2019. From 318 total patients treated during this period, a total of 173 were selected using simple random sampling. 143 patients met the inclusion criteria, of which 91 were male and 50 were female. Details of patient demographics, nutritional status, disease histopathology, tumor stage, treatment details, and follow-up data were then entered into customized data abstraction charts. Data was analyzed using SPSS version 23 and a p-value of < 0.05 was considered significant.

Results: The most commonly affected age group for NPC was between 30-39years, followed closely by 18-29 years with a median age of 47years. The majority of the patients presented with advanced disease, with stage III and IVA accounting for 48% and 35% of cases, respectively. The 2-year overall survival, LRFFS and DMFS were 36%, 84% and 86% respectively. 2D-EBRT was associated with more locoregional recurrences compared to 3D-CRT but there was no difference in the rate of distant metastasis between the two modalities. Age was the only significant prognostic factor for overall survival. Common treatment toxicities included odynophagia, mucositis and xerostomia.

Conclusion: The 2-year OS outcomes in this study were inferior to studies in endemic regions. This may be due to late disease presentation, delay in starting treatment, more use of 2D-EBRT, which limits the dose of radiation safely delivered, and fewer cycles of concurrent chemotherapy.

Recommendations: There is need to formulate policies for cancer screening and early diagnosis. Patients should be managed with conformal radiotherapy techniques such as IMRT and measures should be taken to ensure the recommended doses and schedules of chemoradiotherapy are delivered.

CHAPTER ONE

1.0 INTRODUCTION

Nasopharyngeal carcinoma is endemic in Southeast Asia, Southern China, and North Africa but occurs less commonly in other areas of the world.[1] It ranks 23rd worldwide amongst all cancers with 133,354 cases and 80,008 deaths reported by GLOBOCAN in the year 2020.[2] According to Lee et al, the incidence of NPC is 10 to 15/100,000 in Southeast Asia, Native Arctic, Northern Africa, and the Middle East, 20 to 50/100,000 per year in Southern China, and 0.2 to 0.5/100,000 in North America and other Western countries. In Kenya, it is the leading head and neck malignancy and the 11th commonest cancer. GLOBOCAN reported 931 new cases and 621 deaths in the year 2020.[2, 3]

Kenya has an incidence approximately 5 times higher than Europe, making it a medium risk area for nasopharyngeal carcinoma.[4] Musibi et al. carried out a four-year population data review of the Nairobi Cancer Registry and found that majority of head and neck cancers were oral cancers and nasopharyngeal carcinoma at 40.6% and 20.8% respectively.[5] Studies done in other African countries have also confirmed the rising incidence of this disease. Bukola et al. in a study done in Ibadan, Southwest Nigeria showed that cancer of the nasopharynx was the second commonest head and neck malignancy in the region, occurring at a frequency of 16.4%.[6]

EBV is the major etiologic factor for NPC with environmental and dietary factors also contributing to the disease. Studies implicating EBV as a cancer causative virus have been done extensively for Burkitt's lymphoma in malaria-endemic regions of Western Kenya.[7] In a prospective study carried out at KNH from 2015-2018, Aswan et al found a 100% prevalence of EBV among the 62 NPC patients studied.[8]

Definitive chemoradiotherapy is the main modality of treatment for stages II-IVA NPC.[9, 10] Some patients with limited metastasis in stage IVB NPC also receive chemoradiotherapy but the main treatment is chemotherapy.[10] Radiotherapy alone is recommended for stage I disease. Induction chemotherapy has also been accepted as a standard of treatment and is widely used in

most parts of the world.[9, 32, 33]Adjuvant chemotherapy remains controversial but is still used in some centers.

Studies have shown that concurrent Cisplatin-based chemotherapy with radiotherapy improves overall survival and progression-free survival in patients with nasopharyngeal carcinoma compared to receiving radiotherapy alone.[11] NCCN recommends the use of induction chemotherapy followed by concurrent chemoradiotherapy or chemoradiotherapy followed by adjuvant chemotherapy, giving it category 2A for NPC stages II-IVA.[10]

Conformal radiotherapy with 3-D conformal radiotherapy (3D-CRT) and intensity modulated radiotherapy (IMRT) have been associated with improved overall survival and locoregional control, with a reduction in acute toxicity profile compared to 2D-EBRT treatment.[12] The use of CT simulation with MRI co-registration has been shown to improve treatment planning compared to conventional simulation.[15] Other radiotherapy modalities, such as proton therapy, and techniques such as SBRT and brachytherapy are less frequently utilized.[15] Salvage surgery and re-irradiation are used in cases of recurrent nasopharyngeal carcinoma but are not widely practiced.[14]

According to Murat et al, nasopharyngeal carcinoma has 35% to 50% 5-year overall survival, with stages I to II having 5-year survival of 70–80% and Stages III to IV having 5-year survival of 10–40%.[16] Outcomes of treatment for NPC have been widely studied in the endemic regions but there is a paucity of data on the same in Kenya. This study, therefore, aims to bridge the gap in research on the treatment outcomes for NPC and will help to improve patient management.

CHAPTER TWO

2.1 LITERATURE REVIEW

Background

Nasopharyngeal carcinoma arises in the lining of the nasopharynx. It most commonly occurs within the fossa of Rosen muller in the lateral nasopharyngeal wall.[17, 18]The first study on NPC in Kenya was carried out by Clifford et al. at the King Georges VI hospital between the years 1959 and 1962, where it was noted to be the commonest head and neck malignancy in the country. The primary histologic type was anaplastic carcinoma with clinical presentation resembling that seen in other endemic regions.[4]

Most patients with NPC present late with locally advanced disease because of the indeterminate presentation of symptoms and lack of screening efforts.[4, 20]This scenario contributes to poor prognosis despite advances in treatment options and access to care. Ogun et al carried out a retrospective study from January 2007 to December 2016 at Ibadan University college hospital in Nigeria and found that 54.8% of the patients presented with stages III to IV NPC.[6]

The average time from onset of symptoms to the first clinical presentation is approximately 6 months.[17] Nasopharyngeal carcinoma has a bimodal age distribution in low-risk populations, with a peak between 15-25 years and 50-59 years according to GLOBOCAN 2008 cancer incidence and mortality report.[19] In the high-risk populations, patients in the fourth and fifth decade have the highest incidence of disease. In a demographic study carried out at Kenyatta National hospital by M. Muchiri, NPC was found to occur at a higher frequency in patients between 31-40years, with a male to female ratio of 2.2: 1.[20] In the study on patients with nasopharyngeal carcinoma at Khartoum Teaching Hospital, El Hassan et.al found a bimodal age distribution of the disease, with the first peak at 15 to 19 years and the second peak at 50 to 54 years.[21]

Survival outcomes have improved internationally due to treatment advances with chemotherapy delivery and advanced radiation techniques, such as IMRT. Negative prognostic factors for nasopharyngeal carcinoma include lymph node involvement, presence of distant metastasis,

cranial nerve involvement, and extent of local invasion.[22]Despite the advances in treatment techniques, most of the patients at KNH still receive treatment with 2D-EBRT which may negatively impact survival outcomes.

2.2 Classification and Staging

Three histologic subtypes of nasopharyngeal carcinoma have been classified by WHO, with Type III being the most common type in NPC endemic regions. [23]

Table 1: NPC WHO Classification

Type 1: Keratinizing squamous cell carcinoma
Type 2: Non-keratinizing differentiated carcinoma
Type 3: Undifferentiated carcinoma

The staging system currently in use is the 8th edition of UICC/AJCC TNM staging.[10] The HO's staging system is of historical importance and is no longer used.

Table 2: AJCC Stage Groups

Stage 0	Tis N0 M0
Stage I	T1 N0 M0
Stages II-IVA	T1-T4, N1-N3, M0
Stage IVB	Any T, any N, M1

2.3 Etiology

Nasopharyngeal carcinoma arises as a result of multifactorial causes. The major etiologic agent which has been widely studied is the Epstein Barr virus, a member of herpes viruses. [24] This virus has been mostly associated with undifferentiated WHO type III NPC. Hausen et al. used DNA hybridization technology to show that EBV DNA was present in Burkitt's lymphoma and Nasopharyngeal carcinoma that had been extracted from patients. It has been postulated that the initial infection results in the attachment of the virus to B-cells. The virus remains in a latent

phase for a prolonged period and causes B-cells to become immortal. The proliferation is kept in check by cytotoxic T cells, lack of which causes transformation into cancer.[24, 26] Lawrence et al. suggested that loss of heterozygosity as a result of environmental exposures results in low-grade pre-invasive lesions. Subsequent infection with the EBV virus then drives progression to the development of NPC. [24] EBV DNA titers can be used to predict treatment response and recurrence when monitored before and after treatment.[24, 25]Screening for NPC has been implemented in endemic countries and it makes use of ELISA to measure IgA levels against viral EBNA1 and VCA.[25]

Recently, p16 positive but EBV negative variant of NPC has also been described. Maxwell JH et al. carried out a study on 89 NPC patients and found that four of the patients had tumors that were positive for HPV but negative for EBV. [27] Other Risk factors which have been linked to NPC include consumption of salt-cured fish, exposure to dust, cigarette smoking, alcohol intake, formaldehyde, wood dust, and genetic predisposition. The HLA locus, particularly serotypes B17, BW46, and A2 have been associated with an increased risk of nasopharyngeal carcinoma.[28]

2.4 Clinical Presentation

The nasopharynx has a rich lymphatic network and therefore most patients present with cervical lymphadenopathy as the first symptom. Other symptoms include nasal blockage, epistaxis, tinnitus, decreased hearing, headache, and cranial nerve palsies (especially CN VI and CN VII).[29,30] NPC is also associated with paraneoplastic syndromes including endocrine, dermatologic, hematologic, and neurologic presentation.[30]Cranial nerve syndromes associated with NPC are shown in the table below: [31]

Table 3: Cranial Nerve Syndromes

Trotters syndrome	Triad of unilateral conductive deafness, immobility of soft palate, and trigeminal neuralgia
Vernet syndrome	CN IX, X, XI palsies
Villaret syndrome	CN IX, X, XI, XII palsies

Jaccoud syndrome	Trigeminal neuralgia, ophthalmoplegia, and sensorineural loss

2.5 Diagnosis

Nasopharyngeal carcinoma is diagnosed late due to the challenge in visualizing the nasopharynx and the fact that symptoms are nonspecific. The initial workup in the diagnosis is shown in the table below: [9, 10]

Table 4: Initial Work Up

A thorough history and physical examination	CT scan or MRI with contrast enhancement, from skull base to clavicle
Nasopharyngoscopy	Chest x-ray or chest CT scan for N3 disease
Mirror examination	PET-CT scan
Fibreoptic examination	Baseline audiogram
Endoscopic biopsy	Dental review
FNA of suspicious nodes	Speech, swallowing, and nutritional review

2.6 Chemotherapy and Radiotherapy Technique

The standard of care for nasopharyngeal carcinoma is chemoradiotherapy. There are several radiotherapy modalities, with the commonest being 2D-external beam radiotherapy (2D-EBRT), 3D-CRT, and IMRT. At KNH, the modalities in use are 2D-EBRT and 3D-CRT. Induction chemotherapy is recommended before initiating CCRT and mostly consists of 3 cycles of TPF regimen. CCRT is commenced within 3weeks of completing induction chemotherapy. Cisplatin is the main chemotherapy administered concurrently with radiotherapy because it has been shown to improve locoregional control and overall survival.[9]When adjuvant chemotherapy is indicated, Cisplatin and 5-FU are commonly prescribed.[9]

