UNIVERSITY OF NAIROBI

Barriers to timely initiation and completion of guideline concordance treatment for patients with carcinoma of the cervix stage 1b2-IVa at Cancer Treatment Centre, Kenyatta National Hospital.

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A THESIS RESEARCH SUBMITTED TO THE DEPARTMENT OF RADIOLOGY IN PARTIAL FULFILLMENT FOR THE AWARD OF THE DEGREE OF MASTER OF MEDICINE IN RADIATION ONCOLOGY, FACULTY OF HEALTH SCIENCES, UNIVERSITY OF NAIROBI

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Declaration

This research is my original work and has not been presented for a degree in any other institution.No part of this research may be reproduced without the prior written approval of the author and/ or the University of Nairobi.

Signature: _____   **Date:** 7th November, 2023

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Supervisor' Approval

This research has been submitted to the Department of Diagnostic and Radiation Medicine, University of Nairobi, with our approval as university supervisors.

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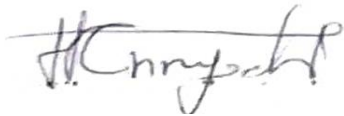
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CERTIFICATE OF AUTHENTICITY

This is to certify that this dissertation is the original work of **Dr. Collin Masolo Nandasaba,** MMed student, Registration number **H58/34005/2019**, Department of Diagnostic Imaging and Radiation Medicine. This research was carried out at the Kenyatta National Hospital, Cancer Treatment Centre. It has not been presented to any other institution or university for a ward of degree or diploma.

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DEDICATION

I would like to dedicate this dissertation to my lovely wife Centrine and our lovely children,

Barak and Trizabeth for being there through this journey and offering me support every step of

the way. I would also like to dedicate this dissertation to my sisters Namweyi and Nakhungu for

being my best critics and supporters. Finally, I would like to dedicate this dissertation to my

parents for the support they have given me and for believing in me.   This journey would not

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List of abbreviations and acronyms

- EBRT- External Beam Radiotherapy

- FIGO- Fédération Internationale de Gynécologie Obstétrique (International Federation of Gynecology and Obstetrics)

- HIV- Human Immunodeficiency Virus.

- HDR- High Dose Rate

- HPV – Human Papillomavirus

- KNH- Kenyatta National Hospital

- KNH_UoN ERC-Kenyatta National Hospital /University of Nairobi Ethics and Research Committee.

- NHIF- National Health Insurance Fund

- SPSS-statistical Package for Social Sciences.

List of tables, charts and graphs

Operational definitions

- Gray -the derived SI unit of absorbed ionizing radiation dose equivalent to absorption per unit mass of one joule per kilogram of irradiated materials (symbol Gy).

- Chemoradiotherapy- combined treatment modality using chemotherapy and radiotherapy concurrently.

- Brachytherapy- this is a form of internal radiotherapy making use of a radioactive source embedded within the body i.e., in a cavity, lumen, on the surface or a short distance from the surface.

- Simulation- in cancer treatment, this is the process by which radiation treatment is planned by accurately locating and marking the target area

- First specialist assessment – the date the patient was first seen by a specialist radiation oncology physician.

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Abstract

Background.

Cervical carcinoma is the second most common cancer among women in Kenya, with an incidence of 2454 per year according to Globocan 2020. Most patients (80.5%) present with locally advanced form of carcinoma of the cervix. The standard treatment paradigm involves chemo-radiotherapy and brachytherapy delivered in less than 56 days. Exceeding this time period has been associated with poor local control of the disease and poor disease specific survival. Studies assessing the treatment timing patterns have observed that less than 50% of the patients complete treatment within the 56 days. A combination of patient, and system related factors seem to affect the overall treatment timings.

Justification for the study

Although studies have shown that the total time taken to complete treatment in locally advanced cervical carcinoma affects treatment outcomes, no study in Kenya has yet evaluated the treatment timing patterns in patients with this disease and the factors affecting these patterns. This study sought to shed some light on this topic and identify areas of improvement in the treatment of these patients.

Study design

The study was a retrospective analytical study analyzing the treatment timing patterns for patients with cervical carcinoma stage Ib2-IVA treated at the cancer treatment center (KNH) between January 2016- December 2020. A structured questionnaire was used to excerpt data from randomly sampled patient files and uploaded to Excel for cleaning and subsequently SPSS for analysis. Descriptive analysis was grouped into continuous and categorical variables, with categorical variables analyzed using frequencies and percentage. Continuous variables were

analyzed using mean and median. Inferential analysis was using univariate, bivariate and multivariate analysis.

Data findings

The median treatment starting time was 71 days with 58.5% of the patients starting their treatment within ninenty days of a histologically confirmed diagnosis. Being employed and having a residence outside Nairobi positively influenced treatment starting times whereas longer duration of symptoms negatively influenced treatment starting times.

The median definitive treatment time was 80 days, with 34.5% of the patients completing their treatment within the guideline concordance period of 56 days. Having a secondary or higher education and having residence outside Nairobi positively influenced definitive treatment timelines.

Study limitations

Considering that the study was retrospective in design, some qualitative data was found to be missing from patient files or was poorly and inconsistently recorded and could not be traced. Consequent to this, variables such as treatment related factors, logistical administrative factors, did not reach the statistical threshold for meaningful analysis and thus were excluded from the final analysis.

Recommendations

- Extension of patient navigation program to the point of histological diagnosis can be used in an attempt to shorten the treatment initiation timelines.

- Prospective qualitative studies should be done to identify actionable qualitative factors influencing these timelines for example treatment related factors.

- Prospective multicenter studies should be done to audit the treatment timelines given that the number of public facilities offering cancer treatment (radiotherapy and brachytherapy) have increased from one (during the study period) to five currently.

- Institute proper and comprehensive documentation in the medical informatics to avoid loss of qualitative data that can be used in medical audits to better healthcare through policy changes.

CHAPTER 1-BACKGROUND:

Cervical carcinoma is the development of abnormal cells along the lining of the uterine cervix. It is the second commonest form of cancer in female gender in the developing world, with breast cancer being the commonest. The WHO in 2018, estimated that about 33 per 100000 women in Kenya had cervical carcinoma and about 22 per 100000 died from it. Furthermore, according to GLOBOCAN 2020, it is estimated that the annual incidence of this disease stands at 2454 women per year. This is projected to rise to 4261 per year, with estimated 2955 deaths by 2025 if urgent interventions for screening, early detection, and treatment are not initiated. This is an unfortunate situation given that it is not only preventable, but also curable in its early stages (Sung et al., 2021).

Majority of the patients in sub-Saharan Africa present with locally advanced form of the disease. A study done in Kenya demonstrated that up to 80.5% of patients presented whistle in stage 2b and above (Maranga et al., n.d.). For stages 1b2-IVa, chemo radiotherapy, with high dose rate brachytherapy, has come to be accepted as the most recommended combined treatment modality (Morris et al., 1999; Pearcey et al., 1999; Rose et al., 1999; Thomas, 1999). Moreover, its timely delivery has been associated with excellent local control of the disease. It has been demonstrated in past studies that extension of the total time taken to treat patients with an intact carcinoma of the cervix, getting chemo-radiotherapy with brachytherapy beyond 8 weeks (56 days) is detrimental to the local pelvic control of the disease (S. W. Chen et al., 2003; Perez et al., 1995; Song et al., 2013).

In Kenya, a study done in 2013 looking at the "treatment outcomes of advanced cervical carcinoma" revealed that only 6.7 % of the patients underwent chemo radiotherapy and brachytherapy to completion (Maranga et al., n.d.). An updated review of treatment outcomes

done in 2018 by Osok et al. revealed that up to 62.1% of the women completed their radiotherapy treatment. It is not clear whether this included brachytherapy. The projected survival estimate for five years was 59%, based on one year observation considering that over 82.3% of the patients were subsequently lost to follow-up after the first year with no deaths observed during this period (Osok et al., n.d.). In both studies, the treatment timings patterns were not analyzed.

It is with this in mind that this study intents to analyze the treatment timelines of this disease and identify modifiable factors, if any, affecting treatment timing patterns of patients diagnosed with locally advanced cervical carcinoma treated at the Cancer Treatment Center, KNH. It is hoped that the study may create avenues for remedial actions if, and where modifiable factors that are adversely affecting treatment timing for this cohort of patients are identified.

The Cancer Treatment Centre at Kenyatta National Hospital was established in 1968 and has grown since then. It currently has two cobalt 60 machines, and one linear accelerator (Linac). The Linac is an Elekta, able to treat with two photon energies, 6MV and 15 MV. Planning images are obtained from the diagnostic CT scans using setups similar to the treatment machine and transferred to the Oncentra planning system. 2 dimensional(2D) simulation for the cobalt 60 machines is done on two machines, a Nucleotron and Imagin simulator.

In addition, the unit has a single brachytherapy machine, the Microseletron HDR that uses iridium 192, with a half-life of 74 days. Brachytherapy is planned via the Oncentra 2D planning system. In terms of human resource, the unit has 4 medical physicists, 21 radiation therapists, and 6 consultant clinical oncologists.

Treatment sites treated at the facility include the cranium, head and neck, chest wall, and thoracic cavity, spine, abdomen, pelvis, and all limbs.

