THE CLINICOPATHOLOGY, TREATMENT PATTERN AND SURVIVAL OF NASOPHARYNGEAL CARCINOMA PATIENTS AT TIKUR ANBESSA SPECIALIZED HOSPITAL, ONCOLOGY DEPARTMENT, ADDIS ABABA, ETHIOPIA

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ACRONYMS

AAU	Addis Ababa University
ACT	Adjuvant Chemotherapy
AJCC	American Joint Committee on Cancer
CCRT	Concurrent Chemo Radiotherapy
CHS	College of Health Sciences
CI	Confidence Interval
Co-60	Cobalt 60
CT-Scan	Computed Tomography
CT	Chemotherapy
CXR	Chest X-Ray
DM	Diabetes Mellitus
ECOG	Eastern Cooperative Oncology Group
ENT	Ear, Nose and Throat Specialty
FMOH	Federal Ministry of Health
FNAC	Fine Needle Aspiration Cytology
5–FU	5 Fluorouracil
Gy	Gray
HIV	Human Immunodeficiency Virus
HMIS	Health Management Information System
HNC	Head and neck cancers
HR	Hazard Ratio
HTN	Hypertension
IAEA	International Atomic Energy Agency
IQR	Interquartile range
MRI	Magnetic Resonance Imaging
MRN	Medical Record Number
NCD	Non-Communicable Disease

NPC	Nasopharyngeal carcinoma
OR	Odds Ratio
OS	Overall survival
PFS	Progression Free Survival
RR	Relative Risk
RT	Radiotherapy
RVI	Retro Viral Infection
RX	Treatment
SCC	Squamous cell carcinoma
SNNPR	Southern Nations, Nationalities, and Peoples' Region
SPH	School of Public Health
SPSS	Statistical Package for Social Science
TASH	Tikur Anbessa Specialized Hospital
TNM	Tumor Size, Nodal involvement, Metastasis
TPF	Chemo regimen of cisplatin/5Fluorouracil/Docetaxel
WHO	World Health Organization

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Abstract

Background: Nasopharyngeal carcinoma is one of the most common head and neck cancers worldwide and its incidence is reported to be increasing both in developed and developing countries. There is, however, lack of published data on nasopharyngeal carcinoma in Ethiopia.

Objective: To assess the clinicopathology, treatment patterns and median survival of patients diagnosed with nasopharyngeal carcinoma at Tikur Anbessa Specialized Hospital (TASH), Oncology Department, Ethiopia

Methodology: A retrospective cohort study design of histopathologic proven nasopharyngeal carcinoma patients seen at the Oncology Department of TASH from September 11, 2014 and September 10, 2017 and followed for vital status up until October 2020. Descriptive statistics (mean, SD, frequency, percentage) were calculated and chi-square tests were performed using SPSS version 26, with $P<05$ for level of statistical significance. Survival curves were analyzed using the Kaplan-Meier method, and survival curves between groups of patients were compared using a log-rank test. A multivariable Cox proportional hazard model was used to identify prognostic factors.

Results: A total of 170 patients with histopathological confirmed nasopharyngeal cancer were seen in the Oncology Department during the study period. The mean age of the patients was 37.73 ±17.7 SD years, with 2:1 male to female ratio. Majority 77 (56.6%) of the histology types were taken from Lymphnode with 36 (26.5%) showing secondary carcinoma from nasopharynx. Generally 113 (83.31%) of the patients presented with stage III-IV. 23.5 % of the patients did not take any form of treatment. Of those who received treatment, the most common form of treatment was induction chemotherapy (19.1%), followed by concurrent chemo radiotherapy (16.9%). Patients had to wait on average 3.24 months to get any types of treatment. The median waiting periods were 8.4 months for any form of radiation and 3.3 months for chemotherapy. The median followup period was 23.3 months, and the median survival was 33 months. Survival was statistically significantly associated with advancing age, keratinizing histologic type, lack of receipt of treatment, suboptimal dose of RT and nodal disease. However, Sex, Tumor stage, metastasis, group stage, waiting time to treatment and performance status were not significantly affecting the survival time of patients.

Conclusion: Majority of patients with nasopharyngeal cancer seen at TASH in Addis Ababa are presented at advanced stage of the disease, and with exceedingly long waiting period for receipt of radiotherapy and poor survival outcomes. These findings underscore the need for development of public health plans for early diagnosis and treatment of nasopharyngeal cancer and for expansion of radiotherapy services in the country.

1. INTRODUCTION

1.1 Background

Nasopharyngeal carcinoma (NPC) is a disease of the nasopharynx, which is a component of the upper airway system, connecting the nasal cavity to the oropharynx and contains the Eustachian tube openings and adenoids. The nasopharynx represents the most superior portion of the pharynx, bounded superiorly by the skull base and inferiorly by the soft palate. It mainly functions as an airway passage and its intrinsic muscles control the opening of the eustachian tubes, which help control ventilation and equilibrium of atmospheric pressure between the middle ear cavity and nasopharynx. The nasopharynx contributes to voice resonance and production. Obstruction of the nasopharynx leads to voice changes (hyponasality). As inspired air is filtered and humidified within the nasal cavity, dust particles are trapped in nasal mucus and transported via the "mucociliary elevator," which beats towards the nasopharynx. From there, nasal debris drains to the oropharynx. In addition, the nasopharyngeal isthmus blocks the nasopharynx during swallowing (1).

The nasopharynx contains several types of tissue, and each tissue type contains several types of cells. Benign and malignant lesions can occur in the nasopharynx. Under malignant lesions, carcinomas compose about 85% and lymphomas, about 10% [2]. Nasopharyngeal carcinomas are classified as follows: keratinizing SCC (WHO type I), differentiated nonkeratinizing carcinoma and, undifferentiated non-keratinizing carcinoma including lymphoepithelioma and anaplastic variants (WHO type II) and Basaloid SCC (WHO type III). Keratinizing squamous cell carcinoma is distinguished by the presence of keratin pearls or intracellular keratin. Non-keratinizing carcinoma is characterized by the complete absence of keratin formation. The WHO type III subtype is the commonest form of NPC in endemic areas and differs from squamous type of NPC in its association with the Epstein Barr virus (EBV) and sensitivity to chemotherapy and radiotherapy (RT) (3). In addition, a miscellaneous group of malignant tumors can occur in the nasopharynx including melanoma, plasmacytoma, juvenile angiofibroma, carcinosarcoma, sarcomas, nonchromaffin paragangliomas, and minor salivary gland tumors (4).

The most important risk factors for nasopharyngeal cancer were Epstein-Barr virus (EBV), heredity, human leukocyte antigen (HLA) genes, salt-preserved fish consumption, history of

chronic respiratory diseases, tobacco smoking, occupational dusts, formaldehyde and low socioeconomic status (5).

In most cases, diagnosis is made by biopsy of the primary lesion performed under local anesthetic in the clinic. An alternative to a biopsy of the primary lesion is to obtain a fine-needle aspirate (FNA) biopsy of a clinically suspicious neck node on the ipsilateral side of the primary tumor. The staging of NPC is based on the depth of invasion of the soft tissue, cranial nerves and bony structures at and near the nasopharynx, the involvement of local and regional lymph nodes of the head and neck, and the presence of distant metastases (3). There is an 80% to 90% incidence of metastatic neck nodes on presentation; approximately 50% are bilateral (2).

1.2 Statement of the problem

The annual incidence of head and neck cancers worldwide is more than 550,000 cases with around 300,000 deaths each year (6). Globally, NPC has approximately 80,000 new cases reported each year and accounts for 0.7% of all cancers (3). The standard incidence of nasopharyngeal cancer in the world was 1.2 per 100,000 (in men, 1.7 per 100,000; in women, 0.7 per 100,000). The standardized mortality rate for nasopharyngeal cancer in the world was 0.7 per 100,000 (in men
1.0 per 100,000; in women 0.4 per 100,000) (5).

In North America and Europe, the incidence rate is less than 1 case per 100,000 populations, but in endemic areas like Southern China (e.g., Hong Kong) and Southeast Asia, the annual agestandardized incidence rates are as high as 20 to 30 cases per 100,000 population in men and 8 to 15 cases per 100,000 population in women (3).

Cancer is an emerging public health problem in Africa. About 715,000 new cancer cases and 542,000 cancer deaths occurred in 2008 in the continent, with these numbers expected to double in the next 20 years simply because of the aging and growth of the population. Despite the increment of cancer burden, much attention is still on the communicable diseases like HIV/AIDS, malaria, and tuberculosis (7). For many reasons, cancers in Africa are diagnosed at late stages. Study shows that about 95% of cancer cases present at late and end-stage. Delayed diagnosis of these patients is due to low level of awareness of the population and health workers

and cultural constraints on access to specialized care (8). In 2008, nasopharyngeal carcinoma in Africa showed an estimated 8,700 incidence and 5,500 deaths. The incidence rates are twice as high in men as in women. The highest incidence rates are in the Republic of South Africa, and in the countries of the Maghreb (Morocco, Algeria, and Tunisia) (7).

Ethiopia is one of the east African countries with an estimated population of 112,079,000 based on the United Nation's midyear World Population Prospects of 2019 (9). It is expected to become the 8th most populous country in the world by 2050 (10). It is estimated that about 60,000 new cancer cases are diagnosed each year in the country (11). The common challenges of cancer treatment are, the lack of awareness of the signs and symptoms of cancer, shortage of traveling cost to hospital, financial deficiency for diagnosis and treatment costs, which thus leads many to seek traditional treatments instead (12).

Head and neck cancers (HNC) are one of the commonest types of cancers in Ethiopia. The finding from a study done at Tikur Anbessa Specialized Hospital (TASH) on pattern of cancer from 1998 to 2010, HNC was the leading malignancy in male (22%) (13). However, the study didn't separately analyze the clinicopathology and pattern of treatments of head and neck cancers.

According to the report from the Addis Ababa population-based cancer registry of 2015, on the estimated number of cases of the commonest cancer types in Ethiopia, nasopharyngeal cancer has a crude incidence rate of 1 per 100,000 people in male and 0.6 per 100,000 in females. The age standardized ratio of 1.2 per 100,000 people in male and 0.8 per 100,000 in females. The total annual new cases were 497 and 277 in male and female, respectively (11).