Radiotherapy treatment planning involves either conventional or conformal simulation. Conventional simulation makes use of bony landmarks. Conformal simulation is done using a CT simulator and images are taken from the vertex to arch of the aorta with 3-5 mm slices. [9, 16]The patient is positioned lying supine with the head, neck, and shoulder immobilized with a 5-point thermoplastic or Perspex shell.[9, 16]

Conformal treatment includes delineation of a gross tumor volume (GTV) as defined by imaging scans and initial clinical exam. A high dose clinical target volume (CTV) is created to encompass the primary tumor and involved nodes, often treated to 66 to 70 Gy. An elective CTV includes areas at high risk for microscopic disease such as sphenoid sinus, skull base, pterygoid plates, and parapharyngeal space and is treated to 60 Gy.[9, 10, 16] A lower dose CTV covers the elective, uninvolved nodal regions with a dose to 50 Gy. A shrinking field technique is used during treatment to spare the spinal cord and other organs at risk from a high dose of radiotherapy. Phase one includes treatment of a larger facial-cervical field with lateral opposed fields up to 40Gy in 20fractions. The spinal cord is shielded after 40Gy and the posterior neck is boosted with electrons up to 50Gy. The second phase treats the nasopharynx up to 60Gy and the treatment field is reduced further to deliver a final boost of 10Gy to the primary tumor.[16] With IMRT, a shrinking field or simultaneous integrated boost technique are standard options. Radiotherapy dose of 70Gy at conventional fractionation (1.8Gy-2Gy) has been associated with improved local control. The level II-V cervical nodes are always treated prophylactically because of the high likelihood of nodal metastasis even in early N0 disease.[10, 16]

2.7 Treatment Outcomes

2.7.1 Induction Chemotherapy

Randomized clinical trials have shown the benefit of induction chemotherapy and this modality of treatment has been widely accepted. In our setting, only a proportion of patients receive induction chemotherapy with the TPF regimen.

The efficacy of induction chemotherapy was demonstrated by Zhang et al in a study on 109 patients with locoregionally advanced stages III to IVB NPC at Sun Yat-Sen University Cancer Center between December 2010 and January 2015. Patients whose ages ranged from 18 to 69 years received 3cycles of induction TPF followed by two to three cycles of Cisplatin administered concurrently with radiotherapy. IMRT was delivered at a dose of 70 Gy in 33

fractions or 68Gy in 30 fractions. The results of the study showed an improved 3-year FFS of 76.8%, OS of 85.1%, LRFFS of 88.3%, and DFFS of 84.1% with the addition of induction chemotherapy. Total time of treatment and patient age were found to be important prognostic factors with influence on overall survival and FFS. The commonest toxicities seen were neutropenia, liver injury, and loose stools. There was increased disease recurrence and metastasis witnessed in the first year after treatment[32]

Additional trials have supported the role of induction chemotherapy in improving both local and distant control. In a meta-analysis of randomized controlled trials of 2628 patients with locally advanced stages III to IV NPC, Lucheng et al. compared patients who received induction chemotherapy and chemoradiotherapy with those that received chemoradiotherapy alone. The Induction chemotherapy arm had better locoregional control, improved overall survival, and distant metastasis-free survival compared to the chemoradiotherapy alone arm. However, there were more acute toxicities in the induction chemotherapy arm compared to CCRT alone.[33]

Moreover, patients with high-risk stages III and IV disease experience more benefit from induction chemotherapy compared to stages I and II NPC, irrespective of the radiotherapy technique. Palazzi et al. conducted a study of 87patients with stage III and IV NPC in Milan, whereby Patients who received induction chemotherapy and CCRT had improved distant control of 92% at 3years compared to 56% for the CCRT alone arm. Patients with stages I and II had no local or regional failure in this series.[34]

2.7.2 Concurrent Chemoradiotherapy

Concurrent chemoradiotherapy is associated with improved locoregional control and overall survival in stages II-IVA NPC. The majority of patients at KNH receive concurrent chemoradiotherapy but the number of chemotherapy cycles varies according to factors such as patient tolerance and compliance.

The landmark trial which established the practice of concurrent chemoradiotherapy was the Phase III randomized intergroup study by Al-Sarraf et al. In this study, 147 patients were randomized to CCRT or RT alone at a radiotherapy dose of 70Gy in 35 to 39 fractions using conventional fractionation (1.8 to 2Gy per fraction). 69 patients received radiotherapy alone while 78 patients received Cisplatin-based chemoradiotherapy followed by 3cycles of adjuvant Cisplatin and 5-FU. Study results showed that chemoradiotherapy is superior to radiotherapy

alone for patients with advanced nasopharyngeal cancer. The 3-year PFS was 24% for the radiotherapy arm versus 69% for the chemoradiotherapy arm, and the 3-year survival rate was 46% for the RT arm vs 76% for the chemoradiotherapy arm. The major limitation of the study was the fact that it was carried out in a non-endemic region and results could not be directly replicated to NPC endemic regions due to differences in histology and presentation of the disease.[11] Attempts to replicate this study in 3 Japanese patients resulted in discontinuation of chemotherapy due to severe acute toxicities. The patients experienced grade 3 to 4 skin toxicity, difficulty in swallowing, pharyngitis and two died of recurrent disease a few months after treatment.[35]

To further test the efficacy of concurrent chemoradiotherapy, Yong et al. carried out a Prospective randomized trial of 316 patients with locoregional NPC in endemic regions of China from July 2002 to September 2005. The patients were randomized to receive RT alone or Cisplatin-based chemoradiotherapy followed by adjuvant Cisplatin/5-FU. The CCRT arm experienced more acute toxicity compared to the RT arm (62.6% vs. 32% respectively). There was improved 2-year overall survival of 89.8% vs 79.7%, FFSR of 84.6% vs. 72.5%, DFFS of 86.5% vs. 78.7%, and LFFS of 98.0% vs. 91.9% for the CCRT and RT groups respectively[36]

Studies done in Africa have demonstrated poorer survival outcomes for NPC following CCRT compared to endemic regions. Usman et al. analyzed 161 patients from 2000-2009 in a retrospective study carried out in the University College Hospital of Ibadan in Nigeria. 93.7% of patients presented with late disease (stage III and IV) and 6.3% had an early disease. 113 men and 48 women each received RT with concurrent Cisplatin and 5-FU. The overall DFS was 67% and 46% at 12 and 24months respectively.[6]

2.7.3 Adjuvant Chemotherapy

The benefit of adjuvant chemotherapy has been shown in a few clinical trials but the practice is not common in our setting. Other studies have failed to demonstrate a survival advantage of adjuvant chemotherapy and the practice is shrouded in controversy. The intergroup study by Al-Sarraf et al. used both concurrent chemoradiotherapy and adjuvant chemotherapy but there was no clear separation to indicate which of the two modalities contributed to the favorable treatment outcomes.[11] Consequently, NCCN incorporated adjuvant chemotherapy as a standard of treatment for patients who receive CCRT without induction chemotherapy.[10]

Moreover, Chappell et al. provided evidence that adjuvant chemotherapy may improve survival outcomes for patients with NPC who are managed with CCRT. He conducted a Multicenter phase 3 randomized trial of 348 patients with regionally advanced NPC, where 170 patients received CCRT followed by Adjuvant Cisplatin/5-FU while 174 received RT alone from March1999 to January 2004. The CCRT and adjuvant chemotherapy group had higher 10-year overall failure-free survival (62% vs 42%), progression-free survival (56% Vs 42%), and superior locoregional control (87% Vs 74%) compared to RT alone.[37]

2.7.4 Surgery

Nasopharyngeal carcinoma is not amenable to surgery as the first modality of treatment due to inaccessibility of the nasopharynx and the propensity for locoregional spread by the time patients are diagnosed.[9, 16] Surgery is only carried out as a salvage treatment in patients with residual or recurrent disease after definitive chemoradiotherapy and it is not widely practiced. In a study by Wei et al., he proposed a maxillary swing surgery for the management of recurrent tumors.[38]There have been no reports of surgery for NPC at KNH up to date.

2.8 Comparison of radiation modalities and techniques

IMRT has replaced conventional treatment as the radiotherapy modality of choice for NPC and is increasingly being used in most developed countries. In a study carried out in China on 749 patients with early NPC, Jun ma et al. demonstrated an improved locoregional control with IMRT but no difference in distant control. There was an improved DFS of 75.1%; LRFS of 94.6%; DMFS of 82.6%, and overall survival of 82.0%.[38]

Studies have also demonstrated the benefit of 3D-CRT over conventional 2D-EBRT treatment. Leibel et al. showed that 3D-CRT improves tumor coverage compared to 2D treatment. He further demonstrated that 2D plans under-dosed 22% of the target volume at the 95% isodose level compared to 7% with the 3D plans. Both IMRT and 3D-CRT are associated with improved locoregional control and better OS compared to 2D-EBRT in NPC.[39]

IMRT has also been shown to improve locoregional disease control with better quality of life and parotid sparing compared to 3D-CRT.[40, 41]A phase II trial by RTOG showed that IMRT used together with chemotherapy leads to improved locoregional control in patients with NPC stage II and above.[42] Moreover, Mao et al. conducted a study on patients with early NPC treated with IMRT and the results of the study showed that the median time to distant metastases was 18.9

and the median relapse time was 25.2 months. The 5-year local failure rate was 5.4%, regional failure of 3.0%, loco regional failure of 7.4%, and distant failure rates of 17.4%.[38] However, distant metastasis remains a major challenge that needs to be addressed in prospective trials.

Brachytherapy is used to deliver a boost dose in the treatment of T1 to T3 tumors after EBRT. Treatment is delivered with intracavitary or interstitial implants. Jade et al. conducted a study on Seventeen patients with NPC stage I and II, and the patients were treated with EBRT followed by two fractions of boost HDRIB. The local control rate was 93.6% at 2 years of follow-up.[44]Stereotactic radiosurgery is an alternative method for delivering a boost after EBRT, with improved local control.[45]

2.9 Treatment Complications

Treatment with chemotherapy and radiotherapy is associated with both early and late toxicities. Organs at risk include but are not limited to optic apparatus, pituitary gland, brainstem, and spinal cord. Tolerance of the organs at risk must be observed during radiotherapy to prevent debilitating toxicities**.** The commonest radiotherapy treatment complications include radiation dermatitis, hypopituitarism, brainstem injury, cranial nerve palsies, mucositis, xerostomia, otitis media, temporal lobe necrosis, and osteoradionecrosis.[46, 47]

2.10 Statement of Problem, Justification, and Objectives

2.10.1 Statement of the Problem

Nasopharyngeal carcinoma is the most common head and neck malignancy in Kenya. This is the first study analyzing the outcomes of chemoradiotherapy for patients with nasopharyngeal carcinoma managed at the KNH cancer treatment center.

Studies on nasopharyngeal carcinoma carried out in other countries have shown that definitive chemoradiotherapy leads to better locoregional control and improved overall survival compared to radiotherapy alone. IMRT is the established standard of treatment in most developed countries and it has been shown to have better outcomes compared to conventional treatment. The majority of patients in our facility are managed with concurrent chemoradiotherapy and the treatment modality used is mostly 2D-EBRT with a few being managed with 3D-CRT. Delays in patient referral, poor patient compliance, machine breakdown, treatment interruptions and failure to complete the required cycles of chemotherapy all contribute to poor outcomes.

2.10.2 Study Justification

There are no studies available in the country on the trends and outcomes of treatment for nasopharyngeal carcinoma. This study sought to establish the prevalence of nasopharyngeal carcinoma, the clinical presentation, treatment modalities, complications of treatment, outcomes of treatment, and the relevant prognostic factors for patients with nasopharyngeal carcinoma managed with chemoradiotherapy at KNH. The study will also help to identify the barriers to favorable treatment outcomes. The data obtained will guide the development of treatment protocols for the management of patients to improve treatment outcomes for NPC.