CHAPTER 2-LITERATURE REVIEW

Cervical carcinoma is a form of cancer that affects the cervix in women. It mainly presents as squamous cell carcinoma, though other histological types do exist. Carcinoma of the cervix is staged as per the FIGO system. Each stage together with the histological subtype informs the treatment paradigm. Human papilloma virus (HPV) has been implicated together with other co-factors in the causation of cervical carcinoma in humans. Twelve oncogenic types have been identified and classified as class I carcinogens (Mabruk, 2014). Other factors that may contribute to the causation of cervical carcinoma include Human Immunodeficiency Virus (HIV), smoking, multiparity, and long-term use of oral contraceptives (Singh et al., 2012).

Globally, cervical cancer is the fourth most commonly diagnosed cancer in women and likewise, it is the fourth leading cause of mortality in women with cancer, with an estimated 604,000 new cases and 342,006 deaths in 2020 (Sung et al., 2021). According to Globocan 2020, the estimated annual incidence of cervical carcinoma in Kenya stood at 2454 women per year. This is projected to rise to 4,261 per year, with estimated 2,955 deaths by 2025 if urgent interventions for screening, early detection, and timely treatment are not initiated (Sung et al., 2021). Maranga et.al., 2013 noted that in Kenya about 80.5% of the women present with locally advanced carcinoma stage IIb and above. Of these, only 6.7 % received the then-recommended optimal treatment comprising external beam radiotherapy, brachytherapy, and adjuvant chemotherapy. Furthermore, it was noted that the projected two-year survival stood at less than 20% (Maranga et al., n.d.). A more recent review of treatment outcomes in KNH done in 2018 by Osok et al. revealed that up to 62.1% of the women completed their radiotherapy treatment up from the

hitherto observed 6.7%. It is not clear whether this included brachytherapy. The projected survival estimate for five years was 59%, based on one year observation considering that over 82.3% of the patients were subsequently lost to follow-up after the antecedent year of follow up, with no deaths observed during this period (Osok et al., n.d.).

Although the incidence and the mortality of cancer of the cervix have both been on the decline especially in the 1st world countries such as Europe and North America due to aggressive cervical cancer screening programs (Bray et al., 2005), the same has not been observed in sub-Saharan countries, Kenya included, where the very opposite has been observed (Jedy-Agba et al., n.d.). This may be due to the low level of national HPV vaccine implementation and low level of screening that has been observed in not only low but also middle-income countries of which the Sub-Saharan countries fall under (*"Global HPV Vaccine Introduction Overview | PATH"*, n.d.; Lemp et al., 2020).

Locally advanced carcinoma of the cervix is treated using a combination of concurrent chemotherapy and radiotherapy (Morris et al., 1999; Pearcey et al., 1999; Rose et al., 1999; Thomas, 1999). This involves a sensitizer in the form of a platinum-based chemotherapeutic agent. Cisplatin has been the preferred choice (Morris et al., 1999; Rose et al., 1999). It is combined with brachytherapy with the aim of achieving a target dose of between 85-90 Gray. Moreover, it is recommended that the total actual treatment time should be less than 56 days(S. W. Chen et al., 2003; Perez et al., 1995; Song et al., 2013).

Various investigators have analyzed the effect of the extension of the total treatment time of radiation therapy, concurrently with chenotherapy for patients with carcinoma of the cervix and

have associated a high risk of poor pelvic control with a time exceeding 56 days (Song et al., 2013).

Moreover, similar outcomes were observed by other investigators using different timelines. Perez et.al investigated 1,224 patients between stage 1b and III as per the FIGO staging system who were given external beam radiotherapy and 2 sessions of intracavitary brachytherapy with the aim of delivering between 70 and 90 Gray to point A. It was a multivariate analysis where the associative relationship between the overall total treatment and the timing of brachytherapy and treatment outcome were analyzed with respect to the tumor stage, size, or extent. They concluded that the overall total treatment time has a significant effect on the local pelvic disease control and the disease-specific survival in all cases in the study except for tumors below 3cm (Perez et al., 1995).

Chen et.al also came to a similar conclusion noting that prolongation of treatment time beyond 63 days adversely affected not only the case-specific survival, but also the pelvic control rates for patient treated with external pelvic radiotherapy with either low dose rate or high dose rate forms of intracavitary brachytherapy. It was noted that prolongation decreased pelvic control rate by 0.67% daily (S. W. Chen et al., 2003).

Given the importance of timely completion of chemoradiotherapy within the timeframes defined by various guidelines and studies, previous studies have noted that less than 50% of patients complete their treatment within this defined overall treatment time of 56 days.

Valakh V. et.al. carried out a retrospective study of 104 patients in which only 34% of the patients completed their treatment within 56 days. 56.7% completed within 63 days. The median time of treatment was 60 days. No significant relationship between the treatment timings

and potentially modifiable patient factors were noted (Valakh & Coopey, 2019). However, transition of a radiation oncology doctor at the study facility from a private non-integrated practice to a larger integrated practice had the effect of reducing the mean overall treatment duration from 68 days to 61 days (p-0.007). The modifiable patient-related factors investigated in this study included distance to the treatment center, driving time and income levels. It was further noted that unscheduled external beam radiotherapy treatment breaks were few and furthermore, high-grade toxicity related to treatment following completion of radiotherapy was equally low. Based on this it was postulated that the delays in the administration of brachytherapy due to physician and program related factors were the main cause of treatment prolongation.

Cohen J. et.al. similarly carried out a retrospective study of 43 patients with cervical carcinoma receiving chemo-radiotherapy and brachytherapy and observed that 45.5% completed treatment in 56 days with 53.5 failing to do so. In the cohort that failed to complete treatment within 56 days, 43.5 % were due to noncompliance and psychosocial factors such as inadequate transport (9.1%), mental health challenges (9.1%), substance abuse (18.2%), (independently or as a mixture of the above factors), with financial and childcare issues (27.3%). Poor psychosocial support and profound dementia were observed too (9.1%) (Cohen et al., 2017).

In addition, in the absence of the above, delays in the initiation and protracted brachytherapy treatment were identified as other causes for treatment prolongation. This contributed to 34.8% of the patients failing to complete their treatment in under fifty-six days. Factors contributing to this delay included tumor related factors that required modification from intracavitary brachytherapy to interstitial brachytherapy, minimal or slow response to external beam radiotherapy, medical complications that required treatment prior to, or during brachytherapy,

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toxicity, or unsuccessful placement or intra-treatment displacement of the Smit sleeve device, necessitating replacement and failure of the patient to return for scheduled treatment sessions(Cohen et al., 2017).

No significant associations between race, age, language, , employment status, marital status, HIV status, substance abuse or mental health issues, the FIGO stage, performance status at diagnosis, body mass index, income by zip code, distance traveled to the hospital and overall treatment delay were observed. Though distance traveled had borderline significance (p=0.07) and thus requires more research. The study did generate interesting observations but was limited by the sample size (Cohen et al., 2017).

In contrast to the above, Govardhan HB. et al. in a prospective study on 200 patients observed that 34% of patients experienced quaternary treatment delay; this was designated as treatment prolongation due to patient and treatment related causes. Primary delay was defined as the time between the appearance of the first sign and the first clinician review. Secondary delay as the time between the first clinical review and diagnosis, and tertiary delay and time between diagnosis and initiation of treatment. Correlations were made between the above treatment delays, calculated overall treatment time and overall survival. Overall survival of 0.087, 0.036, and 0.087 was observed for primary, secondary, and tertiary delays, respectively. The author concluded that delay in treatment was the major cause of poor treatment outcomes and survival in developing countries. It was recommended that proper education be provided to patients/ caregivers, and health care providers at all levels from the initial point of diagnosis and referral, on the backbone of a cancer network program that can navigate patients from remote areas to specialist care providers (Govardhan & Sarkar, 2017).

Spees LP. et.al. assessed the relationship of distance to care and correlated this with treatment timelines as regards treatment initiation and completion within 56 days for patients with cervical carcinoma stage 1b2 -IVa. It was observed that whereas 48% of the patients were initiated within 6 weeks of diagnosis, only 37% completed treatment within the guideline concordance recommended 56 days. In urban areas, those residing more than 15 miles from care centres were unlikely to initiate treatment in a timely manner as compared to those within 5 miles of the care centre: risk ratio 0.72; 95% confidence interval (0.54-0.95). On the flip side, in the rural areas, those residing more than 15 miles and beyond from the care centre were more certain to complete treatment within 56 days: Risk ratio -2.49: 95% confidence interval (1.12-5.51). It was concluded that geographical distance was differentially influencing treatment initiation and completion in the two settings. This contrasts with the findings from the study carried out by Valakh and Coopey, 2019 where such correlation was not realized (Spees et al., 2019).

In a broadened scope, both Ferreira Da Silva et.al and Shen S.C. et.al. defined treatment delay as failure to complete conventional treatment (surgery, radiotherapy, chemotherapy in their various combinations) within 120 days from the time of diagnosis. In both studies, age was significantly associated with delay in the initiation of treatment. In addition, Ferreira Da Silva et.al. observed that less than 10 % of the patients were initiated on treatment in less than 60 days, with delays beyond 30 days between diagnosis and first specialist assessment being a main driver. Patients scheduled for chemotherapy, or a combination involving surgery and radiotherapy were more prone to having treatment delays. On the flip side, stage at diagnosis was negatively associated with treatment delays since these patients with advanced disease tended to be started earlier and put on shorter treatment schedules as compared to early-stage patients that were more likely to

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undergo more extensive treatment and thus experience delays in the initiation and completion of treatment in less than 120 days from the time of diagnosis (Ferreira Da Silva et al., 2019; Shen et al., 2016).