Tikur Anbessa Specialized Hospital, the country's largest tertiary hospital, is the only radiation treatment center in the country. Up until the recent establishment of other oncology centers in the country, it has served as the sole oncology center since 1990. Similar to other cancer cases, NPC patients don't get timely treatment in the hospital. The waiting list for chemotherapy is around 24 months. According to a recent International Atomic Energy Agency (IAEA) report, the waiting time for radiotherapy treatment at TASH is one year, and by the time patients get access to

radiotherapy, 70% of the patients are in the final stages of the diseases and requiring palliative care

(14).

1.3 Significance of the Study

According to literature, there has not been any study done on the patterns of treatment and survival outcome of patients with NPC in Ethiopia. Therefore, this study will try to address this knowledge gap by assessing the burden of the disease, the treatment modalities and the survival outcome of NPC at the largest cancer care center in the country. The findings of this study will inform future practices to improve the management of such curable disease. It will also provide baseline information for governmental and non-governmental organizations which work in the area of noncommunicable diseases at national and regional levels. Finally, this study will be able to stimulate further research on nasopharyngeal cancer.

2. LITERATURE REVIEW

The incidence of NPC gradually increases with age, peaking at 50-59 years of age, and then tends to decrease. Furthermore, the prognosis for those with NPC tends to worsen with age (15). Nour *et al.* conducted a retrospective study at Tikur Anbessa Specialized Hospital on the imaging patterns of 80 newly diagnosed nasopharyngeal carcinoma patients, who came to the Hospital from January 2016 to August 2017. In that study, the commonest initial clinical symptoms were neck swelling seen in 61 (81.3%) of patients, Nasal obstruction in 32 (40%) and headache 19 (23.8%) of patients. The average time of presentation of symptoms was 6 (IQR 8) months. The study showed that 56 (70.0%) were diagnosed with non-keratinizing undifferentiated nasopharyngeal carcinoma while 15 (3.8%) had keratinizing nasopharyngeal carcinoma. Sixty-nine (86.3%) patients had nodal metastasis; 22.5% had invasion into the paranasal sinuses; 47.5% had T4 with T1, T2 and T3 stages being 18.8%, 17.5% and 7.5%, respectively at time of diagnosis. Ninety percent of the cases had a diagnosis of nasopharyngeal carcinoma on imaging, but 10% were given alternative diagnosis (16).

Nasopharyngeal carcinoma is anatomically deep and occurs close to important neurovascular structures making surgical resection very difficult. Thus, the mainstay strategies for treatment of

NPC are radiotherapy-based, comprehensive therapies, including concurrent chemoradiotherapy, as well as induction or adjuvant chemotherapy and palliative chemotherapy following radiotherapy
(17).

The 2020 National Comprehensive Cancer Network (NCCN) states that the standard of care for the treatment of stage I NPC is radiotherapy and for nonmetastatic stage II-IV NPC, the treatment is concurrent chemo-radiotherapy with or without induction and adjuvant chemotherapy. For optimal RT, depending on different radiation fractionation techniques, a total dose of 66-70 Gy is needed for eradication of gross tumor and 44–63 Gy for elective treatment of potential sites at risk. For RT delivery, three dimensional RT is the minimum requirement, while intensity-modulated radiation therapy (IMRT) is the preferred approach in expert centers. Neoadjuvant chemotherapy is sometimes used to down-stage those locally advanced NPCs that cannot be encompassed readily within the radiation field without incurring significant risks to adjacent normal tissues. For metastatic NPC, the standard first-line therapy is a platinum-based 'doublet' that commonly consists of cisplatin or carboplatin in combination with one of the following drugs: 5-fluorouracil, gemcitabine, paclitaxel and docetaxel. Other drugs such as Capecitabine, Methotrexate and targeted agents like cetuximab, Nivolumab and pembrolizumab are also used (18).

Prognosis is affected by treatment approach, race, histological type, and disease stage [19–21]. According to a 5 year retrospective analysis of nasopharyngeal carcinoma done by Arthur *et al.* in China, clinical staging appeared to be the most important prognostic factor for NPC. As the stage number increases, both the 5-year OS and PFS significantly decrease. The 5-year overall survival rates for patients in stages I, II, III and IV were 66.7%, 55.6%, 41.8% and 25.9%, respectively (P=0.026), while the respective 5-year progression-free survival (PFS) rates were 60.0%, 51.1%, 36.6% and 18.6% (P=0.044). Age was also found to be an independent prognostic factor with age less than 50-years stated as a good prognostic factor (22). This Chinese study further revealed that females have favorable prognostic factors demonstrating that gender is a major factor in the incidence of NPC and slightly indicative of an independent prognostic factor affecting overall survival (OS) and progression free survival (PFS). The occurrence of NPC in males is 2-3 times higher than that in females; this is similar to two other studies [23,24].

Similarly, in a retrospective Japanese study, patients with non-keratinizing NPC (WHO Types III and II) were found to have higher 5-year OS and PFS rates than those with the keratinizing type (WHO Type I) (23). A retrospective study conducted in Malaysia showed that the risk of death was 1.97 times greater in patients with WHO Types I and II NPC than in patients with type III (25).

The Retrospective Analysis of 5-Year Survival Rate of Nasopharyngeal Carcinoma by Arthur *et al.* also showed that patients with stages I or II NPC will likely not benefit from the addition of chemotherapy, in terms of long-term survival and PFS (22). However, for patients with stage III NPC, adding chemotherapy can improve PFS to a certain degree though it may not improve OS and in patients with stage IV NPC, the addition of chemotherapy can significantly prolong both OS and PFS [22,26].

A retrospective analysis by Chua *et al*. also found that radiotherapy combined with induction chemotherapy resulted in only a mild improvement in PFS and in the relapse rate and no improvement in OS when compared with radiotherapy alone (27). A phase III clinical trial conducted in patients with locally advanced NPC in China showed that adding adjuvant chemotherapy did not result in improved OS or relapse-free survival when compared with using concurrent chemo-radiotherapy (28).

Aliyu *et al*. studied the treatment outcome of patients with nasopharyngeal carcinoma treated with CCRT in Nigeria. During the analysis stage, only the 2-year survival analysis was carried out due to the high rate of loss to follow up among patients after 2 years. With 2-year follow up, compliance of approximately 75% was obtained in this study, whereas the follow-up compliance decreased to 20% after 5 years. The log–rank test showed a significant association between the stage of the disease at presentation and the overall 2-year survival ($P<0.0001$). Patients with stage II disease survived more than those with stages III and IV, with a 24-month survival rate of 58%, 52%, and 20%, respectively. Patients with nonkeratinizing differentiated carcinoma had a higher overall disease-free survival rate, followed by patients with keratinizing squamous cell carcinoma. Although the majority of the patients were diagnosed with non-keratinizing undifferentiated carcinoma, this condition was associated with a relatively poor survival rate.

Age, sex and radiotherapy dose were also independent prognostic factors for the overall survival of patients

(29).

A related study was done by Siti-Azrin et al. on the median survival and overall five-year survival rate of 134 patients who took radiotherapy and chemotherapy. The overall median survival time was found to be 31.30 months (95%CI: 23.76, 38.84) and the 5 year Overall survival was 38.0% (95% confidence interval (CI): 29.1, 46.9). The median survival of NPC patients was significantly longer for age ≤50 years, no cranial nerve involvement, and early stage and is dependent on treatment modalities (30).

3. OBJECTIVES

3.1 General objective

- To assess clinicopathology, treatment patterns and median survival of nasopharyngeal carcinoma patients at Tikur Anbessa Specialized Hospital, Oncology Center.

3.2 Specific objectives:

- To describe the distribution of NPC patients by age, sex and region;
- To determine the clinical stages of NPC patients at diagnosis;
- To identify the histological patterns of NPC patients at diagnosis;
- To describe the pattern of treatment delivered to NPC patients at TASH;
- To evaluate the waiting time of NPC patients to get chemotherapy and/or radiotherapy;
- To determine the median survival of NPC patients treated at Oncology Center of TASH and
- To assess factors that determine the median survival.

4. METHODS

4.1 Study area

The study area was the Oncology Department of School of Medicine, College of Health Sciences,

Addis Ababa University (AAU) located in the premises of Tikur Anbessa Specialized Hospital, Addis Ababa, Ethiopia. The department was established in 1990 G.C and currently has an

outpatient department (OPD), inpatient ward with 28 beds, daycare chemotherapy, and radiotherapy facilities. It has two cobalt-60 External beam radiotherapy machines, of which only one iwas functional at the time of the study and one Co-60 source HDR brachytherapy machine. The center also performs three-dimensional (3D) radiotherapy planning and virtual simulation under CT scan. It has installed a linear accelerator machine (LINAC) which was undergoing acceptance and commissioning test during the conduct of this study.

4.2 Study design

An institution based retrospective cohort study design was used.

4.3 Source of data

Data was collected from patient registration log books, patients' charts and radiotherapy treatment sheets. Patient survival was assessed by directly contacting the patients or their close attendants using the phone numbers registered on their respective charts after asking for their consent. At least three phone calls were attempted (two on weekends and one on weekday) before a call was labeled 'unanswered'.

4.4 Source population

The source population was cancer cases treated at the Oncology Department of TASH.

4.5 Study population

The study population was histopathologically confirmed cases of NPC that were treated at the Oncology Department of TASH from September 11, 2014 and September 10, 2017.

4.6 Inclusion criteria

All histopathologically confirmed NPC cases.

4.7 Exclusion criteria

1. Incomplete charts (if no card number, age, sex, residency, phone number)
2. Diagnosis not confirmed by histopathology
3. Nasopharyngeal hematolymphoid tumors, soft tissue neoplasms, salivary gland type tumors, bone and cartilage tumors, secondary tumors or nasopharyngeal benign tumors. 4. Cancers of two or more primary sites

4.8 Variables

4.8.1 Dependent variable

- Median survival

4.8.2 Independent variable

- Age at diagnosis
- Sex
- Histopathology types
- Clinical stage of cancers at diagnosis (Both TNM and Group stage).
- Performance status (ECOG)
- Treatment pattern (chemotherapy, radiotherapy, surgery or their combinations)

4.9 Sample size determination

All NPC patients who were treated at the Oncology Department of TASH from September 11, 2014 to September 10, 2017 and fulfilled the inclusion criteria were considered in the study without the need to do a separate sample size calculation.