2.10.3 Research Questions

1. What are the outcomes of treatment with chemoradiotherapy for nasopharyngeal carcinoma?

2. What are the significant prognostic factors for nasopharyngeal carcinoma?

2.10.4 Study Objectives

Broad Objective:

To determine the outcomes of nasopharyngeal carcinoma after chemoradiotherapy

Specific Objectives:

1. To determine the clinical characteristics of patients with nasopharyngeal carcinoma
2. To determine the treatment modalities used and overall treatment time
3. To determine treatment-related complications
4. To establish the failure patterns and 2-year overall survival for nasopharyngeal carcinoma
5. To determine relevant prognostic factors that influence the outcomes in nasopharyngeal carcinoma

CHAPTER 3

3.0 METHODOLOGY

3.1 Study Design

This was a retrospective cross-sectional study analyzing treatment outcomes of patients with nasopharyngeal carcinoma managed with chemoradiotherapy at Kenyatta National Hospital between 1st January 2015 and 30th December 2019.

3.2 Study Site

The study was conducted at Kenyatta National Hospital cancer treatment center. KNH is the largest national referral hospital in Kenya and also serves neighboring East African countries. The hospital is located within Nairobi and is among the top Government facilities offering radiotherapy and chemotherapy services to cancer patients. It has a capacity of 2,000 beds with an annual average of 70,000 inpatients and 500,000 outpatients. Most cancer patients seen at the facility are referrals from secondary facilities.

3.3 Study Population

The study population included patients with biopsy-confirmed stage II to stage IVA nasopharyngeal carcinoma

3.4 Selection Criteria

3.4.1 Inclusion Criteria

1. Biopsy-confirmed nasopharyngeal carcinoma

2. Stages II to IVA NPC

3. Age 18-80 years

3.4.2 Exclusion Criteria

1. Stage I and IVB NPC

2. History of prior malignancy

3.5 Sample Size Determination

The sample size for this study was determined using the sample size calculation for proportions, with a finite population correction formula according to (Naing, Winn, & Rusli, 2006).

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

Where:

n = Sample size

Z = Z statistic for a level of confidence

P = Expected prevalence or proportion (in proportion of one; if 50%, P = 0.5)

d = Precision (in proportion of one; if 5%, d = 0.05)

According to (Naing et al., 2006) the conventional Z value used is for the level of confidence of 95% which is 1.96. The population size is 318 according to the KNH cancer registry for the specified period.

$n = \frac{1.96^2 0.5(0.5)}{0.05^2}$ $n = \frac{3.8416*0.5(0.5)}{0.05^2}$ $n = 384$

The finite correction factor is:

$n = \frac{n_0 N}{n_0+(N-1)}$ $n = \frac{384*318}{384+(318-1)}$ $n = \frac{122{,}112}{701}$ $n = 174$

3.6 Sampling Procedure

Simple random sampling method was used to obtain the desired sample size in order to minimize bias. Patients who did not meet the inclusion criteria were consequently excluded from the study.

3.7 Data Collection

The principal investigator and trained research assistants used data abstraction tools to collect data from patient files, physician notes, and nurses' Kardex. Data on patient demographics, disease histopathology, TNM stage, treatment details, follow-up findings, and date of last contact or death was captured. Treatment complications and prognostic factors that influence outcomes were also documented. Patients were analyzed based on those who received induction chemotherapy followed by concurrent chemoradiotherapy and those who received upfront chemoradiotherapy. Patients were divided into two cohorts, based on whether they received treatment with 2D-EBRT or 3D-CRT. Patients who received adjuvant chemotherapy were also analyzed. The information was then entered into a computer excel sheet and later exported to the SPSS version 23 for further analysis.

3.8 Study Variables

Independent Variables:

1. Age
2. Gender
3. TNM stage
4. Nutritional status

Dependent Variables

1. Type of chemotherapy
2. Radiotherapy modalities
3. Radiation treatment time
4. Follow-up data

3.9 Materials and Methods

Clinical records of patients with nasopharyngeal carcinoma seen between 1st January 2015 and 30th December 2019 were retrieved and analyzed for necessary study variables. A simple random sampling method was used to achieve the desired sample size, thereby avoiding

sampling bias. Data on patient and disease-related factors was collected and filled in the data abstraction charts.

3.10 Quality Assurance

The study was undertaken under strict guidelines on the conduct of research provided by the KNH-UON Research and Ethics Committee. Data was collected with abstraction charts which were specially formulated to encompass the necessary study variables

3.11 Ethical Consideration

Data was collected after approval by the Department of Diagnostic Imaging and Radiation Medicine at the University of Nairobi. Being a retrospective study, permission to access patient medical records was granted by the KNH Cancer Treatment Center administration. Approval of the KNH Ethics and Research committee was also obtained. Patient information was handled with utmost care, therefore ensuring patient confidentiality. Patient files were only made accessible to the principal investigator and specially trained research assistants.

3.12 Data Protection and Management

Data abstraction charts had special serial numbers, which excluded patient names to maintain patient confidentiality. Data collection tools were stored in locked cabinets to avoid the loss of data. Patient data was entered into a computer excel sheet and later transferred to the SPSS version 23 system, both of which had password encryption. Only the principal investigator and authorized statistician had access to the data entry and analysis systems.

3.13 Study Limitations

This study was not without limitations:

1. There were many files with missing information and incomplete documentation

2. Some patient files could not be traced from the records department

3. Data was spread out between radiotherapy treatment files and patient admission files, which made harmonization of patient treatment information a tedious process

4. Many patients, including those who were still alive during the study period were lost to follow up after treatment

CHAPTER 4

INTRODUCTION

A total of 318 patients with histology-proven NPC were treated at Kenyatta National Hospital Cancer Treatment Center from 1st January 2015 to 30th December 2019. Out of a sample size of 174, only 143 patients met the inclusion criteria for my study. The medical records of these patients were reviewed with the approval of the Ethics and Research Committee. Information on patient demographics, medical history, staging investigations, treatment modalities, treatment outcomes and follow up data was captured in customized questionnaires.

4.1 TREATMENT TECHNIQUES

4.1.1 Radiotherapy

All the patients were treated in the supine position and immobilized with a customized thermoplastic mask. Patients treated with 3D-CRT were scanned with 3mm CT slices from the skull vertex to the middle of the chest. The CT images were transferred to the treatment planning system for contouring and planning of treatment. Organs at risk were contoured and dose constraints taken into consideration. Targets volumes, including gross tumor volumes and nodal CTVs were contoured on all axial CT slices. The high dose CTV 66-70 encompassed the primary tumor and involved nodes whereas the areas at high risk for microscopic disease (the posterior third of nasal cavity, the entire nasopharynx, and posterior third of maxillary sinus, sphenoid sinus and skull base) were covered under the intermediate risk CTV 60. Low risk nodes were covered by CTV 50. The target volumes were defined using the International Commission on Radiation Units and Measurements (ICRU) reports 50 and 62. The GTV was expanded with a 5–10 mm margin to create the CTV1. The planning target volume (PTV) was generated by adding a margin of 3–5 mm around the CTV to account for patient movement and set-up uncertainties. Level II to level V cervical nodes were contoured bilaterally and a margin of 5mm was added around the nodal CTV to generate a nodal PTV. Patients receiving 3D-CRT were treated with an Elekta linear accelerator. Patients who received treatment with 2D-EBRT were simulated with a conventional simulator. Anterior and lateral tattoos were marked on the thermoplastic mask and aligned with orthogonal lasers to avoid lateral rotation of the patient. Bony landmarks were used as references and treatment volumes outlined on the thermoplastic mask. Lead shields were used

to block organs at risk such as the spinal cord and larynx from treatment field. Simulation films were then taken and treatment delivered with a cobalt-60 radiotherapy machine.

4.1.2 Induction Chemotherapy

Induction chemotherapy was administered to 51% of patients with stage II, III, and IVA NPC using various schedules and treatment regimens. The most commonly used chemotherapy regimen was Cisplatin and paclitaxel. The Mean ± SD from time of diagnosis to the start of Induction Chemotherapy was 2.6119 ± 4.366 months with a median of 1 month. This was however not statistically significant. The treatment modalities are illustrated by the table below.

Table 5: Induction Chemotherapy Regimens

	Frequency	Percentage
TPF	22	31%
Cisplatin/Paclitaxel	37	52%
Carboplatin/Paclitaxel	3	4%
Docetaxel/Cisplatin	8	11%
Carboplatin/Docetaxel	1	1%

A further analysis on cycles per treatment modality was done and represented by the frequency table below.

Table 6: Induction Chemotherapy Cycles

	Cycle I	Cycle II	Cycle III	Cycle IV	Cycle V	Cycle VI
Carboplatin/Docetaxel				1	1	1
Cisplatin/Paclitaxel	2	6	12	2		7
Docetaxel/Cisplatin			3	2	1	2
TPF			13		1	

4.1.3 Chemoradiotherapy

All the eligible patients were treated with concurrent chemoradiotherapy. Patients underwent dental assessment and baseline audiogram before starting treatment. In this study, 58% of patients were managed with 2D- EBRT and 42% were treated with 3D-CRT. The majority of patients received 2D-EBRT as there were two cobalt machines and only one linear accelerator available during the period of the study. Patients who initially started treatment with the cobalt

machine and who required electron boost to the posterior neck nodes were eventually transferred to the LINAC machine for further treatment. The number of concurrent chemotherapy sessions varied widely with majority of patients receiving only one cycle of concurrent cisplatin. Some patients received cisplatin at 100mg/m2 at an interval of 3 weeks, while others received weekly cisplatin at 40mg/m2. Patients with creatinine clearance of <60ml/min received Carboplatin instead of Cisplatin. The most common radiotherapy dose fractionation was 66 Gy at 47.6%, followed by 60 Gy at 39.2%. Only 8.4% of the patients received 70 Gy in 35 fractions. The Mean ± SD for treatment time in weeks was 8.10 ± 7.111. The calculated standard deviation above may not be a reliable measure of the true variability of the population since the sample size is small.

The dose and fractionation are represented below.

Table 7: Chemoradiotherapy Dosage and Fractionation

Dose and Fractionation	Frequency	Percentage
60Gy/30 + 1 Cycle Cisplatin	23	16%
60Gy/30 + 2 Cycle Cisplatin	4	3%
60Gy/30 + 3 Cycle Cisplatin	19	13%
60Gy/30 + 4 Cycle Cisplatin	6	4%
60Gy/30 + 5 Cycle Cisplatin	1	1%
60Gy/30 + 6 Cycle Cisplatin	3	2%
62Gy/31 + 1 Cycle Cisplatin	1	1%
64Gy/32 + 2 Cycle Cisplatin	3	2%
64Gy/32 + 3 Cycle Cisplatin	2	1%
66Gy/33 + 1 Cycle Cisplatin	15	11%
66Gy/33 + 2 Cycle Cisplatin	21	15%
66Gy/33 + 3 Cycle Cisplatin	15	11%
66Gy/33 + 4 Cycle Cisplatin	9	6%
66Gy/33 + 5 Cycle Cisplatin	4	3%
66Gy/33 + 6 Cycle Cisplatin	2	1%
70Gy/35 + 1 Cycle Cisplatin	3	2%
70Gy/35 + 2 Cycle Cisplatin	2	1%
70Gy/35 + 3 Cycle Cisplatin	4	3%
70Gy/35 + 4 Cycle Cisplatin	1	1%
70Gy/35 + 6 Cycle Cisplatin	2	1%
70Gy/35 + 7 Cycle Cisplatin	1	1%

Notably, the ideal treatment time without break for radiotherapy with accordance to fractionation would be 6 weeks, 6.4 weeks, 6.6 weeks and 7 weeks for 60Gy/30, 64Gy/32, 66Gy/33 and 70Gy/35 respectively. However, the respective median time for each fractionation was 7 weeks, 9 weeks, 7 weeks and 7 weeks. Therefore, for 60Gy/30 the average interruption time was 1 week, for 64Gy/32 the interruption time was 2.6 weeks, for 66Gy/33 the interruption time was 0.4 weeks and 70Gy/35 did not have an interruption time.