Interestingly, Shen S. C. et.al. observed that in addition to age, severe comorbidity (as per the Charlson comorbidity index) disease stage IV and diagnosing hospital level were also associated with treatment initiation delay. It was noted further that this delay was associated with 2.3 times greater risk of mortality as compared to those who got timely treatment (p<0.05) (Shen et al., 2016). In a population-based survey in Taiwan by Chen et.al. it was observed that 96% of patients started their definitive treatment within 90 days. Furthermore, it was noted that for patients delayed beyond 90 days, there was an increased risk of death; HR 1.33.(1.02-1.72) 95% CI (C. P. Chen et al., 2019). Timothy P Hanna in a systematic review and meta-analysis also noted that even a four-week delay in the initiation of treatment across seven cancers (cervical cancer included) was significantly associated with increased mortality across different modalities of treatment (Hanna et al., 2020). In context, it seems that delaying the timely initiation of treatment could be carrying an increased risk of death.

From the above studies we can conclude that overall, less than 50% of patients seem to complete treatment in under 56 days. This is despite a clear demonstration of the adverse effects of treatment prolongation. Although Maranga et.al in 2013 observed that only 6.7% of the women treated at Kenyatta National Hospital (KNH) got the optimal treatment of external beam radiotherapy, brachytherapy (intracavitary) and adjuvant chemotherapy with the figures improving to 62.1% in 2018 as realized by Osok et al, no audit of the treatment timelines has been conducted in Kenya for the same.

It would be important that this is done and factors affecting this, if any, be identified and addressed.

Problem statement

Majority of patients treated with cervical carcinoma at KNH present with locally advanced disease (Maranga et al., n.d.; Osok et al., n.d.).

Combined chemo-radiotherapy and intracavitary/interstitial brachytherapy is the recommended treatment modality for these patients (Rose et al., 1999). Treatment timings have been shown to affect treatment outcomes with the guideline concordance treatment time recommended as less than 56 days (Song et al., 2013). Although antecedent studies have investigated the outcomes of patients with locally advanced cancer of the cervix getting definitive chemo-radiotherapy and brachytherapy, an audit of the treatment timing patterns in this setting and factors affecting them has not been done. This study set out to shed light on this.

Justification for the study

Several antecedent studies have shown that overall total treatment time in locally advanced cervical carcinoma has been shown to affect treatment outcomes. However, no study in Kenya has yet evaluated the factors affecting treatment timing patterns in patients with locally advanced carcinoma of the cervix. As such, this study aimed to shed light on this topic and possibly identify areas of improvement in the timings of the treatment of patients with locally advanced cancer of the cervix.

Research question-

What are the treatment timing patterns for patients with locally advanced carcinoma of the cervix treated at the Cancer Treatment Center at KNH?

Null hypothesis

More than 40% of patients with locally advanced carcinoma of the cervix at KNH are completing definitive treatment within the guideline concordance recommendation of 56 days.

Broad objective

To determine the factors affecting the overall treatment timing patterns of patients with cervical carcinoma stage 1b2-Iva undergoing chemo-radiotherapy plus brachytherapy at Kenyatta National Hospital.

Specific objectives

1. To determine the demographic and clinical characteristics of patients with locally advanced carcinoma of the cervix treated at the Cancer Treatment Centre, Kenyatta National Hospital between 2016-2020.

2. To determine what proportion of patients completed their definitive treatment within the guideline concordance overall treatment time of 56 days and the converse between 2016-2020.

3. To determine what proportion of patients started their definitive treatment within 90 days of a histologically confirmed diagnosis and the converse between 2016-2020.

4. To investigate the factors that affected the treatment timing patterns for patients with locally advanced carcinoma of the cervix treated with chemo-radiotherapy and brachytherapy at KNH between 2016-2020.

CHAPTER 3-METHODOLOGY

Study design

The study was a retrospective analytical study done on patients treated at the cancer treatment centre, KNH between 2016 -2020 using routinely collected patient information in patient charts. The data from the patient chart was abstracted using a data collection tool. Univariate and multivariate analysis using statistical software packages SPSS was done to investigate correlations between dependent and independent variables. The strength of these correlations were analysed using chi square and t-tests.

Study setting

The study was a hospital-based study carried out at the Cancer Treatment Centre, Kenyatta National Hospital. Kenyatta National Hospital is a level 6 referral hospital located in Nairobi County on 45.7 hectares of land. It was established in 1901 and has a bed capacity of 1800. It became a state cooperation in 1987 furnished with a board of management. It is equipped with 50 wards, 22 outpatient clinics, 24 theaters, (16 specialized) and an accident and emergency department. Because of its location, it is accessible to most of the Kenyan population. The cancer treatment centre is one the of the specialist clinics at Kenyatta national hospital. It was established in 1968 and has grown since then. It currently attends to about 3000 new patients annually. During the study period, the unit had two cobalt 60 machines, and one linear accelerator (Linac). The Linac was an Elekta, able to treat with two photon energies, 6MV and 15 MV. The clinic was also equipped with a planning CT scan from which planning images were abstracted before being transferred to the planning console at the linear accelerator. The planning system used for the treatment planning and setup was Oncentra. This could deliver 3D

conformal radiotherapy treatment plans. 2D simulation for the cobalt 60 machines was done on two machines, a Nucleotron and Imagin simulator. In addition, the unit had a single brachytherapy machine, the Microseletron HDR that used iridium 192, with a half-life of 74 days. Brachytherapy was planned via the Oncentra 2D planning system. In terms of human resource, the unit had 4 medical physicists, 21 radiation therapists, and 6 consultant clinical oncologists. Treatment sites treated at the facility included the cranium, head and neck, the chest wall, and thoracic cavity, the spine, the abdomen, pelvis, and all limbs.

Study population

Patients with a histologically confirmed carcinoma of the cervix (stages 1b2-IVa) treated at the Cancer Treatment Center , KNH aged between 18 and 80 years.

Selection criteria

Medical charts were included or excluded from the study based on the following criteria.

Inclusion criteria	Exclusion criteria
Patients with histologically confirmed diagnosis of cervical carcinoma, stage 1b2-IVa , as per the FIGO classification system, treated at the Cancer Treatment Center between 2016-2020.	Patients planned for radiotherapy alone
Patients planned for chemo-radiotherapy and brachytherapy	Patients transferring in after having started their treatment elsewhere
	Patients without a histological diagnosis

Duration of the study

The study was conducted on patients treated at the cancer treatment centre, KNH between the years 2016-2020.

Sampling determination

The sample size was determined as follows.

Sample size was calculated using Fisher's formula; (Machin, 1995)

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

Where,

n = Desired sample size

Z = value from standard normal distribution corresponding to desired confidence level (Z=1.96 for 95% CI)

P = expected true proportion (put at 40.0%,)

d = desired precision (0.05)

$$n_0 = \frac{1.96^2 x\ 0.40(1 - 0.40)}{0.05^2} = 368.79$$

Since the study population was a finite figure of 2940. And considering that the above sample size as a proportion exceeded 5% of the finite population (@11.56%, a sample size calculation

for proportions with finite population correction formula according to Niang, Winn & Rusli (2006) (Nordin, n.d.) was used to modify it

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

where

n' = sample size with finite population correction,

N = Population size,

Z = Z statistic for a level of confidence,

P = Expected proportion (in proportion of one), and

d = Precision (in proportion of one).

This gave a final sample of 328.

Sampling procedure and data collection.

Simple random sampling was used to select the patient charts meeting the eligibility criteria for the study as follows.

The file numbers of patients with cervical carcinoma that have undergone chemo radiotherapy and brachytherapy at the cancer treatment centre were obtained from the patient treatment registries. These file numbers were then used to obtain the relevant files from the KNH health information department. The abtained files were examined for completeness and those meeting the eligibility criteria were selected for the years 2016-2020. The eligible files were sorted according to year of treatment i.e., 2016, 2017, 2018, 2019 and 2020. Afterwards the proportion of the sample size against the total number of patients treated was calculated. This figure came to 11.56%. This proportion was used to calculate the number of files to be sampled from each year.

The file numbers of each of the eligible files were written on a piece of paper, concealed, and put in a basket for each year. The pieces of paper with the file numbers were drawn out randomly from each basket representing the different years until the proportioned sample size for each year was obtained. The corresponding files/medical charts were selected, and data was abstracted from them using a structured data extraction form.

The data was uploaded and cleaned in Excel before being transferred to a central database in a statistical software i.e., SPSS for analysis. A statistician was consulted to assist in the data analysis.

Research assistants (medical doctors) were instructed and trained on methodology of data collection. They subsequently assisted the principal investigator in the collection of data.

Variables

Dependent variables-

Proportion of patients completing treatment in less than 56 days and vice versa.

Proportion of patients starting treatment within 90 days from a histologically confirmed diagnosis and vise versa.

Independent variables

Patient demographics, socioeconomic status, residence (urban versus rural) the patient NHIF status and the patient HIV status will constitute the patient factors whereas treatment toxicity, Delay in initiation of 1st brachytherapy implant if any and the hemoglobin levels of the patient will constitute treatment related factors under independent variables

Ethical considerations

Since the study design was a retrospective design, consent for the study was given by the "Ethics and Research Committee (ERC) at Kenyatta National Hospital /University of Nairobi". The administrative clearance required to conduct this study was sought from "Kenyatta National Hospital Health Information Department", and the "University of Nairobi, College of Health Sciences, Department of Diagnostic Imaging and Radiation Medicine".