4.10 Data collection tool and procedure

A team was formed consisting of two chart finders from the chart room; two data collecting oncology residents and one supervisor. They received two days training from the primary investigator concerning the purpose and the goal of the study and data extraction techniques for the data collecting residents. Pretesting of the data extraction format was performed by the principal investigator along with the data collectors prior to the actual study on 10% of the nasopharyngeal patient's charts which were not included in the study. Appropriate modification was made based on the pre-test result. The chart numbers of all NPC patients in the study period were selected from the HMIS record and were given to the chart finders. They collected all the charts and those charts that were not in accordance with the inclusion criteria were discarded by the supervisor. The filled review checklist was collected on daily basis and checked for completeness by the supervisor. The principal investigator also ensured that each form was filled

correctly by the data collectors and the supervisor. There were regular discussions with the principal investigator/supervisor and data collectors during the data collection process.

4.11 Operational definitions

Clinical Diagnosis and staging: Diagnosis with nasopharyngeal fiberoptic examination, FNAC and physical examination, imaging with CT scan, MRI, Ultrasound, X-ray and others.

ECOG Performance Status: Eastern cooperative oncology Group is a scale used to assess how patient's disease is progressing, assess how the disease affects the daily living abilities of the patient, and determine appropriate treatment and prognosis and is developed by the Eastern Cooperative Oncology Group.

Follow-up period: The period from the date of diagnosis until death or until the last follow-up time. Patients with disease recurrence, progression, and those that were lost to follow up were considered to have died on the day of their last follow-up.

Group stage: this explains the combined score of T, N & M stages (T describes the size of the tumor and any spread of cancer into nearby tissue; N describes spread of cancer to nearby lymph nodes; and M describes metastasis or the spread of cancer to other parts of the body).

Histology grade: is a description of a tumor based on how abnormal cancer cell and tissue look under a microscope and how quickly the cancer cells are likely to grow and spread.

Histopathology: refers to microscopic study of tissue from biopsy or surgical specimen.

Nasopharyngeal carcinoma (NPC): a tumor arising from the epithelium of the nasopharynx.

Metastatic disease (M1) - the presence of the disease outside of the nasopharyngeal anatomy and regional lymph nodes at presentation or follow-up.

Median survival: The time at which the survival curve crosses 50% survival.

Overall survival (OS): The time from diagnosis to the time of death from any cause. The cut-off time for patients who survived will be defined as the day of a phone call made to confirm their alive status, date of death or as the time of last visit if phone calls were not answered.

Optimal Radical Radiotherapy Dose: A total dose of 66-70 Gy given for eradication of nasopharyngeal gross tumor and 44–63 Gy for elective treatment of potential sites at risk depending on different radiation fractionation techniques. Those below this dose range are suboptimal Radical Radiation doses.

Palliative Radiotherapy: Radiotherapy given for palliating symptoms with dose usually <30Gy.

Palliative Treatment: Treatment given to relieve the symptoms and reduce the suffering caused by cancer.

Radical Treatment: Vigorous treatment that aims at the complete cure of a disease rather than the mere relief of symptoms.

Progression-free survival (PFS): Referrers to the time from the start of treatment until recurrence, disease progression or death from any cause. The cut-off time for the cases without disease progression was defined as the time of last visit.

Treatment patterns: Treatment types given including surgery, radiotherapy, chemotherapy or combination of two or more of these treatment options in a certain order.

4.12 Data processing and Analysis

The data collected was analyzed using SPSS statistics software version 26 (SPSS Inc., Chicago, IL). Basic descriptive analyses like frequency, mean, median, percentile and Quartile ranks were used. Binary logistic regression was done for variables having two possible outcomes, and also chi-square test was done for test of association using level of significance set at 5%. The survival analysis was done only in those patients who have received the treatment and this was correlated to other factors using Kaplan–Meier method and comparison between two survival curves was done using log-rank test. The results were considered statistically significant at P value < 0.05.

4.13 Ethical Consideration

Ethical clearance for the proposed study was obtained from the department's Institutional Review Board. All data collectors were informed to respect the data confidentiality throughout the study and the data were used only for the purpose of the proposed study.

5. RESULTS

5.1 Socio-demographic characteristics

A total of 170 patients with pathologically confirmed diagnosis of NPC were identified in the specified period from the Oncology Department's Health Management Information System (HMIS) index data. Of these, 136 patients were found to be eligible for the study. Out of the 136 patients, men accounted for 92 (67.6%) and women were 44 (32.4%) of the cases. The ratio of male to female in this study was (2:1). Of these patients, 97 (71.3%) of them were above the age of 50. Majority of the study participants were married, 75 (55.1%) [Table 1]. The mean age of patients was 37.73 ±17.7 SD years old. The youngest patient was 12 and the oldest was 80 years old. In terms of regional distribution, majority of the patients, 45 (33.1%) were from Oromia region followed by Addis Ababa, 35 (25.7%) [Figure 1].

Table 1: Socio-demographic characteristics of Nasopharyngeal carcinoma patients treated at the Oncology Department of Tikur Anbessa Specialized Hospital between September 11, 2014 and September 10, 2017, Addis Ababa, Ethiopia (n= 136)

Demographic character		**Frequency**	**Percent**
Sex	Male	92	67.6
	Female	44	32.4
Age group	Below 50 years old	97	71.3
	50 and above years old	39	28.7
Marital status	Divorced	2	1.5
	Married	75	55.1
	Single	49	36.0
	Unknown	10	7.4

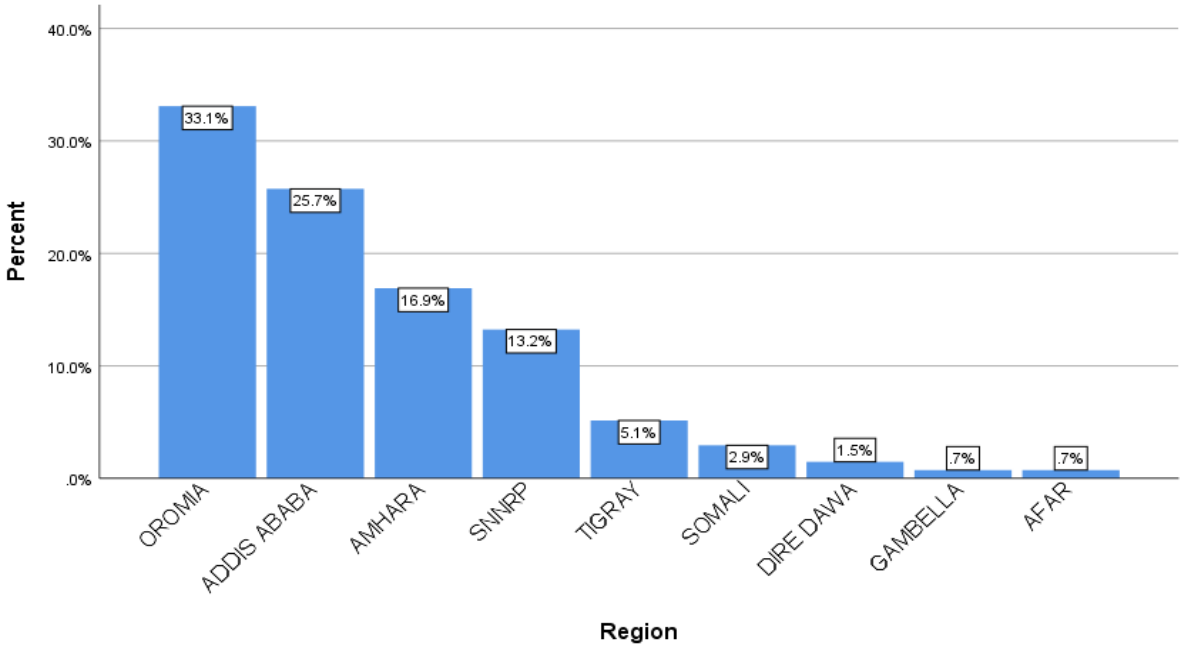

Figure 1: Distribution of Nasopharyngeal carcinoma patients treated at the Oncology Department of Tikur Anbessa Specialized Hospital between September 11, 2014 and September 10, 2017 by regions and city administrations (n=136).

5.2 Clinicopathologic data

Of the 136 patients, 79 (58.1%) presented with duration of symptoms lasting for more than 6 months. The commonest symptoms at presentation were neck swelling (n=121, 89%), nasal obstruction (n=86, 63.2%) and Epistaxis (n=45, 33.1%). Of the 136 patients, 101 (74.3%) had ECOG performance of 1. In almost all, 133 (97.8%), cases, source of diagnosis was from both pathology and imaging [Table 2]. The clinical staging showed majority of the patients had locally advanced disease at diagnosis. For instance, 68 (50%) of the patients were stage IVA. The commonest T stage was T4 accounting for 63 (46.3%), and 62 (45.6%) of them had N2 disease. 123 (90.4%) of the patients had no metastasis (M0) at the time of presentation [Figure 2]. The commonest site of metastasis was bone 6 (4.3%) located mainly on the vertebral bone. The next common sites of metastasis were the liver and the lungs, each composed of 2.2% [Table 2].

Table 2: Description of clinicopathology of nasopharyngeal carcinoma patients treated at the Oncology Department of Tikur Anbessa Specialized Hospital between September 11, 2014 and September 10, 2017, Addis Ababa, Ethiopia (n= 136).