Adjuvant chemotherapy was administered less often, with only 4.2% (n=6) patients documented to have received treatment. The Mean ± SD for treatment time in weeks was 19.45 ± 8.825. There was no re-irradiation nor surgery conducted for patients with local-regional disease recurrence during this study period.

4.2 PATIENT FOLLOW-UP

Patients were followed up weekly during treatment and side effects managed accordingly. Patients were required to do follow up at 3-4 monthly intervals for the first 2 years, 4 to 6 monthly up to year 5 and yearly thereafter. Each follow-up appointment comprised a clinical history and physical examination. Hematology and biochemistry investigations were ordered whenever necessary. Re-staging scans (CT scan, MRI, Chest radiography, and abdominal sonography) were ordered when necessary to assess for treatment response, recurrent disease or distant metastases. Local-regional recurrence was confirmed using biopsies of nasopharyngeal lesions and lymphadenopathy. None of the patients received PET/CT scanning as it was not available. Patients were also assessed for early and late side effects of radiotherapy. None of the patients were investigated for hypothyroidism as a side effect of radiotherapy.

4.3 RESULTS

4.3.1 Patient demographics

The summary of the findings are presented in tables and figures shown below:

Table 8: Clinicopathologic Characteristics of Patients

Characteristics	No. of patients	Percentage
Age		
18-29	27	19%
30-39	40	28%
40-49	25	17%
50-59	24	17%
60-69	19	13%
70-80	8	6%
Gender		
Male	91	65%
Female	50	35%
AJCC stage		
Stage II	24	17%
Stage III	67	48%
Stage Iva	50	35%

Table 9: Distribution of T and N categories

TNM Stage	Frequency	Percentage
T0,T1 N1 M0	10	7%
T2 N0,N1 M0	13	9%
T0,T1,T2 N2 M0	30	21%
T3 N0,N1,N2 M0	39	28%
T4 N0,N1,N2 M0	34	24%
Any T N3 M0	14	10%

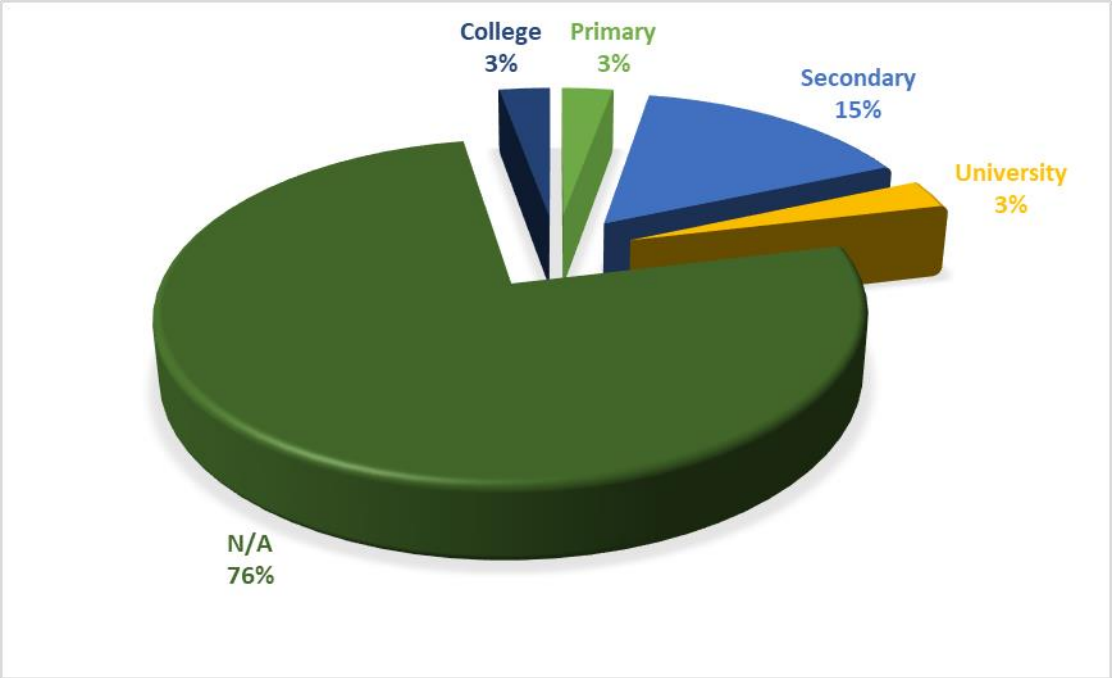
The results of the study show that the most commonly affected age group for NPC was between 30-39years, followed closely by 18-29 years. The mean age of presentation was 48.9 years and median age of 47years with a SD of 16.1. Males were more commonly affected compared to females with a ratio 1.9:1. The majority of the patients presented with advanced disease, with stage III NPC accounting for 48% of the cases and stage IVA accounting for 35% of cases.

Table 10: Patient Residence

County	Frequency	Percentage
Meru	5	4%
Embu	5	4%
Kitui	6	4%
Machakos	7	5%
Makueni	5	4%
Nyeri	6	4%
Muranga	5	4%
Kiambu	10	7%
Kakamega	6	4%
Siaya	6	4%
Kisumu	10	7%
Kisii	13	10%
Nairobi	5	4%
Others	47	35%

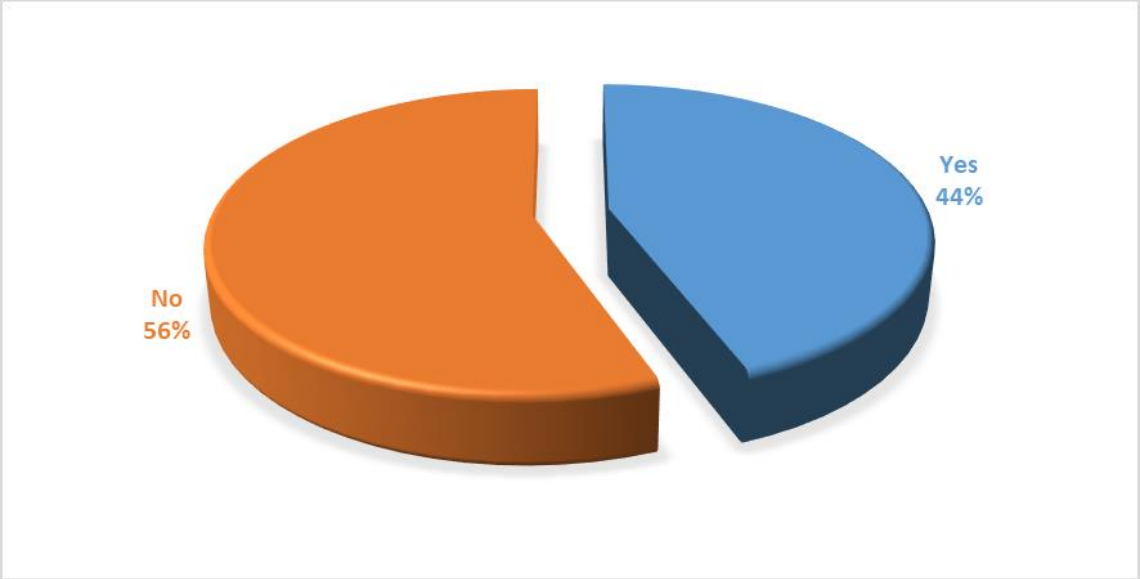
Interestingly, Kisii County had the highest number of patients diagnosed with NPC (10%) followed by Kiambu and Kisumu, both with 7%.

Figure 1: Level of education



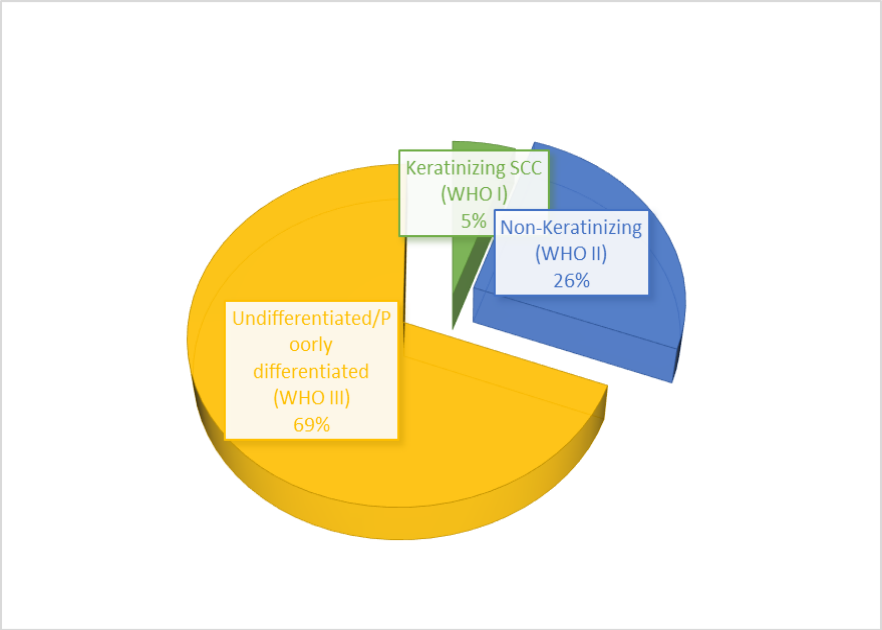
Most of the patients whose education background was captured only had basic secondary education.

Figure 2: Patients referred to KNH



Fifty-six percent of the patients were not referred to the facility meaning most of them were self-referrals.

Figure 3: Histopathology



Core biopsy was the most common method of cancer diagnosis at 93%. FNA of cervical nodes was only used 7% of the time. The commonest histologic subtype in our study was undifferentiated nasopharyngeal carcinoma (WHO grade III) at 69%.

The most common imaging modalities used for staging in this study were CT scan (34%), chest radiograph (33%), abdominal ultrasound (32%) and MRI head/neck (1%).

Risk factors for nasopharyngeal carcinoma according to this study include a history of smoking at 22% and history of alcohol consumption (32%). However, the frequency of alcohol intake and pack years of smoking was not documented. Only 1% had EBV DNA titers documented. When it came to presenting signs & symptoms, nasal blockage was the most prevalent at 28%, followed closely by neck swelling at 24%. Other symptoms worth mentioning were epistaxis (19%), headaches (13%), hearing difficulties (8%) and visual disturbance (3%). The Mean ± SD for duration of presenting symptoms in months was 11.63 ± 8.820.

In this study, 14.7% of patients were lost to follow up. Among patients still on follow up, the majority were followed up between 0-12 months, accounting for 53.2% of the cases. The median

follow-up was 10 months, with mean ± SD of 11.07 ± 5.96 months. The table below further illustrates this information.

