

DISPARITIES IN RECEIPT OF RADIOTHERAPY AND OUTCOMES AMONG CERVICAL CANCER PATIENTS SEEN IN TIKURANBESSA HOSPITAL, ETHIOPIA

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A Thesis submitted to Department of Clinical Oncology, Addis Ababa University, College of
Health Sciences in the Partial Fulfillments of the Requirements for the Certificate of Clinical
Oncology

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This is to certify that the thesis prepared by Dr Biniyam Tefera Deressa, entitled: “**Disparities in Receipt of Radiotherapy and Outcomes among Cervical Cancer Patients Seen in Tikur Anbessa Hospital, Ethiopia**” submitted in partial fulfillment of the requirements for the certificate of specialization in Clinical Oncology complies with the regulations of the University and meets the accepted standards with respect to originality and quality.

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ABSTRACT

Introduction: Ethiopia is among countries with the highest burden of cervical cancer worldwide. Up to 6,000 new cervical cancer patients are diagnosed each year. The primary objective of this study was to evaluate the survival of cervical cancer patients in general and compare the difference in survival, waiting time and stage migration among patients treated with radiotherapy in Tikur Anbessa Hospital on private wing and regular sides.

Methodology: Women with histologically verified cervical cancer, who received radiotherapy in 2014, were included. All patient characteristics, tumor characteristics, and information concerning therapy and outcome were extracted from the patients' medical record files. Vital status was obtained through telephone contact or patient cards.

Result: Out of 249 patients treated in 2014, the patient file of 242 could be retrieved. 152 (63%) were treated on the regular service side and 90 (37%) were treated on Private wing side. The median age at diagnosis was 45 years and 48 years for patients with private wing side and regular service side. After first oncologist consultation private wing patients waited more (92 days) than regular side patients (39 days) to receive radiotherapy. During this time, stage migration was seen more in private wing (20%) than regular side (8.6%) patients. In general, the estimated of 52 months overall survival probabilities were 21.5% (14.6% in worst-case scenario). The median overall survival time was 21 months (18 months in worst-case scenario). The median survival was 23 months (19 months in worst-case) and 19 months (17 months in worst-case) between private wing and regular side patients, respectively. The FIGO stage, intension of radiotherapy, one-year tumor control rate, comorbidity and concurrent chemotherapy were the factors, which has found to be significant association with survival.

Conclusion: The survival of cervical cancer patients remains low in Ethiopia, despite the higher cure rate of the disease. The reason for poor survival were advanced stage at presentation, very long waiting time for treatment and as a result stage migration, the old treatment machine and technique and absence of brachytherapy are some of the reason. Therefore, the parallel oriented efforts in all direction such as prevention, early detection and improving access to standardized care are required.

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DEDICATION

To my Mother

ACRONYMS

LMICs - Low and Middle-Income Countries

RT - Radiotherapy

WHO – World Health Organization

HPV – Human Papilloma Virus

TASH -TikurAmbesa Specialized Hospital

CR – Complete Response

PR – Partial Response

PD – Progressive disease

SD – Stable Disease

HIV – Human Immuno-Deficiency Virus

Gy – Gray (unit)

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INTRODUCTION

Cancer continues as a medical challenge to humankind. For all cancers combined (excluding non-melanoma skin cancer), the highest incidence rates are found in high-income countries of North America and Western Europe. But more than 70% cancer deaths occur in low and middle countries.(1) The continuing global demographic and epidemiologic transitions indicates an ever-increasing cancer burden over the next decades, particularly in low and middle-income countries (LMIC), with over 20 million new cancer cases expected annually as early as 2025.(2)

It is known that there are marked differences in cancer burden across countries and regional boundaries, particularly when considering specific cancer types. For example, data from low-resource countries (LMIC) show that cervical cancer is still one of the most common cancer among women, but not in developed world.(1) Historically, cervical cancer was the leading cause of death from cancer in women at the beginning of the 20th century worldwide. Nowadays it is the fourth most common cancer in women, due the significant reduction of cervical cancer incidence in developed world largely because of wide utilization of screening which allows the detection and removal of precancerous lesions, (3) as well as the detection of early stage diseases for successful treatment through surgery, radiotherapy, and chemotherapy. In many developing countries, however, cervical cancer remains the most frequently diagnosed cancer and a leading cause of cancer death because of lack of screening. A majority of cervical cancer in these countries are diagnosed at advanced stage when the choice of treatment is limited and the chance of survival is poor.(4) Of the 500,000 cervical cancer cases and 270,000 deaths estimated to occur worldwide each year, 85% of them occur in LMICs, which are least equipped to screen and treat these patients because of poor healthcare infrastructure. (5)

Cervical cancer is the most curable form of cancer if detected and treated early. (6, 7) In most developing countries, however, 80% of cervical cancer patients seek medical care at advanced stage of the disease and that there is long waiting time for treatment because of limited healthcare infrastructure. (8) Delays in diagnosis and treatment continue to be the greatest challenge to reducing the disproportionately high burden of the disease in these countries.(9)

STATEMENT OF THE PROBLEM

Ethiopia is among countries with the highest burden of cervical cancer worldwide. It is the second most commonly diagnosed and the second leading cause of cancer death in the country, with age standardized incidence and mortality rate of 26.4 and 18.4 per 100,000 population each year, respectively (GLOBOCAN 2012). (1) According to cases series data from Tikur Anbessa Hospital, the majority of the cases are presented at advanced stage of the disease. (10-12)

It is known that radiotherapy is an essential part of treatment for cervical cancer, especially for locally or loco regionally advanced disease. (13, 14) It can cure cervical cancer alone, or when used in conjunction with surgery or chemotherapy. Furthermore, radiotherapy can relieve symptoms in patients with far advanced and incurable disease (palliation). (15) However, there is only one radiotherapy center in Ethiopia, housed in TikurAnbessa hospital, to provide radiotherapy for all cancer patients in the country, including cervical cancer patients. (10, 12) Because of large volume of patients and one functioning radiotherapy machine in the radiotherapy center, waiting time for receipt of radiation treatment could be very long. (9, 16)

There are two types of services for cancer patients in Tikur Anbessa Hospital radiotherapy center: regular service weekdays from 8 am -5 PM and private wing service in the evening and on the weekend. Private wing service in public hospitals began in 2008 as part of the Ethiopian government's health sector financial reform program, with intension of retention of qualified health staff in the country. (17) Payment for receipt of treatment in the private wing is substantially higher than that for regular services. Because of the low per capita income of the country and because cervical cancer patients are tended to be poorer compared to the general population, most cervical cancer patients receive radiotherapy in regular services where the waiting time period presumed to be longer compared to those patients receiving treatment in the private wing.

However, it is unknown whether there is difference in delay in receipt of radiotherapy between cervical cancer patients treated in regular and private services in the center, and whether there are differences in stage migration during waiting period for radiotherapy and in local control of the disease between the two groups of patients.