Variables	**Categories**	**Frequency (%)**
Duration of symptom	Six months and below	57 (41.9%)
	More than six months	79 (58.1%)
Source of diagnosis	Both pathology and imaging	133 (97.8%)
	Pathology from lymph node	3 (2.2%)
Neck swelling	No	15 (11.0%)
	Yes	121 (89.0%)
Nasal obstruction	No	50 (36.8%)
	Yes	86 (63.2%)
Epistaxis	No	91 (66.9%)
	Yes	45 (33.1%)
Headache	No	99 (72.8%)
	Yes	37 (27.2%)
Ear complaint	No	109 (80.1%)
	Yes	27 (19.9%)
Vision complaint	No	121 (89.0%)
	Yes	15 (11.0%)
Voice change	No	126 (92.6%)
	Yes	10 (7.4%)
Dysphagia	No	121 (89.0%)
	Yes	15 (11.0%)
ECOG performance	None	5 (3.7%)
	One	101 (74.3%)
	Two	25 (18.4%)
	Three	5 (3.7%)
Site of metastasis	No	123 (90.4%)
	Liver	3 (2.2%)
	Lung	3 (2.2%)
	Vertebra, Femoral, Iliac, Humeral bone	6 (4.3%)
	Pleura	1 (0.7%)

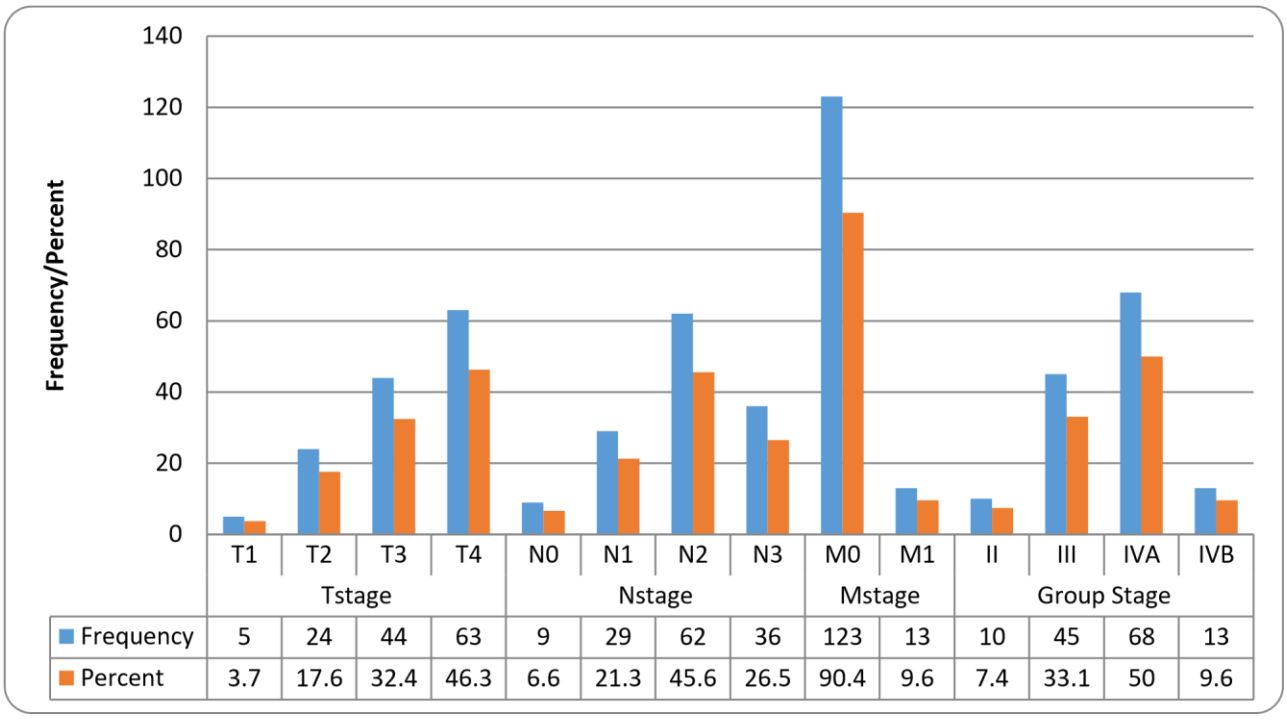

Figure 2. The distribution by TNM and Group stage at diagnosis of nasopharyngeal cancer patients treated at the Oncology Department of Tikur Anbessa Specialized Hospital between September 11, 2014 and September 10, 2017, Addis Ababa, Ethiopia (n= 136).

5.3 Histologic Types

From this study, we found that 77 (56.6%) of the biopsies were taken from Lymph nodes. 36 (26.5%) of the lymph node pathologies showed secondary carcinoma from nasopharynx and 32 (23.5%) showed secondary undifferentiated carcinoma [Figure 3]. The rest of the biopsies were taken from the Nasopharynx and the commonest subtype was undifferentiated carcinoma (30, 22.1%) followed by keratinizing squamous cell carcinoma (18, 13.2%) and non-keratinizing carcinoma (11, 8.1%) with no basaloid subtype identified [Figure 3].

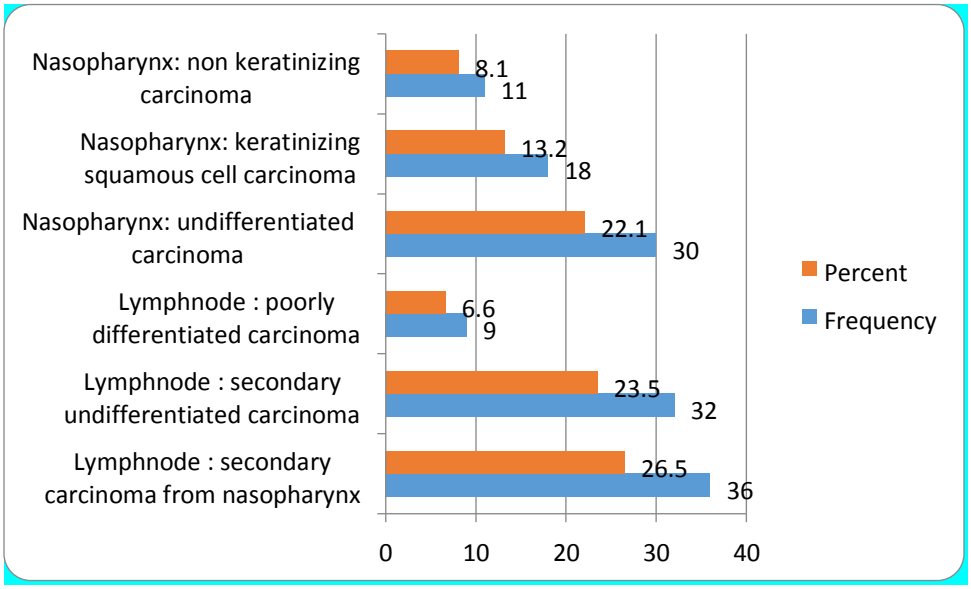

Figure 3: Histological types of nasopharyngeal carcinoma patients treated at the Oncology Department of Tikur Anbessa Specialized Hospital between September 11, 2014 and September 10, 2017, Addis Ababa, Ethiopia (n= 136).

5.4 Treatment pattern

Among the 136 nasopharyngeal carcinoma patients, 32 (23.5%) didn't receive any chemotherapy or radiotherapy treatment. Of those who received treatment, 86 (63.2%) received treatment in the form of radical approach and the rest, 18 (13.2%) received palliative treatment. Sixty one (44.9%) of the patients didn't receive any form of radiotherapy. Of those who received RT, 30 (22.1%) received adequate radical RT dose of ≥ 66 Gy, 27 (19.9%) with inadequate radical dose of 40-65 Gy and 18 (13.2%) the palliative doses of ≤ 30 Gy [Table 3].

Of those patients who received treatment, 10 (7.3%) received upfront CCRT followed with or without CT, while 23 (16.9%) received induction CT before receiving CCRT. Twenty four (17.6%) patients had induction followed by radical RT without concurrent CT; 3 (2.2%) patients received CCRT followed by Adjuvant CT; 26 (19.1%) patients received induction CT only; 11 (8%) patients received both palliative CT and palliative RT, while 4 (2.9%) received palliative RT only and 3 (2.2%) received palliative CT only. Of those who took chemotherapy for radical or palliative reason, the commonest chemotherapy regimen was Cisplatin/5FU 54 (39.7%) followed by Cisplatin/Paclitaxel 35 (25.7%). Carboplatin/Paclitaxel was only used in 3 (2.2%) patients and about 44 (32.4%) patients had no chemotherapy. [Table 3].

The median time gap between first presentation to the hospital and initiation of any form of RT was 8.4 ± 4.9 SD months, and 8 months for radical RT and 5.7 months for palliative RT [Table 4]. The median time gap between first presentation and commencement of any form of CT was 3.3 months with 3.5 months for palliative CT and 2.9 month for radical CT [Table 5]. After completion of primary treatment, 65 (47.8%) of the patients didn't have any follow up recorded on their charts. Of those who had follow up, the average number of follow up they had was 4 [Table 4].

Table 3. The pattern of treatment delivered for patients with nasopharyngeal carcinoma presented to the Oncology Department of Tikur Anbessa Specialized Hospital between September 11, 2014 and September 10, 2017, Addis Ababa, Ethiopia (n= 136).

Variables	**Categories**	**Frequency**	**Percent**
Treatment Received	No treatment	32 (23.5%)	
	Palliative	18 (13.2%)	
	Radical	86 (63.2%)	
Type of Treatment received	CCRT	6	4.4
	CCRT+ Adjuvant CT	3	2.2
	CCRT+ Palliative CT	1	0.7
	Induction CT	26	19.1
	INDUCTION CT+ CCRT	23	16.9
	INDUCTION CT+ RT	24	17.6
	INDUCTION CT+ PALLIATIVE RT	3	2.2
	PALLIATIVE RT	4	2.9
	PALLIATIVE CT	3	2.2
	PALLIATIVE CT + PALLIATIVE RT	11	8
	NO TREATMENT	32	23.5
Type of Chemotherapy	Cisplatin/ 5FU	54	39.7
	Cisplatin /paclitaxel	35	25.7
	Carboplatin/ paclitaxel	3	2.2
	No	44	32.4
RT dose	No	61	44.9
	≤ 30 Gy (Palliative)	18	13.2
	40-65 Gy (Suboptimal radical)	27	19.9
	≥ 66 Gy (Optimal radical)	30	22.1
	Total	**136**	**100.0**

Table 4: The pattern of treatment and the time gap for starting treatment for patients with nasopharyngeal carcinoma presented to the Oncology Department of Tikur Anbessa Specialized Hospital between September 11, 2014 and September 10, 2017, Addis Ababa, Ethiopia (n= 136).