In order to garrison the confidentiality of the patient information and data, the investigators ensured that any patient specific identifiers were excluded from the dataset during data collection (patient names, numbers). In addition, no other person(s) except the principal investigator and the research assistants were allowed access to patient records. All records were locked in a safe cabinet at the medical records department and were accessed by authorized persons only.

There was no anticipated risk of physical, economic and/or social harm to patients whose files were used in this study.

In the fulfillment of social justice, the findings realized from this study were shared with the cancer treatment centre KNH, University of Nairobi, and the health community through dissemination to peer reviewed journals.

Data handling.

Pieces of papers used in random sampling of the eligible files were destroyed after sampling.

Unique numbers were generated for each data record transcribed from the data collection tool to the statistical analysis software in order to safeguard patient confidentiality.

The databases were secured in a password protected computer and were also backed up on an external memory device which was kept in custody of the principal investigator.

Data extraction charts were filed and subsequently stored in a secured cabinet ensuring that verification of the data could be done as maybe required. At the conclusion of the study these data extraction forms were destroyed.

Data analysis

Descriptive analysis was grouped into continuous and categorical variables with categorical variables analyzed using frequencies and percentages. Continuous variables were analyzed using mean and median.

Inferential analysis was done using univariate, bivariate and multivariate analysis.

Study limitation

Since the study was a retrospective study, some data/information was found to be missing or excluded from the patient files. This information could not be traced.

Study delimitations.

All laboratory investigations, biopsies, and imaging investigations were interpreted as equally accurate and valid in this study.

Study closure plan and procedure.

Closure procedures of the study were initiated, once data collection, verification and analysis had been completed whereby a requisite closure application form was duly filled and submitted to the KNH-UoN ERC for verification and approval.

All links to identifiers in health records were removed and destroyed and all original records, including the data collection sheets were safely stored for anonymity and completion. The final database on which data analysis and publication was based was properly labeled for archiving.

CHAPTER 4-RESULTS

Introduction

The study sought to determine the factors affecting the overall treatment timing patterns of patients with cervical carcinoma stage 1b2-Iva undergoing chemo-radiotherapy plus brachytherapy at Kenyatta National Hospital. A total of 328 patients with locally advanced carcinoma of the cervix treated at the Cancer Treatment Centre, Kenyatta National Hospital between 2016-2020 were included in this study.

Demographic characteristics of patients with locally advanced carcinoma of the cervix treated at the Cancer Treatment Centre, Kenyatta National Hospital between 2016-2020.

The median age of patients in the study was 50 (IQR: 41 – 60) years, 58.8% (n =193) were HIV negative, 77.7%(n=255) of the respondents were married. 73.8% (n =242) of the respondents had secondary level education. Further, 64.9% (n =213) of the respondents were not employed. Majority, 92.4% (n =303) of the patients were residing outside Nairobi as shown in Table 1.

I-Table 1: Demographic characteristics of patients with locally advanced carcinoma of the cervix treated at the Cancer Treatment Centre, Kenyatta National Hospital between 2016-2020.

Demographic factors	Frequency	Percentage (%)
Age, Median(IQR) years	50(IQR:41 - 60)	
HIV status		
Negative	193	58.8
Positive	59	18.0

Missing	76	23.2
Marital status		
Single	15	4.6
Married	255	77.7
Separated/widowed	48	14.6
Missing	10	3.0
Level of education		
Primary level	83	25.3
Secondary level	242	73.8
Tertiary level	3	0.9
Occupation		
Employed	60	18.3
Not employed	213	64.9
Missing	55	16.8
Residence		
Within Nairobi	25	7.6
Outside Nairobi	303	92.4

Clinical and histological characteristics of patients with locally advanced carcinoma of the cervix treated at the Cancer Treatment Centre, Kenyatta National Hospital between 2016-2020.

The histology findings showed that 89.6% (n =294) of the patients had Squamous cell carcinoma while 6.7% (n =22) had Adenocarcinoma. In investigating cancer staging, 46.6% (n =153) had Stage 2a – b. The median duration of illness prior to diagnosis was 7(IQR: 4 – 12) as shown in Table 2.

II-Table 2: Clinical characteristics of patients with locally advanced carcinoma of the cervix treated at the Cancer Treatment Centre, Kenyatta National Hospital between 2016-2020.

Clinical factors	Frequency	Percentage (%)
Diagnosis		
Squamous cell carcinoma	294	89.6
Adenocarcinoma	22	6.7
Others	12	3.7
Staging		
Stage 1a -b	13	4.0
Stage 2a - b	153	46.6
Stage 3a - c	133	40.5
Stage 4a - c	28	8.5
Unstaged	1	0.3

Duration of illness, Median (IQR)	7(IQR: 4 - 12)

III-Pie chart 1: showing disease distribution by histological subtypes
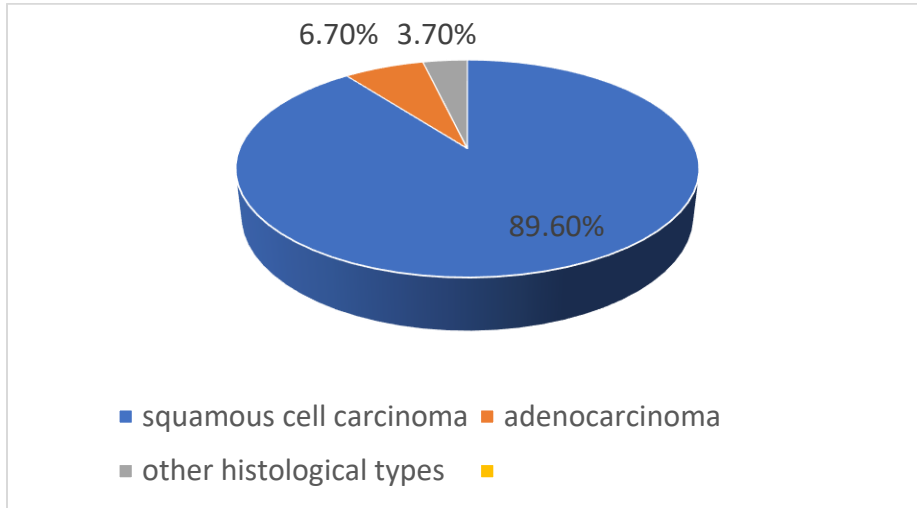
IV-Bar graph 1: showing disease distribution by clinical stage.
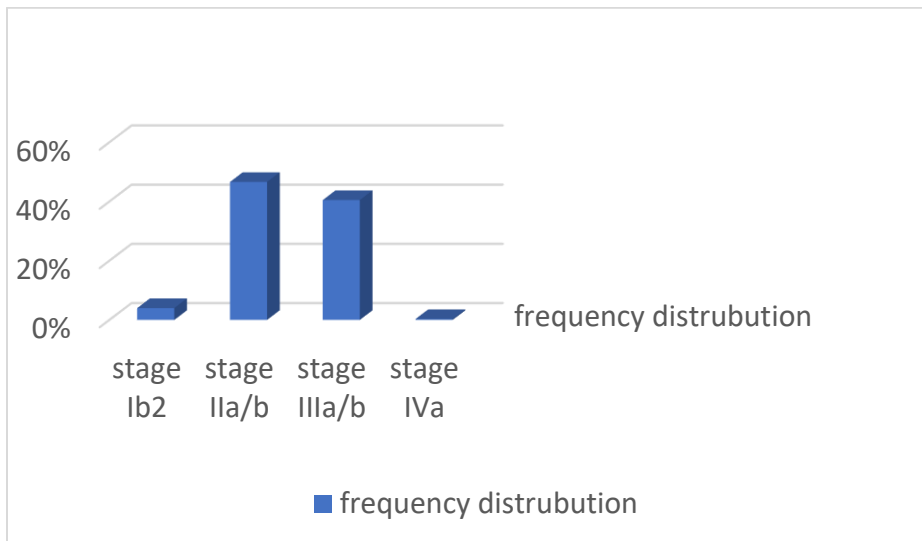
Proportion of patients who started their definitive treatment within 90 days of a histologically confirmed diagnosis and the converse between 2016-2020

The median time for starting definitive treatment was 71 (IQR: 49 – 110) days. Further analysis revealed that 58.5% (n =192) of the patients started their definitive treatment within 90 days of a histologically confirmed diagnosis and the converse as shown in Table 3.

