TREATMENT OUTCOME OF NEOADJUVANT THERAPY FOR LOCALLY ADVANCED RECTAL CANCER A SINGLE INSTITUTION EXPERIENCE

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DECLARATION AND RECOMMENDATION

Declaration

This thesis is my original work and has not been presented to any other institution of learning for award of a degree or any an academic certificate.

Signature:  **Date:** 07/09/23

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Supervisors' Recommendation

This thesis has been submitted for examination with our approval as university supervisors

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TABLE OF CONTENTS

DEFINITION OF TERMS

Local recurrence: Means that the cancer has come back in the same place it first started. **Regional recurrence:** Means that the cancer has come back in the lymph nodes near the place it first started.

Locally Advanced Rectal cancer (LARC): Is characterized as tumors invading or extending close to the mesorectal fascia.

Neoadjuvant therapy: Refers to the systemic treatmen**t** of LARC cancer prior to definitive surgical therapy.

Overall Survival: Is the duration of patient survival from the time of treatment initiation and a universally-accepted measure of lifespan after treatment(1).

Progression Free survival: Is the length of time during and after the treatment of a disease, such as cancer, that a patient lives with the disease without relapse

LIST OF ABBREVIATIONS

CEA: Carcinoembryonic antigen

CRT: Chemoradiation Therapy

CTC: Cancer Treatment Center

EORTC: European Organisation for Research and Treatment of Cancer

Gy: Gray Unit

KNH: Kenyatta National Hospital

LARC : Locally Advanced Rectal Cancer

LCRT: Long Course Radiotherapy

pCR: Pathologic complete response

SCRT: Short course Radiotherapy

TME: Total Mesorectal Excision

TNT: Total Neoadjuvant Therapy

WHO: World Health Organization

ABSTRACT

Background: Rectal cancer is daunting disease that has been significantly associated with high rate of recurrence and metastasis. According to Globocan report in 2020, rectal cancer is among the top ten cancers in Kenya with an incidence of 2.3% and 2.5% mortality rate. Locally advanced rectal cancer (LARC) involve tumours that extend to the mesorectal fascia. Thus, in management of this condition, a complete removal of the tumour and mesorectum is essential on local control and survival. The use of neoadjuvant therapy has been observed as essential in management of LARC resulting in improved overall survival, progression free survival, and local control. However, the outcomes of neoadjuvant therapy in management of LARC have not been fully investigated in the Kenyan setting.

Broad Objective: To establish the outcomes of neoadjuvant therapy in LARC a single institution study at the Cancer Treatment Centre, Kenyatta National hospital between January 2016 and January 2020.

Methodology: The study adopted a retrospective study design. A complete enumeration was be done where all 182 patient files were targeted between January 2016 and January 2020. The inclusion criteria comprised patients treated for locally advanced rectal cancer diagnosed in Kenyatta National Hospital, patients who completed neoadjuvant therapy, and a histological subtype of adenocarcinoma. A structured data abstraction tool was developed to help in data extraction from patients with LARC. The data that was extracted from the files.

Results: The average age of 54.2 years, more than half of the patients, 52.5% were female. More than half of the patients, 57.5% were at T3 at diagnosis. Progression free survival and overall survival were investigated. The median progression free survival after neoadjuvant treatment was 24 (IQR: 23 – 25) months. The overall survival median was 36 (IQR: 24 – 36) months. The bivariate analysis revealed that presence of comorbidities ($\beta = -4.2$, $p = 0.041$), tumor staging ($\beta = -4.4$, $p = 0.003$), Duration of symptoms before diagnosis ($\beta = -0.07$, $p = 0.028$), and treatment modality ($\beta = -7.2$, $p = 0.026$), were predictors of overall survival. Multiple regression analysis revealed that presence of comorbidities ($\beta = -4.6$, $p = 0.023$), tumor staging ($\beta = -6$, $p = 0.009$) and duration of symptom before diagnosis ($\beta = -0.1$, $p = 0.039$) were independent predictors of overall survival.

Conclusion and recommendations: The findings have showed that presence of comorbidities, tumor staging at diagnosis and the longer duration of symptoms before diagnosis were independent predictors of poor overall survival. Thus, there is need to ensure regular screening for rectal cancer should be done across all ages to control late diagnosis of the disease at advanced stage.

CHAPTER 1: INTRODUCTION

1.1.Background

The global trends show that there are approximately 1.6 million patients diagnosed with colorectal cancer. Thirty percent of these tumours occur in the rectum (2). In the United States, the American Cancer Society (ACS) highlight that there has been an increasing incidence of rectal cancer with an estimated 45,230 cases likely to occur by the end of 2021 with higher incidence expected in men with an estimate of 26,000 and 18,230 in women (3).

According to Globocan Rectal cancer in Kenya is ranked 10th with an incidence rate of 2.3% and a mortality rate of 2.5% and a five-year prevalence of 3.56 per 100,000. This indeed shows the need to address the treatment outcomes and evaluate reasons why the mortality rate high. Locally advanced rectal cancer (LARC), which includes T3 and T4 tumours as well as tumours comprising locoregional lymph nodes, has proven difficult to treat and cure. The proximity of the sphincter to the borders of the bony pelvis, as well as the need to protect autonomic nerves, have made surgical resection difficult and morbidity high.

The management plan for rectal cancer has shifted in the recent past, to chemoradiation as the common management approach in patients with LARC. However, the outcomes have not been fully assessed in the form of research to determine the efficacy of chemoradiation as first line treatment in management of this type of cancer (4).

The common management approaches of cancer include radiotherapy, chemotherapy, chemo-radiation and surgery have been associated with different outcomes. However, the manner in which these approaches are integrated into patient management care has been subject for discussion since there are no well outlined outlines in management of different types of cancer. However, there have been various clinical trials conducted with an aim to obtain a more efficient management approach. LARC had adopted both neoadjuvant and adjuvant

management techniques which have been associated with diverse outcomes. Neoadjuvant radiotherapy and chemo-radiation have been associated with higher positive outcomes which include longer progression free survival and reduced recurrence (5).

A study conducted in Japan in 2019 by Shiraishi et al. in predicting prognosis of patients with LARC revealed that neoadjuvant was associated with a higher five-year recurrence free survival , 89% and overall survival rate of 93.8%. Poor recurrence was associated with extramural venous invasion on the imaging after ADT (6). Similarly, Cercek et al. found that 36 percent of 61 LARC patients who received induction chemotherapy together with Chemo-radiotherapy had better five-year recurrence free survival. The results further revealed that there were no observed side effects in any of the patients who had a R0 resection (7).