	Date of starting treatment (months)	Time gap of starting Chemotherapy (months)	Time gap of starting RT (months)	No of follow up (In days)
Mean	4.3	4.4	7.3	25.8
Median	3.2	3.3	8.4	23.3
Std. Deviation	3.6	3.7	4.9	14.1
Minimum	0.5	0.5	0.5	4.7
Maximum	15.9	15.9	25.1	51.7

Table 5: The mean and Median time gap in months from presentation to Tikur Anbessa Specialized Hospital, Oncology department and starting either RT or CT in the form of palliative and radical intent.

		Time gap of starting RT (months)	**Time gap of starting CT (months)**
Palliative Intent	Mean	6.2	4.4
	Median	**5.7**	**3.5**
Radical Intent	Mean	8.8	3.9
	Median	**8.0**	**2.9**

5.5 Survival analysis

After 23.3 months of median follow up, 81 (59.6%) were dead at the time of data collection with 95% CI (51.5, 67.6) and 55 (40.4%) of the patients were alive with 95% CI (32.4, 48.5) [Figure 4]. Specifically, 48 (35.3%) of the patients were alive with no recurrence and 7 (5.1%) with distant recurrences [Table 7]. The median survival was 33 months [Figure 4].

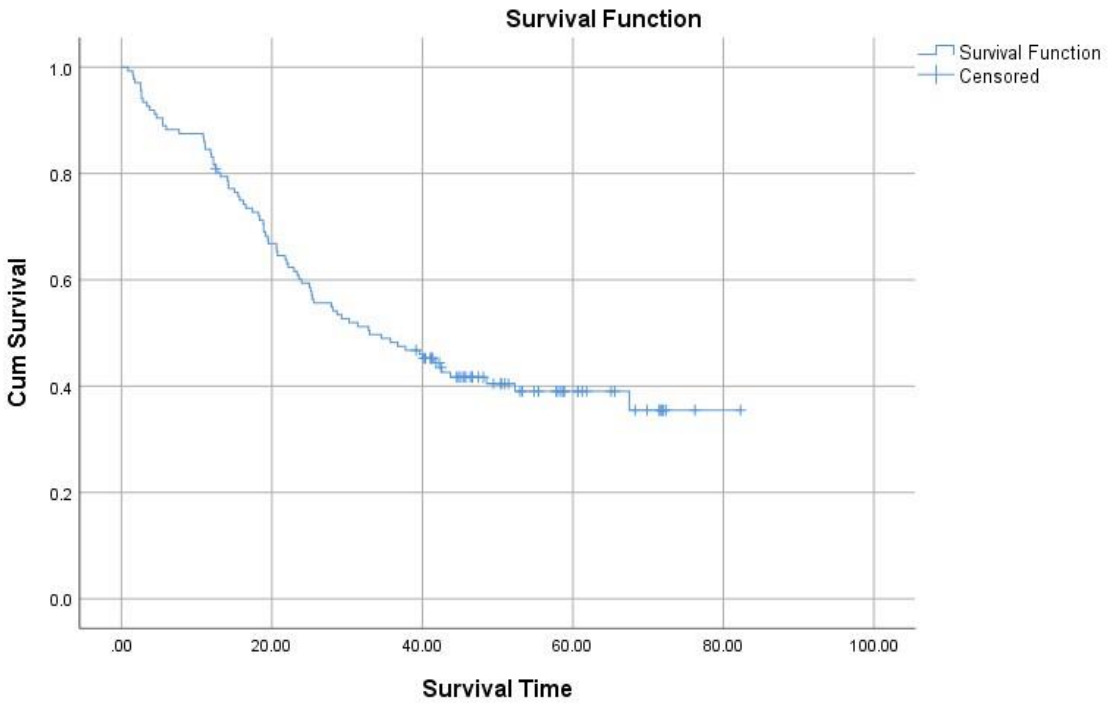

Figure 4. Kaplan Meier Plot for survival function in months of nasopharyngeal carcinoma patients presented to the Oncology Department of Tikur Anbessa Specialized Hospital between September 11, 2014 and September 10, 2017, Addis Ababa, Ethiopia (n= 136).

Mean and Median for Survival Time							
Mean[a]				Median			
Estimate	Std. Error	95% Confidence Interval		Estimate	Std. Error	95% Confidence Interval	
		Lower Bound	Upper Bound			Lower Bound	Upper Bound
44.1	2.8	38.6	49.5	33.0	6.1	21.1	44.9
a. Estimation is limited to the largest survival time if it is censored.							

5.6 Association of survival with variables

We have entered all variables into bivariate cox regression and selected those variables that were found to have association with survival fit for the final model. Group stage was not passed for multivariate analysis as its p value was 0.25.

5.6.1 **Survival based on Type of Treatment**

In this specific study, the median survival was 33 months with 95% CI (21.1, 44.9) and overall survival rate of 30.39% with 95% CI (20.74, 40.05).

The median survival was only 14.65 months for those with no treatment. The median of survival was 47.18 months for those who took radical treatment and 32.72 months for those who took palliative treatment. The survival time of radical treatment was 3.2 times and 1.4 times higher from patients without treatment and palliative treatment respectively [Figure 5 and Table 6].

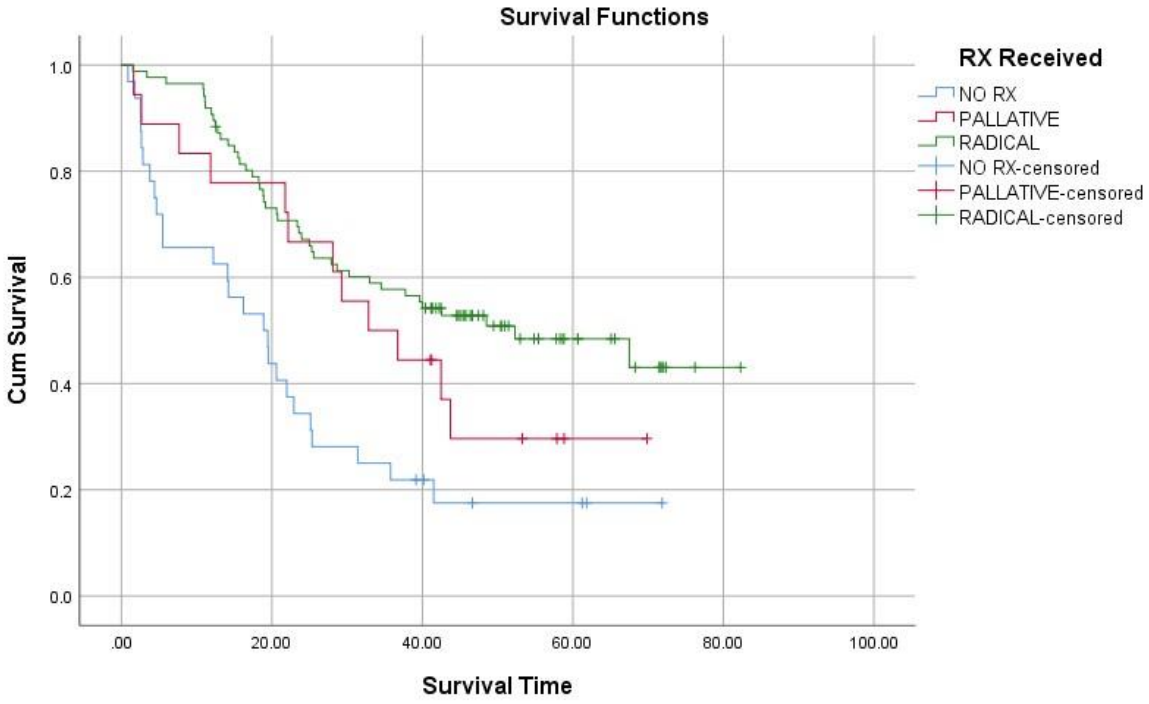

Figure 5: The survival analysis compared to the type of treatment of patients with nasopharyngeal carcinoma presented to the Oncology Department of Tikur Anbessa Specialized Hospital between September 11, 2014 and September 10, 2017, Addis Ababa, Ethiopia (n= 136).

Table 6. The survival analysis based on type of treatment in patients with nasopharyngeal carcinoma presented to the Oncology Department of Tikur Anbessa Specialized Hospital between September 11, 2014 and September 10, 2017, Addis Ababa, Ethiopia (n= 136).

RX received/ Age	Median survival			
	Estimate (month)	Std. Error	95% Confidence Interval	
			Lower Bound (month)	Upper Bound (month)
Overall survival	30.39	4.93	20.74	40.05
Median survival	32.986	6.085	21.059	44.913
No treatment	14.65	3.25	8.28	21.03
Palliative	32.72	9.2	14.69	50.75
Radical	47.18	3.4	43.78	50.58
< 50 years old	41.495	10.834	20.259	62.730
≥ 50 years old	22.177	1.702	18.840	25.513

5.6.2 **Survival and pattern of treatment**

Significant difference was obtained between CCRT and induction CT (P= 0.014). The survival time for CCRT was 22 months more as compared to induction CT only. RT with induction CT had significantly less survival time as compared to all and on the contrary CCRT + Adjuvant CT has been significantly increasing the survival time of patients. The survival time for CCRT+ Adjuvant CT was 5.3, 27.3 and 13.7 months more as compared to CCRT, Induction CT and Induction CT+CCRT, respectively [Figure 6 and 7].

