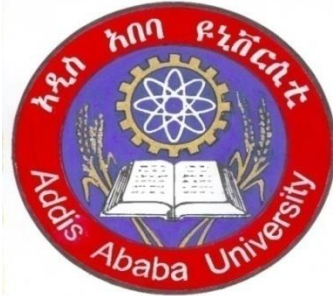


SURVIVAL OF NONMETASTATIC NASOPHARYNGEAL CANCER PATIENTS TREATED RADICALLY BY TWO DIMENSIONAL EXTERNAL BEAM RADIOTHERAPY AT TIKUR ANBESSA SPECIALIZED HOSPITAL, RADIOTHERAPY CENTER, ADDIS ABABA, ETHIOPIA, 2020: A RETROSPECTIVE COHORT STUDY



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ABSTRACT

Introduction: Globally, an estimated 51,000 deaths from nasopharyngeal carcinoma were reported in 2012. In Africa, 8700 new nasopharyngeal cancer cases and 5500 deaths occurred in 2008. A 22 months median survival was seen in post concurrent chemoradiation Nigerian cases and two year cure rate of 16% was achieved in East African post radiotherapy cases. There are no, however, data on survival of nonmetastatic nasopharyngeal cancer in Ethiopia.

Objective: To examine survival time of non-metastatic nasopharyngeal cancer patients treated radically by concurrent chemoradiation using 2 dimensional external beam radiotherapy at Tikur Anbessa Specialized Hospital, Radiotherapy Center, Ethiopia, 2020.

Methodology: A retrospective cohort study was conducted among all nonmetastatic nasopharyngeal cancer cases treated radically by 2 dimensional external beam radiotherapy from January 2013 to August 2018 at Tikur Anbessa Specialized Hospital, Radiotherapy center. Descriptive and frequency analysis was done to calculate mean, median, standard deviation and percentile. Kaplan meier analysis was used for survival analysis. Bivariate and multivariate cox regression done to assess association between dependent and independent variables. Multicollinearity test ($T < 0.1$, $VIF < 10$) was assessed among the variables with significant association on multivariate cox regression.

Results: Mean age at diagnosis was 33 ± 16 years. Most patients (97.1%) presented with loco-regionally advanced disease. The median survival was 31 months with 95% CI (27, 35) & overall survival rate of 37.9% after 31 months of median follow up. Patients who took 4 cycles of concurrent chemotherapy were more likely to have longer survival with Crude Hazard Ratio of 0.28, 95% CI (0.11, 0.72). Post treatment recurrence, distant metastasis or bone metastasis were associated with lower survival on multivariate cox regression.

Conclusion/recommendation: Although the median overall survival outcome of our patients (37.9%) was low as compared to most reports of developed countries, it might be acceptable given the higher stages of most patients, technique of treatment delivery & long waiting list for treatment. So, we should design a policy to increase public awareness & expand cancer centers to increase access to recent treatment modalities.

Key words: non- metastatic nasopharyngeal cancer, locoregional, patterns of treatments, survival, Tikur Anbessa Specialized Hospital, Ethiopia.

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ABBREVIATIONS AND ACRONYMS

AAU	Addis Ababa University
AC	Adjuvant Chemotherapy
ACS	American Cancer Society
AJCC	American Joint Committee on Cancer
CCRT	Concurrent Chemo Radiotherapy
CHR	Crude Hazard Ratio
CHS	College of Health Science
CI	Confidence Interval
Co-60	Cobalt 60
CXR	Chest X-Ray
CT	Computed Tomography
DM	Diabetes Mellitus
EBRT	External Beam Radiotherapy
EBV	Epstein Bar Virus
ECOG	Eastern Cooperative Oncology Group
FMOH	Federal Ministry of Health
FNAC	Fine Needle Aspiration Cytology
5 – FU	5 Fluorouracil
GLOBOCAN	Global Burden of Cancer
Gy	Gray
HR	Hazard Ratio
HTN	Hypertension
IC	Induction Chemotherapy
LRC	Loco-regional Control
MeV	Mega electro volt
MRI	Magnetic Resonance Imaging
NCD	Non-Communicable Disease
NMNPC	Non-metastatic Nasopharyngeal Cancer
NPC	Nasopharyngeal Cancer

OS	Overall Survival
PFS	Progression Free Survival
RT	Radiotherapy
RTOG	Radiation Therapy Oncology Group
RVI	Retro Viral Infection
SPH	School of Public Health
SPSS	Statistical Package for Social Science
TASH	Tikur Anbessa Specialized Hospital
TNM	Tumor Size, Nodal involvement, Metastasis
UICC	Union of International Cancer Control
WHO	World Health Organization

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CHAPTER ONE: INTRODUCTION

1.1 Background

Nasopharyngeal cancer (NPC) is a relatively rare disease with worldwide incidence of 1.2 per 100,000 (1.7 per 100,000 in men and 0.7 per 100,000 in women), and the standardized mortality rate is 0.7 per 100,000. But, there is geographic variation in its distribution. About 81% of the new cases occur in Asia and 9% in Africa; the rest are from elsewhere in the world. Southeast Asian countries account for 67% of the global burden of cancer. The disease is more common in Southern China, Micronesia/Polynesia, Eastern Asia, and North Africa. The lowest incidence of NPC has been reported from the United States of America and Europe, accounting for less than 1% of all cases of cancer (1-4). In Africa, Kenya, Tunisia and Algeria have higher incidences than non-Mongolian races. In a review of articles on cancer burden in Africa, largely based on the Global Burden of cancer (GLOBOCAN) 2008 data estimates, 8700 incident NPC cases and 5500 deaths occurred in 2008. The male to female ratio was 2:1. The highest incidence rates were in the Republic of South Africa, Morocco, Tunisia & Algeria (4-8).

NPC is the most common malignant tumor arising from the nasopharynx. The most important risk factors for nasopharyngeal cancer include: Epstein-Barr virus (EBV), heredity, presence of weak human leukocyte antigen (HLA) allele, salt-preserved fish, cigarette smoking, alcohol consumption, exposure to wood dust, low socioeconomic status and history of respiratory diseases. Fruit and vegetable consumption is known as a protective agent for this cancer. Although its etiology remains unclear, the EBV, also called human herpes virus, is evidently associated with endemic Burkitt's lymphoma and the undifferentiated form of NPC, which is characterized by the presence of EBV encoded early Ribonucleic Acids (RNAs) in nearly all tumor cells (4,9).

Histopathologically, NPC is classified into 3 types according to the World Health Organization (WHO) classification, 2005 edition: (i) keratinizing squamous cell carcinoma, which is characterized by intracellular keratin formation; (ii) nonkeratinizing carcinoma, which is characterized by the total absence of keratin formation, and further classified into differentiated and undifferentiated subtypes; and (iii) basaloid squamous cell carcinoma, which is characterized by closely packed cells forming a lobular or palisading pattern with a focal squamous cell component. NPC rapidly spreads through the rich lymphatic vessels of the head and neck region,

and to contiguous structures, including the cranial nerves. Due to the aforementioned and early metastatic nature of the disease, radiotherapy (RT) is considered the primary treatment, and adjuvant chemotherapy (AC) as a supportive modality to improve patient response (9).

The treatment of these malignancies vary based on stage of the tumor, the availability of facility and expertise in the treating center & performance status of the patient. Patients with T1,No,Mo disease should be treated with definitive RT alone. Currently available evidence shows trends favoring the addition of chemotherapy to concurrent chemoradiotherapy (CCRT) in patients with loco-regionally advanced NPC; however, it remains unclear whether to administer chemotherapy to these patients before or after CCRT (10-12).

Like other centers, treatment delivered in Black Lion Hospital Radiotherapy center is based on the stage of the disease and performance status of the patient. Because of limited resources and long waiting list for upfront RT, majority of the patients received chemotherapy as induction chemotherapy (IC) or palliative therapy. RT or CCRT is also delivered based on the indications.

1.2 Statement of the problem

Even though NPC is a relatively rare malignancy worldwide, it has a significantly higher incidence in endemic areas like Southern China (20–50/100 000 person-years). The survival rates also vary among patients depending on differences in geographic regions worldwide, stage of the disease at presentation, histological subtype, radiotherapy dose & age (9).