However, management of LARC in local setting has not been fully investigated which present clear gaps that exist in management of this type of cancer. Research has shown that neoadjuvant therapy for LARC patients is vital in improving positive outcomes (8).Thus integration into the local setting should essential in guiding positive outcomes in cancer patients.(9)

CHAPTER TWO: LITERATURE REVIEW

2.1.Locally Advanced Rectal cancer

Rectal cancer is a highly variable disease associated with varied prognostic effects and results. Unclear decision-making approach has had an adverse influence on controlling the recurrence rate which is crucial in management of the condition globally. The need for radiation therapy prior to surgery has shown positive outcomes in advanced settings. This has also been driven by the need to control local pelvic recurrence. The commonly occurring symptoms of local recurrence include intractable pelvic pain, mucinous discharge, intestinal obstruction (10). In addition to pelvic recurrence, distant spread remains a concern and a a pooled study involving five European countries and a sample of 2,795 showed that a five year period distant metastasis rate was 31percent (11).

The initial attempts to improve results in LARC patients mainly focused on pathological staging because of poor preoperative imaging. The treatment in recent past has significantly shifted from upfront surgical based interventions to a neoadjuvant radiation or chemo-radiation which have been associated with improved outcomes (12). Treatment failure has been associated with distant recurrence in LARC patients (13).

Rectal cancer that has progressed locally necessitates multidisciplinary treatment. The United States has adopted neoadjuvant treatment plan in management of LARC patients. Additional therapies have also been adopted include full mesorectal excision as well as four months of adjuvant chemotherapy. Neoadjuvant radiotherapy occurs for around 25 and 28 days. The trimodal approach has been largely successful although longer duration of management is required to achieve maximum outcomes. Alternative methods for reducing patient time without compromising oncologic results have arisen. Preoperative chemotherapy with targeted radiation, short-course radiotherapy administered over 5 days, and complete neoadjuvant

therapy with nonoperative organ preservation management are examples of these approaches (14).

2.2.Standard of care for LARC

Management of LARC has evolved over the years with key emphasis on proper mechanisms that can help improve patient outcomes. A recent clinical trial conducted by EORTC including 22,921 rectal cancer patients found that patients who were given preoperative chemo-radiation therapy had the lowest rate of local recurrence at 8 percent (15). These findings illustrate that fluorouracil-based chemotherapy reduced the risk of local recurrence, but that adjuvant chemotherapy had no effect on survival

Alternative agents for neoadjuvant radiosensitizing chemotherapy have been studied in several studies. Capecitabine was found to be noninferior to fluorouracil in the NSABP-R04 experiment. Multiple studies have shown that oxaliplatin combined with neoadjuvant fluorouracil is not reliably effective and is associated with increased toxicity. For neoadjuvant chemo-radiation therapy, fluorouracil is still the preferred agent (16). Although preoperative chemo-radiation therapy and TME are generally recognized as the gold standard, the relative benefits of SCRT and LCRT are still debated.

2.3.Characteristics of patients with LARC

While rectum cancer is thought to be a disease that affects the elderly, it can also affect people in their younger years (17). The likelihood of occurrence at younger age is associated with the genetic arm of causation leading to development of several screening methods and criteria which include the Bethesda and Amsterdam. These screening methods have been utilized in classifying the population at risk (18). The diagnosis of rectal cancer in patients who are aged 40 years and below has also been associated with wrong prognosis and advanced stage at the patient presentation stage (19). There has been a regular need to understand the underlying

epidemiology of the tumor in relation to the different geographical settings to understand essential interventions for management of adverse outcomes.

In a retrospective descriptive study conducted in Los Angeles revealed that approximately 4% of the patients were aged below 40 years (20). Thus, the lower prevalence of rectal cancer patients in younger individuals is based on the diagnosis at late stage in life when the presenting symptoms begin to show. Similarly, another observational study conducted in New Orleans found that 3.6% of the population were aged below 40 years (21). However, there is contrast in another study conducted in India which found that 36% of patients with rectal cancer were young (22). Most of the diagnosis among older patients occurs at later stage of disease development which shows that early screening is likely to find a higher prevalence of the disease in younger patients at early stages of the tumour development.

In a retrospective cohort study conducted in Canada by Reguena et al. investigating the outcomes of elderly patients receiving neoadjuvant chemoradiation, 25% were aged more than 75 years. The findings further revealed that, 85% aged below 70 years completed neoadjuvant therapy compared to 75.6% who were aged 75 years who completed neoadjuvant treatment. When comparing cancer staging based on age groups, 66.2% and 59.3% of patients aged less than 75 and greater than 75% respectively were at stage 3 (23).

Peng et al. investigated clinical features of LARC patients undergoing neoadjuvant treatment in a retrospective review in China. There were 297 patients in total, with 207 males (69.7%) and 90 females (30.3%) with a median age of 56 years and a range of 15 to 80 years, according to the results. CEA levels ranged from 0.2 to 249.6 ng/ml, with the median being 4.5 ng/ml. Low-lying tumours had a median tumour position of 5 cm. There were 90 (30.3%) and 207 (69.7%) patients with clinical stage II and III, respectively. After neo-CRT, a complete mesorectal excision was performed 45 days or within the next 20 to 142 days (24). In a

retrospective study conducted in Japan, Shiraichi et al discovered that 68 percent of the 102 patients enrolled were female, with an average age of 60 years (6). These findings reveal that rectal cancer is more prevalent in women as well as individuals aged 60 years and above.

2.4.Treatment modalities and Outcomes

2.4.1. Radiotherapy as neoadjuvant treatment

Short course radiotherapy includes 25 Gy which is given for a period of five days while the Long course radiotherapy includes approximately 45 to 50.4 Gy which are given over a five- or six-week period in addition to the sensitizing fluoropyrimidine-based chemotherapy and surgery which is conducted later after an eight to twelve-week period. Preoperative SRCT is more widely used in European countries because it is less costly, takes less time, and is more convenient for patients than LCRT. Although SCRT has the same tumour-killing ability as LCRT, the shorter time to surgery reduces the chance of tumour downstaging and adequate pathologic response.

A clinical trial conducted by Bujko et al compared the outcomes of short course radiotherapy followed by surgery within the first seven days and the long course radiotherapy followed by surgery within the first four to six weeks. The findings from the study revealed that at four years, both groups had findings that were comparable based on overall survival, disease free survival and local recurrence levels. These findings show that SCRT can help attain the needed outcomes if it is immediately followed by surgery within first seven days (25).

Stockholm II noninferiority trial including 840 patients with rectal cancer were assigned randomly to three groups which were investigated. The groups include SCRT with immediate surgery, SCRT with surgery after four to six weeks, or LCRT with surgery between the first four to six weeks. The findings from the study found that patients who had SCRT with surgery after six weeks had lower incidence of postoperative complications, higher tumor regression

as well a higher rate of pCR of 12% compared to 2% in patients who had SCRT with immediate surgery(26). The results have shown that SCRT with surgery later is a significant alternative to LCRT. It is also essential to note that while these trials haven't shown whether SCRT or LCRT leads to better tumour control, they have successfully shown that delaying surgery after radiotherapy maximizes tumour response.