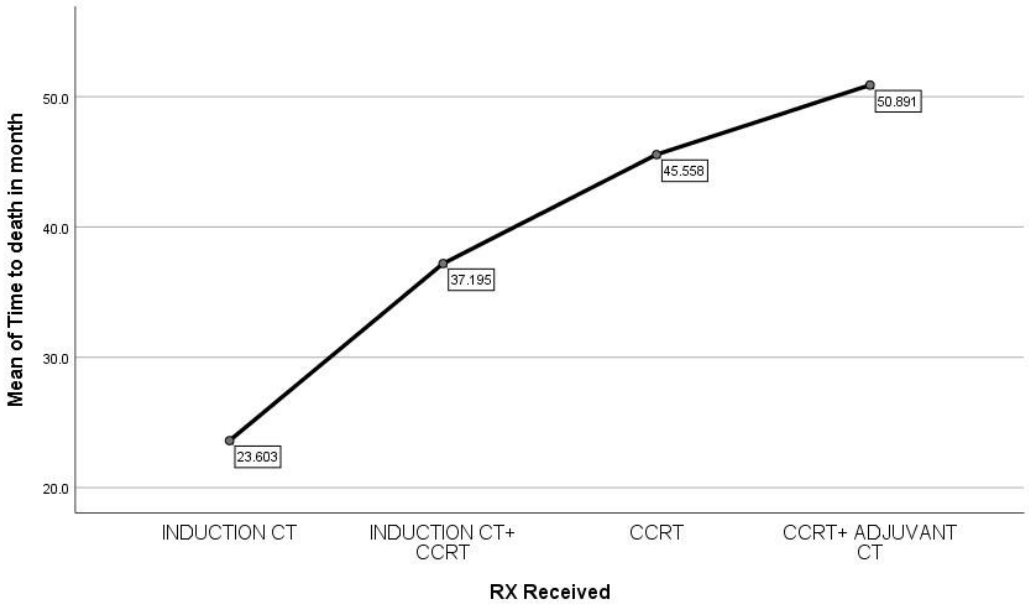

Figure 6: The survival of patients with nasopharyngeal carcinoma with different patterns of treatment presented to the Oncology Department of Tikur Anbessa Specialized Hospital between September 11, 2014 and September 10, 2017, Addis Ababa, Ethiopia (n= 136).

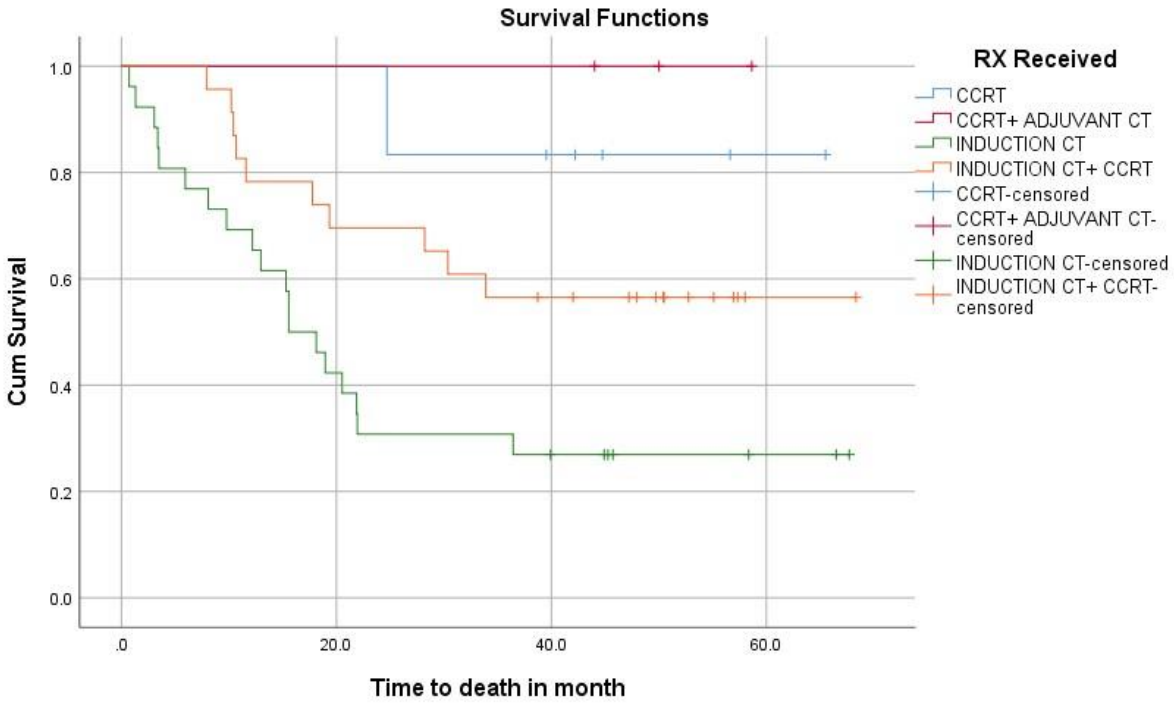

Figure 7: The survival analysis of patients with nasopharyngeal carcinoma presented to the Oncology Department of Tikur Anbessa Specialized Hospital between September 11, 2014 and September 10, 2017 compared to their treatment patterns, Addis Ababa, Ethiopia (n= 136).

5.6.3 **Miscellaneous factors associated with survival**

Based on multivariate Cox regression analysis, age, histology, RT dose, N staging were found to have significant impact on survival ($p < 0.05$) while sex, duration of symptoms, T and M staging, ECOG and group stages were found to be statistically insignificant.

Patient who had no RT dose (AOR: 4.98, 95%CI: 2.25-11.03) were 4.98 times significantly more likely to die as compared to those who received more than 66 Gy (adequate radical). Similarly, patients who had palliative RT dose were 4.3 times more likely (AOR: 4.3, 95%CI: 1.51-12.28) to die more quickly as compared to those who received more than 66 Gy (adequate radical) [Table
7].

Histology group was also significantly associated with survival time. Nasopharynx: keratinizing squamous cell carcinoma has 4.02 times less survival time as compared to Nasopharynx: undifferentiated carcinoma (AOR: 4.02, 95% CI: 1.74, 9.24).
N0 or patients with no nodal metastasis were associated with 5.66 times increased in death rate than N3 (AOR: 5.66, 95% CI (1.80, 17.79).

In the current study, age was affecting the survival time of patients. The result shows that those patients whose age were 50 and above (22 months) were almost surviving half of those whose ages were under 50 years old (41.5 months).

Table 7: Multivariate Cox regression analysis of variables of nasopharyngeal cancer patients presented to the Oncology Department of Tikur Anbessa Specialized Hospital between September 11, 2014 and September 10, 2017, Addis Ababa, Ethiopia (n= 136).

Variables	Current status		COR (95%CI)	AOR (95%CI)	P
	Alive	Dead			
Age					
Below 50 years old	45 (46.4)	52 (53.6)	0.57 (0.36-0.91)	0.55 (0.31-0.98)	**0.04***
50 and above years old	10 (25.6)	29 (74.4)	1	1	
Sex					
Female	18 (40.9)	26 (59.1)	0.84 (0.52-1.33)	1.29 (0.75-2.22)	0.36
Male	37 (40.2)	55 (59.8)	1	1	
Duration of symptoms (months)					
<= 6 months	21 (36.8)	36 (63.2)	1.15 (0.74-1.78)	0.83 (0.48-1.44)	0.50
More than 6 months	34 (43)	45 (57)	1	1	
T Stage					0.20
T1	2 (40)	3 (60)	1.02 (0.32-3.31)	2.73 (0.71-10.53)	0.14
T2	9 (37.5)	15 (62.5)	0.89 (0.49-1.61)	0.58 (0.27-1.24)	0.16
T3	21 (47.7)	23 (52.3)	0.80 (0.48-1.33)	1.01 (0.52-1.98)	0.97
T4	23 (36.5)	40 (63.5)	1	1	
N Stage					**0.02***
N0	0 (0)	9 (100)	2.56 (1.17-5.60)	5.66 (1.80-17.79)	0.00
N1	13 (44.8)	16 (55.2)	0.99 (0.52-1.89)	1.02 (0.46-2.25)	0.96
N2	28 (45.2)	34 (54.8)	0.97 (0.57-1.67)	1.28 (0.67-2.46)	0.45
N3	14 (38.9)	22 (61.1)	1	1	
M Stage					
M0	50 (40.7)	73 (59.3)	0.96 (0.46-2.00)	2.30 (0.91-5.84)	0.08
M1	5 (38.5)	8 (61.5)	1	1	
Histology groups					**0.03***
Lymph node: poorly differentiated carcinoma	3 (33.3)	6 (66.7)	1.26 (0.49-3.22)	1.19 (0.40-3.55)	0.76
Lymph node: secondary carcinoma from nasopharynx	15 (41.7)	21 (58.3)	1.17 (0.61-2.25)	1.55 (0.68-3.55)	0.30
Lymph node: secondary undifferentiated carcinoma	16 (50)	16 (50)	0.86 (0.43-1.71)	1.14 (0.48-2.73)	0.77
Nasopharynx: keratinizing squamous cell carcinoma	2 (11.1)	16 (88.9)	1.84 (0.92-3.68)	4.02 (1.74-9.24)	0.00
Nasopharynx: non keratinizing carcinoma	5 (45.5)	6 (54.5)	1.01 (0.40-2.59)	1.54 (0.52-4.59)	0.44
Nasopharynx: undifferentiated carcinoma	14 (46.7)	16 (53.3)	1	1	
ECOG					0.06

0	2 (40)	3 (60)	0.24 (0.06-1.00)	0.71 (0.13-3.85)	0.69
1	40 (39.6)	61 (60.4)	0.24 (0.10-0.61)	0.27 (0.09-0.86)	0.03
2	13 (52)	12 (48)	0.19 (0.07-0.55)	0.23 (0.06-0.82)	0.02
3	0 (0)	5 (100)	1	1	
RT dose					**<0.001***
No	15 (24.6)	46 (75.4)	3.57 (1.80-7.09)	4.98 (2.25-11.03)	0.00
Palliative	5 (27.8)	13 (72.2)	2.54 (1.11-5.79)	4.30 (1.51-12.28)	0.01
40-65 (Inadequate radical)	15 (55.6)	12 (44.4)	1.16 (0.50-2.69)	0.47 (0.17-1.31)	0.15
≥66 (Adequate radical)	20 (66.7)	10 (33.3)	1	1	
Group Stage					0.325
II	2 (20)	8 (80)	1.50 (0.56_3.99)	2.4 (0.42-13.162)	0.325
III	24 (53.3)	21 (46.7)	0.71 (0.31_1.59)	2.0 (0.7-5.72)	0.195
IVA	24 (35.3)	44 (64.7)	1.08 (0.51_2.30)	3.0 (0.84-10.38)	0.092
IVB	5 (38.5)	8 (61.5)	1	1	

Footnote: * (star) implies significant variables at 0.05 level of significance

6. DISCUSSION

Out of the 136 patients, men accounted for 92 (67.6%) and women 44 (32.4%) of the cases. The ratio of male to female in this study was (2:1) which is similar to the study done in Nigeria and China (22,29). In the current study, 97 (71.3%) of the patients were above the age of 50 similar to a study conducted by Sun et al. evaluating the prevalence of nasopharyngeal carcinoma across multiple institutions around the world including Chinese, non-Hispanic White, Black, and Filipino populations where patients above the age 50 constituted 64.9% (15).