Table 11: Follow up Periods

	Frequency	Percentage
0-6 months	38	26.6
7-12 months	38	26.6
13-18 months	16	11.2
19-24 months	9	6.3
>25 months	31	21.7

4.4 STATISTICS

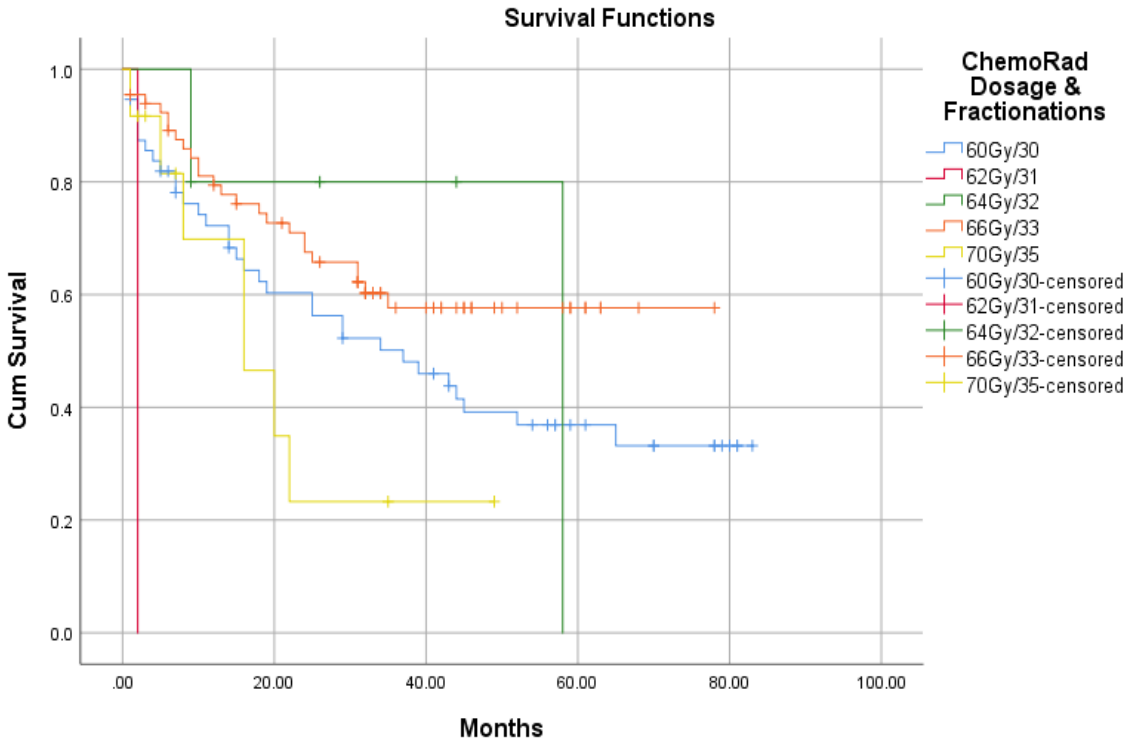
Overall survival (OS) was measured from the start of diagnosis up to the time of death. Local-regional failure-free survival (LRFFS) was calculated from the beginning of treatment to the first loco-regional tumor detection. Distant metastases-free survival (DMFS) was assessed separately. Patients without tumor recurrence were censored at the last follow-up contact. Significance was defined as a $P<0.05$. Survival curves were plotted using the Kaplan–Meier method. Univariate and multivariate analysis was performed using the log-rank (Mantel–Cox) test and Cox regression respectively. Statistical analysis was performed using the SPSS Version 23 programme.

4.4.1 Overall Survival

At the time of this retrospective analysis, Fifty-two (36.4%) patients were still alive and 70 (49%) patients had died. The 2-year OS rate for the total group of patients was 36%. Only age was a significant prognostic factor for overall survival in the univariate analysis. Patients between 30-49 years had a higher 2-year overall survival compared to other age groups. T category, N category, AJCC stage, and body mass index were insignificant prognostic factors. The independent prognostic importance of the variables was verified by multivariate analysis of

age, AJCC stage, and BMI. The log-rank p-Value of the OS in relation to the commencement of diagnosis was statistically significant with a p value <0.003. All the other tests are also <0.05, indicating that there is a statistically significant difference in time to incident. From the figure below, patients who received 62Gy in 31 fractions had the worst outcome with 100% rate of death in the 2-year duration. This is however due to the fact that only a single patient received this radiotherapy dose.

Figure 4: Overall Survival



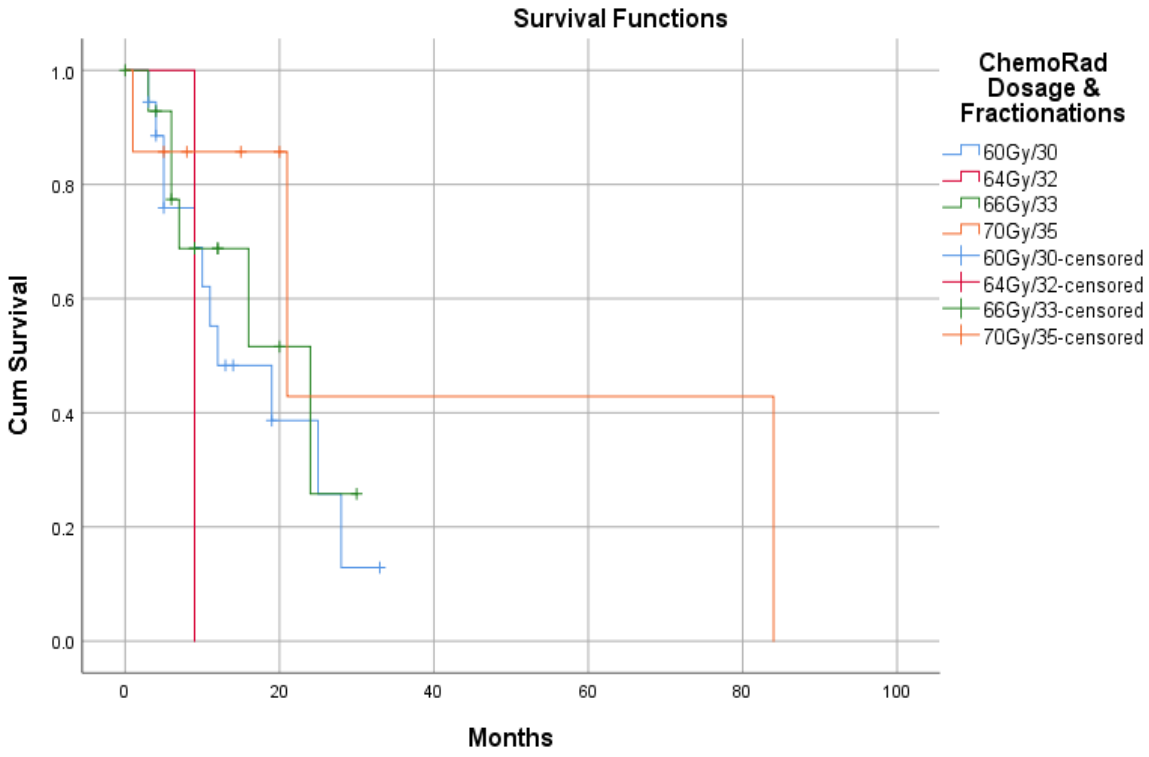
4.4.2 Local- Regional Failure-Free Survival (LRFFS)

During the follow-up period, 24 individuals experienced locoregional recurrence. The overall cohort of patients had a 2-year LRFFS rate of 84 percent. 8% of the total patients experienced local recurrence and 8% experienced regional recurrence. Age, T category, N category, AJCC stage, and body mass index were not predictive for LRFFS in univariate analysis.

The independent prognostic importance of the following variables was verified by multivariate analysis: Age, AJCC stage, and BMI. The p-Value of the LRFFS in relation to the start of

treatment was p=0.310, which is >0.05 and thus statistically insignificant, according to the log-rank. All of the tests are also >0.05, indicating no significant difference in time to event.

Figure 5: LRFFS

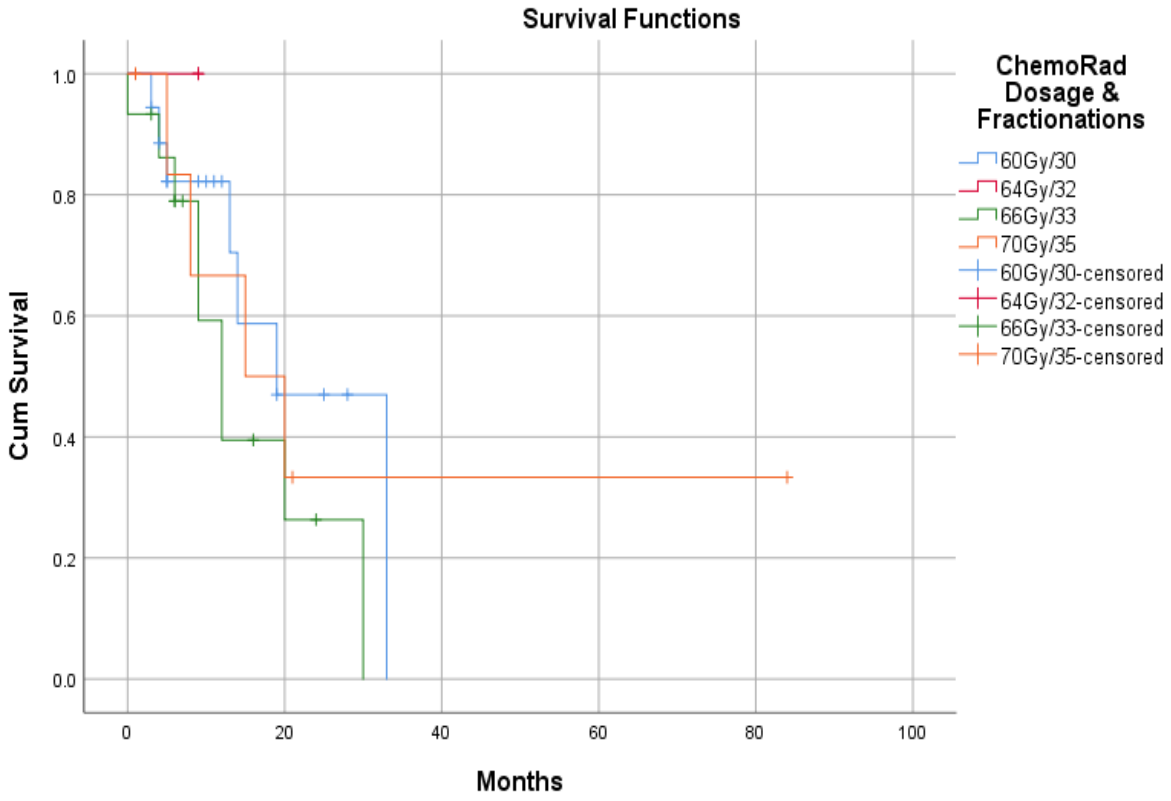


4.4.3 Distant Metastasis-Free Survival (DMFS)

During the follow-up period, 20 individuals had distant metastases. Metastatic recurrence was seen in 14% of the total number of patients. The overall cohort of patients had an 86% 2-year DMFS rate. Age, T category, N category, AJCC stage, and body mass index were not predictive for DMFS in univariate analysis. The independent prognostic importance of these variables was

verified by multivariate analysis of age, AJCC stage, and BMI. No other variables were associated with DMFS.

Figure 6: DMFS



Tables 12 and 13 detail the results of the univariate and multivariate analyses.

