# COMPARISON OF PRE AND POST TREATMENT MAGNETIC RESONANCE FEATURES OF RECTAL CANCER BETWEEN PATIENTS UNDERGOING LONG AND SHORT COURSE NEOADJUVANT TREATMENT AT THE KENYATTA NATIONAL HOSPITAL

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I, **Dr. Tabitha Muthoni Karuri,** do, hereby declare that this dissertation as purely my own original work and has not been presented for a degree in any other university. Where I have used another person's work, I have carefully acknowledged and referenced.

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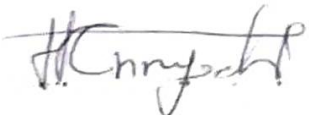
**Signature:**  **Date: 5**th November, 2023

# DEDICATION

To **Joe** (My Rock) and **Rish** (My Sunshine).

Your love and support give me the energy and determination to aim higher.

To Me.

For pushing through and finishing what seemed impossible.

*"My mission in life is not merely to survive, but to thrive; and to do so with some passion, some compassion, some humor, and some style."*

***— Maya Angelou***

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# ACRONYMS

| | |
|---|---|
| **AJCC-** | American Joint Committee on Cancer |
| **CI-** | Confidence Interval |
| **CRM-** | Circumferential Resection Margin |
| **CRT-** | Chemo radiation |
| **DCE-** | Dynamic Contrast Enhancement |
| **DWI-** | Diffusion Weighted Imaging |
| **ESGAR-** | European Society of Gastrointestinal and Abdominal Radiology |
| **FSE-** | Fast Spin Echo |
| **KNH-** | Kenyatta National Hospital |
| **MOH-** | Ministry of Health |
| **MRF-** | Mesorectal Fascia |
| **MRI-** | Magnetic Resonance Imaging |
| **mrTRG-** | Magnetic resonance Tumor Regression Grade |
| **NPV-** | Negative Predictive Value |
| **PPV-** | Positive Predictive value |
| **RC-** | Rectal Carcinoma |
| **RECIST-** | Response Evaluation Criteria in Solid Tumors |
| **SPSS-** | Statistical Package for Social Sciences |
| **T-** | Tesla |
| **T2WI-** | T2 Weighted Imaging |
| **TME-** | Total Mesorectal Excision |
| **TNM-** | Tumor-Node-Metastasis |
| **UON-** | University of Nairobi |

# ABSTRACT

**Study Background:** The treatment of locally advanced rectal carcinoma involves the use of neoadjuvant chemo radiation. The types of neoadjuvant treatment offered to these patients can be long-term or short-term. The choice of course of treatment to be undertaken remains under debate. No clear reason for the choice of treatment is given. Short course treatment can be preferred in cases of proximally located tumors, cost-effectiveness or convenience since it takes a shorter time. Long course treatment is preferred in cases of more distal tumors. Thereafter, MRI is used for follow-up evaluation of the disease to assess for response to the neoadjuvant treatment. During MRI evaluation, restaging of the disease is done which then determines the next step treatment / management following neoadjuvant therapy and eventually determines the treatment outcome/success of treatment for these patients. Evaluation of rectal carcinoma using MRI involves the use of anatomical and functional techniques to assess the morphology and biology of the tumor therefore increasing the confidence of assessing for tumor response on MRI. There is no local study done to assess the MRI findings of rectal tumor response post CRT or compare the tumor response between patients who have undergone long course and short course treatment.

**Study Objective:** This study assessed the pre-treatment and post-treatment MRI features of rectal tumors that underwent either long course or short course treatment, categorized and compared the treatment response categories between the two groups.

**Study design and site:** This was a comparative cross-sectional study done at the Kenyatta National Hospital Radiology and cancer treatment center department with the MRI treatment response category as the outcome and the treatment duration as the exposure of treatment.