The finding of average time of presentation of symptoms being 6 months (IQR 8) and the commonest T and N stages being T4 with 63 (46.3%), and N2 with 62 (45.6%) patients, respectively, which was similar with a retrospective study done on Imaging Patterns at Tikur Anbessa Specialized Hospital (16). Another study in Malaysia also found similar T4 stages in 48.1% of patients at presentation (30). Abdullah et al. reported the possible factors of late presentation of NPC include delay in seeking medical advice, confusing nature of presenting symptoms, difficult nature of clinical examination and silent spread of submucosal lesion with normal nasopharynx (31). For this, prospective study is needed to justify the above-mentioned reasons.

The commonest symptoms at presentation were neck swelling in 121 (89%), Nasal obstruction in 86 (63.2%) of patients. This was found to be similar in another related study by Siti-Azrin the commonest initial clinical symptoms were neck swelling 61 (73%) and Nasal complaints in 60% (30).

Major site of metastasis in our study was bone 6 (4.3%), common site being the vertebral bone. This was comparable to a related study conducted in Nigeria where just 11 (6.3%) patients were presented with metastatic disease of which 6 had metastasis to the bones, of which the vertebrae were mostly affected (29).

In our study, 77 (56.6%) of the histology types were taken from lymph nodes showing 26.5% secondary carcinoma from nasopharynx, 23.5% lymph node: secondary undifferentiated carcinoma. The commonest histologies taken from nasopharynx subtype were undifferentiated carcinoma (22.1%) followed by keratinizing squamous cell carcinoma (13.2%) and nonkeratinizing carcinoma (8.1%) and no basaloid subtype was identified. Similar to a study done by Aliyu *et al*., the highest number of cases (n=111, 69%) were patients with nonkeratinizing undifferentiated histology, 32 (20%) with keratinizing squamous cell carcinoma and 18 (11%) had the non-keratinizing differentiated type (29).

Majority of chemotherapy regimen used in the study period was Cisplatin/5FU 54 (39.7%) followed by Cisplatin/Paclitaxel 35 (25.7%) similar to a multi-institutional survey done in Japan on the effectiveness of chemotherapy combined with radiotherapy for patients with nasopharyngeal carcinoma (23). In this study, the proportion of patients who received radical RT were only 86 (63.2%) which is low since radiotherapy still remains the standard care for NPC treatment, either alone or in combination with chemotherapy (18). This could have affected the treatment outcome in our study. The reason could be due to the lack of radiotherapy centers and machines in Ethiopia resulting in the average time of 8.4 months gap between first presentations to the hospital and starting radiotherapy.

After a median follow up of 23.3 months, results from this retrospective cohort study showed that the overall median survival for the eligible 136 patients was 33 months with 95% CI (21.1, 44.9) and overall survival rate of 30.39% with 95% CI (20.74, 40.05). The magnitude of death was 59.6% with 95% CI (51.5, 67.6). Similar to this study, a hospital-based retrospective study was

conducted in Indonesia on the survival outcome and prognostic factors of patients with nasopharyngeal cancer which followed patients taking similar treatment like our study for a median time of 14.39 months and the median survival time for the whole cohort was 31.08 months (32).

Factors that were found to be significantly associated with survival were age, histology type, nodal stage, treatment pattern and dose of RT.

Our study showed that patients whose age was 50 and above were almost surviving half of those whose ages were under 50 years old which was found similar to a study done by Arthur *et al*. where age was found to be an independent prognostic factor with age less than 50-years stated as a good prognostic factor than > 50 yrs (22).

Histology group was found to have significant association with survival time. Nasopharynx: keratinizing squamous cell carcinoma had 3.94 times less survival time as compared to Nasopharynx: undifferentiated carcinoma (AOR: 3.94, 95% CI: 1.69, 9.18) which is similar to the study done by Aliyu *et al.* showing worse survival outcome in keratinizing than non-keratinizing histology (29). In another retrospective Japanese study, patients with the non-keratinizing type of NPC (WHO Types III and II) were found to have higher 5-year OS and PFS rates than those with the keratinizing type (WHO Type I) (23). A retrospective study conducted in Malaysia also showed that the risk of death was 1.97 times greater in patients with WHO Types I and II NPC than in patients with type III (25).N stage was also significantly affecting the survival time of patients with p-value of 0.01 which is found to be comparable to a study done by Phua *et al*. (25).

Patient who had no radical or palliative Radiotherapy (AOR: 5.43, 95%CI: 2.48, 11.89) were 5.43 times significantly more likely to die as compared to those who had more than 66GY. Similarly, patients who had palliative RT dose were 6 times more likely (AOR: 6.02, 95%CI: 2.16-16.77) to die quickly as compared to those who had more than 65 GY. A significant dose–response has been observed in the majority of retrospective studies, based on patients irradiated with 2-D techniques. Marks *et al.* and Vikram *et al*. showed that local control was significantly improved in patients who received >67 Gy to the tumor target (33,34). Similar finding was found in a study done in Nigeria where all patients included in the study received RT dose to the Gross tumor between 50

- 70 Gy. The dose had a prognostic significance in survival that a minimum dose of 66 Gy to the GTV had comparable and satisfactory 5-year survival rates of >75%. The radiation dose of ≤60 Gy had a worse response than those receiving doses >60 Gy (HR; 0.32 - 95% confidence interval 0.16,0.63; P < 0.001 (35,36).

Tumor staging was not significantly associated with survival in contrary to two similar studies conducted in China showing clinical staging to be the most important prognostic factor for NPC. As the stage number increases, both the 5-year OS and PFS significantly decrease (22,25,26). One of the trials, by Clemet *et al*. showed that the 5-year overall survival (OS) rates for patients in stages I, II, III and IV were 66.7%, 55.6%, 41.8% and 25.9%, respectively (P=0.026) (22).

Patients with ECOG 1 and 2 performance status were 65% and 77% less likely to die sooner than those with ECOG 3. This is similar to a study done in Indonesia where patients receiving similar pattern of treatment as the current study showed a significant association with ECOG status and survival that patients with ECOG 3 had a 4.6 times higher rate of mortality (HR: 4.668, 95%CI: 2.277 -9.57) than patients with ECOG of 1-2 (32).

The survival time for CCRT+Adjuvant CT was 5.3, 27.3 and 13.7 months more as compared to CCRT, Induction CT and Induction CT+CCRT, respectively. Intergroup trial 0099, a randomized phase III trial compared CCRT+Adjuvant CT vs RT alone in 185 patients with stages III & IV nasopharyngeal cancers, with the median follow-up of 2.7 years, the 3-year survival rate was 76%, and 46% (P <0.001), respectively (37). Although results of this trial cannot be directly compared to our study due to different study designs and use of post chemoradiation Adjuvant CT, the superiority of CCRT over RT alone has been clearly demonstrated.

In this, study, we observed that combined CT or RT treatment strategies had a better survival compared with no treatment. This was comparable to a study done by Hilda *et al*. which showed that compared with radiation alone or chemotherapy alone, a combination of chemotherapy and radiation either in a form of concurrent chemoradiotherapy (CCRT), sequential chemotherapy and radiation, or induction chemotherapy followed by CCRT demonstrated a better OS (time ratio/TR
3.108, 95% CI 1.274–4.942 and TR 2.531, 95% CI 1.829–3.233) (p values < 0.01) (32).

7. STRENGTHS AND LIMITATIONS OF THE STUDY

7.1 Strengths

- This is the first study to analyze all the treatment pattern and the median survival of nasopharyngeal carcinoma in Ethiopia.
- This study is done at Tikur Anbessa Specialized Hospital Radiotherapy Center which is the only radiotherapy center for the country and may represent the majority of the society of the country at large.
- We took all patients in the study time to increase the sample size which increases the representativeness of the results.

7.2 Limitations

- ✓ This is retrospective study which is less powerful than prospective study.
- ✓ The study didn't assess risk factors responsible for causing nasopharyngeal carcinoma.
- ✓ Associated confounding factors that might affect survival like diet and life style were not assessed.
- ✓ The study evaluated treatments performed using the outdated conventional (2D) radiotherapy.

8. CONCLUSIONS AND RECOMMENDATIONS

This study showed that nasopharyngeal cancers at Black Tikur Anbessa Specialized Hospital present at advanced stage of the disease. Most patients 57(41.9%) presented with symptoms lasting for more than 6 months. The median follow-up time was 23.3 months and the median survival was 33 months. Patients wait on average 3.24 months to get any treatment and of those, only 63.2% took radical treatment. Patients had to wait 8.4 months on average to take any form of radiation. Survival was also affected by age, histologic type, treatment pattern, intake and radiotherapy and the nodal status. However, in the current study sex, Tumor stage, metastasis, group stage, duration of symptoms and waiting time to treatment were not significantly affecting the survival time. The government and other stakeholders should give due attention and work on expanding cancer centers in the country to increase the quality of health care in early diagnosis and treatment of nasopharyngeal carcinoma.