Alves et al. found that parents with rectal cancer who were treated with preoperative SCRT and total mesorectal excision (TME) surgery had lower risk of local recurrence at two years than those who had total mesorectal excision alone (27).These results, however, were in contrast to those of a previous Swedish study that looked at overall survival in rectal cancer patients. According to the study's results, patients who received preoperative SCRT plus surgery had a higher five-year survival rate than patients who received surgery alone, with 58 percent and 48 percent, respectively (28).

2.4.2. Total neoadjuvant therapy

Total neoadjuvant therapy is a multimodal new approach in management of LARC and involves the use of systemic chemotherapy. Using this approach, chemotherapy can be given as either induction or consolidation chemoradiotherapy prior to curative surgery approach. The use of preoperative chemotherapy has significant benefits which include facilitation of tumour down staging and control of distant recurrence which has been associated with high mortality among rectal cancer patients (21).

Another retrospective cohort design was conducted in the United States revealed that induction chemotherapy patients had higher rate of complete response than those who utilized adjuvant therapy. Similarly, the study revealed that 78% of patients of induction chemotherapy completed eight cycles (29). Patients with high risk LARC had higher response to induction therapy together with chemo-radiotherapy. In the two trials, the rate of pCR was 20%, and T

and N downstaging occurred in 56 percent and 43 percent of patients, respectively. Despite the lack of a chemo-RT control group in the trials, they did show persistent tumour regression in a high-risk population (30).

A randomized control trial involving 920 patients comparing chemotherapy followed with TME and LCRT followed with TME found that patients in the total neoadjuvant therapy were associated with higher pCR as well as reduced three year distant recurrence compared to LCRT with TME group (31).

2.4.3. Chemotherapy addition in the Neoadjuvant treatment protocols

Induction prior to chemoradiation is an increasingly common method of combining chemotherapy that results in high rates of symptomatic improvement (65 percent)(32). Induction chemotherapy has a clinical response rate of 28 percent. When cetuximab was introduced, the percentages increased to 41% and 59 percent, respectively, with no patients showing signs of disease progression (33). According to phase II randomised trials, TNT prior to chemoradiation is feasible and can be delivered with minimum radiation or surgery compromise (34).

Similarly, chemo-radiation before operation with LCRT with 50.4Gy over a five-week period and fluorouaracil were compared to post-operative chemotherapy alone before surgery among rectal cancer patients. The findings revealed patients who had preoperative chemo-radiation had reduced rates of grade 3 as well as grade 4 acute and long-term toxicities. However, the findings revealed that there was no significant difference in overall survival, distant recurrence as well as disease free survival. Importantly, there was a high rate of adherence to chemotherapy and RT, as well as sphincter preservation (35). This trial was essential in establishing preoperative chemo-radiation therapy as the standard of care for LARC.

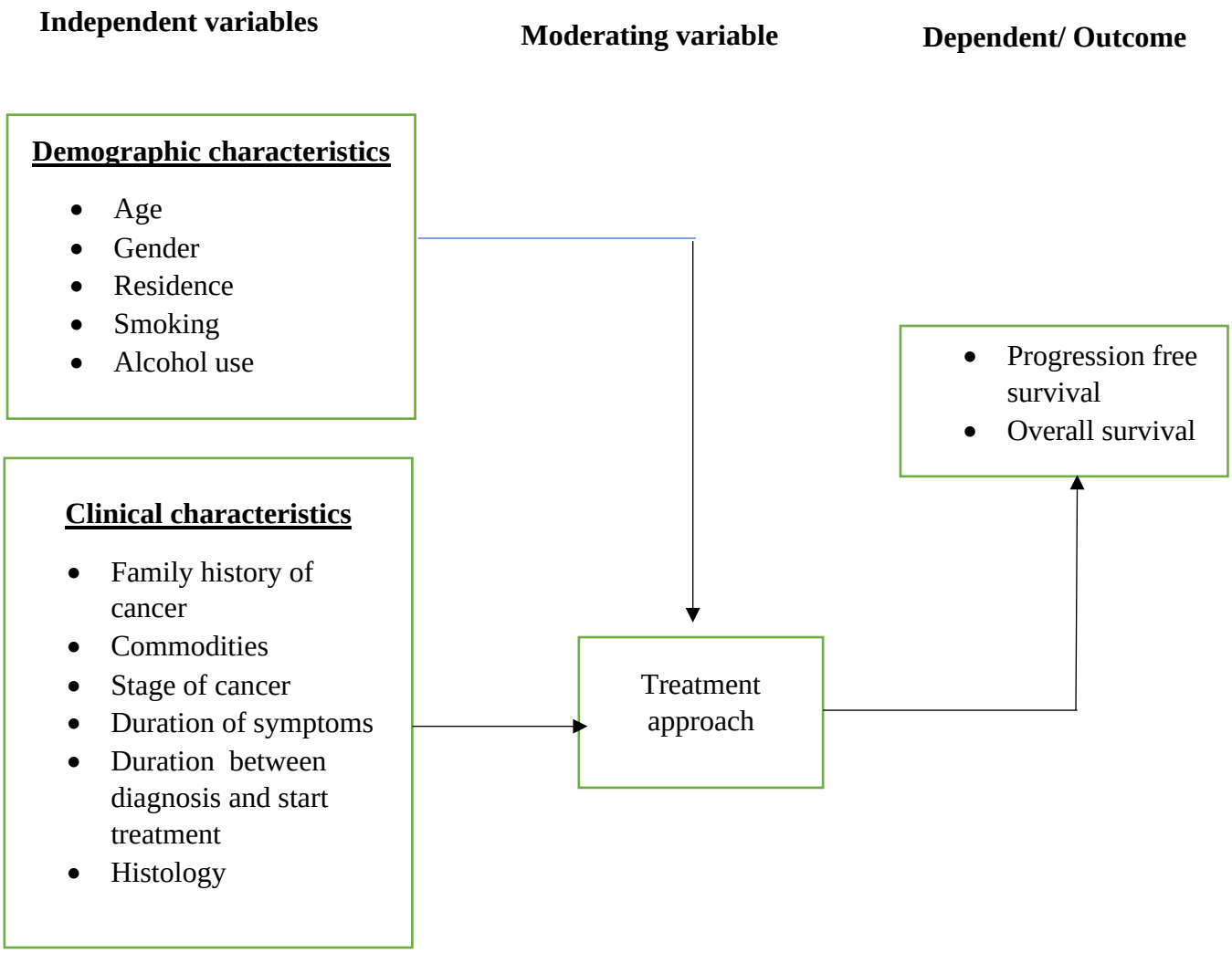
Another retrospective cohort study conducted in Spain investigating the outcomes in rectal cancer patients based on chemoradiation therapy followed with TME and adjuvant chemotherapy, the results showed that there were higher positive outcomes in the preoperative treatment group with neoadjuvant and TME (36).