REVIEW OF LITERATURES

In spite of being preventable, cervical cancer is the fourth most common type of cancer among women worldwide. (18) In 2012, 528,000 new cases were reported, accounting for an age-adjusted incidence rate of 14.0 per 100,000 women in the world. (3, 18) Out of these 85% were occurred in less developed world. (3) The top of the High-risk regions (with estimated age-standardized incidence rates of >30 per 100,000 women) is eastern Africa, where the incidence rate is up to 42.7 per 100,000 women. (18, 19) In this regions cervical cancer remains the most common cause of cancer deaths, accounting for 10.4%, which represents one in five of all cancer deaths in the women. (20) The incidence and mortality of cervical cancer has plummeted in the developed countries mainly due to the implementation of national screening programs and human papilloma virus vaccination. (21) Due to these interventions, there has been a 75 percent decrease in the incidence and mortality of cervical cancer over the past 50 years in these countries. (22, 23)

In Ethiopia, the incidence of cervical cancer is one of the highest in the world. According to the 2009 World Health Organization (WHO) report, the age-adjusted incidence rate of cervical cancer in Ethiopia is 35.9 per 100,000 patients with 7619 annual number of new cases and 6081 deaths every year. (11) Currently, Cervical cancer is the second most common cancer in Ethiopia followed by breast cancer. (24, 25) Since TASH is the only oncology center for the radiotherapy treatment of cervical cancer patients in Ethiopia, all patients are referred to this hospital from all over the country. (12) However, the number of cervical patients are continuously increasing from year to year. (11) Majority of the patients have advanced stage of the disease at presentation, which make the outcome poor. (11, 12)

According to the study of Kantelhardt et al, among 1,059 cervical cancer patients treated in Tikur Anbessa Hospital thorough 4-year overview of treated patients (from 2008 to 2012), the 1- and 2-year overall survival probabilities were 90.4% and 73.6% (in worst-case scenario 45.4%). According to the study, advanced stage at presentation and stage migration due to long waiting (median 3.8 months), where the factors associated affecting survival negatively. (9) Another study of Moelle et al, among cervical cancer patients treated in Tikur Anbessa Hospital in the same period (2008-2012) performed to assess adherence of radiotherapy treatment and survival. The study found that, the estimated overall survival after 1 and 2 years was 84% and 64%, respectively, and decreased to 54% and 35% in the assumption of worst-case scenario. Those patients had lower survival probabilities in the case of discontinuation. According to the study, reasons for discontinuation were toxicities, economic background, and Radiotherapy machine breakdown. The waiting time was not mentioned in the study. (26) Similar to this Aynalem et al, assess the impact of the optimal radiation dose on survival of cervical cancer in this hospital. The study found that patients those took higher doses of radiotherapy had better survival probability. Among patients treated on curative intent, the one-year survival probability

(OS) was higher 96.1% versus 88.4% for patients who took 72 Gy versus who discontinued, respectively. Among patients treated with palliative intent, those who received radiation more than 42 Gy was better survival than who took less; 1-year survival probability was 86.1 % versus 72.9%, respectively. The reason for discontinuation and received a non-optimal radiation dose was due to limited radiation facilities, socio-economic reasons, side effects or progression of disease. The waiting time was not mentioned in this study. (27)

Studies on cancer treatment waiting times for are not common around the world, the fact that they differ on the definition for intervals used and types of tumors and therapy administered makes comparing them difficult. In Ontario, Canada, the median was of 5.7 weeks from surgery or biopsy to the first radiotherapy session for cervical cancer diagnosed in 2001 and 2002. (28) From 2011, the Canadian Institute for Health Information established 28 days as the standard time limit for treating cancer with radiotherapy regardless of the site. (29) The definition of optimal waiting time in care for cervical cancer involves numerous services and depends on the availability of different technologies, which are essential for defining the stage and the clinical recovery of patients and thus, varies among different countries. (30) For example, since 2012 the problem of time spent waiting to begin cancer treatment has understandably been given special attention by government authorities in Brazil and a maximum of 60 days waiting time before effectively beginning the treatment of malignant neoplasms including cervical cancer was applicable by law. (31)

OBJECTIVE OF THE STUDY

GENERAL OBJECTIVE

To estimate waiting time for initiation of radiotherapy after first oncologic consultations, one year tumor control rate, and survival for patients treated in the regular and private wing services of the radiotherapy center and whether these estimates differ between the two groups of patients.

SPECIFIC OBJECTIVES

- To estimate and compare waiting time for initiation of radiotherapy since first oncological consultation between patients treated in the regular and private wing services
- To determine the extent of stage migration while waiting for initiation of radiotherapy in patients treated in the regular and private wing services and whether stage migration differ between the two groups of patients

- To estimate the extent of tumor control at 1 year after radiotherapy in patients treated in the regular and private wing services and whether the estimates vary between the two sets of patients
- To compare survival between patients treated in the regular and private wing services

METHODOLOGY

STUDY SETTING AND TREATMENT MODALITY

The study was carried out in adult oncology department of Tikur Anbesa Specialized Hospital (TASH) radiotherapy center, under the Addis Ababa University. The department has currently three full time oncologists, three physicists, six radiotherapists, thirty residents and other supportive staffs. In 2014, during the study period there were three oncologists, six residents and one General practitioner and palliative care physician. The center offers outpatient services for all types of solid tumors, selected hematologic cancers, and inpatient services with 19 beds. The department had two cobalt 60 machines and no brachytherapy machine. Since 2015 the brachytherapy machine was installed for treatment cervical cancer patients.

Patients with cervical cancer were referred from all over Ethiopia to Tikur Anbesa Hospital Radiotherapy center for radiotherapy. Up on first oncologist consultation and/or radiotherapy planning, tumor stage were classified according to the International Federation of Gynecology and Obstetrics (FIGO) staging system. (32) The stage was based mainly on clinical pelvic examination by at least one clinical oncologist from radiotherapy center. The routine radiological examination such as chest X-ray and abdomino pelvic ultrasound examination will aid to classify the FIGO stage further more, in case of hydronephrosis or metastatic lesion was detected.

According to the treatment protocol of the center, cervical cancer patients FIGO stage IIa and lower were treated surgically with radical hysterectomy and pelvic lymphadenectomy (Wertheim). Patients with FIGO stage IIb and above without surgery or patients who undergone surgery but has positive surgical margins and positive lymph nodes required radiotherapy. Patients with early stage disease but unable to undergo surgery due to other medical conditions also treated with radiotherapy. The radiotherapy planning techniques were two-dimensional (2D-technique) in two phases. In the first phase, opposing-field techniques (anterior-posterior/posterior-anterior) were used, and in the second phase, four-field box techniques were applied. 40-46Gy radiotherapy was given in the first phase and then 20-26 Gy given in the second phase with 2Gy per day fractions. Generally, patients with early

stage IIIB or less with good general condition treated with curative dose radiotherapy in two phases. However, for patients with palliative intent, palliative radiotherapy is usually offered for patients with FIGO stage above late stage IIIB. The radiation dose and fractionation was different from curative intent cases, which depends on general status of the patient, state of renal failure or uremia and presence or absence of Fistula. In addition to stage, patients with poor medical condition or in emergency state might be offered palliative radiotherapy. The palliative radiotherapy dose and fractionation might be 10 Gy, 12 Gy, 30 Gy or 32 Gy with different fractionation, according to the clinical scenario. Chemotherapy was recommended together with radiotherapy in curative setting and as palliation of symptoms in stage IV disease.

STUDY DESIGN

An institutional based retrospective study of cervical cancer patients treated in 2014 in Tikur Anbessa Hospital, Oncology Center, with the data systematically abstracted from patients' medical records.

SOURCE POPULATION

Women with histologically verified cancer of the cervix uteri (International Classification of Disease-Oncology (ICD-O-3) codes C53.0–9) who were diagnosed and treated at the Radiotherapy Center at Tikur Anbessa Hospital in Addis Ababa, Ethiopia, were included in the study.

STUDY POPULATION

Women with histologically verified cancer of the cervix uteri (International Classification of Disease-Oncology (ICD-O-3) codes C53.0–9) who were treated at the Radiotherapy Center at Tikur Anbessa Hospital in Addis Ababa, Ethiopia as regular or private wing between January 1st to December 31st, 2014.

INCLUSION AND EXCLUSION CRITERIA

All medical charts of patients with cervical cancer treated with radiotherapy from January 1st to December 31st, 2014 was included. Those medical charts with unknown regular or private wing was excluded.

STUDY VARIABLES

DEPENDENT VARIABLES

Stage Migration

Tumor control rate at one year

Survival

INDEPENDENT VARIABLES

Age

Histology

Private wing treatment

Regular side treatment

Curative intent treatment

Palliative intent treatment

OPERATIONAL DEFINITIONS

FIGO staging: FIGO staging is a clinical staging system for cervical cancer developed by International Federation of Gynecology and Obstetrics revised in 2009. (32) (See Annex 1)

Stage Migration: The change in the stage between the first radiotherapy session or radiotherapy planning and the stage at first oncologist consultation

One-year tumor control rate: response to treatment after one year of Radiotherapy as per RECIST criteria. (33) (See Annex 3)

Radiotherapy Treatment planning: the process of patient positioning, simulating and Target volume and organ at risk definition prior to radiotherapy treatment.