From our routine observation, most of our NPC patients have locoregional advanced disease at presentation. In a retrospective analysis of 80 patients with newly diagnosed NPC who came to Tikur Anbessa Specialized Hospital (TASH) from January 2016 to August 2017, the average time of presentation of symptoms was interquartile range [IQR 8] months. 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 being 18.8%, 17.5% and 7.5% stage respectively at time of diagnosis (13). The possible reasons for late stages of the disease may be: lack of adequate awareness of our society on cancer, lack of nearby cancer centers, economic problems and social stigma on cancer patients.

In addition to this, even after they get referred to TASH, which is the only radiotherapy center in the country; they wait for months before starting RT. In a retrospective cross sectional study of 1,823 patients of different cancer types treated with cobalt RT in Black Lion Hospital, Addis Ababa, Ethiopia, from May 2015 through January 2018, the wait times were the shortest for

short palliative treatment cases (median, 0 days; [IQR], 0-15 days; n = 1,138), whereas wait times were long for patients who received radical/curative treatment (median, 150 days; IQR, 60-210 days; n = 685) (14).

Despite the seemingly significant numbers of nonmetastatic nasopharyngeal cancer (NMNPC) patients getting treated in TASH, there is no data showing outcome of such cases in this center and even in Ethiopia. Therefore, knowing the survival outcome of these groups of patients is important & in fact, this retrospective cohort study will help to determine the overall survival (OS) of NMNPC cases treated radically by CCRT using 2D EBRT in TASH.

1.3 Significances of the Study

There is lack of awareness on NPC in Ethiopia. So, this study will be used as an input by policy makers and concerned bodies to increase awareness on NMNPC and then improve their patterns of care. This in turn helps for evidence based decision making, prioritizing, designing and initiating interventions at facility level. Additionally, this study will add information to the already existing literature and used as a base line for further research on NPC cases.

CHAPTER TWO: LITERATURE REVIEW

2.1 Epidemiology of Nasopharyngeal Cancer

Nasopharyngeal cancer, a rare cancer arising from a cuboidal structure called the nasopharynx, accounting for 0.6% of all cancers diagnosed worldwide in 2012(1). However, there are areas of the world with endemic disease; global incidence rates are highest in Southeast Asia (especially southern China), Micronesia/Polynesia, Eastern Asia, and North Africa(1, 2). In Africa, Kenya, Tunisia and Algeria have higher incidences than non-Mongolian races. As to GLOBOCAN 2008 data estimates, there were 8700 incident NPC cases and 5500 deaths occurred in 2008, with the highest incidence rates being in the Republic of South Africa, Morocco, Tunisia & Algeria(5-8).

Rates are 2 to 3 times higher in men than in women. NPC is one of the head and neck cancers with the highest propensities to metastasize to distant sites. Regional recurrences are uncommon, occurring only in 10% to 19% of the cases(15, 16).

Non-communicable diseases (NCDs) are now responsible for the majority of global deaths. And cancer is expected to rank as the leading cause of death and the single most important barrier to increasing life expectancy in every country of the world in the 21st century. According to estimates from the World Health Organization(WHO) in 2015, cancer is the first or second leading cause of death before age70 years in 91 of 172 countries, and it ranks third or fourth in an additional 22Countries(GLOBOCAN2018) (17).Based on estimates of cancer incidence in Ethiopia in 2015 using population based registry data, it was estimated that 21,563 (95% CI, 17,416 to 25,660) and 42,722 (95% CI, 37,412 to 48,040) incident cancer cases were diagnosed in males and females, respectively. The most common adult cancers were: cancers of the breast and cervix, colorectal cancer, non-Hodgkin lymphoma, leukemia, and cancers of the prostate, thyroid, lung, stomach, and liver (18).

In Ethiopia, the real burden of NPC and its treatment outcomes including survival are not yet studied. Some of the literatures with regard to treatment and outcome of NMNPCs conducted in different parts of the world are mentioned below.

2.2. Survival of non-metastatic nasopharyngeal cancer

In 1998, in the landmark intergroup study 0099, the Southwest Oncology Group (SWOG) coordinated an intergroup study with the participation of Radiation Therapy Oncology Group

(RTOG), and Eastern Cooperative Oncology Group (ECOG). This randomized phase III trial compared chemotherapy plus EBRT versus EBRT alone in patients with NPCs and was closed early when an interim analysis disclosed a significant survival advantage favoring the chemoradiation group. It was the first of its kind that proved the benefit of chemotherapy on progression free survival and overall survival(19). The addition of chemotherapy also decreased local, regional and distant recurrence rates.

Subsequent randomized phase III trials in Asia confirmed that concurrent chemoradiation increased survival as compared to RT alone (20-23). In one of these trials, 5 year OS was 70% versus 59% in the CCRT group and RT alone groups respectively (20). The randomized study conducted in Singapore, which was modeled after the Intergroup 0099 treatment regimen, also demonstrated the benefit of adding chemotherapy to RT. In this study, adjuvant Cisplatin/5FU (5-Fluorouracil) regimen was added after Cisplatin based chemoradiation and appeared to decrease toxicity while still increasing antitumor effect (22). In contrary to this, a phase III randomized trial from China comparing Cisplatin/RT with (or without) adjuvant Cisplatin/5FU demonstrated that adjuvant chemotherapy did not show significant improvement in survival following CCRT (HR, 0.74; 95% CI, 0.49-1.10; p= 0.13) (24).

Both adjuvant chemotherapy (AC) following CCRT and CCRT without AC were associated with better OS (HR, 0.65; 95% CI, 0.56-0.76 and HR, 0.80; 95% CI, 0.70-0.93 respectively) and progression free survival (PFS) (HR, 0.62; 95% CI, 0.53-0.72 and HR, 0.81; 95% CI, 0.71-0.92, respectively) in an individual patient data meta-analysis (25) which included 19 trials and 4806 patients with NMNPC. However, differences between the included studies assessing CCRT with and without adjuvant chemotherapy (eg. Different length of follow up, fewer patients with stage II disease in trials assessing adjuvant chemotherapy) limited the ability to make a firm conclusion regarding the efficacy of one treatment modality over the other. The relative benefit of additional chemotherapy over CCRT alone was demonstrated in a network meta-analysis based on this individual patient data meta-analysis of all chemotherapy (25) (including 20 trials and 5144 patients), where all randomized trials of radiotherapy with or without chemotherapy in NMNPC were considered. The three treatments with the highest probability of benefit on overall survival (OS) were CCRT-AC, followed by CCRT and IC-CCRT, with respective hazard ratios (HRs [95% CIs]) compared with RT alone of 0.65 (0.56 to 0.75), 0.77 (0.64 to 0.92), and 0.81 (0.63 to 1.04). HRs (95% CIs) of CCRT-AC compared with CCRT for OS, progression-free

survival (PFS), locoregional control (LRC), and distant control (DC) were, respectively, 0.85 (0.68 to 1.05), 0.81 (0.66 to 0.98), 0.70 (0.48 to 1.02), and 0.87 (0.61 to 1.25). IC-CCRT ranked second for PFS and the best for DC. CCRT never ranked first. HRs of CCRT compared with IC-CCRT for OS, PFS, LRC, and DC were, respectively, 0.95 (0.72 to 1.25), 1.13 (0.88 to 1.46), 1.05 (0.70 to 1.59), and 1.55 (0.94 to 2.56). Regimens with more chemotherapy were associated with increased risk of acute toxicity. In conclusion, the addition of AC to CCRT achieved the highest survival benefit and consistent improvement for all end points. The addition of IC to CCRT achieved the highest effect on DC. And the authors argued that more chemotherapy in addition to CCRT could reduce recurrence rates (25, 26).

As to the currently available evidences, there is a trend favoring the addition of chemotherapy to CCRT. However, it remains unclear whether to administer chemotherapy before or after CCRT (26, 28).