2.5. Factors associated with treatment outcomes

There are varied demographic and clinical characteristics that have an influence on LARC treatment outcome. Thus, it is essential to understand these factors in the context of past studies. A retrospective study conducted in China revealed that, Patients with clinical T1-3 and a pre-treatment CEA level less than 5.33 ng/ml had a higher chance of achieving pCR after neo-CRT, according to univariate analysis. Sex, age, pre-treatment haemoglobin level, distance between the anal verge and the lower tumour edge, pathological differentiation, clinical N stage, and time between neo-CRT and complete mesorectal excision were also found to be unrelated to pCR. Pre-treatment CEA levels and clinical T1-3 were linked to pCR in multivariate analyses (24).

Shiraishi et al. in a study conducted in Japan in the year 2019 seeking to predict prognosis in patients with LARC, it was found that significant positive response to neoadjuvant was linked to higher five-year recurrence free survival. Poor recurrence free survival was associated with extramural venous invasion on the imaging after neoadjuvant therapy and tumor volume reduction of less than 60.The best 5-year recurrence-free and overall survival rates were 89 percent and 93.8 percent, respectively, for good responders without extramural venous invasion. Extramural venous invasion poor responders had the lowest 5-year recurrence-free and overall survival rates of 21.4 and 50.0 percent, respectively (6).

2.6.Conceptual Framework



2.7.Problem statement

Patients with locally advanced rectal cancer have reported increased disease progression even after initial cancer treatment intervention. Management of rectal cancer has been predominantly a combination of chemotherapy and radiotherapy. The changing guidelines on locally advanced rectal cancer present the need to assess the underlying outcomes based on the approaches that have been defined. Neoadjuvant therapy has been observed to positively influence patient outcomes based on clinical trials conducted globally. However, there is limited information on the treatment outcomes of neoadjuvant in locally advanced cancer of the rectum in Kenya which has prompted the need to understand this aspect with an aim to improve rectal cancer management.

2.8.Justification

Management of locally advanced rectal cancer has been subject to diverse intervention approaches which have sought to present a clearer approach to improve health outcomes of patients. Prior clinical trials have shown that primary management of LARC using neoadjuvant therapy has been linked with improved outcomes which present the need to understand this management approach in local setting and outcomes. There is less focus on the efficacy or importance of neoadjuvant therapy in management of LARC. This study provided essential knowledge on the protocol adopted in our setting, efficiency of neoadjuvant treatment, as well as overall survival of patients with locally advanced cancer based on chemoradiation care.

2.9.Research question

What are the outcomes of neoadjuvant therapy for locally advanced Rectal Cancer treated at the Kenyatta Cancer Treatment Center Jan 2016 and Jan 2020?

2.10. Objectives

2.10.1. Specific objectives

1. To describe demographic and clinical characteristics of patients with locally advanced rectal cancer at Kenyatta National Hospital between Jan 2016 and Jan 2021.

2. To determine the neoadjuvant modalities utilized at the Kenyatta Cancer Treatment Center
3. To determine treatment outcomes associated with neoadjuvant modalities utilized at Kenyatta National Hospital

2.10.2. Secondary objective

4. To investigate factors associated with treatment outcomes of patients with locally advanced rectal cancer at Kenyatta National Hospital between Jan 2016 and Jan 2020.

CHAPTER THREE: METHODOLOGY

3.1.Research Design

This was a retrospective cross-sectional study design.

3.2.Study setting

The study was carried out at the Cancer Treatment Center, Kenyatta National Hospital (KNH). The hospital has a bed capacity of 1,800 and more than 6,000 staff. KNH cancer treatment center is a specialized unit for cancer management. The unit has two Cobalt machines and one Linac Machine. There are seven Radiation Oncologists and eight medical officers in The Kenyatta National Hospital Cancer Treatment Center. The unit operates from Monday to Friday. The Cancer treatment Center was chosen as the study setting because of the availability of rectal cancer patients on neoadjuvant therapy and it is one of the best cancer care centers in the country.

3.3.Study population

The study included patients with locally advanced rectal cancer on neoadjuvant therapy between 2016 and 2020. The focus on a five-year period present a well elaborate basis within which it is possible to make strong and informed scientific decisions pertaining the effectiveness of neoadjuvant therapy in management of locally advanced rectal cancer.

3.4.Inclusion Criteria

- Patients treated for locally advanced rectal cancer diagnosed in Kenyatta National Hospital.
- Patient who completed neoadjuvant therapy
- Histology- Adenocarcinoma
- T3 and T4 tumors

3.5.Exclusion criteria

- Patients that do not have a histological ddiagnosis

- Incomplete files (Without a treatment outcome)

3.6.Sample size and sampling technique

3.6.1. Sample size determination

The total rectal cancer patients who sought care at KNH-CTC between 2016 and 2020 were 274. A census method was used where 181 files were retrieved.

3.6.2. Sampling technique

A complete enumeration was done where all files of patients within the study period were selected to form the study sample.

3.7.Study variables

Independent variables included in this study included age, gender, residence, smoking, alcohol, histology, imaging, time from diagnosis to treatment. The dependent variable included Progression free survival and overall survival

3.8.Data collection tool

A structured questionnaire was used in data extraction from patient files. The structure of the questionnaire included patients' demographics, clinical characteristics, treatment modality and treatment outcomes.

3.9.Data Collection Procedure

The data collection process began after approval from KNH-UoN Ethics Committee and permission from Kenyatta National Hospital to access patient files between 2016 and 2020 of rectal cancer patients. The PI sought permission for CTC to access files of patients from the department at the Health information department who are custodians. Patient register from CTC was obtained to identify patients who were diagnosed with LARC. The PI proceeded to the KNH health information archive to retrieve the files based on the IP numbers listed. The targeted files in the Health information department are stored under CTC files and grouped yearly. The retrieval of the patient files was done using the IP number list from the CTC register. The PI then reviewed the files and select files that meet the inclusion criteria

systematically every 2nd file. Once the patient file was selected, the PI extracted vital information using the developed questionnaire. Once relevant information was extracted from the patient file, they were returned to archive for safe keeping.

3.10. Data Management

All data collected was kept locked and confidential at all times and only accessible to the investigator and data manager. Once data was collected, Epi data version 3.1 was used to enter data and then exported to Stata version 14 for data analysis. Only the Principal investigator and the authorized biostatistician were allowed to access the information.

3.11. Data analysis

Descriptive analysis was grouped into categorical and continuous variables.