**Study participants and methods:** Adult patients with rectal cancer who had undergone both long and short courses of neoadjuvant treatment were included in this study. A complete enumeration was done where all patients on post treatment follow up were included in the study; 25 patients on long neoadjuvant treatment group and 15 patients on short course neoadjuvant treatment group.

**Data management:** Statistical Package for Social Sciences version 28 was used for analysis. Demographic and clinical characteristics of the patients were analyzed and presented as frequencies and percentage for categorical data, and as means with standard deviation or median with interquartile range for continous data. Assessment for the response by comparing the changes in tumor size, T2w signal intensity, DWI/ADC map, ADC values on the ADC map were done with the use of McNemar's test and Paired Sample t-test. The difference in tumor response in those who had long course versus short course CRT was done with the use of Pearson Chi-square test. All statistical tests were considered significant where the p-value < 0.05.

**Significance of the study:** This study will aid in assessing the MRI treatment features and give surrogate information on whether either of the two treatment forms are similar in their outcome or not.

**Results:** Of the 40 patients included in the study, 65% were female and 35% were male. The median age was 54.7 years with the youngest being 24 years and the oldest being 90 years. The

average time to repeat MRI was 7.05 weeks. Majority of the patients undergoing long course treatment were noted to have bulkier low level disease with the majority having T3d staging. A larger diameter of residual disease (mean=2.37 cm) and higher fibrosis (mr-TRG mean of 3.83) was seen in the long course group. An improvement in the CRM status was noted in the short course group which could be attributed to less bulky disease initially. A rise in ADC value was also seen in the patients who underwent long course treatment (M= 1.91). An overall improvement in nodal disease was noted. However residual nodal disease was present in the long course group.

**Conclusion:** This study established that the overall radiological response to treatment was better in the long course group when compared to the short course group. This result may however have been secondary to the smaller number of short course patients sampled. Less bulky disease (T3a-T3c tumours) were more likely to have short course treatment recommended while low level, bulky disease with sphincter involvement were more likely to have long course treatment recommended. An increase in ADC values was established to have a role in the indication of tumour response to treatment.

# 1.0 CHAPTER ONE: INTRODUCTION

## 1.1 Background Information

Rectal cancer is a common and lethal disease. It is the third most commonly diagnosed disease in males and the second most commonly diagnosed in females globally. Rectal cancer is the 13th most common cancer in Kenya making up 3% of the malignancies[1]. It is a leading cause of morbidity and mortality in the Kenyan population. Its incidence is rising with a recorded increase of 12.3 to 12.9 per 100,000 people[2].

MRI is the gold standard of imaging the rectum due to its superior soft tissue contrast. It is able to depict the rectal wall layers, mesorectal fat, mesorectal fascia and pelvic floor as well as show invasion of the tumor into surrounding tissues.

In Kenya, once a patient is diagnosed with rectal cancer, a pre-treatment MRI is done to stage the disease. Those with T1 and T2 disease proceed for surgical resection. Those with T3 and T4 disease or any T stage with nodal disease are sent for neoadjuvant chemo radiation. After chemo radiation, the patients wait 6-12 weeks and then have a repeat MRI scan done to restage the disease for further treatment planning.

Neoadjuvant chemo radiation can be given in two ways. There is the long course CRT whereby a long course of radiotherapy (5-6) weeks) and radio sensitizing chemotherapy is given. For short course chemo radiation, a short course of radiotherapy is administered (1 week) with no radio sensitizing chemotherapy given[3] The reason for the choice of either course of treatment remains debatable with no clear reason given to favor the use of one course over the other. Short course of treatment can be favored in cases of proximally located tumors. It is also convenient for the patient since it takes a shorter time with an eventual benefit of being cost-effective. Long course of treatment can be favored in cases of distally located tumors. Normally, long course chemo radiation is preferred as treatment. No clear cut reason is yet to be given for this. Some studies have also shown the benefit of short course CRT with a good response in 73% of cases noted[4]

Staging of the disease is important in the treatment planning of the patient. TNM staging is most widely used. T1 and T2 tumors with no nodal disease are treated by surgical resection. T3, T4 tumors and any T stage with nodal disease are first subjected to neoadjuvant chemo radiotherapy.