In a retrospective study of outcome of nasopharyngeal carcinoma cases treated by radical concurrent chemoradiotherapy using cisplatin and 5-FU, at the University College Hospital, Ibadan, Nigeria, between 2000 and 2009 in Nigeria, a total of 161 patients were included in the analysis, of which 113 (70%) were men and 48 (30%) were women. The mean age of the patients was 41.7 years (range 15–89 years). Ten (6.3%) patients presented with early-stage disease, whereas 149 (93.7%) had late-stage disease. The median survival time was 22 months, and the overall disease-free survival rates were 67% and 46% at 12 and 24 months, respectively. Late side-effects included chronic otitis ($n = 21$, 13.2%), change in voice ($n = 11$, 6.8%), trismus ($n = 7$, 4.4%), neck and facial edema ($n = 27$, 16.7%), and neck fibrosis ($n = 8$, 4.9%). The treatment outcome in this study is worse than in previous studies in developed countries. This is likely because most patients presented with late-stage disease (9).

In a study of RT of NPC cases, conducted between late 1968 & 1970, in Kenyatta National Hospital, Kenya, 64 East African patients were treated by RT. The primary site of the tumor received, in most cases, a dose of 55 to 67 Gy in 30 to 55 days and the cervical region received 45 to 65 Gy during the same time. Both the primary tumor and the neck were irradiated daily during 5 days per week. The primary site was irradiated by 2 lateral opposing fields, sometimes supplemented by one anterior field. The neck region was usually irradiated by two large anterior and posterior opposing fields. About 40 Gy of prophylactic RT was also given to the

mediastinum and both axillae in most patients. They were observed for 1 to 3 years. The minimum cure rates in the total series after 1 & 2 years were 31% and 16% respectively (29).

CHAPTER THREE: OBJECTIVE

3.1 General objective

- To determine the survival outcome of non-metastatic nasopharyngeal cancer patients treated radically by 2 dimensional external beam radiotherapy at Tikur Anbessa Specialized Hospital, Radiotherapy Center, Ethiopia, 2020.

CHAPTER FOUR: METHODOLOGY

4.1 Study area and period

The study area was at Addis Ababa University (AAU), Tikur Anbessa specialized Hospital, oncology department, which is found in Addis Ababa city administration, Addis Ababa, Ethiopia. The department was established in 1990 G.C serving its referral and non-referral services. It has outpatient department, 18 beds for inpatient, day care chemotherapy, and RT facility. It has two cobalt-60 EBRT (External Beam Radiotherapy) machines and one brachytherapy machine which are in use. The center also started Computed Tomography (CT) scan simulation and installed linear accelerator machine (LINAC). Data collection period for this study was from March 2020 to August 2020.



Black Lion Hospital, Addis Ababa, houses Ethiopia's only cancer referral centre

Figure 1: Study area (Black lion hospital, Addis Ababa, houses of Ethiopia's only radiotherapy center)

4.2 Study design

A hospital based retrospective cohort study was employed from secondary data recorded in the time period from January 2013 to August 2018.

4.3 Source population

All histopathologically confirmed cases of NMNPC treated radically by concurrent CCRT, using 2D EBRT (2 Dimensional External Beam Radiotherapy) at TASH, Radiotherapy Center

4.5 Study population

All histopathologically confirmed cases of nonmetastatic nasopharyngeal cancer treated radically by CCRT using 2D EBRT at TASH, Radiotherapy Center during January 2013 to August 2018.

4.6 Inclusion criteria

All histopathologically confirmed NMNPC cases registered and radically treated by CCRT using 2D EBRT at TASH, radiotherapy center from 2013 to August 2018.

4.7 Exclusion criteria:

- ✓ Incomplete charts (if no age, sex, region, residency, card number)
- ✓ Poor performance status (if ECOG is not 0-2)
- ✓ Cancers of two or more primary sites
- ✓ If patients are absent from follow up for more than 6 months & cannot be reached on phone call

4.8 Sample size determination

The sample size required for this study included all NMNPC patients treated radically by CCRT using 2D EBRT during January 2013 to August 2018.

For sample size determination, we used a single proportion formula

$$\text{Sample Size} = n_1 = \frac{(Z_{\alpha/2})^2 P(1-P)}{d^2}$$

n = minimum sample size required for the study

Z = standard normal distribution with confidence interval of 95%, Z = 1.96

d = Absolute precision or tolerable margin of error (d = 0.05)

P = is the proportion (P) value of Nasopharyngeal cancer in Ethiopia according GLOBOCAN 2018, which is 0.9

$$\text{Sample Size} = (1.96^2 \times 0.9(1-0.9)) / 0.05^2 = \mathbf{138}$$

According to GLOBOCAN 2018, the total number of new cases of NPC diagnosed in 2018 was 608. This is less than 10,000 which requires correction formula

When sample size is less than 10,000, we use a correction formula called Cochran's Formula.

$$n_2 = n / 1 + (n-1)/N = 138 / 1 + ((138-1)/608)$$

$$n_2 = \mathbf{113}$$

Considering 10% incomplete charts the final sample size will be

$$N_{\text{final}} = n_2 + 10 \% (n_2) = 113 + 10 \% (113) = \mathbf{124} \text{ patients}$$

4.9 Sampling procedure

Patient chart numbers and names registered from January 2013 to August 2018 were identified from log books. These charts were collected from chart room. As all NPC cases are registered together, the eligible charts were selected for data source after reviewing all charts. After identifying all eligible medical cards, all were counted as the final desired sample size.

4.10 Data collection tool and procedure

Data was collected by using pretested structured checklist. The data collecting team consisted of two chart finders from chart room, two data collector oncology residents and one supervising oncology resident.

4.11 Data Quality assurance

Pretest was done on 10% of the sample to evaluate the data collection tool for further modification of checklist prior to actual data collection. Appropriate modification was taken based on the pretest results. One day training was given to the data collectors and chart finders by the principal investigator (PI). The training covered the study objective through the review of the checklist, how to extract data. For completeness and consistency of the daily collected data, it was checked every night after data collection by the supervisors.

4.12 Data processing and Analysis

Data was coded and entered to the Epidemiological Data (EPI- Data) version 3.1 computer software package and the soft copy was compared with the hard copy for data consistency. Then cross checking and cleaning was done. Finally cleaned data was exported to Statistical Package for Social Sciences (SPSS) version 25 software packages for analysis. First descriptive statistics of the study variables was done. Proportion and frequency were used to represent results of categorical variables. Mean and Standard deviation were used to represent continuous variables after normality of distribution checked and for those non-normally distributed population median and inter-quartile range was reported. Chi-square test was conducted to determine if there were adequate cell counts for each categorical variable. Kaplan Meier was used to estimate median

survival time, cumulative probability of survival. Log-rank test was also used to compare statistical survival difference between categories of different explanatory variables.

4.13 Ethical Consideration

Ethical approval was obtained from Addis Ababa University, School of public health, office of research ethical committee before conducting the study. Consent from medical director and cancer treatment center focal person of Black Lion Hospital was obtained. Confidentiality was ensured by keeping all the information obtained in strict confidence throughout the study by excluding names as identification in the data extraction form and by using only for purpose of the study.

4.14 Dissemination of Result

Upon accomplishment, the findings of this study were submitted and presented to oncology department, Addis Ababa University College of Health Science. The result will also be disseminated for those organizations that are engaging on activities related to area of the study like that of Federal Ministry of Health (FMOH). The document will also be presented to school of public health cancer research groups, NCDs department, in different meetings, seminars. It will be published in peer reviewed journals so that it could be used as a reference.

4.15 Operational definitions

Clinical stage: staging with physical examination and imaging like CT scan, ultrasound, endoscopy, MRI, X-ray and others.

Overall Survival (Time to death): the overall survival time from the date of first presentation in the clinic with the histological diagnosis of nasopharyngeal carcinoma to the date of death, or date of last follow-up visit for patients who are absent on phone call (if it was within the last 6 months).

Median Overall Survival: the length of time from the date of first presentation with histological diagnosis of nasopharyngeal carcinoma that 50% of the patients in the group diagnosed with the disease is still alive.

Lost from follow up- if the patients did not have a follow up data on their medical charts for more than 6 months & were not reachable on phone call (the patients or their relatives)

Second line chemotherapy: the need for giving the patients palliative chemotherapy for either local or distant recurrence.

TNM stage: T (Tumor) describes the original or primary tumor extent, N (Node) tells whether the cancer has spread to nearby lymph nodes, and M (Metastasis) tells whether the cancer has spread to distant parts of the body.