Demographic and clinical characteristics of patients with locally advanced rectal cancer at Kenyatta National Hospital between Jan 2016 and Jan 2021.

This was analyzed descriptively. Categorical variables was analyzed using frequencies (n) and percentages (%). Continuous variables was analyzed using mean (SD) and Median (IQR).

Neoadjuvant modalities utilized at the Kenyatta Cancer Treatment Center

This objective was analysed descriptively involving categorical variables where frequencies (n) and percentages (%).

Treatment associated with neoadjuvant modalities utilized at Kenyatta National Hospital

Bivariate and multivariate linear regression analysis were conducted to identify predictors of overall survival. P values of 0.05 shall be considered statistically significant.

3.12. Ethical considerations

This research underwent ethical review and approval at the KNH-UON ERC. Permission to carry out the study was sought from the hospital administration. Principles of confidentiality and privacy of information were maintained throughout the research process. Patients' data was kept confidential at all data abstraction, processing, and analysis stages. Data was anonymized and key patient identifiers like names, residence and age among others were de-identified.

Anonymity and Confidentiality: The researcher also maintained anonymity and confidentiality by using no identifiers such as codes that cannot link a participant with the information provided during the study. The information obtained was solely for the purpose of this study and improving the implement of service integration policy and not to divulge personal information to the public. Recorded data was under custody of the principal researcher until validation within one year after which the data will be destroyed.

3.13. Study Limitations

Missing data. However, meticulous searching of hospital records was done as well as collation of data from the patient files.

3.14. Dissemination plan

Results will be presented in the department of Diagnostic imaging and radiology Medicine. Further, the findings will further be shared with the Kenyatta National Hospital in improving the outcomes of patients with LARC. A Manuscript will be developed and published in globally renowned Oncology peer reviewed journal to share the results from our local setting and allow comparison with findings from other settings.

CHAPTER FOUR RESULTS

4.1.Introduction

The study sought to investigate outcomes of neoadjuvant therapy for locally advanced rectal cancer treated at the Kenyatta National Hospital between January 2016 and December 2020. A total of 181 sample was retrieved for analysis. The study flow chart is shown in Figure 1.

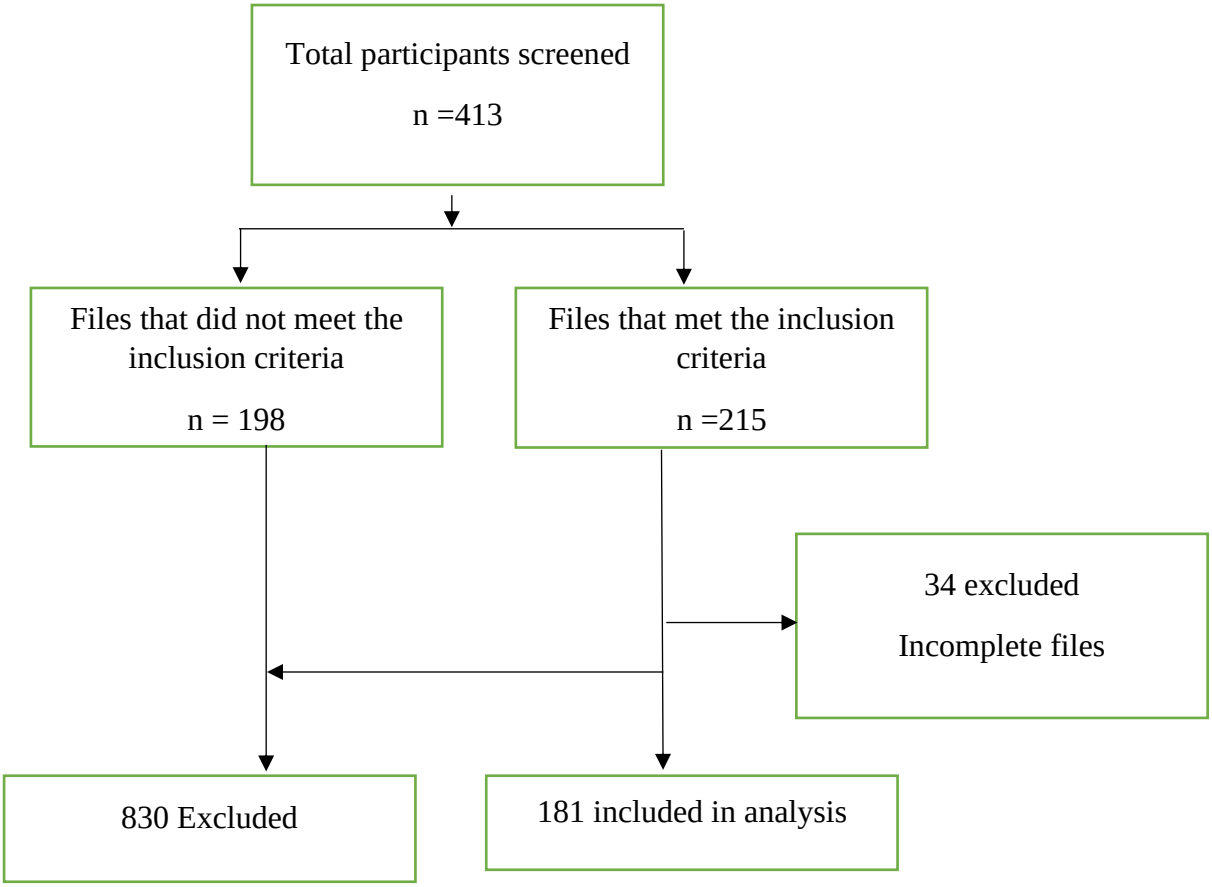


Figure 1: Study Flowchart

4.2.Demographic and clinical characteristics of patients with locally advanced rectal cancer at Kenyatta National Hospital

Demographic and clinical characteristics of patients with LARC were investigated as shown in Table 1. The findings from analysis revealed that the average age of patients with LARC were aged 54.2 years SD =13.82. More than half of the patients, 52.5% (n =95) were female, 76.2% (n =138) were residing in rural areas.

Table 1:Demographic and clinical characteristics of patients with locally advanced rectal cancer at Kenyatta National Hospital

Characteristics	Frequency (n)	Percent (%)
Age (Mean± SD)	54.2±13.82	
Gender of patient		
Male	86	47.5
Female	95	52.5
Residence		
Urban	43	23.8
Rural	138	76.2
Cigarette smoking		
Yes	47	26.0
No	134	74.0
Average number of packs (Mean ±SD)	3±1	
Alcohol intake		
Yes	47	26.0
No	134	74.0
Family history of cancer		
Yes	33	18.2
No	148	81.8
Presence of comorbidities		
Yes	39	21.5
No	148	78.5

4.3.Disease characteristics among patients with locally advanced rectal cancer seeking treatment at Kenyatta National Hospital

More than half of the patients, 57.5% (n =104) were at T3 at diagnosis. The lymph node assessment revealed that among 53.6% (n =97) of the patients had one lymph node containing cancer as shown in Table 2.