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Annex

ANNEX I: DATA EXTRACTION TOOLS

Demographic data

Serial No	Variable	Category
1.	MRN	
2.	Phone number	
3.	AGE	
4.	GENDER	1. MALE 2. FEMALE
5.	REGION	1. OROMIA 2. AMHARA 3. TIGRAY 4. SNNPR 5. ADDIS ABEBA 6. DIRE DAWA 7. HARARI 8. SOMALI 9. GAMBELA 10. BENISHANGUL GUMUZ 11. AFAR

6.	**Marital Status**	**1. SINGLE** **2. MARRIED** **3. DIVORCED** **4. SEPARATED**
		5. WIDOWED 6. UNSPECIFIED
Clinicopathologic Data		
1.	**DATE OF FIRST DIAGNOSIS (DD/MM/YY)**	
2.	**DATE OF FIRST VISIT TO ONCOLOGY (DD/MM/YY)**	
3.	**SOURCE OF DIAGNOSIS**	**1. PATHOLOGY FROM NASOPHARYNX** **2. PATHOLOGY FROM NECK LYMPHNODE** **3. PATHOLOGY FROM BOTH** **4. IMAGING** **5. BOTH IMAGING AND PATHOLOGY** **6. OTHER (PLEASE SPECIFY)**
4.	**HISTOLOGICAL TYPES**	**1.WHO GRADE I** **SQUAMOUS CELL CARCINOMA**

		0 **2. WHO GRADE II** **KERATINIZING UNDIFFERENTIATED CARCINOMA** **3. WHO GRADE III** **NON KERATINIZING UNDIFFERENTIATED CARCINOMA** **4. LYMPHNODE: POORLY DIFFERENTIATED CARCINOMA**
		5. NASOPHARYNGEAL CARCINOMA **6. LYMPHNODE: SECONDARY CARCINOMA FROM NASOPHARYNX** **7. LYMPHNODE : UNDIFFERENTIATED CARCINOMA** **8. Others (please specify).**
5.	**CLINICAL SYMPTOM AT PRESENTATION** **NECK SWELLING**	**1. YES 2. NO**
6.	**NASAL OBSTRUCTION**	**1. YES 2. NO**
7.	**EPITAXIES**	**1. YES 2. NO**
8.	**HEADACHE**	**1. YES 2. NO**
9.	**HEARING COMPLAINT**	**1. YES 2. NO**
10.	**VISION COMPLAINT**	**1. YES 2. NO**
11.	**DYSPHAGIA**	**1. YES 2. NO**
12.	**VOICE CHANGE**	**1. YES 2. NO**

13.	**Duration of Symptoms**	
14.	**TUMOR (T)STAGE at diagnosis**	**1. TX** **2. T1** **3. T2** **4. T3** **5. T4**
15.	**N STAGE at diagnosis**	**1. NX** **2. N0**
		3. N1 **4. N2** **5. N3**
16.	**M STAGE at diagnosis**	**1. MO 2. M1 3.Mx**
17.	**IF THERE IS METASTASIS, WHAT'S THE SITE OF METASTASIS?**	**1. BONE** **2. LIVER** **3. LUNG** **4. BRAIN** **5. OTHER SITE**

18.	**GROUP STAGE (8th AJCC)**	**1. I** **2. II** **3. III** **4. IVA** **5. IVB** **6. IVC**
19.	**PERFORMANCE STATUS (ECOG)**	**1. 0** **2. I** **3. II** **4. III** **5. IV** **6. Unknown**
20.	**TREATMENT RECEIVED**	**<u>CURATIVE</u>** **1. INDUCTION CT ONLY** **2. INDUCTION CT + CCRT**

		3. INDUCTION CT + RT **4. CCRT+ ACT 5. RT ALONE** **<u>PALLIATIVE</u>** **6. PALLATIVE CT** **7. PALLATIVE RT** **8. NO RX** **9. INDUCTION CT+ PALLATIVE RT** **10. INDUCTION CT+ PALLATIVE RT** **11. OTHER (PLEASE SPECIFY)**
21.	**IF CHEMOTHERAPHY WAS TAKEN SPECIFY THE TYPE OF CT**	**1. CISPLATIN /5FU** **2. CARBOPLATIN/5FU** **3. CISPLATIN/PACLITAXEL** **4. CARBOPLATIN/PACLITAXEL** **5. CISPLATIN/GEMCITABINE** **6. TPF** **7. AT LEAST 2 OF THE ABOVE** **8. OTHER (PLEASE SPECIFY)** **9. NO CT**
22.	**IF PATIENT RECEIVED RT, WHATS THE DOSE RECEIVED IN GY?**	

23.	**TIME GAP BETWEEN DIAGNOSIS AT ONCOLOGY DEPARTMENT**	
	AND FIRST TREATMENT (CT /RT) (IN MONTHS)	
24.	**Day of start of RT**	
25.	**NO OF FOLLOW UPS AFTER RX COMPLITION**	
26.	**LAST FOLLOW UP TIME (SPECIFIED IN MONTHS FROM FIRST DIAGNOSIS)**	
27.	**CURRENT STATUS** **(PLEASE MENTION THE DATES BASED ON THE LAST KNOWN STATUS OF THE PATIENT)**	**1.ALIVE WITHOUT RECURRENCE** **2.ALIVE WITH LOCAL-REGIONAL RECURRENCE** **3. ALIVE WITH DISTANT METASTASIS** **4. DEAD**
28.	**IF THERE IS RECURRENCE, MENTION THE SITE OF RECURRENCE.**	
29.	**DATE OF DATA COLLECTION (DD/MM/YY)**	

ANNEX II: CONSENT FORM AND INTERVIEW GUIDE

My name is Dr. Ruth Shimeles and I am a final year Oncology resident at the College of Health Sciences, Addis Ababa University. I am currently working on a research titled "THE CLINICOPATHOLOGY, TREATMENT PATTERN AND SURVIVAL OF NASOPHARYNGEAL CARCINOMA PATIENTS AT TIKUR ANBESSA SPECIALIZED HOSPITAL, ONCOLOGY DEPARTMENT, ADDIS ABABA, ETHIOPIA." This research is intended to study the clinicopathology, treatment pattern and survival of nasopharyngeal carcinoma patients treated at Tikur Anbessa Specialized Hospital, Oncology center, Addis Ababa, Ethiopia. The study will be conducted through reviewing secondary data from patients' medical charts, log books and radiotherapy treatment sheets. The data extraction will be performed by two trained oncology residents working in the cancer treatment center of Tikur Anbessa specialized hospital. The study also involves communicating patients/family members through phone call to check the current health status of patients. The

Information you provide and the data extracted from patients' medical charts will be treated with strict confidentiality. Moreover, no personal identifiers will be used on data collection form. The study will provide important information for governmental and non-governmental organizations which work in the area of non-communicable diseases specifically on nasopharyngeal carcinoma at national and regional levels that could possibly help to improve the oncology service in the country. I am thus contacting you to request your willingness for a brief interview to discuss about your current health status (in case the interviewee is the patients) or your family member's health status who has been a patient of nasopharyngeal carcinoma (in case interviewee is family member). Your participation is voluntary and you may refuse to participate in the interview or choose to stop the interview at any time.

Do you agree for the interview?

YES ☐ NO ☐ If yes, continue with the interview.

1. What is the current health status of the patient?

   Follow up: If patient's health has improved, encourage the patient to maintain healthy life style.

   If patient's health has deteriorated, encourage the patient to visit the oncology center for follow up.
2. If the patient has passed away, console with the family member for their loss and ask when the patient passed away?

Thank the interviewee and finish the interview.

ANNEX III: TNM STAGING FOR NASOPHARYNGEAL CARCINOMA

American Joint Committee on Cancer (AJCC)
TNM Staging System for the Nasopharynx (8th ed., 2017)
(The following types of cancer are not included: Mucosal melanoma, lymphoma, sarcoma of the soft tissue, bone and cartilage.)

Primary Tumor (T)

TX	Primary tumor cannot be assessed
T0	No tumor identified, but EBV-positive cervical node(s) involvement
Tis	Carcinoma *in situ*
T1	Tumor confined to nasopharynx, or extension to oropharynx and/or nasal cavity without parapharyngeal involvement
T2	Tumor with extension to parapharyngeal space, and/or adjacent soft tissue involvement (medial pterygoid, lateral pterygoid, prevertebral muscles)
T3	Tumor with infiltration of bony structures at skull base, cervical vertebra, pterygoid structures, and/or paranasal sinuses
T4	Tumor with intracranial extension, involvement of cranial nerves, hypopharynx, orbit, parotid gland, and/ or extensive soft tissue infiltration beyond the lateral surface of the lateral pterygoid muscle

Regional Lymph Nodes (N)

NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Unilateral metastasis in cervical lymph node(s) and/or unilateral or bilateral metastasis in retropharyngeal lymph node(s), 6 cm or smaller in greatest dimension, above the caudal border of cricoid cartilage
N2	Bilateral metastasis in cervical lymph node(s), 6 cm or smaller in greatest dimension, above the caudal border of cricoid cartilage
N3	Unilateral or bilateral metastasis in cervical lymph node(s), larger than 6 cm in greatest dimension, and/or extension below the caudal border of cricoid cartilage

Distant Metastasis (M)

M0	No distant metastasis
M1	Distant metastasis

Histologic Grade (G)
A grading system is not used for NPCs.

Anatomic Stage/Prognostic Groups

Stage 0	Tis	N0	M0
Stage I	T1	N0	M0
Stage II	T0,T1	N1	M0
	T2	N0,N1	M0
Stage III	T0,T1,T2	N2	M0
	T3	N0,N1,N2	M0
Stage IVA	T4	N0,N1,N2	M0
	Any T	N3	M0
Stage IVB	Any T	Any N	M1

ANNEX IV: ECOG PERFORMANCE STATUS

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

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

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

ANNEX V: ASSURANCE OF THE INVESTIGATOR

I, the undersigned Clinical Oncology Resident agree to accept responsibility for the scientific, ethical and technical conduct of the research project and for provision of required progress reports as per terms and conditions of the research and publications office of the Addis Ababa University.

Name of the Investigator: Dr. Ruth Shimeles (4th Year Clinical Oncology Resident)

Signature_____ Date_____/_____/_____

APPROVAL OF THE PRIMARY ADVISOR

Advisor's Name:

Signature_____ Date _____/_____/_____

Evaluator's Name:

Signature_____ Date _____/_____/_____