The first oncologist consultation: The time at which the patient is evaluated by senior oncologist with history, physical examination, all necessary lab tests and diagnostic imaging is done for and final treatment decision is made.

Curative intent treatment: a treatment plan with intension of cure the cancer

Palliative intent treatment: a treatment plan with intension of alleviating pain and improving quality of life of the patient where cure is impossible.

DATA COLLECTION TOOLS AND PROCEDURE

One supervisor, the investigator and one resident was participate in data collection. After consensus was reached with data collectors on the purpose of the study, data extraction techniques, and codes, pretesting of the data extraction format was done prior to the actual study. Pre-test was done on 42 patient record charts, which will not be included in the study (20 private wing and 22 regular side patients). Appropriate modifications was made based on the pre-test result. Prior to data collection, each included patient's chart was given code numbers. The medical chart of each patient will be compared for the presence or absence and

details of essential parameters listed in the study checklist (Annex 1 and 3) jointly by the investigator and the adviser. In addition, discrepancy between the information of patients on private wing service and regular service was evaluated and corrections was made as needed. Data collection was took place between 01.02.2018 and 10.03.2018.

All patient characteristics, tumor characteristics, and information concerning therapy and outcome were extracted from the patients' medical record files. The date of diagnosis was assigned as the date of referral with the suspicion of cervical cancer or the date of biopsy confirmation, whichever is first. The waiting time was calculated between each paths of the patient in the hospital as it was documented on the chart. The information on the date of last follow-up or date of death (if documented) was also extracted from the chart. The information on vital status was obtained from the patients or –in case of death- from the relatives through telephone calls. If patients or relatives were not reached by telephone, the last date of personal contact in Tikur Anbessa hospital was taken from the patients' files. For these patients the additional worst-case scenario analysis was performed with assumption of dead after 6 months of last follow-up date registered on their medical record.

DATA PROCESSING AND ANALYSIS

The revised patient record charts was checked for completeness, cleaned manually, entered in to excel, 2016 statistical software, and then transferred to SPSS windows version 20 for further analysis.

Results are presented as count (%), means \pm standard deviation or median (25th-75thPercentile) depending on data type and distribution. Groups are compared using parametric (t test) and nonparametric (Chi-square, Mann-Whitney U test) tests. Kaplan-Meier curve and survival analysis was performed using Log-rank test to assess significant differences between groups regarding survival. All p values less than 0.05 were considered significant. All data was analyzed using SPSS 20.0 (IBM Corp. Released 2011. IBM SPSS Statistics for Windows, Version 20.0. Armonk, NY: IBM Corp.) and R 3.4.2. (R Core Team (2017). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL <https://www.R-project.org/>.)

ETHICAL CONSIDERATIONS

Ethical clearance was obtained from the Ethical review committee of the Radiotherapy unit of Tikur Anbessa Hospital under Addis Ababa University College of Health Sciences (AAU CHS). To maintain Confidentiality, the name and other personal identification was omitted.

RESULT

In 2014, the estimated number of cervical cancer patients who received radiotherapy was 349. Of those, 242 patient files could be retrieved. Of 242 patients, 152 (63%) were treated on the regular service side and 90 (37%) were treated on Private wing side.

Patient characteristics

The median age at diagnosis was 45 years (range 27 to 75) and 48 years (range 27 to 86) for patients with private wing side and regular service side, respectively ($p=0.8$). Majority of the patients were married. Among these 83 (92%) of private wing and 126 (91%) of regular side patients were living with their partner ($p=0.806$). The rest were either divorced or widowed. Parity ranged from 0 to 13 children. The average number of birth they gave was 5.52 (± 2.86) and 5.72 (± 2.90) on private wing and regular side, respectively ($p=0.565$). In addition to their cervical cancer, 18 (20%) of patients on private wing and 26 (17.1%) on regular side patients had comorbidity ($p=0.573$). HIV was relatively the commonest comorbidity, in which 8 (9%) patients from the private wing and 18 (11%) patients from the regular side patients were HIV Positive ($p=0.66$). (See table 1 for Detail information)

Table 1. Basic demographic and disease-specific data of patients

		Private wing		Regular side		P-value
		patients		patients		
		N	%	N	%	
Marital status	Married	83	92.2%	126	91.3%	0.549
	Divorced	1	1.1%	5	3.6%	
	Widowed	6	6.7%	7	5.1%	
Histology	Adeno-squamous	1	1.1%	1	0.7%	1.000
	Adenocarcinoma	2	2.2%	5	3.3%	

	Squamous Carcinoma	Cell	87	96.7%	146	96.1%	
Comorbidity	Hypertension		7	38.9%	7	26.9%	0.066
	HIV		8	44.4%	18	69.2%	
	Diabetes mellites		3	16.7%	-	-	
	Breast cancer		-	-	1	3.8%	
Address	Oromia		31	34%	53	35%	
	Addis Ababa		24	27%	37	24%	
	Amhara		17	19%	46	30%	
	SNNPR		10	11%	8	5%	
	Tigray		7	8%	7	5%	
	Somali		1	1%	1	1%	
Prior surgery	No		82	91.1%	134	88.2%	0.473
	Yes		8	8.9%	18	11.8%	
Prior Chemo	No		87	96.7%	148	97.4%	1.000
	Yes		3	3.3%	4	2.6%	
Stage at First Oncologist Consultation	I/II		33	36.7%	49	32.2%	0.058 /
	III		45	50.0%	63	41.4%	0.075
	IV		12	13.3%	40	26.3%	
Stage at Start RT	I/II		24	26.7%	40	26.3%	0.157 /
	III		51	56.7%	71	46.7%	0.256
	IV		15	16.7%	41	27.0%	
	no		72	80.0%	139	91.4%	0.010

Stage migration	yes	18	20.0%	13	8.6%	
Concurrent chemo	no	79	87.8%	129	84.9%	0.529
	yes	11	12.2%	23	15.1%	
Brachytherapy Boost	no	90	100.0%	152	100.0%	-
	yes	0	0.0%	0	0.0%	
Intent of RT	curative	67	74.4%	84	55.3%	0.003
	palliative	23	25.6%	68	44.7%	
Tumor Control at 1 year (RECIST)	SD	1	2.4%	12	21.1%	0.013
	PR	0	0.0%	2	3.5%	
	PD	10	24.4%	8	14.0%	
	CR	30	73.2%	35	61.4%	

Waiting time and stage Migration

Waiting time for radiotherapy at different paths, which was evaluated using the median of the interval between the diagnostic confirmation and the first radiotherapy session, was summarized in figure 1 below. The median time from first diagnosis to referral to Tikur Anbessa hospital was 3 days (range 0 to 20 days) and 1 day (range 0 to 13.5 days) for private wing and regular side patients, respectively ($p=0.045$). The median time took to the patients to report to Tikur Anbessa hospital triage center after referral was 5.50 days (range 2 to 29 days) for private wing and 4 days (range 1.5 to 10.5) for regular patients ($p=0.079$). After the triage center the private wing patients clerked faster than regular side patients; the median of waiting time was 23 days (9 to 59 days) in private wing and 56 days (range 16.5 to 109 days) in regular side patients ($p < 0.001$). After the first physician evaluation the median time it took to be seen by oncologist for first time was 4 days (range 1 to 13 days) for private wing and 7 days (range 5 to 15.5 days) for regular side patients ($p=0.001$). However, after the first oncologist consultation the private wing patients waited more time than the regular side patients to receive Radiation treatment; the median of 92.5 days (range 12 to 153 days) and 39 days (8.5 to 108 days) for private wing and regular patients, respectively ($p=0.023$). The overall

waiting time from the first date of diagnosis to the first session of Radiotherapy treatment was a median of 185 days or ~ 6 months (range 102 to 255 days or ~3 to 0 months) and 164 days or ~ 5 months (range 86 to 267 days or ~ 2 to 8 months) for private wing and regular side patients, respectively (p=0.522). (Figure 1)