Table 12: Univariate Analysis

	No.	2-year OS	2-year DMFS	2-year LRFS
Age		P<0.001	P=0.221	P=0.791
18-29	27	52%	67%	33%
30-39	38	66%	57%	43%
40-49	25	60%	50%	50%
50-59	24	50%	27%	73%
60-69	19	21%	40%	60%
70-80	8	25%	N/A	N/A
T category		P=0.101	P=0.227	P=0.949
T0	2	0%	100%	0%
T1	22	41%	43%	57%
T2	31	64%	67%	33%
T3	44	39%	44%	56%
T4	42	47%	42%	58%
N category		P=0.126	P=0.647	P=0.933
N0	16	63%	0%	100%
N1	30	60%	38%	63%
N2	70	36%	52%	48%
N3	25	54%	57%	43%
Stage		P=0.064	P=0.549	P=0.979
II	24	75%	33%	67%
III	67	43%	48%	52%
IVa	50	50%	53%	47%
BMI		P=0.638	P=0.928	P=0.154
≤25	117	50%	43%	57%
≥26	24	54%	71%	29%

BMI, body mass index; OS, overall survival; LRFS, loco regional failure-free survival; DMFS, distant metastasis-free survival.

Table 13: Multivariate Analysis

		P value	HR	95.0% CI	
Overall survival rate:					
Age		<0.001	1.86	1.366	2.532
Stage		0.408	1.318	0.685	2.535
BMI		0.503	0.686	0.228	2.066
Local control rate:					
T category		0.743	1.339	0.234	7.642
Regional control rate:					
N category		0.474	0.025	<0.001	606.264
Distant metastasis-free survival rate:					
BMI		0.759	0.953	0.702	1.295
N category		0.392	2.584	0.294	22.728

HR, hazard ratio; CI, confidence interval; BMI, body mass index

The results of this study show that 30.8% of patients experienced recurrence. From the time of the last chemoradiotherapy treatment, the mean time to recurrence was 41.35 ± 33.6 weeks. Forty-six percent of these recurrences were metastatic, and 27% for both regional and local recurrence. The liver was the commonest site of distant metastasis at 38%, followed by skeletal metastasis (27%), lungs (23%) and brain (12%). Patients managed with 2D-EBRT had more local-regional recurrence than those treated with 3D-CRT. The rate of distant metastasis between the two radiotherapy modalities was almost similar.

Table 14: 2D vs 3D Treatment with Reference to Recurrences

	Local	Regional	Metastatic
2D-EBRT	7(58%)	10(83%)	8(40%)
3D-CRT	5(42%)	2(17%)	12(60%)

4.4.4 Treatment Toxicity

Treatment related toxicity for chemotherapy and radiotherapy was assessed using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) and the Radiation Therapy Oncology Group (RTOG) toxicity criteria respectively. In relation to treatment toxicities, mucositis was the most common treatment related side effect at 33%, followed closely by odynophagia at 29%. Xerostomia was the commonest side effect which persisted after treatment and was reported during patient follow up. For more references, check the table below.

Table 15: Treatment Toxicities

Toxicities	Frequency	Percentage
Mucositis	60	33%
Dermatitis	24	13%
Hearing deficits	4	2%
Cranial nerve palsy	2	1%
Dysphagia	7	4%
Xerostomia	27	15%
Odynophagia	52	29%
Neuropathy	1	1%
Oral Condiasis	1	1%
Skin Hyperpigmentation	1	1%
Tinnitus	1	1%
Vomiting	1	1%

Of the mentioned toxicities only mucositis and dermatitis were graded, with grade II mucositis being the most commonly reported. Refer to the table for frequencies.

Table 16: Toxicity Grades

	Mucositis	Dermatitis
Grade I	12	8
Grade II	13	3
Grade III	4	8

CHAPTER 5

DISCUSSION

Nasopharyngeal carcinoma is the most common head and neck malignancy in Kenya and it contributes to significant morbidity and mortality. Studies have been carried out over the years to investigate treatment outcomes for patients with NPC in endemic regions, with very good outcomes achieved with conformal radiotherapy such as 3D-CRT and IMRT. This study investigated the treatment outcomes for patients who received chemoradiotherapy at KNH Cancer treatment center between 1st January 2015 and 30th December 2019.

The results of the study showed that the most affected age group was between 30-39years, followed closely by 18-29 years with a median age of 47years. This finding is similar to the finding by Muchiri et al. at KNH, where the commonest age group was 31-40yrs. This is in contrast to the GLOBOCAN 2008 report which showed a bimodal age of distribution in low risk areas, with a peak between 15-25years and 50-59years. Males were more commonly affected compared to females with a ratio of 1.9:1. This is in keeping with the study by Muchiri et al. at the ENT department of KNH which confirmed that males had a higher prevalence of NPC than their female counterparts. [20]

The risk factors that were identified for NPC in this study were alcohol and cigarette smoking. EBV titer assessment was only carried out in 1% of the patients. The low uptake for EBV testing in our population might be due to lack of awareness. In studies carried out elsewhere, EBV has been identified as the major causative agent for NPC and has prognostic value. [24] The most common histology in our study was undifferentiated NPC at 69%, with the least common histology being non-keratinizing SCC at 5%. Studies in endemic regions have also shown a higher prevalence of undifferentiated NPC, which is mostly EBV associated. [25] Aswan et al. found that there was 100% prevalence of EBV among the 62 NPC patients who were studied in a prospective study carried out at KNH from 2015-2018. This stresses the importance of EBV DNA screening within our population as it may be the primary etiologic agent for nasopharyngeal cancer.

The majority of the patients in our study presented with advanced disease, with stage III NPC accounting for 48% of the cases and stage IVA accounting for 35% of cases. This finding is

similar to the study by Ogun et al where 54.8% of the patients managed at a University hospital in Ibadan- Nigeria presented with stage 3 or 4 disease. Nutritional status was not found to be a significant factor affecting treatment outcomes in our study. In contrast, Tang et al found that underweight patients had inferior survival compared to both overweight and obese patients, who had similar survival to those with normal weight. [49]

Induction chemotherapy has been shown to improve outcomes for patients with locoregionally advanced NPC in some series. The study by Palazzi et al showed that distant control at 3 years was 56% in patients treated with concomitant chemotherapy only and 92% in patients treated with both induction and concomitant CCRT. [34] In our study, only 51% of patients received induction chemotherapy. The commonest chemotherapy used was Cisplatin and paclitaxel, whereas recent studies have shown that TPF is associated with better outcomes for patients with high risk disease. The study by Liu et al showed that TPF improves local control and reduces the rate of distant metastasis compared to the combination of two drug regimens (taxane/ paclitaxel and taxane/5-FU). Similarly, Zhang et al showed that induction TPF was associated with improved 3-year FFS of 76.8%, OS of 85.1%, LRFFS of 88.3%, and DFFS of 84.1%. [32]

In the recent past, IMRT and 3D-CRT have been associated with better locoregional control and overall survival compared to 2D-EBRT [12, 38, 39]. Similarly, the study by Leibel et al. showed that 3D-CRT is associated with better locoregional control compared to 2D-EBRT. In our study, majority of patients were treated with 2D-EBRT (58%) with the rest receiving treatment with 3D-CRT (42%). IMRT was not available at our facility during the study period. Patients managed with 2D-EBRT had more locoregional recurrences compared to 3D-CRT, but there was no difference in distant metastasis between the two modalities. Lee et al. compared treatment outcomes for NPC patients managed with 2D-EBRT, 3D-CRT and IMRT whereby distant metastasis was also identified as the major challenge affecting treatment outcomes in patients with NPC. [48] Therefore, conformal modalities of treatment have been able to address the issue of locoregional control only and distant metastasis remains a major stumbling block when managing NPC patients.

The patients in our study had a poorer 2-year OS of 36% compared to studies in endemic regions. This may be attributed to late diagnosis, treatment with 2D-EBRT and use of lower radiotherapy doses than what is recommended due to the planning technique and prioritization of

normal tissue safety. The majority of patients (30%) received only one cycle of concurrent cisplatin, which may also have contributed to the poorer outcomes. The LRFFS and DMFS were comparable to other reported series, at 84% and 86% respectively. [38] In this study, only age was found to be an independent prognostic factor for overall survival on both univariate and multivariate analyses. Patients between the ages of 30-49 had the best 2-yr overall survival whereas elderly patients (60-80years) had the worst 2-year overall survival. T stage, N stage, AJCC stage and BMI were found to be insignificant prognostic factors for OS, LRFFS and DMFS. In our study only 6 patients were documented to have received adjuvant chemotherapy. It is possible this may have contributed to the poor overall survival. [37] Though the impact of adjuvant chemotherapy on outcomes remains controversial, a few studies have confirmed some benefit.[37] Chen et al found that there was improved 2-year overall survival (89.8% vs. 79.7%), distant failure-free survival (86.5% vs. 78.7%), and locoregional failure-free survival (98.0% vs. 91.9%) for patients who received concurrent chemoradiotherapy followed by adjuvant chemotherapy in a prospective randomized trial carried out in endemic regions of China. [36]

Overall, distant metastasis was the commonest pattern of recurrence at 46%. The Liver was the commonest site of distant metastasis at 38%, followed by skeletal metastasis (27%), lungs (23%) and brain (12%). More treatment related toxicities were observed in patients treated with 2D-EBRT at 58% compared to 3D-CRT at 42%. This is attributable to the less conformal dose distribution with 2D treatment techniques. Hypothyroidism has been reported in other studies as a significant late toxicity following head and neck radiotherapy. However, in our study no patients were actively monitored for subclinical hypothyroidism. The longest treatment interruption time was 2.6 weeks, with treatment related toxicities (such as mucositis), machine breakdown and holidays being the commonest causes of treatment delays. This factor likely contributed to the poor treatment outcomes.

CHAPTER 6

CONCLUSION

In the present study we report the clinical outcomes of patients with stage II-IVA nasopharyngeal carcinoma treated with chemoradiotherapy. While we report similar rates of locoregional control as other studies, distant metastasis remains a major challenge. The 2-year overall survival seen in this study was inferior to other reports from endemic regions. This may be attributed to the advanced stage in which patients present, treatment with 2D-EBRT more than conformal radiotherapy, use of lower doses of radiotherapy, treatment interruptions, and fewer total cycles of concurrent chemotherapy than recommended. We found that patients who received 3D-CRT had better locoregional control and fewer side effects compared to 2D-EBRT. However, there is need for more studies to help reduce the rate of distant metastasis, which was the main mode of treatment failure in our study.

RECOMMENDATIONS

1. Formulate policies for cancer screening & early diagnosis
2. There should be emphasis on proper documentation and filing to avoid loss of patient data
3. Digitization of records department
4. Merging of radiotherapy treatment records with admission files will ensure there is no gap in patient treatment and follow up
5. Incorporate more conformal radiotherapy modalities such as IMRT
6. Ensure patients receive recommended doses and schedules of chemoradiotherapy (minimum RT dose of 66Gy)
7. Mechanisms should be put in place to ensure that patients who are lost to follow up are contacted and enrolled back on follow up
8. EBV DNA titers should be investigated for all patients to assist in diagnosis and prognostication

REFERENCES

1. Chang ET, Adami HO. The enigmatic epidemiology of nasopharyngeal carcinoma. Cancer Epidemiol Biomarkers Prev. 2006; 15(10):1765-1777. doi:10.1158/1055-9965.EPI-06-0353
2. Sung H, Ferlay J, Siegel RL, et al. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. CA Cancer J Clin. 2021; 71(3):209-249. doi:10.3322/caac.21660
3. World Health Organization. https://iarc.who.int/. Accessed June 28, 2021.
4. Larsson LG, Clifford P, Einhorn J, et al. Radiation therapy of nasopharyngeal carcinoma in East Africa. Acta Radiol Ther Phys Biol. 1976; 15(4):305-314.doi: 10.3109/02841867609131967
5. Musibi A, Mutuma G, Gathere S, Korir A. Head and neck cancers four-year trend at the Nairobi cancer registry. . Ogun GO, Olusanya AA, Akinmoladun VI, et al. Nasopharyngeal carcinoma in Ibadan, Nigeria: a clinicopathologic study. Pan Afr Med J. 2020; 36:82. Published 2020 Jun 9. doi:10.11604/pamj.2020.36.82.19657
6. Ogun GO, Olusanya AA, Akinmoladun VI, et al. Nasopharyngeal carcinoma in Ibadan, Nigeria: a clinicopathologic study. Pan Afr Med J. 2020; 36:82. Published 2020 Jun 9. doi:10.11604/pamj.2020.36.82.19657
7. Buckle G, Maranda L, Skiles J, et al. Factors influencing survival among Kenyan children diagnosed with endemic Burkitt lymphoma between 2003 and 2011: A historical cohort study. Int J Cancer. 2016; 139(6):1231-1240. doi:10.1002/ijc.30170
8. Aswani JM, Anzala O, Mwang'ombe JN. Epstein Barr-virus and human papillomavirus co-infection in nasopharyngeal carcinoma at Kenyatta National Hospital. East Central Afr J Otolaryngology Head Neck Surg. 2020; 4(2): 3-7.
9. Barrett A, Morris S, Dobbs J, Roques T. Practical Radiotherapy Planning. 2009. doi: 10.1201/b13373
10. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology. Head and neck cancer. Version 1.2021. Available at: https://www.nccn.org/professionals/physician_gls (Accessed on January 29, 2020).