Table 2: Disease characteristics among patients with locally advanced rectal cancer seeking treatment at Kenyatta National Hospital

	Mean± SD	Frequency	Percent
Tumor staging			
T2		10	5.5
T3		104	57.5
T4		67	37.0
Lymph node			
N0		47	26.0
N1		97	53.6
N2		37	20.4
Time before diagnosis (months)	14.07±11.9		
Time from diagnosis to start of treatment months	3.64±2.64		

4.4.Imaging modality and histology assessment among patients with LARC at Kenyatta National Hospital

Chest, abdominal and pelvis imaging were assessed to identify the modality used in imaging. The results revealed that, 96.7% (n =175) of the chest imaging were done using CT scan while 3.3% (n =6) of the chest imaging were done using X-ray. All of the abdominal imaging was done using CT scan. Pelvis imaging assessment revealed that, 85.1% (n =154) of the pelvis scans were done using MRI while 14.9% (n =27) were done using CT scan. The histology assessment identified that, 80.7% (n =146) of the cells were well differentiated. The results also revealed that MDT was done in 3.3% (n =6) of the cases as shown in Table 3.

Table 3: Imaging modality and histology assessment among patients with LARC at Kenyatta National Hospital

	Frequency	Percent
Imaging		
Chest imaging		
X-ray	6	3.3
CT scan	175	96.7
Abdominal imaging		
CT	181	100.0
Pelvis imaging		
CT Scan	27	14.9
MRI	154	85.1
Histology		
Well differentiated	146	80.7
Moderately differentiated	25	13.8
Poorly differentiated	9	5.0
Undifferentiated	1	0.6
MDT		
Yes	6	3.3
No	175	96.7

4.5.The neoadjuvant modalities utilized at the Kenyatta Cancer Treatment Center

4.5.1. Treatment modality

Majority of the respondents, 91% (n =165) had neoadjuvant as the treatment modality as shown in Figure 2.

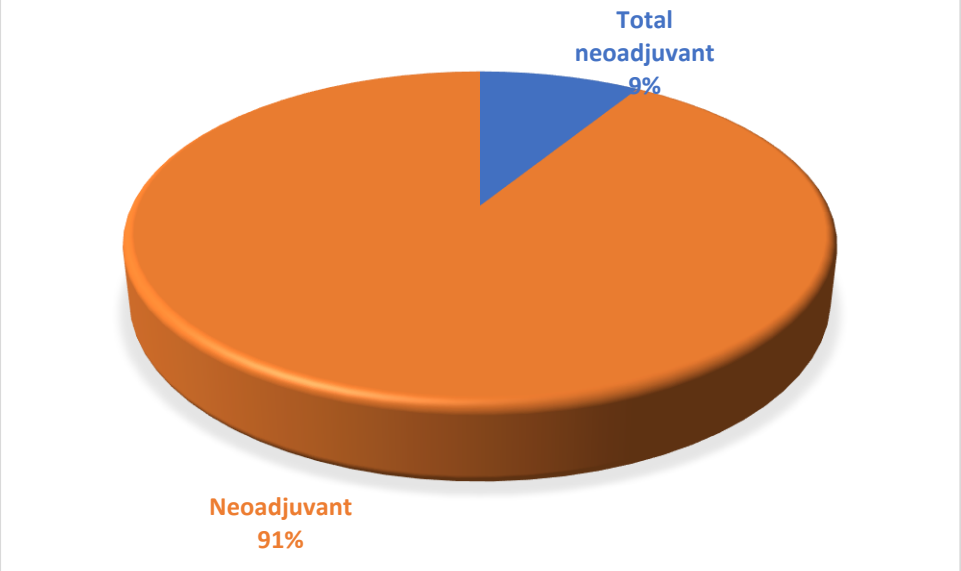


Figure 2: Treatment modality

4.5.2. Treatment course

Almost all patients, 95% (n =172) were on long course treatment as presented in Figure 3.

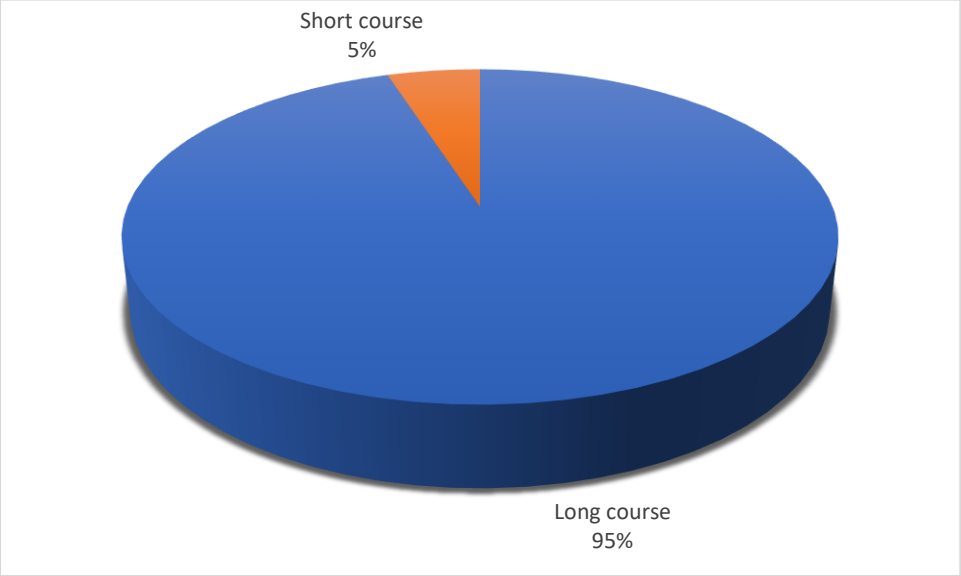


Figure 3: Treatment

4.6.Treatment outcomes among patients with Locally advanced rectal cancer at Kenyatta National Hospital

Treatment outcomes of neoadjuvant among patients with locally advanced rectal cancer were investigated. Progression free survival and overall survival were investigated. The median progression free survival after neoadjuvant treatment was 24 (IQR: 23 – 25) months. The overall survival median was 36 (IQR: 24 – 36) months as shown in Table 4.

Table 4: Treatment outcomes among patients with Locally advanced rectal cancer at Kenyatta National Hospital

	Min	Max	Median	IQR
Progression free survival (months)	3.00	48.00	24	23 - 25
Overall survival (months)	6	72	36	24 - 36

4.7.Factors associated with treatment outcomes of patients with locally advanced rectal cancer at Kenyatta National Hospital between Jan 2016 and Jan 2020.