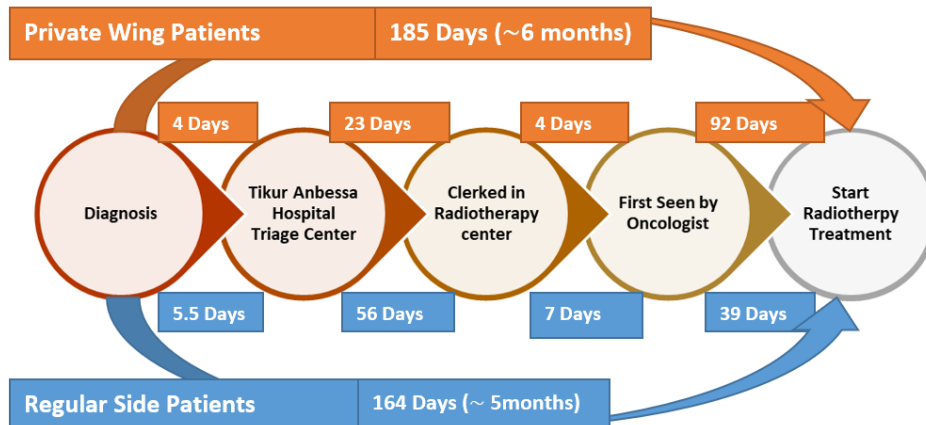
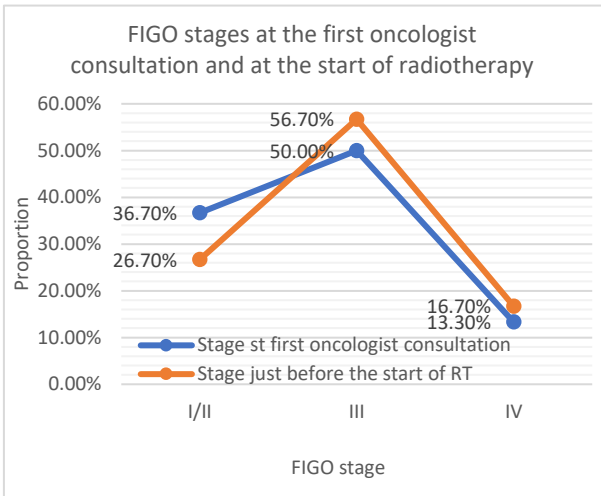


Figure 1: Median waiting time for receipt of Radiotherapy at each treatment path.

The FIGO stage of the patients during the first oncologist consultation was; Stage I/II was 33(36.7%) and 49(32.2%), stage III 45(50.0%) and 63(41.4%) and stage IV was 12(13.3%) and 40(26.3%) in private wing and regular sides, respectively (p=0.058 / 0.075). (Figure 2) During the waiting time, some patients showed stage migration from their baseline at the first oncologist consultation. The stage migration was seen more on private wing side patients, which was 18 (20%) and 13 (8.6%) among private wing and regular side patients, respectively (p=0.010). The restaging of the patients just before the start of radiotherapy was 24(26.7%) and 40 (26.3%) stage I/II, 51(56.7%) and 71 (46.7%) stage III and 15(16.7%) and 41(27.0%) stage IV in private and regular side patients, respectively (p=0.157/0.256). (Figure 2).

a.



b.

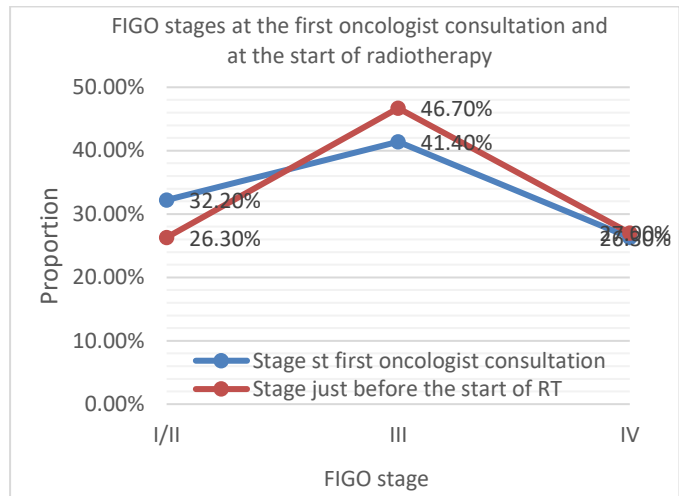


Figure 2: FIGO Stages during the first oncologist consultation and start of radiotherapy (a) private wing patients (b) regular side patients

Treatment Delivery and out come

Most of the patients had no surgery for a cervical cancer treatment prior to their presentation to radiotherapy center. There were eight (8.9%) and eighteen (11.8%) patients underwent surgery from private wing and regular side, respectively ($p=0.473$). In relation to this, three (3.3%) of private wing patient and Four (2.6%) of regular side patients were received chemotherapy prior to their presentation to radiotherapy center ($p= 1.000$).

Since there was no brachytherapy, service in 2014 all the radiotherapy treatment was delivered with EBRT Cobalt 60 machine. Concurrently with Radiotherapy 11(12.2%) and 23 (15.1%) were received chemotherapy from private wing and regular side, respectively ($p=0.529$). Most of the patients on private wing were treated with curative intent relative to regular side patients, 67(74.4%) and 84 (55.3%), respectively ($p=0.003$). In the rest on patients, the intension of treatment was palliative.

Most of the patients had lost from follow-up in Tikur Anbessa hospital before 1 year. The numbers of patients who continue follow-up for at least for 1 year and had recorded response assessment at 1 year after Radiotherapy were 41 (46%) and 57 (38%) in private wing and regular sides, respectively. The proportion of patients with complete responses were higher on private wing side while the proportion of stable diseases were more in regular side patients. According to RECIST criteria complete response 30(73.2%) and 35(61.4%), Partial response 0 and 2 (3.5%), Progressive disease 10(24.4%) and 8(14.0 %) and stable disease 1(2.4%) and 12(21.1%) was seen among private wing and regular side patients, respectively ($p=0.013$) (Table 1)

Survival of patients

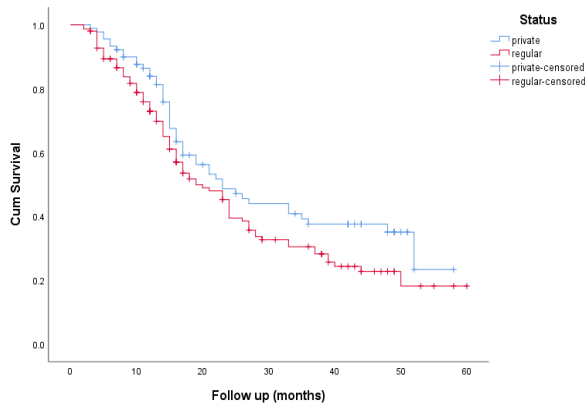
Overall survival

Among 242 patients included in the study, 142 (59%) deaths were registered on the both sides [48 (53%) in private wing and 94 (62%) in regular side patients] and 56 (23%) patients [private wing 26 (29%) and regular side 30 (20%)] were alive. The rest 44 (18%) patients [16 (18%) in private wing and 28 (18%) in regular side] their vital status was unknown; since there was no information regarding the vital status found from their medical record or neither reached by telephone calls during the study. Therefore, these patients were entered as alive and censored at the time of last personal appointment documented in the files. For these patients the additional worst-case scenario analysis was performed with assumption of dead after 6 months of last follow-up date registered on their medical record.