11. Al-Sarraf M, LeBlanc M, Giri PG, et al. chemo radiotherapy versus radiotherapy in patients with advanced nasopharyngeal cancer: phase III randomized intergroup study 0099. J Clin Oncol. 1998; 16(4):1310-1317. doi:10.1200/JCO.1998.16.4.1310
12. Du T, Xiao J, Qiu Z, Wu K. The effectiveness of intensity-modulated radiation therapy versus 2D-RT for the treatment of nasopharyngeal carcinoma: A systematic review and meta-analysis. PLoS One. 2019; 14(7):e0219611. Published 2019 Jul 10. doi:10.1371/journal.pone.0219611.
13. Chen JL, Huang YS, Kuo SH, et al. Intensity-modulated radiation therapy achieves better local control compared to three-dimensional conformal radiation therapy for T4-stage nasopharyngeal carcinoma. Oncotarget. 2017; 8(8):14068-14077. doi:10.18632/oncotarget.12736
14. Perri F, Della Vittoria Scarpati G, Caponigro F, et al. Management of recurrent nasopharyngeal carcinoma: current perspectives. Onco Targets Ther. 2019; 12:1583-1591. Published 2019 Feb 26. doi:10.2147/OTT.S188148
15. Lu JJ, Shakespeare TP, Tan LK, Goh BC, Cooper JS. Adjuvant fractionated high-dose-rate intracavitary brachytherapy after external beam radiotherapy in Tl and T2 nasopharyngeal carcinoma. Head Neck. 2004 May; 26(5):389-95.doi: 10.1002/hed.10398. PMID: 15122654.
16. Basic Radiation Oncology. By Murat Beyzadeoglu, Gokhan Ozyigit, Cuneyt Ebruli New York, 2010
17. Wang KH, Austin SA, Chen SH, Sonne DC, Gurushanthaiah D. Nasopharyngeal Carcinoma Diagnostic Challenge in a Nonendemic Setting: Our Experience with 101 Patients. Perm J. 2017; 21:16-180. doi:10.7812/TPP/16-180
18. Carle LN, Ko CC, Castle JT. Nasopharyngeal carcinoma. Head Neck Pathol. 2012; 6(3):364-368. doi: 10.1007/s12105-012-0333-z
19. Bray F, Haugen M, Moger TA, Tretli S, Aalen OO, Grotmol T. Age-incidence curves of nasopharyngeal carcinoma worldwide: bimodality in low-risk populations and aetiologic implications. Cancer Epidemiol Biomarkers Prev. 2008; 17(9):2356-2365. doi:10.1158/1055-9965.EPI-08-0461
20. Muchiri M. Demographic study of nasopharyngeal carcinoma in a hospital setting. East Afr Med J. 2008; 85(8):406-411. doi:10.4314/eamj.v85i8.9658

21. Abdullah NE, Adam AA, Khalifa EH, et al. Nasopharyngeal cancer in Sudan: epidemiology, clinical and histological characteristics. Clin Med Insights Ear Nose Throat. 2011; 4:5-11. Published 2011 Feb 22. doi:10.4137/CMENT.S5825
22. Perez CA, Devineni VR, Marcial-Vega V, Marks JE, Simpson JR, Kucik N. Carcinoma of the nasopharynx: factors affecting prognosis. Int J Radiat Oncol Biol Phys. 1992; 23(2):271-280. doi: 10.1016/0360-3016(92)90741-y
23. Stelow EB, Wenig BM. Update from the 4th Edition of the World Health Organization Classification of Head and Neck Tumours: Nasopharynx. Head and Neck Pathology. 2017 Mar; 11(1):16-22. doi: 10.1007/s12105-017-0787-0.
24. Young LS, Dawson CW. Epstein-Barr virus and nasopharyngeal carcinoma. Chin J Cancer. 2014; 33(12):581-590. doi:10.5732/cjc.014.10197
25. Price AM, Luftig MA. Dynamic Epstein-Barr virus gene expression on the path to B-cell transformation. Adv Virus Res. 2014; 88:279-313. doi:10.1016/B978-0-12-800098-4.00006-4
26. Pathmanathan R, Prasad U, Chandrika G, Sadler R, Flynn K, Raab-Traub N. Undifferentiated, nonkeratinizing, and squamous cell carcinoma of the nasopharynx. Variants of Epstein-Barr virus-infected neoplasia. Am J Pathol. 1995; 146(6):1355-1367.
27. Maxwell JH, Kumar B, Feng FY, et al. HPV-positive/p16-positive/EBV-negative nasopharyngeal carcinoma in white North Americans. Head & Neck. 2010 May; 32(5):562-567. doi: 10.1002/hed.21216.
28. Okekpa SI, S M N Mydin RB, Mangantig E, et al. Nasopharyngeal Carcinoma (NPC) Risk Factors: A Systematic Review and Meta-Analysis of the Association with Lifestyle, Diets, Socioeconomic and Sociodemographic in Asian Region. Asian Pac J Cancer Prev. 2019; 20(11):3505-3514. Published 2019 Nov 1. doi:10.31557/APJCP.2019.20.11.3505
29. Tiong TS, Selva KS. Clinical presentation of nasopharyngeal carcinoma in Sarawak Malaysia. Med J Malaysia. 2005; 60(5):624-628.
30. Toro C, Rinaldo A, Silver CE, Politi M, Ferlito A. Paraneoplastic syndromes in patients with nasopharyngeal cancer. Auris Nasus Larynx. 2009; 36(5):513-520. doi:10.1016/j.anl.2008.10.006

31. Li JC, Mayr NA, Yuh WT, Wang JZ, Jiang GL. Cranial nerve involvement in nasopharyngeal carcinoma: response to radiotherapy and its clinical impact. Ann Otol Rhinol Laryngol. 2006; 115(5):340-345. doi: 10.1177/000348940611500504
32. Zhang Q, Wang Y, Liao JF, et al. Long-Term Survival and Prognostic Factors in Loco regionally Advanced Nasopharyngeal Carcinoma Patients Treated with TPF Induction Chemotherapy followed by Cisplatin-Combined Concurrent Chemoradiotherapy. J Cancer. 2019; 10(17):3899-3907. Published 2019 Jun 24. doi:10.7150/jca.31663
33. Fang L, Shi L, Wang W, Hu T, Rao X. Which treatment is better than concurrent chemoradiotherapy for the survival of stage III or IV locally advanced nasopharyngeal carcinoma? An updated Bayesian network meta-analysis of randomized controlled trials [published online ahead of print, 2021 Feb 17]. Eur Arch Otorhinolaryngol. 2021; 10.1007/s00405-021-06614-x. doi: 10.1007/s00405-021-06614-x
34. Palazzi M, Orlandi E, Bossi P, et al. Further improvement in outcomes of nasopharyngeal carcinoma with optimized radiotherapy and induction plus concomitant chemotherapy: an update of the Milan experience. Int J Radiat Oncol Biol Phys. 2009; 74(3):774-780. doi:10.1016/j.ijrobp.2008.08.068
35. Isobe K, Kawakami H, Uno T, et al. Concurrent chemoradiotherapy for locoregionally advanced nasopharyngeal carcinoma: is intergroup study 0099 feasible in Japanese patients? Jpn J Clin Oncol. 2003; 33(10):497-500. doi:10.1093/jjco/hyg094
36. Chen Y, Liu MZ, Liang SB, et al. Preliminary results of a prospective randomized trial comparing concurrent chemoradiotherapy plus adjuvant chemotherapy with radiotherapy alone in patients with loco regionally advanced nasopharyngeal carcinoma in endemic regions of China. Int J Radiat Oncol Biol Phys. 2008; 71(5):1356-1364. doi:10.1016/j.ijrobp.2007.12.028
37. Lee AWM, Tung SY, Ng WT, et al. A multicenter, phase 3, randomized trial of concurrent chemoradiotherapy plus adjuvant chemotherapy versus radiotherapy alone in patients with regionally advanced nasopharyngeal carcinoma: 10-year outcomes for efficacy and toxicity. Cancer. 2017; 123(21):4147-4157. doi:10.1002/cncr.30850
38. Mao YP, Tang LL, Chen L, et al. Prognostic factors and failure patterns in non-metastatic nasopharyngeal carcinoma after intensity-modulated radiotherapy. Chin J Cancer. 2016; 35(1):103. Published 2016 Dec 28. doi: 10.1186/s40880-016-0167-2

39. Leibel SA, Kutcher GJ, Harrison LB, et al. Improved dose distributions for 3D conformal boost treatments in carcinoma of the nasopharynx. Int J Radiat Oncol Biol Phys. 1991; 20(4):823-833. doi:10.1016/0360-3016(91)90030-8
40. Abel E, Silander E, and Nyman J, et al. Impact on quality of life of IMRT versus 3-D conformal radiation therapy in head and neck cancer patients: A case-control study. Adv Radiat Oncol. 2017; 2(3):346-353. Published 2017 May 12. doi:10.1016/j.adro.2017.05.002
41. Saleh-Ebrahimi L, Zwicker F, Muenter MW, et al. Intensity-modulated radiotherapy (IMRT) combined with concurrent but not adjuvant chemotherapy in primary nasopharyngeal cancer - a retrospective single-center analysis. Radiat Oncol. 2013; 8:20. Published 2013 Jan 24. doi: 10.1186/1748-717X-8-20
42. Sun PY, Chen YH, Feng XB, Yang CX, Wu F, Wang RS. High-Dose Static and Dynamic Intensity-Modulated Radiotherapy Combined with Chemotherapy for Patients with Locally Advanced Nasopharyngeal Carcinoma Improves Survival and Reduces Brainstem Toxicity. Med Sci Monit. 2018; 24:8849-8859. Published 2018 Dec 7. doi:10.12659/MSM.910465
43. Lai SZ, Li WF, Chen L, et al. How does intensity-modulated radiotherapy versus conventional two-dimensional radiotherapy influence the treatment results in nasopharyngeal carcinoma patients? Int J Radiat Oncol Biol Phys. 2011; 80(3):661-668. doi:10.1016/j.ijrobp.2010.03.024.
44. Lu JJ, Shakespeare TP, Tan LK, Goh BC, Cooper JS. Adjuvant fractionated high-dose-rate intracavitary brachytherapy after external beam radiotherapy in Tl and T2 nasopharyngeal carcinoma. Head Neck. 2004; 26(5):389-395. doi:10.1002/hed.10398
45. Liu F, Xiao JP, Xu GZ, et al. Fractionated stereotactic radiotherapy for 136 patients with locally residual nasopharyngeal carcinoma. Radiat Oncol. 2013; 8:157. Published 2013 Jun 27. doi: 10.1186/1748-717X-8-157
46. King AD, Ahuja AT, Yeung DK, et al. Delayed complications of radiotherapy treatment for nasopharyngeal carcinoma: imaging findings. Clin Radiol. 2007; 62(3):195-203. doi:10.1016/j.crad.2006.10.011