5. RESULTS

5.1 Socio-demographic characteristics and comorbid illnesses of the patients

A total of 150 patients with a pathologically confirmed diagnosis of NPC were identified from Health Management Information System (HMIS) index data. Of these, 103 patients were found to be eligible for our study. Out of the 103 patients, men accounted for 73 (70.9%) of the cases and 30 (29.1%) were women. The mean age of patients was 33 ± 16 years. The majority of the cases (89.3%) were below the age of 55. The youngest patient was 11 years old & the oldest was 73 years old [Table 1].

In terms of regional distribution, majority of the patients (34%) were from Oromia region followed by Addis Ababa (30.1%). The rest were from regions Amhara (14.6%), SNNPR (12.6%), Tigray (7.8%) and Harari (1%). The great majority of the patients (89.3%) were free of any comorbid illnesses. The commonest comorbid illness was RVI (6.8%) followed by HTN (1.9%) and DM (1.9%) [Table 2].

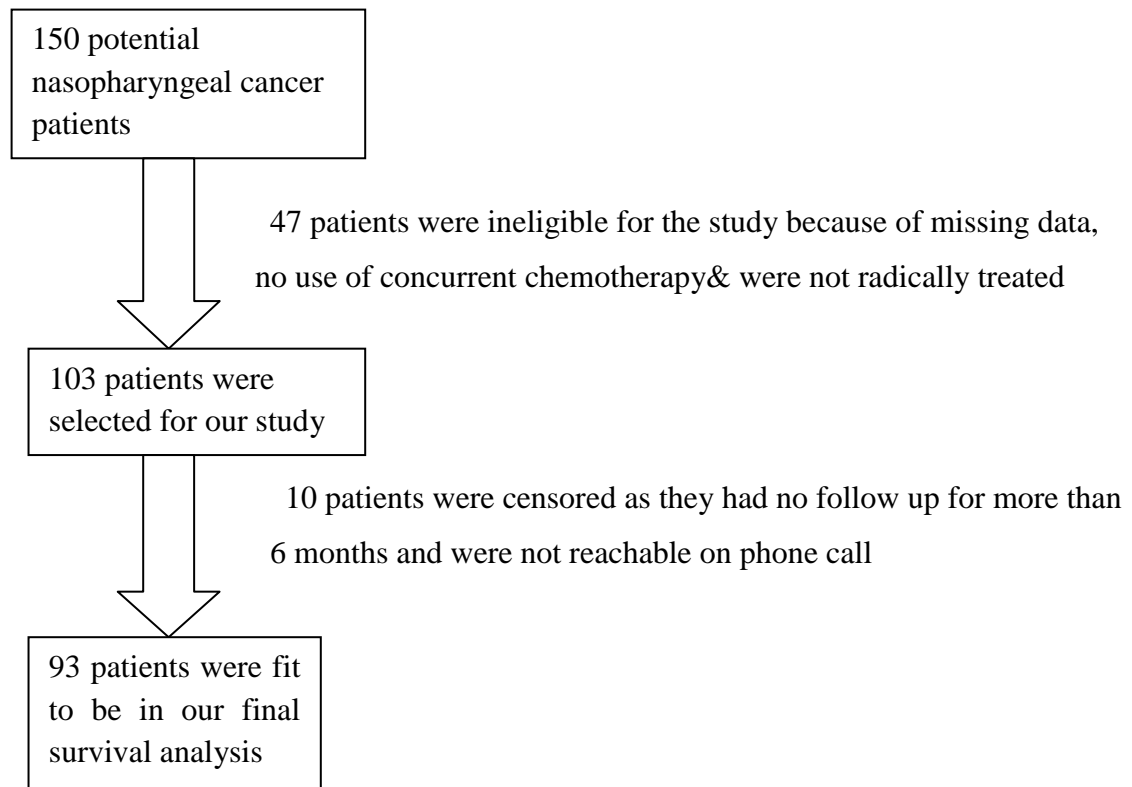


Figure 2: Diagram showing data flow of non-metastatic nasopharyngeal carcinoma patients recruitment in Tikur Anbessa Specialized Hospital, Radiotherapy center (n=103)

Table 1. Extremes of age distribution of nonmetastatic nasopharyngeal cancer patients in Tikur Anbessa Specialized Hospital, Radiotherapy center (n=103)

Age (n=103)	Minimum	Maximum	Mean	Std. Deviation
	11	73	33.17	16.039

Table 2. Distribution of nonmetastatic nasopharyngeal cancer patients by age, gender, address and comorbidity status patients in Tikur Anbessa Specialized Hospital, Radiotherapy center (n=103)

Variable	Category	Frequency	Percentage
Sex (n=103)	Female	30	29.1
	Male	73	70.9
Age category (n=103)	<16	14	13.6
	16-24	24	23.3
	25-34	22	21.4
	35-44	16	15.5
	45-54	16	15.5
	55-64	6	5.8
	65-74	5	4.9
Region (n=103)	AA	31	30.1
	SNNPR	13	12.6
	Tigray	8	7.8
	Amhara	15	14.6
	Harari	1	1.0
	Oromia	35	34.0
Comorbid Illness (n=103)	RVI	7	6.8
	HTN	2	1.9
	DM	2	1.9
	None	92	89.3

5.2 Performance status, Histopathology characteristics & Stage at diagnosis

The great majority of the patients (98%) had ECOG performance status of 1. The commonest histology subtype was non-keratinizing squamous cell carcinoma (86.4%) followed by keratinizing squamous cell carcinoma (13.6%) and no basaloid subtype was identified. Based on the 8th edition AJCC staging for nasopharyngeal cancer, the commonest stage of presentation was group stage IVA (68.9%) followed by stage III (28.2%). Only 2.9% of the patients presented

with stage II and no stage I cases were identified. Similarly, majority of the patients presented with higher T (T3 & T4 combined = 80.6%) & N stages (N2 & N3 combined = 69%). So, most of the patients (97.1%) had loco-regionally advanced disease at presentation.

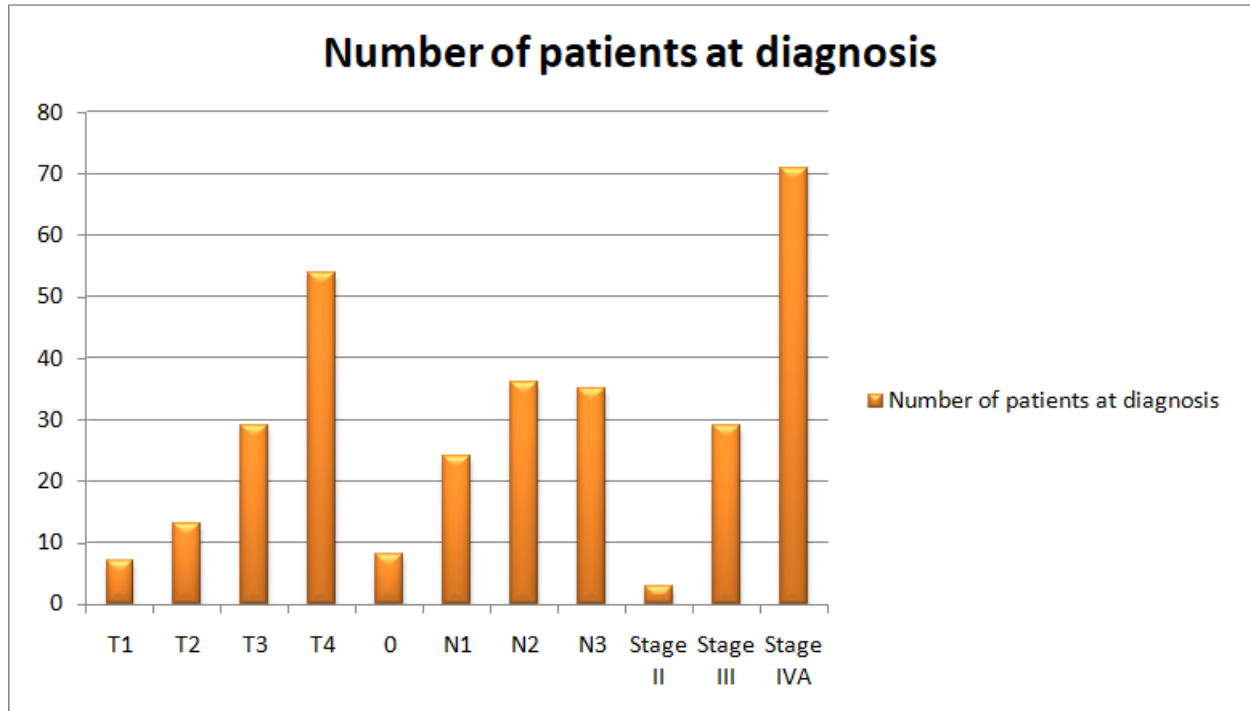


Figure 3. Distribution of nonmetastatic nasopharyngeal cancer patients in TN & group staging at diagnosis in percentage in Tikur Anbessa Specialized Hospital, Radiotherapy center (n=103)