The estimated of 52 months overall survival probabilities were 21.5% in the main analysis. The one-year, two-year, three-year and four-year overall survival probabilities were 77%, 43%, 33.2% and 27.6%, respectively. (Table 2) The median overall survival time was 21 months. There is no statistically significant survival difference between private wing and regular side patients, median time of survival was 23 and 19 months, respectively ($p=0.076$). (Figure 3a)

However, in the worst-case scenario the 52 months overall survival probability was declined to 14.6%. The one-year, two-year, three-year and four-year overall survival probabilities were 75.1%, 33.3%, 24.6% and 20.4%, respectively. (Table 2). The median overall survival time was 18 months. The median time of survival of between private wing and regular side patients was remained statistically non-significant in the worst-case scenario also, which was 19 and 17 months, respectively ($p=0.061$). (Figure 3b)

a.



b.

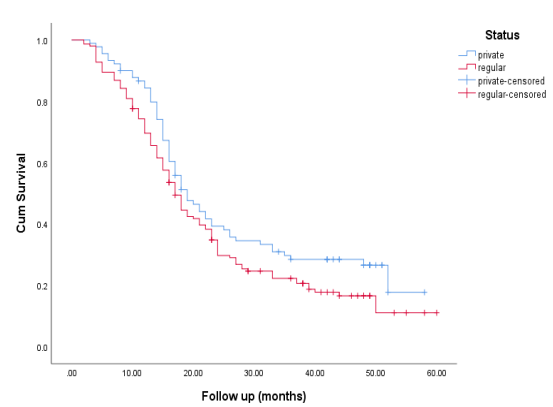


Figure 3: Overall survival of patients according to their treatment side to receive radiotherapy, private wing and regular side: (a) The main Kaplan-Meier analyses, and (b) The worst-case Kaplan-Meier analyses.

Table 2: The survival table showing estimated surviving proportion of patients with time in main and worst-case scenario Kaplan-Meier analysis

	Main Analysis		Worst-case Scenario	
Time (months)	Estimate of surviving proportion	SE	Estimate of surviving proportion	SE
12	77%	0.028	75.1%	0.028
24	43%	0.036	33.3%	0.031
36	33.2%	0.035	24.6%	0.029
48	27.6%	0.035	20.4%	0.028
52	21.5%	0.048	14.6%	0.036

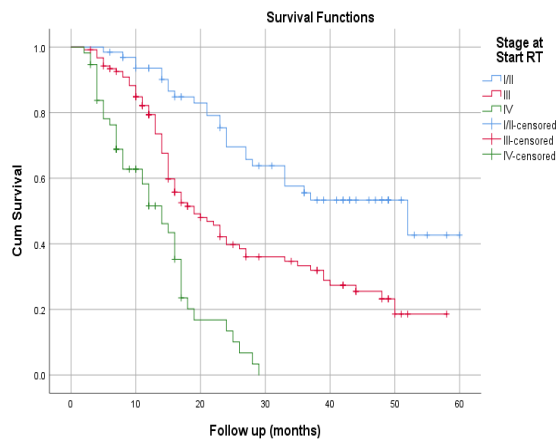
Multi-variate analysis of survival

Table 3 below shows the summary of the median survival time and association for each variable with survival.

FIGO Stage and survival

The FIGO stage of the patients shows significant impact on survival of these patients. The estimated median time of survival based on the stage during the receipt of radiotherapy was 52, 19 and 14 months for stage I/II, stage III and IV, respectively ($p < 0.001$) in main analysis. (Figure 4a). In the worst-case Scenario, the median survival was declined 37, 17 and 13 months for stage I/II, stage III and stage IV patients, respectively ($p < 0.001$) (Figure 4b)

a.



b.

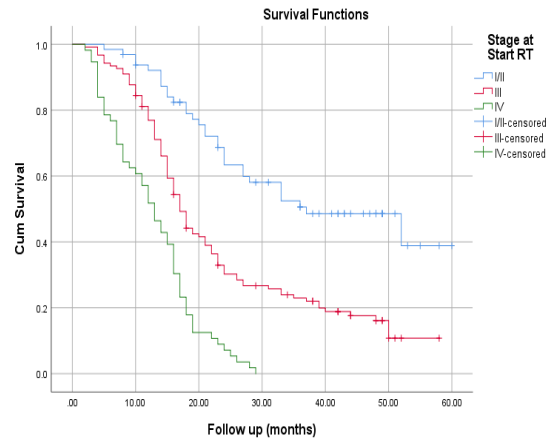
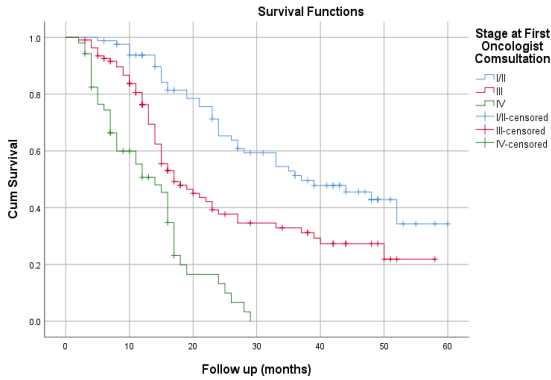


Figure 4: Overall survival of patients according to the stage during receipt of radiotherapy: (a) The main Kaplan-Meier analyses, and (b) The worst-case Kaplan-Meier analyses.

The median survival time according to FIGO stage at the first oncologist consultation was 37, 17 and 14 for stage I/II, III and IV cases in main analysis, respectively ($p < 0.001$). (Figure 5a) In the worst-case scenario, the survival of patients according to the stage at first oncologist consultation was 33, 17 and 12 for stage I/II, III and IV patients, respectively ($p < 0.001$). (Figure 5b)

a.



b.

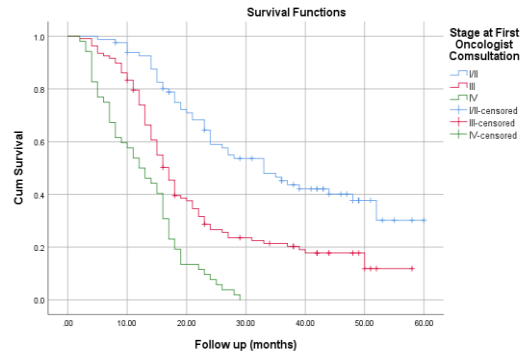


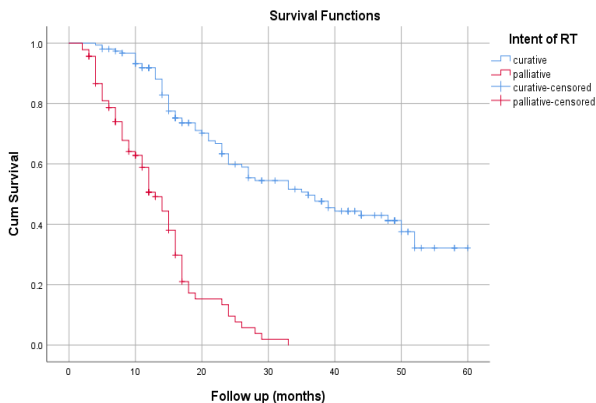
Figure 5: Overall survival of patients according to the FIGO stage during first oncologist consultation: (a) The main Kaplan-Meier analyses, and (b) The worst-case Kaplan-Meier analyses.

The stage migration showed no significant impact on survival of the patients ($p=0.507$ and $p=0.680$ in main and worst-case scenario analysis, respectively). (table 3)

Intent of radiotherapy and survival

As expected the patients treated with curative intent had significantly better survival as compared to those treated with palliative intent. The median survival was 36 and 13 months for patients treated with curative and palliative intent, respectively in main analysis group ($p<0.001$). (Figure 6a). In the worst-case scenario the median survival time was 26 and 12 months for patients treated as curative and palliative intent, respectively ($p<0.001$). (Figure 6b).

a.



b.