47. Lu S, Chang H, Sun X, et al. Long-Term Outcomes of Nasopharyngeal Carcinoma in 148 Children and Adolescents. Medicine (Baltimore). 2016; 95(17):e3445. doi:10.1097/MD.0000000000003445
48. Moon SH, Cho KH, Lee CG, et al. IMRT vs. 2D-radiotherapy or 3D-conformal radiotherapy of nasopharyngeal carcinoma: Survival outcome in a Korean multi-institutional retrospective study (KROG 11-06). IMRT vs. 2D-Strahlentherapie oder konformaler 3D-Strahlentherapie beim Nasopharynxkarzinom: Folgen für das Überleben in einer koreanischen multizentrischen retrospektiven Studie (KROG 11-06). Strahlenther Onkol. 2016; 192(6):377-385. doi:10.1007/s00066-016-0959-y
49. OuYang PY, Zhang LN, Tang J, et al. Evaluation of Body Mass Index and Survival of Nasopharyngeal Carcinoma by Propensity-Matched Analysis: An Observational Case-Control Study. Medicine (Baltimore). 2016; 95(2):e2380. doi:10.1097/MD.0000000000002380

APPENDICES

APPENDIX I: DATA COLLECTION TOOL

OUTCOMES OF PATIENTS WITH NASOPHARYNGEAL CARCINOMA TREATED WITH CHEMO-RADIOTHERAPY

QUESTIONNAIRE NO._____

Tick where appropriate

SECTION 1: GENERAL INFORMATION

1. Age group

   18-29 ☐ 30-39 ☐ 40-49 ☐ 50-59 ☐ 60-69 ☐ 70-80 ☐

2. Gender

   Male ☐ Female ☐

3. BMI…….
4. Date of birth…….
5. Residence…….
6. Level of education Primary ☐ Secondary ☐ University ☐

   Other…….
7. Is the patient a referral? Yes ☐ No ☐

   If yes, from where? ……...

8. Risk factors

   Smoking Yes ☐ No ☐
   If yes, specify pack years…….

   Alcohol Yes ☐ No ☐
   If yes, specify……..
   EBV DNA titers……..

SECTION 2: MEDICAL HISTORY

1. Presenting symptoms	

2. Duration of symptoms(months)	
3. Date of diagnosis	
4. Method of cancer diagnosis	
• FNA of cervical nodes	
• Core biopsy	
• Other	
5. Staging method (specify site)	
• Ct scan	
• MRI	
• X-ray	
• Ultrasound	
• Other	

9. TNM stage
T……. N……. M…….
10. Anatomic Group stage:

Stage II ☐
Stage III ☐

Stage IVa ☐

11. Treatment modality
Induction chemotherapy Yes ☐ No ☐
Specify……
Date started ……...
Date finished…….

Chemo radiotherapy Yes ☐ No ☐
Specify……
Dose and fractionation……
Date Started……
Date finished…….
12. Type of radiotherapy (Tick where appropriate)

2D-EBRT……
3D-CRT……
Adjuvant chemotherapy Yes ☐ No ☐
Specify……
Date started……

Date finished…….

Surgery date…… Yes ☐ No ☐

The intent of surgery (Neck dissection/salvage)……

13. Treatment toxicities and
Common toxicity criteria(where applicable)

Mucositis Yes ☐ ……. No ☐

Dermatitis Yes ☐ ……. No ☐

Hearing deficits Yes ☐…… No ☐

Trismus Yes ☐…. …. No ☐

Hemorrhage Yes ☐…… No ☐

Cranial nerve palsy Yes ☐ ……. No ☐

Xerostomia Yes ☐ …… No ☐

Other ……

14. Follow up duration

0-6 months ☐

7-12 months ☐

13-18 months ☐

19-24 months ☐

> 25 months ☐

15. Disease recurrence Yes ☐ No ☐

Date……

If **yes,** specify the site (local, regional, metastatic) …….

How long after treatment? .....

Last follow-up date…….

Date of death……

APPENDIX II: STUDY BUDGET

Table 17: Study budget

BUDGET ITEM	UNIT COST(Ksh)	QUANTITY	AMOUNT(USD)
1. PERSONNEL			
a. Research assistant(training, data collection& data entry)			1185
b. Statistician			330
2. Ethics committee			33
3. KNH research fee			12
4. Stationery & Other expenses			
a. Airtime			33
b. Data collection tool printing	10/page	174(3pages each)	43
c. Manuscripts printing & binding			63
d. Stationery (pens, clipboards, box files etc.)			41
e. Miscellaneous			83
f. Publishing			165
TOTAL			**$ 1988**

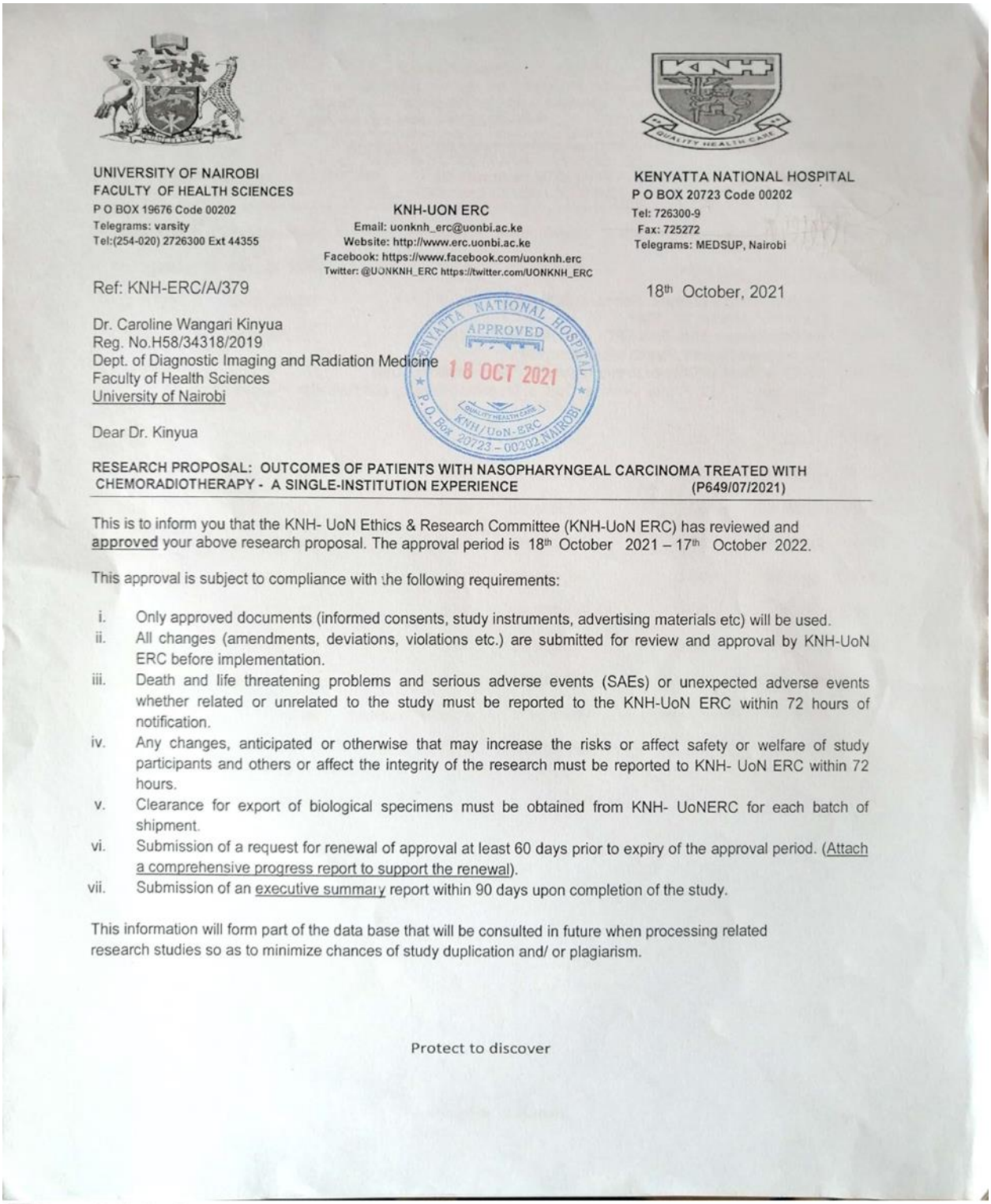
Study sponsored by: Global access to cancer care foundation

APPENDIX III: STUDY TIMEFRAME

The following chart outlines the timeframe of the study:

	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**
PROPOSAL DEVELOPMENT	■	■	■	■	■										
ETHICS COMMITTEE REVIEW						■	■								
DATA COLLECTION								■	■	■					
DATA ANALYSIS											■	■			
WRITING REPORT													■	■	
RESULTS PRESENTATION															■

APPENDIX IV: ERC APPROVAL



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18th October, 2021

KENYATTA NATIONAL HOSPITAL APPROVED 18 OCT 2021 KNH/UoN-ERC P.O. Box 20723 - 00202 NAIROBI

Dr. Caroline Wangari Kinyua
Reg. No.H58/34318/2019
Dept. of Diagnostic Imaging and Radiation Medicine
Faculty of Health Sciences
University of Nairobi

Dear Dr. Kinyua

RESEARCH PROPOSAL: OUTCOMES OF PATIENTS WITH NASOPHARYNGEAL CARCINOMA TREATED WITH CHEMORADIOTHERAPY - A SINGLE-INSTITUTION EXPERIENCE (P649/07/2021)

This is to inform you that the KNH- UoN Ethics & Research Committee (KNH-UoN ERC) has reviewed and approved your above research proposal. The approval period is 18th October 2021 – 17th October 2022.

This approval is subject to compliance with the following requirements:

i. Only approved documents (informed consents, study instruments, advertising materials etc) will be used.
ii. All changes (amendments, deviations, violations etc.) are submitted for review and approval by KNH-UoN ERC before implementation.
iii. Death and life threatening problems and serious adverse events (SAEs) or unexpected adverse events whether related or unrelated to the study must be reported to the KNH-UoN ERC within 72 hours of notification.
iv. Any changes, anticipated or otherwise that may increase the risks or affect safety or welfare of study participants and others or affect the integrity of the research must be reported to KNH- UoN ERC within 72 hours.
v. Clearance for export of biological specimens must be obtained from KNH- UoNERC for each batch of shipment.
vi. Submission of a request for renewal of approval at least 60 days prior to expiry of the approval period. (Attach a comprehensive progress report to support the renewal).
vii. Submission of an executive summary report within 90 days upon completion of the study.

This information will form part of the data base that will be consulted in future when processing related research studies so as to minimize chances of study duplication and/ or plagiarism.

Protect to discover

This information will form part of the data base that will be consulted in future when processing related research studies so as to minimize chances of study duplication and/ or plagiarism.

For more details consult the KNH- UoN ERC website **http://www.erc.uonbi.ac.ke**

Yours sincerely,

PROF. M. J. CHINDIA
SECRETARY, KNH-UoN ERC

c.c. The Principal, College of Health Sciences, UoN
The Senior Director, CS, KNH
The Chair, KNH- UoN ERC
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