V-Table 3: Proportion of patients started their definitive treatment within 90 days of a histologically confirmed diagnosis and the converse between 2016-2020

Duration	Frequency	Percentage (%)
Starting definitive treatment, Median (IQR)	71(IQR:49 - 110)	
Starting definitive treatment within 90 days		
Yes	192	58.5
No	136	41.5

VI-Pie chart 2: showing proportion of patients that started third definitive treatment within 90 days of a histologically confirmed diagnosis.
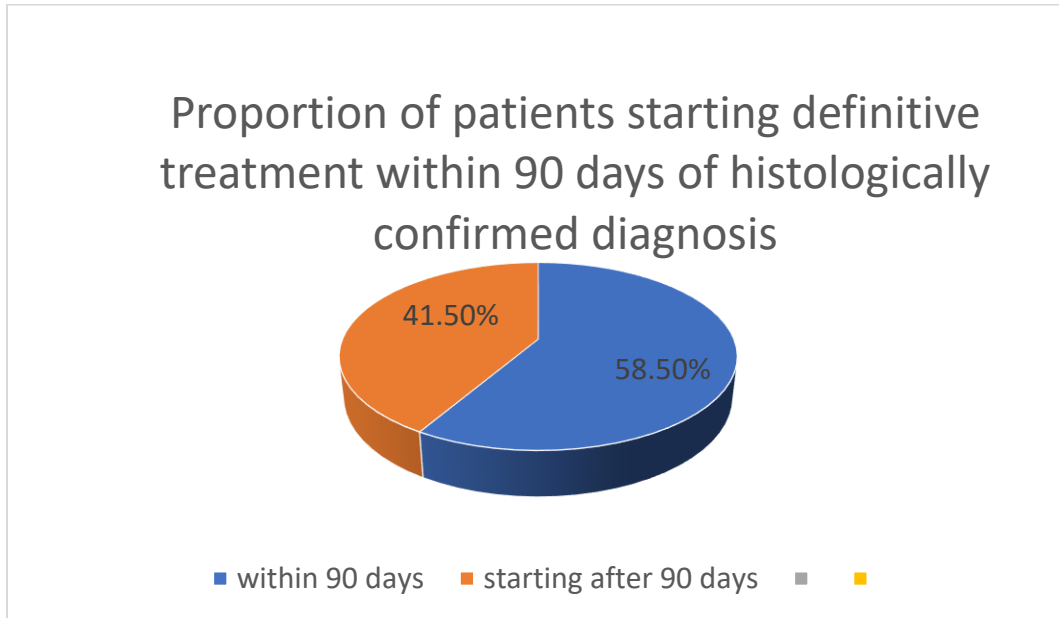
Proportion of patients who completed their definitive treatment within the guideline concordance overall treatment time of 56 days and the converse between 2016-2020

The median time taken to complete their definitive treatment was 80(IQR: 64 – 104) days. Further analysis revealed that 34.5% (n =113) of the patients were treated with the guideline's concordance overall treatment time of 56 days as shown in Table 4.

VII-Table 4: Proportion of patients completed their definitive treatment within the guideline concordance overall treatment time of 56 days and the converse between 2016-2020

| Duration	Frequency	Percentage (%)
Treatment period, Median (IQR) days	80(64 - 104)	
Treatment within 56 days		
Yes	113	34.5
No	215	65.5

VIII-Pie chart 3: showing the proportion of patients that completed their definitive treatment within the guideline concordance overall treatment time of 56 days.

proportion of patients completing definitive treatment within 56 days

34.50%

65.50%

■ within 56 days ■ beyond 56 days
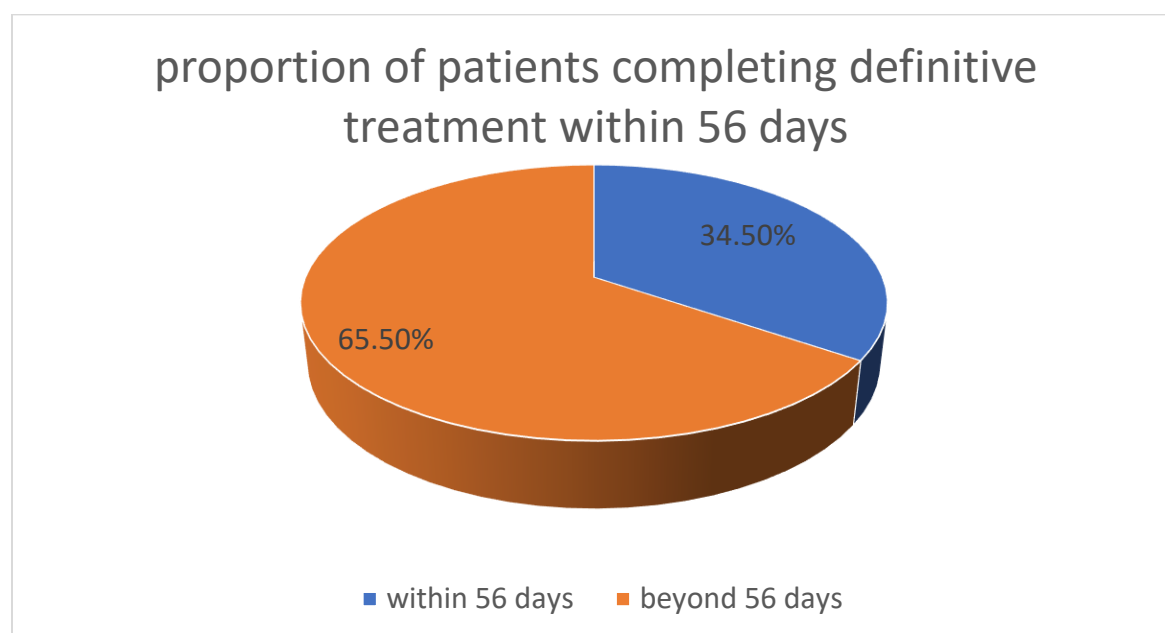
The factors that affected the patient starting treatment within 90 days for patients with locally advanced carcinoma of the cervix treated with chemo-radiotherapy and brachytherapy

Patients who were employed were two times more likely to start treatment within 90 days compared to those who were unemployed, OR =2.0, 95%CI:1.12 – 3.58, p =0.019. Those who resided outside Nairobi were five times more likely to start treatment within 90 days after diagnosis compared to those who were residing in Nairobi, OR =5.03, 95%CI:1.95 – 12.97, p=0.001. Patients who had longer duration of illness were 45% less likely to start treatment within 90 days, OR=0.55, 95%CI:0.12 – 0.88, p=0.008 as shown in Table 5.

IX-Table 5: The factors that affected the patient starting treatment within 90 days for patients with locally advanced carcinoma of the cervix treated with chemo-radiotherapy and brachytherapy

Factors	Started treatment within 90 days			P-value
	Yes n (%)	No n (%)	OR (95%CI)	
Age, Mean (SD)	51.05(11.79)	51.11(13.37)	0.61(0.21 - 2.11)	0.451
HIV status				
Negative	114(59.1)	79(40.9)	0.74(0.40 - 1.36)	0.364
Positive	39(66.1)	20(33.9)	Ref	
Marital status				

Single	9(60)	6(40.0)	1.11(0.34 - 3.64)	0.862
Married	150(58.8)	105(41.2)	1.17(0.62 - 2.20)	0.634
Separated/widowed	30(62.5)	18(37.5)	Ref	
Level of education				
Primary or lower	45(61.6)	28(38.4)	1.18(0.69 - 2.01)	0.591
Secondary or higher	147(57.6)	108(42.4)	Ref	
Occupation				
Employed	30(50.0)	30(50.0)	2.0(1.12 - 3.58)	**0.019**
Not employed	142(66.7)	71(33.3)	Ref	
Residence				
Within Nairobi	6(24.0)	19(76.0)	Ref	
Outside Nairobi	186(61.4)	117(38.6)	5.03(1.95 - 12.97)	**0.001**
Disease diagnosis				
Squamous cell carcinoma	178(60.5)	116(39.5)	0.88(0.36 - 2.16)	0.775
Adenocarcinoma	14(63.6)	8(36.4)	Ref	
Cancer stage				
Stage 1	9(69.2)	4(30.8)	0.51(0.13 - 2.06)	0.347
Stage 2	94(61.4)	59(38.6)	0.72(0.32 - 1.63)	0.435
Stage 3	74(55.6)	59(44.4)	0.92(0.41 - 2.08)	0.842
Stage 4	15(53.6)	13(46.4)	Ref	
Duration of illness, Mean(SD)	9.82	13.42	0.55(0.12 – 0.88)	**0.008**

The factors that affected the treatment within 56 days for patients with locally advanced carcinoma of the cervix treated with chemo-radiotherapy and brachytherapy

Those who had secondary or higher level of education were 2.2 times more likely to have completed treatment within the stipulated 56 days compared to those who had primary or lower level of education, OR =2.19, 95%CI:1.19 – 4.02, p=0.012. Patients who were residing outside Nairobi were four times more likely to complete treatment within the stipulated 56 days compared to those who were residents of Nairobi, OR= 4.18, 95%CI: 1.22 – 14.28, p =0.023 as shown in Table 6.