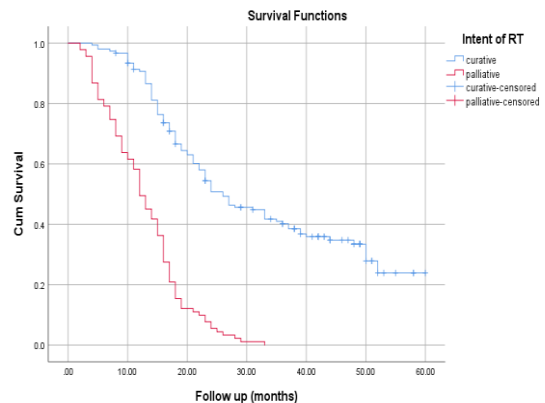
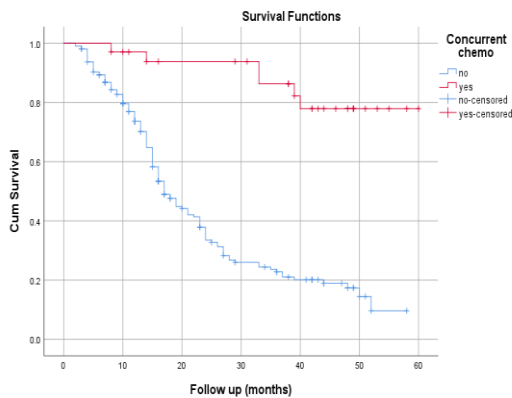


Figure 6: Overall survival of patients according to the intent of radiotherapy: (a) The main Kaplan-Meier analyses, and (b) The worst-case Kaplan-Meier analyses.

Concurrent chemotherapy and survival

As shown in table 1 above, 24 patients (14%) received concurrent chemotherapy with radiotherapy. Even though, the proportion of patients received concurrent chemotherapy was small, they showed significantly better survival. The median survival of these patients is not reached in both main and worst-case analysis. However, for patients who did not received concurrent chemotherapy with radiation the median time of survival was 17 months in both main and worst-case analysis. ($p < 0.001$) (Figure 7a and b).

a.



b.

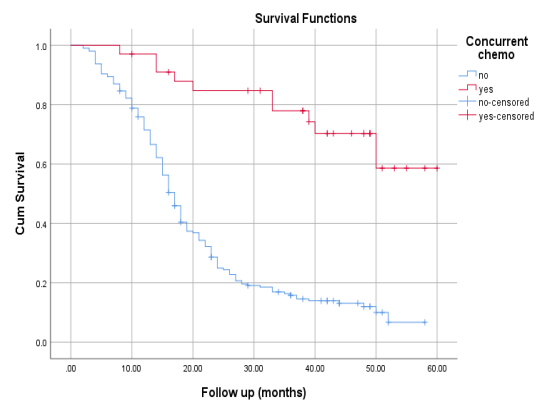
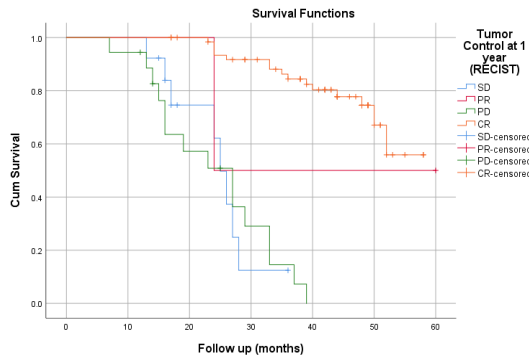


Figure 7: Overall survival of patients according to the receipt of concurrent chemotherapy (a) The main Kaplan-Meier analyses, and (b) The worst-case Kaplan-Meier analyses.

One-year tumor control rate and survival

Among the whole patients 98 (40.5%) had follow-up and recorded response assessment at one-year after radiotherapy. The median time of survival according their response assessment at 1 year was not reached for complete responders in main analysis. The median survival was 27, 25 and 24 months for partial response, stable disease and progressive disease, respectively in main analysis. In the worst-case scenario analysis, the median time of survival was 52, 24, 24 and 20 months for complete responders, partial responders, stable disease and progressive disease, respectively. (Figure 8 a and b)

a.



b.

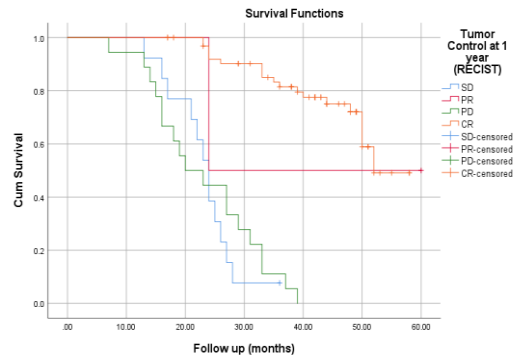
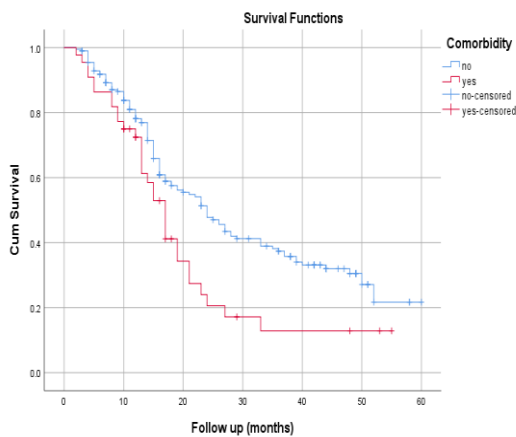


Figure 8: Overall survival of patients according to one-year tumor control rate per RECIST criteria (a) The main Kaplan-Meier analyses, and (b) The worst-case Kaplan-Meier analyses.

Comorbidity and survival

The proportion of patients with comorbidity had significantly lower survival as compared to patients without. The median survival time was 17 and 24 months for patients with and without comorbidity, respectively ($p=0.010$) in the main analysis. In the worst-case scenario, the median survival was 17 and 18 months for patients with and without comorbidity, respectively ($p=0.013$). (Figure 9)

a.



b.

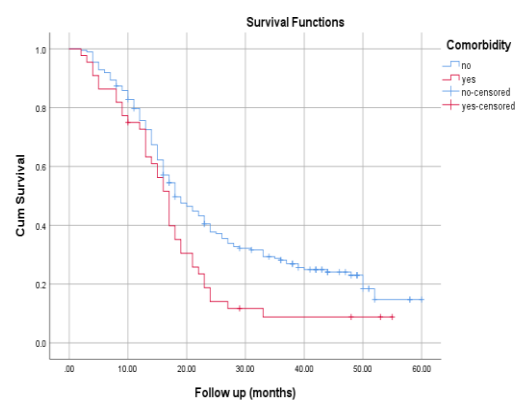
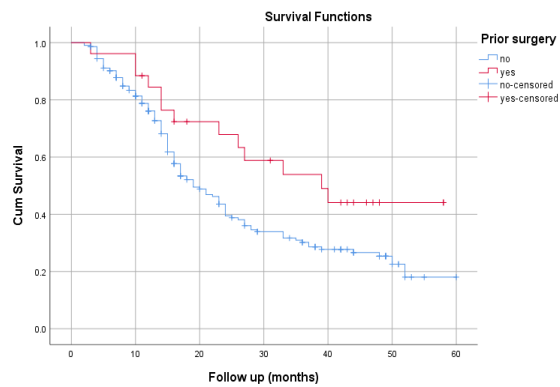


Figure 9: Overall survival of patients according presence or absence of comorbidity (a) The main Kaplan-Meier analyses, and (b) The worst-case Kaplan-Meier analyses.

Prior surgery and survival

Prior surgery for cervical cancer was associated with better survival. The median survival was 39 months for patients underwent prior surgery and 19 months for patients without surgery ($p=0.039$). (Figure 10a) In the worst-case scenario, the median survival of patients who underwent prior surgery was 33 months while for those who had no surgery was 17 months. ($p=0.008$) (Figure 10b)

a.



b.