5.3 Type of treatment given

From the total of 103 patients who took CCRT, 88 (85.4%) of them took IC followed by CCRT, while the rest 15 (14.6%) patients took upfront CCRT. In both arms, single agent Cisplatin was used as a concurrent regimen in 98 (95.1%) of the patients while Cisplatin plus 5FU combination or Carboplatin alone were used in a minority of patients, 2.9% & 1.9% respectively. All 15 patients of upfront CCRT arm took only Cisplatin. Overall, majority of the cases (77.7 %) took 3-5 cycles of concurrent agent where as 12.6% of the patients received 2 cycles and 9.7 % of them took 6 cycles.

In IC followed by CCRT arm, most of the patients (96.6%) took 3-6 cycles of IC while only 3.4% of the cases took 2 cycles. Forty three (48.9%) of the patients took the cisplatin plus 5-Flourouracil regimen and 10 (11.4%) of them took Cisplatin plus Paclitaxol. On the other hand,

the rest of the patients (39.8%) took both regimens as Cisplatin plus 5FU then Cisplatin plus Paclitaxol up on progression or if 5FU was not available.

The time from diagnosis to the start of IC was highly variable, most likely due to the long waiting list. In the IC followed by CCRT group, the time from diagnosis to start of induction chemotherapy (IC) varies from 3 days to 16 months with the mean being 3.3 months. The time from the end of IC to the start of CCRT was also between 3 days and 16.5 months with a mean of 2.5 months.

For the whole group, the mean RT doses given to the primary/craniofacial field & anterior neck/supraclavicular field were 64 ± 4 Gy & 57 ± 9 Gy respectively. The mean duration for radiotherapy course completion was found to be 8 ± 1 week [Table 3].

Table 3. Duration of treatment of nonmetastatic nasopharyngeal cancer patients and RT dose in Tikur Anbessa Specialized Hospital, Radiotherapy center (n=103)

Variable	N	Minimum	Maximum	Mean	Std.Deviation
Time from diagnosis to start of IC (in months)	88	0.10	16.00	3.2734	3.7
Time from end of IC to start of CCRT (in months)	88	0.10	16.30	1.8117	2.5
RT dose to primary/craniofacial field (Gy)	103	40	70.2	63.866	4.2
RT dose to neck/supraclavicular field (Gy)	103	40	70	57.004	9.4
RT duration (in weeks)	103	5	11.1	8.2	1.1

5.4 Treatment Outcome

5.4.1 Response after treatment

After analyzing the 103 patients, 10 (9.7%) cases were excluded because of loss from follow up for more than 6 months and were not accessible for phone interview. After 31 months of median follow up, 37.9% of the patients were alive with no recurrence (23.3%), loco-regional recurrence (9.7%) and distant metastasis (4.9%), whereas around half (52.4%) of the patient were died. Status of the remaining 10 (9.7%) patients was unknown. Overall, distant recurrence was more frequent (52.4%) than loco-regional recurrence (42.7%). Bone was the most common site of distant recurrence (31.1%) [Table 4].

Table 4. Response of non-metastatic nasopharyngeal cancer patients after treatment in Tikur Anbessa Specialized Hospital, Radiotherapy center (n=103)

Variable	Category	Frequency	Percentage
Recurrence status after treatment (n=103)	Alive with no recurrence	24	23.3
	Alive with local recurrence	10	9.7
	Alive with distance recurrence	5	4.9
	Death	54	52.4
	Unknown	10	9.7
Loco-regional recurrence (n=103)	No	59	57.3
	Yes	44	42.7
Distant recurrence (n=103)	No	49	47.6
	Yes	54	52.4
Lung metastases (n=103)	No	77	74.8
	Yes	26	25.2
Bone metastases (n=103)	No	71	68.9
	Yes	32	31.1
Liver metastases (n=103)	No	91	88.3
	Yes	12	11.7
Metastases to other site (n=103)	No	100	97.1
	Yes	3	2.9
Final outcome (n=103)	Alive	39	37.9
	Died	54	52.4
	Unknown	10	9.7

5.4.2 Survival Analysis results

The median follow up period for the entire group was 31 months. The overall median survival time with group staging was 31 months with 95% CI (27, 35) and OS rate of 37.9%. The median survival time for stages II, III and IVA were 30 months, 33 months [95 CI (23,43)] and 31 months [95% CI (28, 34)] respectively. Patients with keratinizing squamous cell carcinoma histology had median survival of 35 months [95 CI (25, 45)] while it was 31 months [95 CI (27, 35)] in those with non-keratinizing SCC subtype.

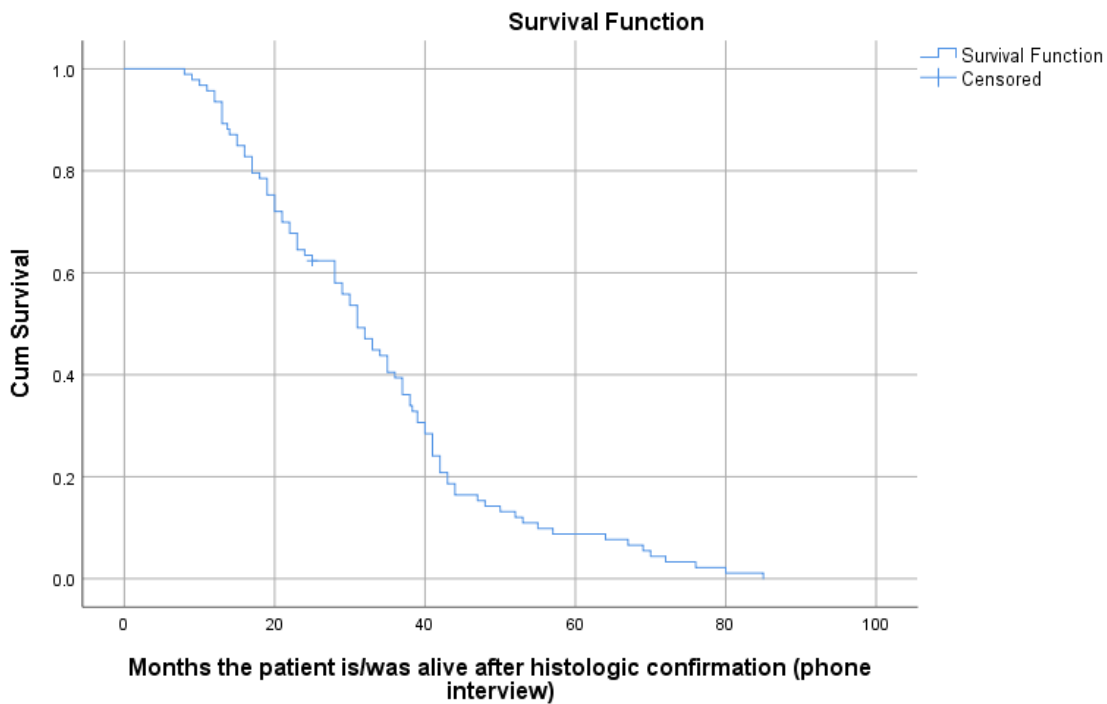


Figure 4. Median survival of non-metastatic nasopharyngeal cancer patients in Tikur Anbessa Specialized Hospital, Radiotherapy center