X-Table 6: The factors that affected the completion of treatment within 56 days for patients with locally advanced carcinoma of the cervix treated with chemo-radiotherapy and brachytherapy

	Treatment within 56 days			
Factors	**Yes n(%)**	**No n(%)**	**OR(95%CI)**	**P-value**
Age	49.7(12.3)	51.9(12.5)	1.01(0.995 - 1.03)	0.141
HIV status				
Negative		70(36.3)	123(63.7)	0.89(0.49 - 1.62)	0.759
Positive		23(39.0)	36(61.0)	Ref	
Marital status				
Single		5(33.3)	10(66.7)	0.74(0.21 - 2.59)	0.641
Married		91(35.7)	164(64.3)	0.67(0.34 - 1.33)	0.252

Separated/widowed		13(27.1)	35(72.9)	Ref	
Level of education					
Primary or lower		16(21.9)	57(78.1)	Ref	
Secondary or higher		97(38.0)	158(62.0)	2.19(1.19 - 4.02)	**0.012**
Occupation					
Employed		26(43.3)	34(56.7)	0.70(0.39 - 1.25)	0.224
Not employed		74(34.7)	139(65.3)	Ref	
Residence					
Within Nairobi		3(12.0)	22(88.0)	Ref	
Outside Nairobi		110(36.3)	193(63.7)	4.18(1.22 - 14.28)	**0.023**
Disease diagnosis					
Squamous cell carcinoma		106(36.1)	188(63.9)	1.21(0.48 - 3.06)	0.69
Adenocarcinoma		7(31.8)	15(68.2)	Ref	
Cancer stage					
Stage 1		7(53.8)	6(46.2)	0.34(0.09 - 1.34)	0.124
Stage 2		57(37.3)	96(62.7)	0.67(0.28 - 1.63)	0.381
Stage 3		41(30.8)	92(69.2)	0.90(0.37 - 2.21)	0.814
Stage 4		8(28.6)	20(71.4)	Ref	
Duration of diagnosis	10.7(7.1)		11.5(7.8)	1.0(0.99 - 1.02)	0.694

CHAPTER 5-DISCUSSION

Introduction-

Cervical cancer is the fourth most common cancer in women worldwide, but the leading cause of death in western, eastern, central and southern Africa (Arbyn et al., 2020) It is the second commonest cancer in Kenya, with the leading being breast cancer (Globocan, 2020). Over 80% of patients with cervical cancer present to the hospital with locally advanced cervical cancer (Maranga et al., n.d.; Osok et al., n.d.). The appropriate treatment of this involves chemoradiotherapy (Enry et al., 1999; Morris et al., 1999; Rose et al., 1999). The timeliness of this treatment and its importance in the outcome of the disease has been well demonstrated in previous studies (S. W. Chen et al., 2003; Perez et al., 1995; Song et al., 2013). According to Perez C. et al. The delay of the definitive treatment beyond 56 days is associated with a 0.85% daily decrease in the risk of pelvic tumour control rate for all disease stages (Perez et al., 1995). On the other hand, time to initiate treatment has been associated with variations in observed disease outcomes. For instance, Chao Ping Chen et al. 2019, noted in a population-based survey in Taiwan that delays in the initiation of treatment beyond 90 days were associated with an increased risk of death HR=1.33 (1.02-1.32) p=<0.05. (C. P. Chen et al., 2019). The same however was not observed by Ramey S et al, 2018 who observed no increased mortality with delays in the initiation of treatment. (Ramey et al., 2018). It should be noted that in the case of the later study, the increased delay in treatment initiation was occasioned by the use of IMRT with its attendant longer treatment planning time requirements. In addition, his treatment initiation timelines were in the range of 38.1 to 49.4 days as compared to the former study where

the same timelines range from over 90 days to over 180 days. Consequently, no adverse effects were associated with delay in starting treatment in this study.

Previous studies done in Kenya looked at the outcomes of patients treated at Kenyatta national hospital (KNH), Maranga et al noted that the projected 5-year survival of patients treated at KNH in 2013 stood at 20%, with only 6.7% completing the entire definitive treatment of chemo radiotherapy and brachytherapy (Maranga et al., n.d.). Osok D. et.al in 2018 reviewed the outcome and noted that 60.6% of the patients getting radiotherapy were completing treatment. This was an improvement given the previous rate observed in 2013 by Maranda et al. He also noted that a majority of the patients (82.3%) were lost to follow-up in the subsequent year post treatment. The projected 5-year survival in this review was projected at 59% based on the one-year data that was available (Osok et al., n.d.). Although these studies looked at the outcomes, none explored the timeliness of the delivery of the treatment, despite it being an important predictor of the outcome of the disease (Perez et al., 1995).

This study is the only one in Kenya that has looked at the treatment timing patterns of patients with cervical carcinoma stage 1b2-Iva undergoing chemo-radiotherapy plus brachytherapy at Kenyatta National Hospital. It looked at the period between a histologically confirmed diagnosis and the associated initiation of treatment (time to treatment initiation) and the overall definitive treatment time being the time between the first fraction of radiotherapy and the last session of brachytherapy. This was done against the established benchmark of 56 days (Perez et al., 1995). The time to initiate treatment was benchmarked against the Taiwan study which demonstrated adverse effects of prolonging treatment initiation beyond 90 days post the histological diagnosis (C. P. Chen et al., 2019).

Demographics

In this study, the median age of the patients was 50 years (IQR:41-60). This is close to the findings in other studies. For instance, the median age in Zambia was noted to be 49 years (IQR+/- 17) (Mumba et al., 2021). This closely echoed the findings realized by Maranga et.al 2013 and Damar Osok et al 2018 in which the median age was also 49 years. (Maranga et al., n.d.; Osok et al., n.d.). Majority of the patients (92.4%) were residing outside Nairobi. This can be explained by the fact during this period, Kenyatta national hospital was the only public institution offering oncology services in the country and thus the majority of these patients were referrals from outside Nairobi. 77.7% were married and 14.6% were widowed. This was comparably different from that observed in Zambia where 57% were married and 26% widowed. (Mumba et al., 2021).

Clinical characteristics

From the study, it emerged that 89.6% of the patients presented with squamous cell carcinoma, while 6.7% were adenocarcinomas and other subtypes accounted for 3.7%. This mirrors the findings in other studies. For instance, Osok et.al noted 93.1% of the patients had squamous cell carcinoma, and 7% had adenocarcinoma whereas Maranda et.al 2013 noted that 89.9% of the patients in his study had squamous cell carcinoma with adenocarcinoma making up 5.3%(Maranga et al., n.d.; Osok et al., n.d.).

About 87.1% of the patients presented in stages II and III, followed by stage `IV at 8.5%|. This is similar to findings by Maranga et al who demonstrated that over 80.5% had stage 2b and above and Mumba J et al who likewise observed in Zambia that over 88.8 % of the patients had stage 2

and above(Maranga et al., n.d.; Mumba et al., 2021). This is in keeping with the epidemiological presentation of the disease in developing countries, where squamous cell carcinoma is the most prevalent histological presentation.

Treatment initiation time

The mean duration of symptoms was seven months (about 28 weeks). In this study, this was associated with significant delays in the initiation of treatment to beyond 90 days from the antecedent date of histological confirmation of the diagnosis. It would seem that the health seeking behavior leading to delays in seeking treatment was similarly at play in delaying the initiation of treatment even after the confirmation of the diagnosis. This could also explain why most of the patients presented with advanced disease. Similar observations were noted in Ethiopia by Matthias B et al. 2019 where the median duration of symptoms was noted to be 30 weeks, with delays more pronounced in the rural areas. This resulted in most of them presenting with advanced disease (Begoihn et al., 2019). This is possibly the same phenomenon observed in this study where a majority of the patients reside outside Nairobi and present with advanced disease. They could have faced similar challenges that could have contributed to this observed prolonged duration of symptoms, the subsequent advanced state of the disease at presentation and the delays in the initiation of treatment. Patients from rural areas face many challenges amongst them financial challenges that may contribute towards delays in seeking health care in a timely manner. Indeed, a study on "the perceptions on financial challenges faced by cervical cancer patients in western Kenya" done by Owenga J et al 2018, confirmed that these patients face many financial related barriers with only a fraction of them having any form of health insurance cover. This cover only catered for the inpatients boarding costs. (Owenga & Nyambedha, 2018).

In addition, other factors besides socioeconomic factors do contribute to delays in seeking health behavior of the patients thus prolonging duration of symptoms. These may include patient related factors such as cultural practices, lack of knowledge, age related factors, the stigma associated with cancer and health care related factors such as inadequate knowledge, poor communication, unnecessary treatment, minimization of patients' symptoms by the health care providers, false diagnosis and healthcare system delays such as inefficient referral systems, and delayed diagnosis. (Benemariya et al., 2018).

From this study, it emerged that the median starting time for patients with locally advanced (stage 1b2-4A) cervical cancer treatment at the Cancer Treatment Centre, Kenyatta National Hospital was 71 days (IQR: 49-110) days with 58.5% of the patients starting their treatment within 90 days of a histologically confirmed diagnosis. This proportion of the patients starting within 90 days was lower than what was observed by Chen et.al. in Taiwan where 96% of the patients were noted to have started within 90 days (C. P. Chen et al., 2019). Furthermore, Chen et al. observed that for patients delayed beyond 90 days, there was a heightened risk of death; HR 1.33.(1.02-1.72) 95% CI. The implication of this is that 41.5% of our patients are facing this increased risk of death even before they start their definitive. This is an adverse prognostic factor that should be improved in order to improve the treatment outcomes. Measures need to be taken to increase awareness and create systems that fast-track the initiation of definitive treatment. As a caveat, it should be noted that during the study period, one public facility (KNH) was offering radiation therapy treatment. However, at the time this study was being done, the number of public faculties offering oncology services has since increased to five centres and thus an audit of treatment initiation timelines needs to be done in a prospective study to find out if they

(treatment initiation timelines) have improved or not and to identify actionable deficiencies if the contrary is found to be true.