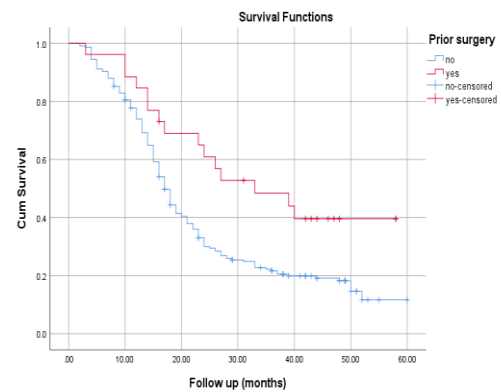


Figure 10: Overall survival of patients according presence or absence of prior surgery for cervical cancer treatment (a) The main Kaplan-Meier analyses, and (b) The worst-case Kaplan-Meier analyses.

The other variables such as age, address, marital status, histology and prior chemotherapy, didn't show significant association with survival in this study. (Table3)

Table 3: The median survival time according to multiple variables and level of statistical significance

Patients	treatment	Median Survival Time in main Analysis			Median survival time in the worst-case scenario				
		Estimate (months)	95% CI		p-value	Estimate (months)	95% CI		p-value
			Lower Bound	Upper Bound			Lower Bound	Upper Bound	
side									
Private wing		23	15.479	30.521	0.073	19	15.446	22.554	0.061
regular side		19	15.031	22.969		17	15.152	18.848	
Prior surgery for cervical cancer									
No surgery prior to RT		19	15.343	22.657	0.039	17	15.642	18.358	0.008
Surgery prior to RT		39	20.743	57.257		33	13.091	52.909	
Chemotherapy before RT									
No chemotherapy before RT		21	17.468	24.532	0.269	18	16.335	19.665	0.112

Received chemotherapy before RT	28	10.036	45.964		28	10.036	45.964	
FIGO stage at the first Oncologist consultation								
Stage I/II	37	22.443	51.557	<0.001	33	24.143	41.857	<0.001
Stage III	17	11.739	22.261		17	15.195	18.805	
Stage IV	14	10.505	17.495		12	7.962	16.038	
FIGO stage at the start of RT								
Stage I/II	52	25.143	78.857	<0.001	37	20.755	53.245	<0.001
Stage III	19	13.997	24.003		17	15.234	18.766	
Stage IV	14	10.144	17.856		13	10.257	15.743	
Stage Migration								
No stage migration	20	16.387	23.613	0.507	18	16.282	19.718	0.68
Has stage migration	26	18.898	33.102		19	13.546	24.454	
Concurrent chemotherapy with RT								
No concurrent chemotherapy	17	14.786	19.214	<0.001	17	15.711	18.289	<0.001
Received concurrent chemotherapy	NR	NR	NR		NR	NR	NR	
Intension of the RT treatment								
Curative intent	36	25.39	46.61	<0.001	26	20.376	31.624	<0.001
Palliative intent	13	10.714	15.286		12	10.13	13.87	
Response assessment at 1-year after RT								
SD	25	22.368	27.632	<0.001	24	21.708	26.292	<0.001
PD	24	NR	NR		20	11.684	28.316	
PR	27	17.656	36.344		24	NR	NR	
CR	NR	NR	NR		52	NR	NR	
Marital status								
Married	23	18.304	27.696	0.474	18	16.338	19.662	0.524
Divorced	8	0	23.363		8	0	26.004	

Widowed	17	12.289	21.711		17	11.495	22.505	
Histology								
SCC	21	17.274	24.726	0.449	18	16.402	19.598	0.209
Others	40	0	103.445		40	0	103.44	
							5	
Presence of comorbidity								
No comorbidity	24	19.497	28.503	0.01	18	15.133	20.867	0.013
with comorbidity	17	14.247	19.753		17	15.215	18.785	
Overall survival	21	17.167	24.833		18	16.369	19.631	

DISCUSSION

Most of our patients had an advanced stage of disease at presentation, as the case of many sub-Saharan African countries (20, 34, 35). Majority of the patients has stage III and IV disease at the time of first oncologist consultation. In several previous publication, advanced stage at presentation was one of the major challenge in the treatment and cure cervical cancer in Ethiopia (9, 26). Some of the reasons for late presentation could be absence of screening, low awareness of the disease, the poverty, less access to modern treatment and low perception of the benefit of modern treatment (9, 26, 36-38). Even though, Survival of cervical cancer patients affected by several factors, one of the major prognostic indicator for survival of cervical cancer is stage at presentation. Since the treatment plan for cervical cancer is mainly stage based, advanced stage at presentation makes those patients suitable only for palliation, which has less impact on survival. (39) The other factors such as the time to treatment, performance status, comorbidity, mode of treatment, and histological subtype, and location are some of the others factors influencing survival. (40)

As we can see from our result, the median waiting time was very long which is 185 days for private wing and 164 days for regular side patients. The bottleneck for long waiting was happen between Triage to first oncologist consultation and first oncologist consultation to start of treatment. This indicate the less number of oncologist and treatment machine, which cannot meet the ever-increasing need. (16) Because of long waiting, about 13% of the patient's experience stage migration from their baseline at first oncologist consultation. As we can see from our result more stage migration was seen in private wing patient than regular patients (20% vs 9%, $p=0.01$) due to long waiting after first oncologist consultation was high

in private wing patients (92 days vs 39 days, $p=0.001$). The stage migration will further compromise survival (9).

One of the most important findings from this study was FIGO stage at start of radiation treatment was the most important determinant of survival. In our finding, there was slightly better but no statistically significant survival difference in the preference of private wing side (median survival 23 vs 19 months, $p=0.076$). This is because; the base line stage at diagnosis could be changed due to long waiting time for treatment. Although, the longer waiting and larger stage migration were seen in private wing patients; the relatively better survival still seen in private wing patients. This is most likely because of more stage IV patients on the regular side patients (16.7% vs 27%, $p=0.256$) which shows the importance of stage at start of radiotherapy in predicting survival. The other explanation, could be due to more curative treatment (74% vs 55%, $p=0.003$) and as a result more complete response rate (73% vs 61%, $p=0.013$) in the private wing patients as compare to regular side patients.

The 1-year and 2 year overall survival probability in our study was lower than previous studies in Tikur Anbessa hospital. According to the study of Kantelhardt et al, which included patients treated between 2008 to 2012, the one year and Two year survival probability was 90% and 74% (45% in the worst-cases analysis), respectively. (9) Similarly in the study of Moelle et al, which included patients treated between 2008 to 2013, the one year and two year survival was 84% (54% in the worst case) and 64% (35% in the worst case), respectively (26). The result of the first 2 years survival in both studies were higher than our findings. Despite the similarity of patient and disease characteristics and treatment method, the main difference between those studies and ours was the waiting time. For example, the waiting time from diagnosis to receipt of radiotherapy was 5/6 month in our study, but in the study of Kantelhardt et al, the waiting was 3.8 month.(9) This show the longer the interval between the diagnostic confirmation and the first radiation session probably have negative impact on survival as it resulted in tumor progression and stage migration.

The reasons for long waiting time in Tikur Anbessa hospital radiotherapy center mainly, the imbalance between the continuously increasing number of patients and limited number of oncologists and supporting professionals as well as treatment machine. The other possible factors for longer waiting could be delay in diagnostic and staging confirmations, such as waiting for biopsy and radiological investigations. Additionally, the increasing number of

patients especially who arrived in poor medical conditions when diagnosed or who are in emergency state at presentation, treated first as they need urgent intervention for keeping them alive. This contributed also for long waiting as they push forward the time to treatment of fit patients.