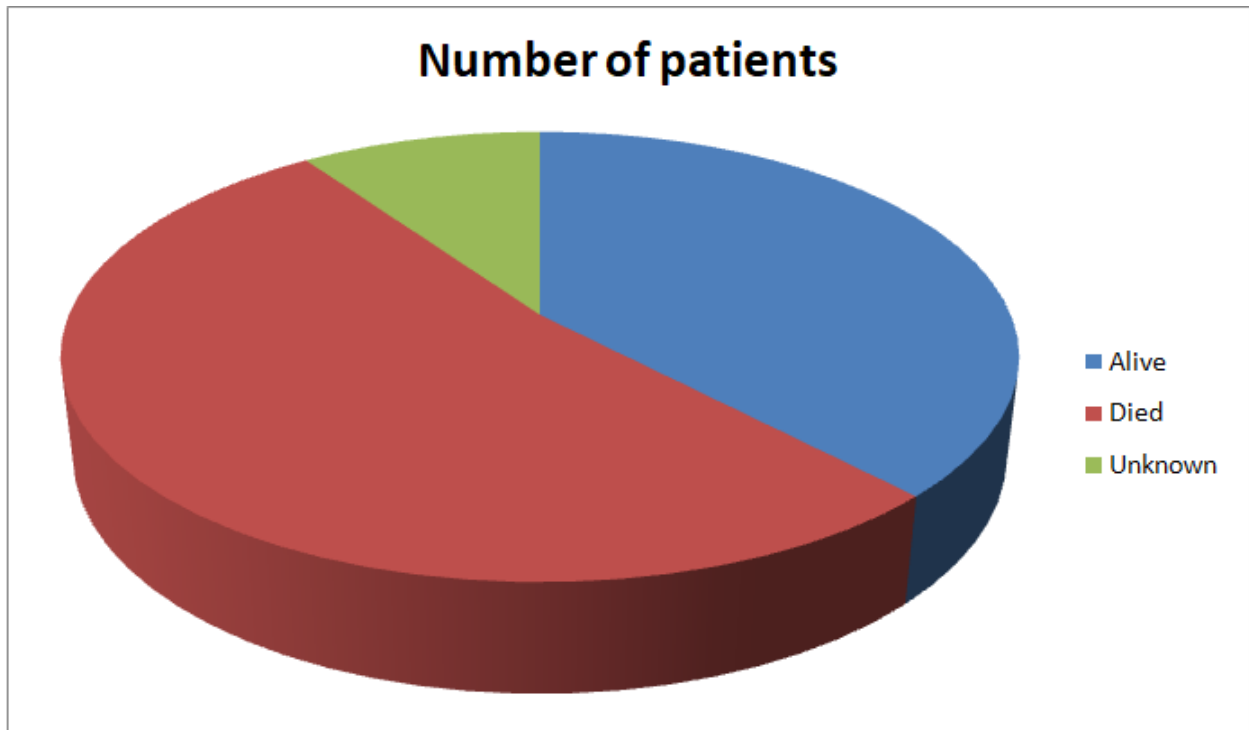


Figure 5. Final outcome of non-metastatic nasopharyngeal cancer patients in Tikur Anbessa Specialized Hospital, Radiotherapy center (n=103)

Table 5. Medians for Survival Time with TN and group staging at diagnosis of non-metastatic nasopharyngeal cancer patients in Tikur Anbessa Specialized Hospital, Radiotherapy center

TN& group staging	Median			
	Estimate	Std. Error	95% Confidence Interval	
			Lower Bound	Upper Bound
T1	37.0	7.9	21.6	52.4
T2	21.0	2.6	15.9	26.1
T3	37.0	2.6	32.0	42.0
T4	28.0	3.8	20.5	35.5
Overall	31.0	1.9	27.3	34.7
N0	33.0	2.8	27.5	38.5
N1	34.0	5.3	23.5	44.5
N2	35.0	7.5	20.4	49.6
N3	28.0	3.8	20.5	35.5
Overall	31.0	1.9	27.3	34.7
Stage II	30.0	.	.	.
Stage III	33.0	5.1	23.0	43.0
Stage IVA	31.0	1.7	27.7	34.3
Overall	31.0	1.9	27.3	34.7

Out of 40 variables entered into bivariate cox regression, 6 variables were found to have an association with survival of NPC patients and found to be fit for the final model. NPC cases with ECOG performance status of 2 were more likely to die than others with Crude Hazard Ratio (CHR) of 0.255, 95% CI (0.094, 0.689). Patients who developed either local or distant recurrence after treatment are more likely to die as compared to those who didn't develop recurrence [CHR=1.554, 95% CI (1.303, 1.854)]. And patients with distant recurrence were more likely to have shorter survival [CHR= 1.940, 95% CI (1.268, 2.970)]. Likewise, individuals with bone metastasis were associated with higher risk of death with [CHR=1.38, 95% CI (1.113, 2.713)] [Table 6].

Table 6. Variables with significant association to outcome variable on bivariate cox regression among non-metastatic nasopharyngeal cancer patients in Tikur Anbessa Specialized Hospital, Radiotherapy center

Variable	Chi square	df	P Value	CHR (Crude Hazard Ratio)	95% CI of CHR	
					Lower M	Upper M
ECOG 0			0.016			
ECOG 1	14.803	2	0.052	4.683	0.984	22.273
ECOG 2			0.007	0.255	0.094	0.689
Cycles of CT given as CCRT in IC group	4.19	1	0.041	1.234	1.008	1.510
Recurrence status after treatment	25.826	1	0.000	1.554	1.303	1.854
Distant recurrence	9.636	1	0.002	1.940	1.268	2.970
Bone metastasis	6.049	1	0.015	1.38	1.113	2.713

Out of the 6 variables entered in to multivariate cox regression, only the number of cycles of chemotherapy given as CCRT was found to have an association with overall survival of NPC cases. Patients who took 4 cycles of CCRT were more likely to have better survival than the others.[CHR=0 .284, 95% CI (0.112, 0.718)] [Table 7].

Table7. Variables entered to Multivariate Cox Regression among non-metastatic nasopharyngeal cancer patients in Tikur Anbessa Specialized Hospital, Radiotherapy center

Variable	df	P value	CHR	95.0% CI for CHR	
				Lower	Upper
ECOG	2	.142			
ECOG(1)	1	.470	3.012	.151	60.146
ECOG(2)	1	.337	.348	.041	2.995
Cycles of CT given as CCRT	4	.021			
Cycles of CT given as CCRT(1)	1	.296	.589	.218	1.592
Cycles of CT given as CCRT(2)	1	.008	.284	.112	.718
Cycles of CT given as CCRT(3)	1	.087	.456	.186	1.121
Cycles of CT given as CCRT(4)	1	.594	.778	.310	1.955
Recurrence status after treatment	4	.001			
No recurrence(1)	1	.900	273.840	.000	2.463
Alive with local recurrence(2)	1	.892	421.021	.000	3.790
Alive with distant metastases(3)	1	.884	668.687	.000	6.054
Death(4)	1	.867	1744.083	.000	1.569
Distant recurrence	1	.373	1.440	.646	3.208
Bone Met	1	.709	.894	.495	1.612

6. Discussions

After a median follow up 31 months, results from this retrospective study show that the overall median survival for the eligible 93 patients was 31 months with 95% CI (27, 35) with overall survival rate of 37.9%. Factors that were found to be significantly associated with survival are performance status of the patients, post treatment recurrence status, distant metastasis and bone metastasis.

Nasopharyngeal carcinomas are highly responsive to chemo- radiotherapy. In the landmark Intergroup trial 0099, a randomized phase III trial which compared chemotherapy plus EBRT versus EBRT alone in 185 patients with stages III & IV nasopharyngeal cancers, the 3-year survival rate was 76%, and 46% ($P < 0.001$) respectively. The median follow-up duration for all randomized patients was 2.7 years. In this trial, a total RT dose of 70 Gy to the primary & 50 to 70 Gy to neck nodes was given in both arms: 1.8- to 2.0-Gy/d fractions Monday to Friday for 35 to 39 fractions. The investigational arm received chemotherapy with cisplatin 100 mg/m² on days 1, 22, and 43 during RT; postradiotherapy, chemotherapy with cisplatin 80 mg/m² on day 1 and 5-FU 1,000 mg/m²/d on days 1 to 4 was administered every 4 weeks for three courses. Although results of this trial cannot be directly compared to our study due to different study design and use of post chemoradiation AC, the superiority of CCRT over RT alone has been demonstrated (19).