Direct comparisons to other studies are challenging to make due to the lack of standardization of treatment initiation times. These variations are as a result of different standards of health care systems with each having varied efficiencies and thus different benchmark timelines for starting treatment. However, in all studies, delays in timely initiation of treatment were observed and actionable factors affecting these starting times were explored and patterns investigated. For instance, Spees et al using a treatment initiation timeline of 6 weeks observed that only 48% of the patients were able to start their treatment on time. It was noted that in urban areas, patients residing more than fifteen miles from the treatment centre, were less likely to start their treatment on time (O.R-0.72 CI 0.54-0.95) (Spees et al., 2019). This is contrary to what was observed in this study where distance from the treatment facility positively influenced the treatment starting times (OR =5.03, 95%CI:1.95 – 12.97, p=0.001). Other factors that positively influenced starting times in this study were the status of employment (OR =2.0, 95%CI:1.12 – 3.58, p =0.019) and the duration of illness (OR=0.55, 95%CI:0.12 – 0.88, p=0.008). Patients employed and thus with a source of income were twice as likely to start their treatment within 90 days. This could be due to the fact that with employment, these patients had income with which to pursue their treatment and/or be able to acquire insurance covers, both factors that were likely to positively influence their health seeking behavior and thus made it possible for them to start their treatment in a relatively timely manner compared to those without employment. As regard the duration of illness negatively influencing starting times, it can be argued that factors at play leading to the delay in seeking treatment could be the same factors at play leading to delays in starting treatment as observed in the study. Given that these delays carry the risk of increased death, it is

imperative that a qualitative prospective study be done to further investigate this and identify modifiable factors contributing to the observed health seeking behavior.

Although age, and the disease stage were not found to significantly affect the treatment starting times, other studies have shown or demonstrated the effect of this on the same. For instance, Ferreira Da 'silva et al. (2019), using a bench mark time of 60 days observed that less than 10% of the patients were initiated within 60 days. Age was noted to be positively associated with delays in time take to initiate treatment. On the other hand, the disease stage was negatively associated with delays in treatment initiation on account that those with advanced disease were more likely to be speedily started on treatment as compared with those with early-stage disease. This could be due to the fact that those with early disease had more investigation done and some were selected for surgical interventions and hence the observed delays. In addition, it was noted that delays beyond 30 days between the date of histological diagnosis and the first specialist assessment also contributed to delays in timely treatment initiation (Ferreira Da Silva et al., 2019)

Shen SC et al. (2016) observed that age and disease stage also negatively affected treatment initiation. It was also noted that severe comorbidity and the status of the diagnosing hospital were significantly associated with treatment initiation delays too (Shen et al., 2016). This is converse to the findings of this study where age and the disease stage were not noted to significantly affect treatment initiation timelines. Comorbidities and the status of the diagnosing and thus referring hospital were not explored in this study thus comparisons cannot be made on these two factors. From the variations in the observed factors causing delays, it can be urged that different factors variably influenced the treatment starting timelines contextually and thus direct comparisons could not be made. Due to a lack of consensus on whether treatment initiation time

is a significant prognostic factor that should inform treatment policy, more prospective studies should be done to explore this area.

The time it takes to initiate treatment from the date of a histologically confirmed diagnosis is a controversial health quality indicator. Its significance has varied from one study to another with some studies noting that it has a significant impact on treatment outcomes while others find no correlation with disease outcomes. For instance, Chen et al in a population-based survey done on patients with cervical cancer in Taiwan noted that delays in initiation of treatment beyond 90 days and 180 days were significantly associated with increased risk of death; HR 1.33.(1.02-1.72) 95% CI, p=,0.05 and 1.36(1.12-1.65)95%CIp=,0.05 respectively (C. P. Chen et al., 2019). Similarly, Timothy P Hanna in a systematic review and meta-analysis noted that even a four-week delay in the initiation of treatment across seven cancers (cervical cancer included) was associated with increased mortality across different modalities of treatment (Hanna et al., 2020). Translating this into our context could mean that the patients delaying the timely initiation of treatment could be at increased risk of death.

Similar sentiments were however not observed by Ramey S et al. 2018 who noted no association between delays in treatment time initiation and mortality. It should be noted that in this study, the delays in the initiation of treatment delays were in the range of 39-49 days and the cause of the delays was a change in the treatment technology where the employment of intensity modulated radiotherapy was associated with long treatment planning times and thus causing delays in treatment initiation (Ramey et al., 2018). This is contextually different from the observation noted in Taiwan and cannot be projected to developing countries such as Kenya where such treatment modalities are yet to take root in most public facilities.

As noted from the above studies, there is no standardized ideal starting time, though countries such as Colombia and the United Kingdom have resorted to utilizing a 30-day bench mark (Hernández Vargas et al., 2021), and 31 days respectively (Hanna et al., 2020). Although direct comparisons could not be made across different studies due to a lack of a standardized treatment initiation timeline, the study managed to establish a benchmark upon which future improvements can be made.

Definitive treatment time.

From the study it emerged the median total treatment time for patients with locally advanced cervical carcinoma treatment at Kenyatta National Hospital between 2016-2020 was 80 days (IQR 64-104), with 34.5%(n=113) of the patients completing their treatment within 56 days. It also emerged that residence also affected the time taken to complete treatment with patients residing outside Nairobi being four times more likely to complete their treatment within 56 days, O.R-4.18 95%CI=1.22-14.28, p=0.0023. Likewise, those with a secondary or higher level of education were twice as likely to complete their treatment in 56 days O.R 2.19 95%CI 1.19-4.02, p=0.0012. Other factors such as age, HIV status, marital status, occupation, histological subtype, and disease stage were not significantly associated with delays in the completion of treatment. The median time observed was longer than that observed by Valakh et al, who observed a median time of 60 days. However, the proportion of patients in this study completing treatment in 56 days was similar to that observed by Valakh et al. in his study where 34% of the patients completed treatment within 56 days. He however did not observe any relationships between treatment timelines and modifiable factors such as distance to the treatment facility, driving times, and income levels (Valakh & Coopey, 2019). Cohen J et al. in a retrospective study of 43

patients observed that 45.5% completed treatment within 56 days. with reference to this study factors associated significantly with delays in completion of treatment included noncompliance on the part of the patient, and psychosocial factors such as inadequate transport, mental health challenges, dementia, substance abuse, financial and childcare challenges. In addition, delays in the initiation and protracted brachytherapy treatment lead to 34% of the patient not completing treatment within 56 days. Tumor factors necessitating a change from intra cavitary to interstitial brachytherapy also contributed to treatment delays. Poor response to external beam radiotherapy, medical complication requiring treatment prior to brachytherapy, treatment toxicity, unsuccessful placement or displacement of the sleeve device were also associated with treatment delays. He observed no significant associations with race, age, language, , employment status, marital status HIV status, disease stage, performance status, body mass index, or distance traveled to the hospital. His study though underpowered revealed a trove of qualitative information especially on the treatment related factors (Cohen et al., 2017). Similar qualitative findings were however not realized in this study due to poor documentation. Spees et al observed that 34% of the patients completed treatment within 56 days. It was further observed that in the rural areas, patients residing more than fifteen miles from the treatment centre were twice more likely to complete their treatment within 56 days (risk ratio 2.46 95%CI 1.12-5.51) (Spees et al., 2019). This is a similar trend to that observed in this study.

Residence as a factor is a vehicle that could encompass more salient confounding factors like socioeconomic status, the presence or absence of specialized medical services, the health seeking behavior intrinsic to each patient, and the efficiency of the referral system. One would argue that the health seeking behavior peculiar to patients seeking oncology services from without Nairobi is such that they are highly motivated to start and complete their treatment as soon as possible

due to the fact they have a sound social support system, are being hosted or are renting facilities while on treatment and thus are highly motivated to see to their treatment without any delays. All this is speculative and can only be ascertained by a prospective qualitative study.

Education is an important socioeconomic factor that has been demonstrated to affect the prognosis of cancer patients. The level of education can affect income, employment status and poverty. These are socioeconomic factors likely to affect the health seeking behavior(s) of patients and thus hold sway in the treatment outcomes. The multivariate Cox analysis by Jiaxuan xu et al, 2022 demonstrated that the level of education is important factor predictive of not only the outcome but also the survival of patients with adenocarcinoma of the stomach. In this study, a high level of education was significantly associated with not only better overall survival rates but also better disease-specific survival rates(J. Xu et al., 2022). Limei Xi, in a similar study on patients with multiple myeloma, observed that lower levels of education were predictive of poor survival outcomes (L. Xu et al., 2020). Both studies demonstrate the importance of the level of education status of the patient(s) on disease outcomes. Drawing from this, it is not surprising that a secondary or higher level of education was significantly associated with better treatment timelines in this study. Being a modifiable factor, it is imperative that measures be taken to improve the education level of Kenyan citizens, given the long-term implications, should they be unfortunate enough to suffer maladies such as cancer.

Conclusions

 From the observations realized in this study, in comparison to findings observed in other studies, it seems that different factors contextually affect the treatment timelines due to the fact that

patients are likely to face a variety of challenges as they seek health care. Some of these factors are modifiable and thus actionable from a health policy point of view whereas others aren't. This study managed to highlight treatment timeline benchmarks upon which future improvements can be based upon. In addition, peculiar patterns emerged between certain factors and the treatment timelines as follows:

- The median age of patients in the study was 50 years with 73.8% (n =242) of the respondents having secondary level education or higher. 64.9% of the patients were unemployed and the majority of the patients (92.4%) were residing outside Nairobi.

- The median definitive treatment time was 80 days, with 34.5% of the patients completing their treatment within the guideline concordance period of 56 days.

- The median treatment starting time was 71 days with 58.5% of the patients starting their treatment within 90 days of a histologically confirmed diagnosis.

- Being employed and residing outside Nairobi at the time of the study period positively influenced treatment starting times whereas longer duration of illness negatively influenced treatment starting times.

- Having a secondary or higher education and residence outside Nairobi positively influenced definitive treatment timelines.

Recommendations

- Extension of the patient navigation program to the point of histological diagnosis can be used in an attempt to shorten the treatment initiation timelines.