In addition to stage at presentation or treatment and timely therapeutic options, lack access of proper treatment technique and equipment, affect overall survival negatively. For example in more developed countries, according to statistics from the American Cancer Society, the five-year survival rate by stage is stage 60 %, 30 % and 16% for stage II, III and IV patients, respectively (41). In our study the survival result we found was 15-20% lower when matched with stage in developed countries (41). This is most probably due to difference in treatment technique, in radiotherapy machine and absence of brachytherapy in our cohort. Brachytherapy was of the important treatment modality, which proved to improve overall survival long time ago, but lacking in our cohort (42). In the single institution experience from Ghana, patients treated with Coblt-60 machine and then with brachytherapy boost has 86% of 3-year overall survival (43), which is much higher than our patients treated with curative intent. However, in the Kenya where the treatment is provided with Coblat-60 machine but without brachytherapy boost, reported median survival of 18, 15 and 11 months for Stage II, III and IV patients, respectively (20). Here, the median survival for stage II patients were higher in our case, however the median survival of stage III and IV is comparable. This shows the influence of brachytherapy on survival of cervical cancer patients even in developing countries like ours. However, since 2015, brachytherapy services have finally been installed and used daily at Tikur anbesa hospital radiotherapy center.

As it is known, several publications at the end of 1990s changed the standard treatment for locally advanced cervical cancer patients, making concomitant chemo-radiotherapy the primary treatment option because it proved that it provided better results than when radiotherapy alone is used (44-46). The fundamental idea behind the use of combined treatment is based on the synergistic effect between both modalities: chemotherapy acts as a radio-sensitizing agent that increases the tumor's susceptibility to the effects of radiation. Since then, concurrent chemotherapy with radiotherapy is the standard of care according to international guidelines (14, 47). The treatment protocol of cervical cancer in Tikur Anbesa hospital radiotherapy center, also recommend concurrent chemo radiotherapy especially in

curative setting (9). However, only 14% of the patients our cohort were able to get combined treatment. Those patients who received concurrent chemotherapy had a very good survival and median survival time is not reached yet. The reason for absence concurrent chemotherapy for most of the patients is most likely financial and logistical obstacles (26).

The presence of comorbidity was also found to be one of the predictors of survival in our study (median 17 months vs 24 months, $p=0.010$). The commonest comorbidity was HIV infection, which was recorded in 11% of our cohort. HIV positive cervical cancer patients have poorer outcome mainly due to late presentation and an increase in treatment related complication, which leads to more frequent interruptions of therapy and lower rates of treatment completion (48, 49). Additionally HIV positive patients also receive concurrent chemotherapy less often due to increase in hematologic toxicity (49). However, even HIV patients with higher CD4+ count and took proper treatment have less good outcome than the non-HIV positive patients treated similarly. One prospective study in HIV patients with cervical cancer shows, HIV infection more than doubled the risk of death among women who received curative guideline-concordant therapy even in the context of good access to and use of ART (50). Patients with cervical cancer who has concomitant HIV infection has higher risk of recurrence than non-HIV infected patients even after complete response rate (51). The mechanism poor survival is not clearly known in such group of patients. However, the residual deficiency in cellular immunity could contribute to poorer responses to cervical cancer therapy in women with HIV infection, since the immune responses from tissue lymphocytes also contribute to the clearance of residual cancerous cells after treatment (50).

STRENGTH OF THE STUDY

To our knowledge this study is the only study reporting the survival of Ethiopian cervical cancer patients beyond 2 years, which is 52 months. The study showed the predictors of cervical cancer survival in Ethiopia. With the other patient and disease related predictors, it also showed the impact of waiting time and stage migration in the overall treatment outcome. Especially with increasing number of patients and unchanged radiation treatment infrastructures the current waiting time is even worse. We hope this study will be used as an evidence to support the effort started to improve cancer care in the country. It can also help as the reference for the future studies and to assess improvements over time in various actions taken to improve access to care.

WEAKNESS OF THE STUDY

Being retrospective study and the loss of many patient records was one of the weakness. Considering the various confounding factors to influence survival, it would have been more complete if the radiotherapy dose and schedules, the toxicities and adherence information's were included.

CONCLUSION

The survival of cervical cancer patients remains low in Ethiopia, despite the higher cure rate of the disease. The reason for poor survival were advanced stage at presentation, very long waiting time for treatment and as a result stage migration, the old treatment machine and technique and absence of brachytherapy are some of the reason. Therefore, the parallel oriented efforts in all direction such as prevention, early detection and improving access to standardized care are required.

RECOMMENDATION:

Advanced stage at presentation and longer waiting after presentation are the major factors for poor survival after treatment. It is very important that to establish more radiotherapy facilities to cope up with the increasing number of patients. It is important to implement the recommendation of the treatment according to the protocol of the department. Patients up to stage IVa should receive curative dose radiotherapy with concomitant chemotherapy. The availability and affordability of chemotherapy and analgesics should be improved. The socio-economic, psychological support, well-trained maintenance and supportive therapies are necessary. The transformation from 2D to 3D treatment technique, replacement of Cobalt-60 machine to Linacs and the proper use of brachytherapy should be applied. In line with improving treatment provided; working on prevention, early detection and improving awareness for the population as well as health professionals is mandatory for better outcome.

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ANNEXES

ANNEX 1: FIGO STAGING

Stage IA Invasive cancers diagnosed by microscopy only

- IA1 Measured stromal invasion ≤ 3.0 mm in depth and extension of ≤ 7.0 mm
- IA2 Measured stromal invasion > 3.0 mm in depth and extension of not > 7.0 mm

Stage IB Clinical visible lesions limited to the cervix

- IB1 Clinical visible lesion ≤ 4.0 cm in greatest dimension
- IB2 Clinical visible lesion > 4.0 cm in greatest dimension

Stage II Invasive cancers extending beyond the uterus, but not to the pelvic wall or the lower one-third

of the vagina

- IIA1 Clinical visible lesion ≤ 4.0 cm in greatest dimension without parametrial invasion
- IIA2 Clinical visible lesion > 4.0 cm in greatest dimension without parametrial invasion
- IIB Clinical visible lesion with obvious parametrial invasion

Stage III Invasive cancer extends to the pelvic sidewall and/or lower one-third of the vagina and/or

causes hydronephrosis

- IIIA Cancer involves the lower one-third of the vagina without extension to the pelvic sidewall
- IIIB Cancer extends to pelvic sidewall and/or causes hydronephrosis and/or non-functioning kidney

Stage IV Invasive cancer involves organs of pelvis or has spread outside the true pelvis

- IVA Cancer involves the mucosa of the bladder or rectum (bullous edema does not categorized lesion as IVA)
- IVB Cancer spreads to distant organs

*International Federation of Gynecology and Obstetrics (32)

ANNEX 2: RECIST Criteria

RECIST	Change in sums of longest diameters
CR	Disappearance the tumor
PR	30% decrease in tumor size
SD	Neither PR nor PD criteria met
PD	20% increase; no CR, PR, or SD documented before

*EUROPEAN JOURNAL OF CANCER, 2009 (33)

ANNEX 3: QUESTIONNAIRE

1. Demographic Data
 - A. Name: _____
 - B. Age : _____
 - C. Adressa: _____
 - D. Tel: _____
 - E. Marrietal Status: _____
 - F. Parity: _____
2. Clinical Data:
 - A. Histology: SCC Adenocarcinoma Other: _____
 - B. Date of biopsy result Known: _____
 - C. Comorbidity: HIV HTN DM
Other: _____
 - D. Date of referral to TAH: _____
 - E. Date of arriving to TAH triage center: _____
 - F. Date of date first seen by RT doctor (Clerked date): _____
 - G. Prior surgery: Yes No
If Yes date: _____
 - H. Prior chemotherapy: Yes No
If Yes date: _____
3. Timing of oncologic treatment
 - A. First oncologist consultation (result):
Date: _____ FIGO Stage: _____
 - B. First day of start Radiotherapy (planning)
Date: _____ FIGO Stage: _____
 - C. Intent of radiotherapy: Radical Palliative Adjuvant
 - D. Concurrent chemotherapy: Yes No
 - E. Brachytherapy boost: Yes No
4. Follow up and vital status
 - A. Tumor control rate at 1 year
CR PR SD PD
 - B. Date of last Follow up: _____
 - C. Current Vital status: Alive Dead
 - D. If Dead:
 - Date of death: _____
 - Cause of death: Cancer Non-cancer Unknown