Linear regression analysis was conducted to investigate the factors associated with treatment outcomes (overall survival) of patients with locally advanced rectal cancer. Both bivariate and multiple linear regression were conducted. The bivariate analysis revealed that presence of comorbidities, tumor staging, Duration of symptoms before diagnosis and treatment modality were predictors of overall survival. Multiple regression analysis revealed that presence of comorbidities, tumor staging and duration of symptom before diagnosis were independent predictors of overall survival. Presence of comorbidity was associated with 4.6 months decrease in overall survival, $\beta = -4.6$, $p = 0.023$. Diagnosis of rectal cancer at later stage was associated with 6 months reduction in patient overall survival, $\beta = -6$, $p = 0.009$. an increase in duration of symptoms prior to diagnosis by one month was associated with 0.1 reduction in overall survival, $\beta = -0.1$, $p = 0.039$ as shown in Table 5.

Table 5: Factors associated with treatment outcomes of patients with locally advanced rectal cancer at Kenyatta National Hospital between Jan 2016 and Jan 2020.

	Unadjusted β coefficients	**95%CI**	**P-value**	**adjusted β coefficients**	**95%CI**	**P-value**
Age	-0.074	(-0.2, 0.05)	0.246			
Gender	1.431	(-2.01, 4.87)	0.413			
Residence	1.747	(-2.01, 5.78)	0.394			
History of cigarette smoking	-0.655	(-4.57, -0.71)	0.742			
Alcohol intake	0.403	(-2.71, 3.58)	0.803			
Presence of comorbidities	-4.245	(-8.31, -0.18)	0.041	-4.554	(-8.48,-0.63)	0.023
Tumor staging	-4.436	(-7.41, -1.37)	0.003	-3.972	(-6.02,-1.92)	0.009
Lymph node	-0.124	(-2.11, 1.90)	0.904			
Duration of symptoms	-0.070	(-0.13, -0.01)	0.028	-0.064	(-0.12, -0.03)	0.039
Duration from diagnosis to start of treatment	-0.234	(-0.88, -0.41)	0.481			
Histology	-1.496	(-0.3, 1.52)	0.330			
Treatment modality	-7.218	(-13.51, -0.86)	0.026	-5.425	(-11.69, 0.84)	0.089
Treatment course	-4.893	(-12.71, 2.99)	0.222			

CHAPTER FIVE: DISCUSSION

The present study examined the outcomes of neoadjuvant therapy for locally advanced rectal cancer in a tertiary hospital in Kenya. The findings from our present study revealed that the average age of the patients was 54 years. These findings are comparable to a study conducted in China by Peng et al. which found that the median age of patients in their study was 56 years (Peng et al., 2018). However, the average age from our present study was higher compared to a study conducted in United states which found that the average age was 40 years. The average age in our present study is lower compared to a study done in Japan by Shiraichi which found that the average age in their study was 60 years. From literature it is evident that the average age of patients with LARC are older adults. This is mainly because of lack of regular screening which means that most of the patients present in a health facility already presenting with symptoms and at advanced stage of the disease. The current study revealed that more than half of the patients were female, 52%. This is consistent with a study conducted in Japan by Shiraichi which found that 68% of the patients with locally advanced rectal cancer (Shiraishi et al., 2019). Although in a study conducted in China by Peng et al, majority of patients with LARC were men. Rectal cancer risk increases with age. A person diagnosed with colorectal cancer is typically 68 years old. Men are more at danger than women. With regular inspections and lifestyle adjustments, the risk of rectal cancer can be lowered, and the disease can be prevented or detected early (Maurie, 2022).

Our findings also revealed that 26% of the patients had history of smoking, and history of alcohol use. Smoking has a significant influence on rectal cancer. Thus cigarette smokers are more likely to develop rectal cancer. These findings from present study are consistent with those from a cohort study conducted in Norway by Parajuli et al. who find that those who had history of cigarette smoking were 25% more likely to develop rectal cancer compared to those

who have never smoked for both men and women (Parajuli et al., 2014). Similarly, Electra et al also found that current smokers were at an increased risk for rectal cancer, but not colon cancer, compared with never smokers. Secondhand exposure to cigarette smoke was not associated with either cancer (Electra, 2007). It has also been identified that alcohol consumption has been related to an increased risk of colon and rectum cancer. The evidence for this is often stronger in men than in women, but studies have revealed a correlation between the two sexes. Overall, it appears that the amount of alcohol consumed over time, rather than the type of alcoholic beverage, is the most relevant factor in increasing cancer risk. The majority of data suggests that it is the ethanol, not other ingredients in the drink, that increases the risk (Scherübl, 2019).

The present study revealed that, 58% were at T3 at diagnosis while 37% were at T4 at diagnosis. These findings show that almost all of the patients were diagnosed with LARC at either stage 3 or stage 4. Symptoms of rectal cancer present late resulting in adverse outcomes and reduced chance of recovery. These findings concur with those from Reguena et al conducted in Canada which found that 75% of the patients were at stage 3 at the time of diagnosis (Reguera Puertas et al., 2016). Peng et al in a study conducted in China also revealed that majority of patients were diagnosed at stage 3 (Peng et al., 2018). These findings show that there is late diagnosis of LARC in both low resource settings and high resource settings thus this could be explained by late occurrence of symptoms which influence health seeking behaviour among patients. There is need for improved awareness on continued level of screening for LARC.

Imaging modality plays a fundamental role in accurate diagnosis of LARC. Chest, abdominal and pelvis imaging are vital in the diagnosis and differentiation of cancer cells. In our present study , 96.7% of the chest imaging were done using CT scan while 3.3% of the chest imaging

were done using X-ray. In addition, all of the abdominal imaging was done using CT scan. Pelvis imaging assessment revealed that, 85.1% of the pelvis scans were done using MRI. These findings show that appropriate imaging is being done which help in histology where 81% of the cancer cells were well differentiated. However, there were few gaps regarding the selection of appropriate imaging. This could be associated with the cost of imaging where MRI and CT scan are costly compared to X-ray hence sometimes patients are unable to afford especially for patients without insurance. In Kenya, the cost of CT scan range between $50 and $100, MRI scan costs between $120 to $300 while an x-ray costs between $12 and $30 (Portal, n.d.).

The findings from the present study revealed that 91% were on neoadjuvant while 9% were on total neoadjuvant. The low proportion of total neoadjuvant treatment in patients with LARC is because it is a multimodal new approach in management of LARC. Keswani et al in a study conducted in New Orleans highlighted that total neoadjuvant is a new approach in LARC management (Keswani et al., 2002). However the use of TNT has been associated with increased positive outcomes such as progression free survival and overall survival (Kasi et al., 2020)(Kasi et al., 2020). Our study also revealed that 95% were on long course treatment. Similar findings were obtained by Dutta et al which found that 99% of the patients were on long course with only 1% on short course treatment (Dutta et al., 2018). Further, Stockholm II non-inferiority trial also found that 2% of patients were on short course (Erlandsson et al., 2017). The higher proportion of long course is mainly due to the fact that it is the standard of care across both low resource and advanced settings.