As compared to the following reports from subsequent trials conducted in Asia, the overall survival result in our study (37.9%) is lower. In the phase III randomized study of loco-regionally advanced NPC cases of Prince of Wales Hospital (PWH) and Queen Elizabeth Hospital (QEH), which compared CCRT versus RT alone in loco-regionally advanced 350 NPC cases, the 5-year overall survival was 70.3% (95% CI = 63.4% to 77.3%) for the CCRT arm versus 58.6% (95% CI = 50.9% to 66.2%) for the RT arm. The median follow up was 5.5 years. The patients were assigned to receive EBRT alone or concurrently with cisplatin at a dosage of 40 mg/m² weekly. The primary endpoint was OS. The nasopharynx was treated to 66 Gy in 33 fractions per 6.5 weeks; parapharyngeal boost was given to patients with parapharyngeal involvement to 20 Gy in 10 fractions in 2 weeks or 10 Gy in five fractions in 1 week. Palpable residual nodes after EBRT were treated with 7.5 Gy in two fractions in 4 days. Any biopsy-proven persistent local disease was treated with intracavitary brachytherapy using iridium-192

sources to 24 Gy in three fractions in 15 days or 21 Gy in three fractions in 15 days. On subgroup analysis, there was no difference between OS in the arms for T1/T2 stage ($P = .74$, HR = 0.93 [95% CI = 0.59 to 1.4]), but for T3/T4 stage ($P = 0.013$, HR = 0.51 [95% CI = 0.3 to 0.88]), favoring the CRT arm(20).The relative lower survival rate in our study may be due to lower mean RT dose.

Similarly, in the Phase III study of CCRT versus RT alone for advanced NPC conducted in Taiwan, the 5-year OS rates were 72.3% for the CCRT arm and 54.2% for the RT-only arm ($P < 0.0022$). In this study, from December 1993 to April 1999, 284 patients with stage III to IV (M0) NPC were randomly allocated into two arms. Most of them were treated via bilateral parallel opposed fields to the primary tumor and upper neck and a single anterior field to the lower neck with a central block. After 40 to 42 Gy, the primary boost field was changed to 10 MV photons delivered from a linear accelerator via bilaterally opposed reduced portals. The bulky nodal area was boosted using a poster anterior neck field of cobalt-60 or an electron beam of appropriate energy. The total planned dose was 70 to 74 Gy/7 to 8 weeks to the primary tumor and positive neck region and 50 to 60 Gy/5 to 6 weeks to the negative neck region. A 3-field combination technique (bilateral opposed and anterior portals) was used if the tumor has anterior extension. Concurrent cisplatin and 5-FU were given at the 1st & 5th weeks of RT. As we can see, even the OS in the RT only arm is better than ours (21).

Likewise, though different in study design, the median survival in our study was found to be much lower than the results of the randomized trial of RT versus CCRT followed AC, conducted between September 1997 and May 2003 in Singapore, in 221 patients with stage III and IV NPC of the endemic variety. The median follow-up time was 3.2 years. The 2- and 3-year OS rates were 78% and 85% and 65% and 80% for RT alone and CCRT, respectively. The HR for OS was 0.51 (95% CI, 0.31 to 0.81; $P < 0.0061$). Patients in both arms received 70 Gy in 7 weeks using standard RT portals and techniques. Patients on CRT received concurrent cisplatin (25 mg/m² on days 1 to 4) on weeks 1, 4, and 7 of RT and 3 cycles of adjuvant cisplatin (20 mg/m² on days 1 to 4) and 5-FU (1,000 mg/m² on days 1 to 4) every 4 weeks (weeks 11, 15, and 19) after completion of RT (22).

Moreover, in the multicenter, phase III, randomized trial of CCRT plus AC versus RT alone in patients with loco-regionally advanced NPC, investigating 10-year outcomes for efficacy & toxicity, the OS rate at 10 years was 62% vs 49% ($P < 0.047$) respectively. And, on subgroup

analysis, the 10 year overall survival rates in stages III (n=206) & IV (n=142) were found to be (74% vs 60%, $p < 0.031$) and (45% vs 31%, $p < 0.28$) respectively. This study was performed by 4 centers from Hong Kong and 1 center from Canada between March 1999 & January 2004 in 348 histologically confirmed non keratinizing (differentiated or undifferentiated) NPC cases with T1-4/N2-3/M0 disease. Patients in both arms were irradiated with megavoltage photons with the same RT technique and dose in line with the treatment policy of each individual center. Those in the CRT arm were given 3 cycles of AC according to the Intergroup 0099 regimen: 3 cycles of cisplatin (100 mg/m²) was given intravenously every 3 weeks, starting with the initiation of RT, and this was followed by adjuvant 3 cycles of combination of cisplatin (80 mg/m²) and 5-FU (1000 mg/m²/d by 96-hour infusion) every 4 weeks(23). Even after 10 years, this OS result is much higher than ours, probably due to the long waiting list in our set up resulting in time delay between diagnosis & IC (mean= 3.3±3.7 months, varying between 3 days & 16 months), time between IC and CCRT(mean = 1.8±2.5 months, varying between 3 days & 16.3 months), longer duration of RT course completion (8 ± 1 weeks, varying between 5 & 11 weeks)and lower mean dose to craniofacial (64 ± 4 Gy)& anterior neck/supraclavicular fields (57 ± 9 Gy).

The overall survival of our study was found to be higher than a study in Nigeria. In a retrospective study of 2 year treatment outcome of patients with NPC in Nigeria that used the records of patients at the University College Hospital, Ibadan, between 2000 and 2009, the median survival time was 22 months. In terms of stage group, more patients with stage II disease survived than those with stages III and IV, with a 2 year survival rate of 58%, 52%, and 20%, respectively. A total of 161 patients were included in the analysis, of which 113 (70%) were men and 48 (30%) were women. Ten (6.3%) patients presented with early-stage disease, whereas 149 (93.7%) had late-stage disease. The treatment regimen of interest was radical CCRT using cisplatin and 5-fluorouracil. All the patients were treated with cobalt-60 2D EBRT (average energy of 1.25 MeV) with standard fractionation. The average central tumor dose to the primary & gross lymph nodes was then maintained at 60 Gy in 30 fractions over 6 weeks, and that to the elective neck nodes was continued at 46 Gy in 23 fractions over 4.5 weeks. Chemotherapy was given every 21 days at days 1, 21 & 42, and continued up to 4-6 courses depending on the extent of the disease (9). In a study of RT of NPC cases, conducted between late 1968 & 1970, in Kenyatta National Hospital, Kenya, 64 East African patients were treated by RT. The primary site of the tumor received, in most cases, a dose of 55 to 67 Gy in 30 to 55 days and the cervical

region received 45 to 65 Gy during the same time. Both the primary tumor and the neck were irradiated daily during 5 days per week. The primary site was irradiated by 2 lateral opposing fields, sometimes supplemented by one anterior field. The neck region was usually irradiated by two large anterior and posterior opposing fields. About 40 Gy of prophylactic RT was also given to the mediastinum and both axillae in most patients. They were observed for 1 to 3 years. The minimum cure rates in the total series after 1 and 2 years were 31% and 16% respectively (29). Overall, the treatment outcome in these studies is worse than the results in developed countries. This is likely because most patients presented with late-stage disease & treatment delay. Additionally, in the East African study, concurrent chemotherapy was not used and both the axillae & mediastinum were unnecessarily irradiated. There are no, however, data on survival of NMNPC in Ethiopia to inform clinical guidelines and public health policy makers.

7. Conclusion and Recommendation

7.1 Conclusion

The overall median survival for the entire population is 31 months, with a survival rate of 37.9%, which is better than the median survival outcome in Nigeria (22 months). But, the treatment outcome in this study is worse than the previous studies in developed countries, likely because most patients presented with late-stage disease. Based on our analysis, significant associations were made between OS and performance status, cycles of concurrent chemotherapy, post treatment recurrence status, distant metastasis & bone metastasis.

7.2 Recommendation

Since concurrent chemotherapy administration, performance status & recurrence status were found to be important factors in determining OS, every effort should be made to increase NPC awareness so that our patients can be diagnosed at early stage with good performance status & proper post treatment follow up is important for early detection & treatment of any recurrence.

We have to expand oncology care in Ethiopia by expanding the facilities & training adequate number of oncology personnel.