- Prospective qualitative studies should be done to identify actionable qualitative factors influencing these timelines e.g. treatment related factors.

- Prospective multicenter studies should be done to audit the treatment timelines given that the number of public facilities offering cancer treatment (radiotherapy and brachytherapy) have increased from one (during the study period) to five currently.

- Encourage proper documentation in medical informatics to avoid loss of qualitative data that can be used in medical audits to better healthcare through policy changes.

Study limitation

Considering that this was a retrospective study, some qualitative data was found missing from patient files or was poorly and inconsistently recorded and as such could not be traced. Consequent to this, variables such as treatment related factors, logistical administrative factors, did not reach the statistical threshold for meaningful analysis and thus were excluded from the final analysis.

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APPENDIX 1.

Study budget

ITEM	QUANTITY	UNIT PRICE	TOTAL
STATIONERY/PRIN TING QUESTIONNAIRES PENS BOX FILES NOTEBOOKS PETTY CASH VOUCHERS	**350** **12** **6** **6** **1**	**5** **15** **250** **100** **250**	**1750** **180** **1500** **600** **250**
FINAL MANUSCRIPTS POSTER PRESENTATION	**7** **1**	**1000** **5000**	**7000** **5000**
RESEARCH **ASSISTANTS** AIRTIME DATA BUNDLES DATA ANALYSIS	**5** **5X2** **5X2**	**10000** **1000** **1000**	**50000** **10000** **10000** **35000**
CONTIGENCIES **(15%)**			**18192**
TOTAL			**139472**

APPENDIX 2.

Data collection tool

Barriers to timely initiation and completion of guideline concordance treatment for patients with cervical carcinoma stage 1b2 –IV A Kenyatta National Hospital	
Form No	
Date	
Age of Participant	
HIV status	Negative ☐ positive ☐
Marital Status	Single ☐ Married ☐ Separated ☐ widowed ☐
Level of Education	none ☐ primary ☐ secondary ☐ tertiary ☐
Occupation	Student ☐ Employed ☐ Not employed ☐
Residence	**(Tick)**
County	
Nairobi Sub Counties	
Westlands	
Dagoretti North	
Dagoretti South	
Langata	

Kibra	
Roysambu	
Kasarani	
Ruaraka	
Embakasi South	
Embakasi North	
Embakasi Central	
Embakasi East	
Embakasi West	
Makadara	
Kamukunji	
Strarehe	
Mathare	
Nairobi Metropolitan Area Counties	
Nairobi County	
Kiambu County	
Muranga County	
Kajiado County	
Machakos County	
Others (Name)	

Medical Information

Duration of illness before diagnosis	
Histology	Date of Histology Diagnosis ………………………… Squamous Cell Carcinoma ☐ Adenocarcinoma ☐

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	Others (name) …………………………….
Stage of disease	
Date of first specialist Assessment	

Treatment Details

Date of Treatment prescription	
Treatment Prescribed	
Date of 2d simulation/CT scan	
Scheduled date of starting radiotherapy	
Concurrent chemotherapy	Given ▭ Not Given ▭

	CHEMO RADIOTHERAPY		
	Visit No	Date	Chemo radiotherapy (Y/N)
1			
2			
3			
4			

5			
6			
7			
8			
9			
1 0			
1 1			
1 2			
1 3			
1 4			
1 5			
1 6			
1 7			
1 8			
1 9			
2 0			
2 1			
2 2			
2 3			

2 4			
2 5			

	BRACHYTHERAPY		
	Visit No	Date	Brachytherapy (Y/N)
1			
2			
3			

REASONS FOR DELAY(tick as appropriate)	RADIO THERAPY	BRACHYTHERAPY
Patient Factors		
Failure to Keep Appointments		
Performance status		
Comorbidities		
Deep Venous thrombosis		
Renal impairment		
Infection		
Diabetes		
Hypertension		
Others (Name)		
Treatment Factors		
Treatment Toxicities		
Anemia and Transfusion requirement		

Neutropenia		
Skin desquamation		
Diarrhea		
Nausea and Vomiting		
System Factors		
NHIF Approval Delays		
Patient Backlog		
Public Holiday		
Machine Downtime		

Treatment outcomes at 3-, 6-, 9-, and 12-months post treatment.

Follow up visit no.	Disease status (via bimanual pelvic examination)	
	Resolved	Present
1st		
2nd		
3rd		
4th		

APPENDIX 3.

Nairobi metropolitan area map (*The-Nairobi-Metropolitan-Region.Jpg (970×1254)*, n.d.)
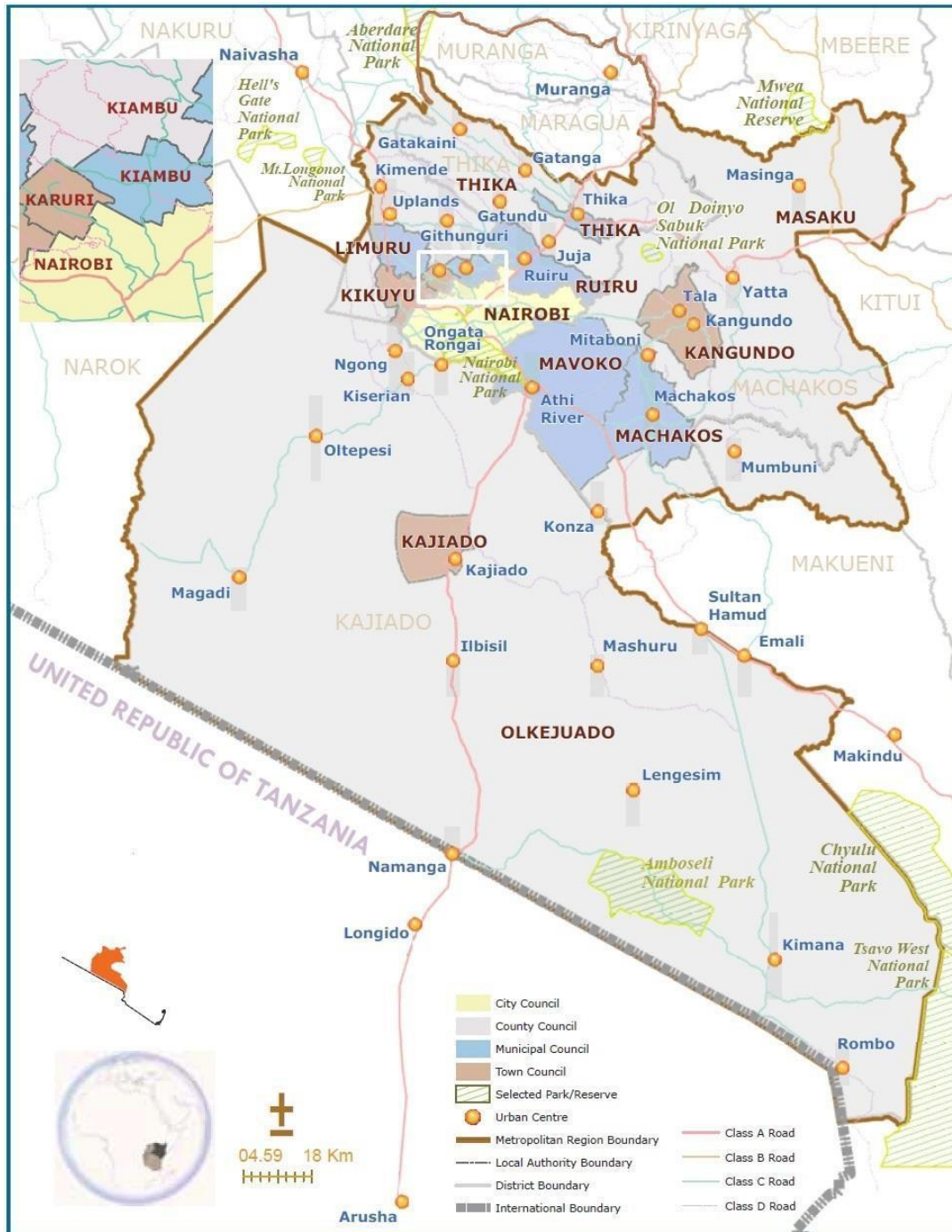
Ref: KNH-ERC/A/423

8th November 2021

Dr. Collins Masolo Nandasaba
Reg. No.H58/34005/2019
Dept. of Diagnostic Imaging and Radiation Medicine
Faculty of Health Sciences
University of Nairobi

Dear Dr. Nandasaba

Research proposal: Barriers to timely initiation and completion of guideline concordance treatment for patients with Carcinoma of the cervix stage Ib2-IVa at Cancer Treatment Centre, Kenyatta National Hospital (P730/09/2021)

This is to inform you that KNH-UoN ERC has reviewed and approved your above research proposal. Your application approval number is **P730/09/2021**. The approval period is 8th November 2021 – 7th November 2022.
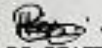
This approval is subject to compliance with the following requirements;

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

Protect to discover

Prior to commencing your study, you will be expected to obtain a research license from National Commission for Science, Technology and Innovation (NACOSTI) https://research-portal.nacosti.go.ke and also obtain other clearances needed.

Yours sincerely,

DR. BEATRICE K.M. AMUGUNE
SECRETARY, KNH-UoN ERC

c.c.   The Dean, Faculty of Health Sciences, UoN
         The Senior Director, CS, KNH
         The Assistant Director, Health Information Dept., KNH
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Protect to discover