Our present study found that the median progression free survival was 24 months while median overall survival was 36 months. Presence of comorbidities, tumor staging and duration of symptom before diagnosis were independent predictors of overall survival. Presence of

comorbidity among LARC patients was associated with poor overall survival. These findings are comparable to a population based study conducted by Kellokumpu et al. which found that high comorbidity burden was significantly associated with poor overall survival (Kellokumpu et al., 2021). Comorbidity does not appear to be linked to more aggressive cancers or other abnormalities in tumor biology. In certain studies, the presence of specific severe comorbidities or psychiatric illnesses was found to be associated with delayed cancer diagnosis, whereas in others, chronic diseases needing regular medical visits were associated with faster cancer detection (Søgaard et al., 2013). Another conclusion is that patients with comorbidity do not obtain standard cancer treatments as frequently as patients without comorbidity, and their chances of completing a course of cancer treatment are lower. Patients with comorbidities have an increased risk of postoperative complications and mortality. According to the literature, it is unclear if the apparent undertreatment reflects an adequate evaluation of increased toxicity risk, worse clinical quality, patient preferences, or poor adherence among patients with comorbidity (Søgaard et al., 2013)(Polanco et al., 2018).

Longer duration of symptoms before diagnosis was associated with poor overall survival. These findings concur with Polanco et al. who found that duration of symptoms is a major factor associated poor overall survival (Polanco et al., 2018). This is also linked to late diagnosis made. Most individuals do not take symptoms seriously due to lack of awareness and knowledge of indications of LARC. The findings from the present study also revealed that higher stage of LARC at diagnosis was associated with poor overall survival. These findings are in line with a study conducted in Canada by Reguena et al. which found that the risk of poor overall survival was significantly associated with stage 3 and stage 4 at diagnosis (Reguera Puertas et al., 2016). Similarly, a population-based study conducted by Zhao et al. found that for stage T3/4N0M0 patients, neoadjuvant RT, adjuvant RT, and surgery plus

chemotherapy resulted in similar OS with better OS observed in these patients than in patients who underwent surgery alone (Zhao et al., 2020).

CHAPTER SIX: CONCLUSION AND RECCOMMENDATIONS

6.1.Conclusion

The average age of 54.2 years, more than half of the patients, 52.5% were female. More than half of the patients, 57.5% were at T3 at diagnosis.

96.7% of the chest imaging were done using CT scan while 3.3% (n =6) of the chest imaging were done using X-ray.

Treatment modality revealed that 91% were on neoadjuvant while 9% were on total neoadjuvant, 95% were on long course treatment.

The median progression free survival was 24 months while median overall survival was 36 months. The presence of comorbidities, tumor staging and duration of symptom before diagnosis were independent predictors of overall survival.

6.2.Recommendations

- Total neoadjuvant treatment modality should be integrated into standard of care among LARC patients to increase overall survival.
- Regular screening for rectal cancer should be done across all ages to control late diagnosis of the disease at advanced stage.
- Create awareness on common symptoms of rectal cancer within the community across both genders.
- Develop a follow up plan to ensure an improved follow-up among patients already diagnosed with LARC to improve treatment outcomes.

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APPENDICES

Appendix 1: Questionnaire
Section 1: Patient Characteristics

1. Age of the patient ……
2. Gender of the respondents

Male [ ]

Female [ ]

3. Residence

Urban [ ]

Rural [ ]

4. Smoking

Yes [ ] Pack years……...

No [ ]

Ex smoker [ ] Years ……..

5. Alcohol intake

Yes [ ]

No [ ]

Ex alcoholic [ ] Years ……..

6. Family history of cancer

Yes [ ]

No [ ]

If yes expound

……
……
…….

7. Co morbidities

Yes [ ]

No [ ]

If yes expound

……
……
…….

Clinical characteristics

8. Stage of cancer ……..
9. Duration of symptoms before diagnosis was made …….
10. Time from diagnosis of rectal cancer to start of treatment (months)……...
11. Imaging
    ……
    ……
    ……
12. Histology assessment
    ……
    …….

Section 2: Treatment approach

13. Treatment modality chosen
    ……
    …….
14. Prescription
    ……
    …….

Section 3: Treatment outcome

15. Post neoadjuvant treatment imaging

……
……
……..

16. RECIST criteria
    …….
17. Progression free survival (years) …….
18. Overall survival (years) …….

Appendix II: The study budgets

Items	Cost	Unit	Total ($)
KNH-UON ERC Submission	20	1	20
STATIONARIES			
Data collection tool printing **Thesis printing**	4 pages * $ 0.1/page 50 pages * $ 0.1/page	100 10	40 50
WAGES			
Research Assistants (RAs)	2.5 / questionnaire	100	250
Data Analysts		1	500
EXPENSES			
Communication	Airtime	1	110
Publication	150		150
Contingencies	15 percent of the total budget		168
TOTAL			**$1,288**

Budget justification

The budget items are priced according to the current marketing rates.

1. KNH-UON Ethical review costs Ksh. 2000 per manuscript.
2. The cost of printing is estimated to be Ksh. 10 per page.
3. Research assistants shall be reimbursed at a rate of Ksh. 250 per file or questionnaire
4. A statistician shall be reimbursed as per market rate to a total of Ksh. 35,000 for data analysis.
5. Communication with research assistants including internet bundles for research to cost Ksh. 2000
6. A 15% contingency fee has been factored in the research in case of other emerging unforeseen expenses.

Appendix III: Study timelines

	Jan 2021 - April 2021	May 2021- July 2021	August 2021 – October 2021	November 2021 - December 2021	January 2022 – February 2022
PROPOSAL DEVELOPMENT					
ETHICAL CLEARANCE					
DATA COLLECTION					
DATA ANALYSIS & REPORT WRITING					
PRESENTATION / PUBLICATION					

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5th January, 2022

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KENYATTA NATIONAL HOSPITAL APPROVED 05 JAN 2022 KNH/UoN-ERC P.O. Box 20723 - 00202 NAIROBI

Dear Dr. Dulcie,

RESEARCH PROPOSAL: TREATMENT OUTCOME OF NEOAJUVANT THERAPY FOR LOCALLY ADVANCED RECTAL CANCER; A SINGLE INSTITUTION EXPERIENCE (P681/08/2021)

This is to inform you that KNH-UoN ERC has reviewed and approved your above research proposal. Your application approval number is **P681/08/2021.** The approval period is 5th January 2022 – 4th January 2023.

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.

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

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