Finally, guidelines for the early diagnosis of nasopharyngeal carcinoma are required, and local studies on treatment regimens that can improve survival should be carried out.

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ANNEXES

ANNEX-I English version of patient information sheet

This patient information collection sheet was intended to determine the survival of nonmetastatic nasopharyngeal cancers cases treated radically by CCRT using 2 dimensional External Beam Radiotherapy at Tikur Anbessa Specialized Hospital, Addis Ababa, Ethiopia. The study was conducted through reviewing secondary data. The study will give some evidence and information for governmental and non-governmental organizations which work in the area of non-communicable disease specifically on NPC at national, regional and district level by providing basic information on the clinical status, pathology and treatments on NPCs. Information which is necessary for the study was taken from patients' chart, log books and radiotherapy treatment sheet. As the study was conducted through review of medical records alone & final interview, the individual patients were not subjected to any harm as far as the confidentiality is kept. To preserve the confidentiality, residents working in cancer treatment center of Tikur Anbessa specialized hospital were selected to extract the data from the medical records. Moreover, no personal identifiers were used on data collection form.

Date of review-----

Date of interview/phone call.....

Day----- month----- year-----

Name of reviewer----- Signature-----

Time started----- Time ended-----

Total number of records reviewed-----

Result; (A) complete (B) incomplete (C) excluded

Action taken for incomplete data-----

Name of supervisor----- Signature-----

Principal investigator address: 0939312994

ANNEX II. Data extraction tools

1.Socio-demographic Data

Ser.No	Item	
101	Card no	
102	Phone no	
103	Sex	1. M 2. F
104	Age in years	
105	Address(Region)	1. Oromia 2. Amhara 3. SNNR 4. Tigray 5. Somalia 6. Gambella 7. BenshangulGumuz 8. Addia Ababa 9. Harar 10. Diredawa 11. Afar

2. Diseases and Treatment Characteristics

201	Associated risk factors and comorbidities	1.Smoking 2.Alcohol 3.Commorbidities: MD,HTN,RVI, Others (mention) 4.None
202	ECOG performance status (0-4)	
203	Date at diagnosis (date of FNAC/biopsy/referral)	
204	Histologic subtype	1.Keratinising SCC 2.Non-keratinising SCC (differentiated & undifferentiated) 3.Basaloid
205	Stage at diagnosis	1.I 2.II 3.III 4.IV
206	Induction + CCRT group	1.Time from diagnosis to starting induction

		chemotherapy 2.Regimen of IC(induction chemo) 3.Number of Cycles of IC 4.Time from end of IC to starting CCRT 5.Regimen in CCRT
207	Upfront CCRT alone group	1.Time from diagnosis to start of CCRT 2.Concurrent chemotherapy regimen 3.Cycles of concurrent chemotherapy
208	Radiotherapy	1.Dose to primary/craniofacial field 2.Dose to anterior neck/supraclavicular field 3. Duration of RT course

3. Survival Data

501	Current status	1.Alive with no recurrence 2.Alive with locoregional recurrence 3.Alive with distant metastasis 4.Died
502	Site of recurrence	1.Locoregional 2.Bone 3.Lung 4.Liver 5.Other site (specify)
503	2 nd line chemotherapy	1.Yes 2.No
504	Time of last follow up from patient's card (months after initial presentation)	
505	Months the patient is/was alive after the date of histologic diagnosis (phone interview)	

ANEX III Eastern cooperative oncology group

These scales and criteria are used by doctors & researchers to assess how a patient's disease is progressing, how the disease affects the daily living abilities of the patient, and determine appropriate treatment and prognosis

Grade	ECOG
0	Fully active, able to carry out 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 self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry out any self-care. Totally confined to bed or chair
5	Dead

As published in Am. J. Clin. Oncol.: Oken, M.M., Creech, R.H., Torney, 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 – IV Assurance of 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. Adonay Gebreslassie (Final Year Clinical Oncology Resident)

Signature _____ Date ____/____/____

APPROVAL OF THE PRIMARY ADVISOR

Advisor Name: Dr. Edom Seife (MD, Consultant Oncologist)

Signature _____ Date ____/____/____

ANNEX-V. Frequency tables for Radiotherapy

Variable	RT dose	Frequency	Percent
RT dose to given to craniofacial fields in Gy (n=103)	40	1	1
	54	1	1
	56	1	1
	60	33	32
	64	5	4.9
	66	52	50.5
	68	2	1.9
	70	7	6.8
	70.2	1	1
	Total	103	100
RT dose given to Anterior neck/supraclavicular field (n=103)	40	16	15.5
	42	1	1
	44	3	2.9
	50	3	2.9
	54	19	18.4
	56	1	1
	59.4	1	1
	60	23	22.3
	64	4	3.9
	66	27	26.2
	68	1	1
	70	4	3.9
	Total	103	100
	RT duration in days (n=103)	35	1
40		1	1
44		1	1
45		1	1
46		4	3.9
47		1	1
48		4	3.9
50		2	1.9
51		1	1
52		7	6.8
53		5	4.9
54		3	2.9
55		6	5.8
56		10	9.7
57		4	3.9
58		15	14.6
59		3	2.9
60		6	5.8

	61	3	2.9
	62	2	1.9
	63	2	1.9
	64	3	2.9
	65	4	3.9
	66	2	1.9
	69	2	1.9
	70	2	1.9
	71	1	1
	72	2	1.9
	73	1	1
	74	1	1
	76	2	1.9
	78	1	1
	Total	103	100

ANNEX VI: All variables entered to bivariate cox regression

Variable	Chi square	df	P Value	CHR	95% CI of COR	
					Lower M	Upper M
Age Category	0.262	1	0.609	0.967	0.849	1.100
Comorbidities	1.026	1	0.314	1.150	0.876	1.509
ECOG 0			0.016			
ECOG 1	14.803	2	0.052	4.683	0.984	22.273
ECOG 2			0.007	0.255	0.094	0.689
Histologic subtype	0.001	1	0.988	0.988	0.525	1.859
T stage T1	3.88	3	0.346			
T2			0.272	0.719	0.398	1.296
T3			0.087	1.525	0.941	2.471
T4					0.602	1.288
N0			0.316			
N1	3.587	3	0.569	0.853	0.494	1.474
N2			0.889	1.023	0.698	1.513
N3			0.365	0.846	0.589	1.215
Group stage II	0.122	2	0.941			
III			0.806	1.125	0.439	2.886
IV			0.907	0.969	0.566	1.658
Induction CT regimen in induction group	1.052	1	0.306	0.885	0.7	1.118
Cycles of CT	0.002	1	0.967	1.004	0.832	1.212

received in induction group						
CCRT regimen in IC group	0.158	1	0.691	0.863	0.418	1.784
Cycles of CT given as CCRT in IC group	4.19	1	0.41	1.234	1.008	1.510
Cis+5FU induction CT cycles	1.230	1	0.268	1.0085	0.939	1.255
Cis+Paclitaxol induction CT cycles	0.062	1	0.803	0.966	0.737	1.267
Total No of cycles of IC	0.002	1	0.967	1.004	0.832	1.212
Concurrent CT cycles	2.669	1	0.103	1.205	0.963	1.509
Concurrent CT cycles in upfront CCRT group	0.971	1	0.325	1.298	0.769	2.191
RT dose to primary site	0.007	1	0.931	1.002	0.9551	1.051
RT dose to the neck	0.08	1	0.777	1.003	0.980	1.027
RT duration in days	0.728	1	0.393	0.988	0.961	1.016
Recurrence status after treatment	25.826	1	0.000	1.554	1.303	1.854
Loco-regional recurrence	0.174	1	0.676	1.093	0.720	1.658
Distant recurrence	9.636	1	0.002	1.940	1.268	2.970
Lung met	0.439	1	0.508	1.170	0.736	1.859
Bone met	6.049	1	0.015	1.38	1.113	2.713
Liver met	1.877	1	0.174	1.532	0.829	2.831
Other met	1.337	1	0.257	1.90	0.613	6.269
2 nd line chemo	0.66	1	0.797	1.056	0.696	1.603
Time from diagnosis to start of IC	1.816	1	0.180	0.956	0.895	1.021
Time from end of IC to CCRT	0.103	1	.748	1.013	.937	1.095
RT Duration of in days	0.728	1	.393	.988	.961	1.016