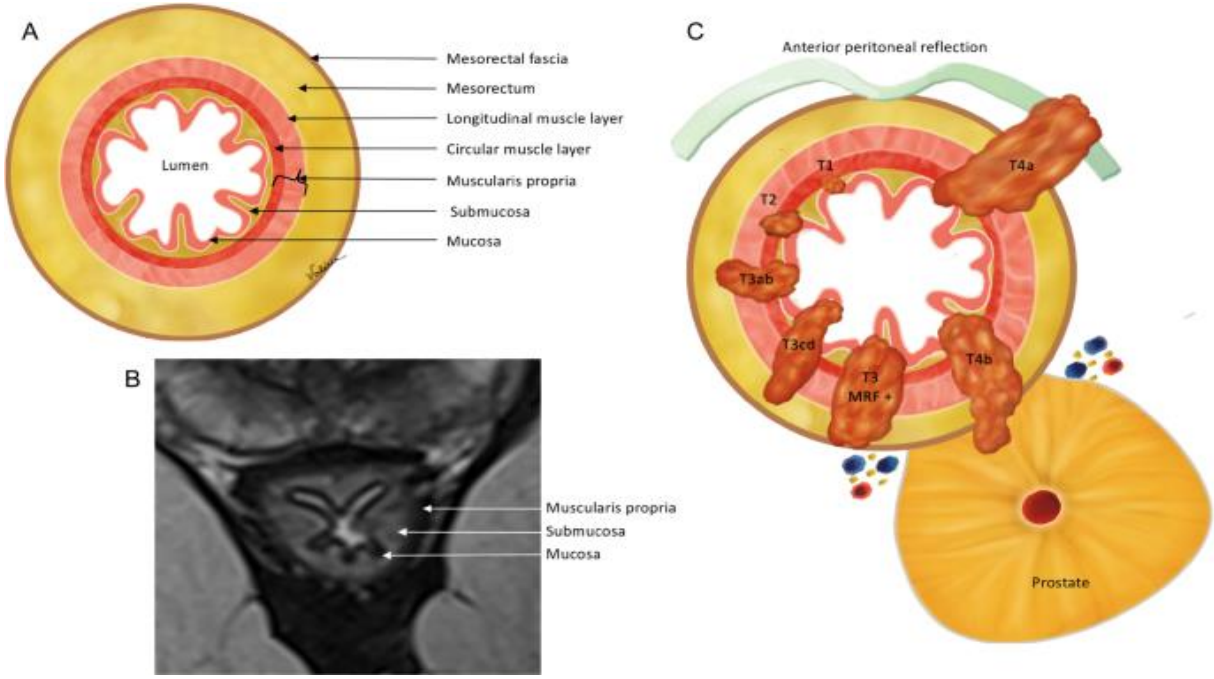


**Figure 1: Pictorial showing different T stages of rectal tumors.**[5]

Currently, neoadjuvant treatment with chemo- and radiotherapy is applied for rectal cancers in the locally advanced stage. Neoadjuvant chemo radiation causes tumor shrinkage and has also been shown to reduce recurrence and increase disease-free survival. Response to neoadjuvant CRT is also assessed by MRI 6-8 weeks once the CRT is completed. The sensitivity of conventional MRI alone in detecting tumor response is less when compared with the sensitivity value of the pre-treatment staging.

Response to neoadjuvant therapy can be assessed by MRI. In the last few years, there has been great effort to increase the capability of MRI in the evaluation of neoadjuvant treatment response. About 15-27% of patients have been shown to exhibit complete response post neoadjuvant therapy. With this in mind, it is important to be able to evaluate for response in that it influences the management the patient will receive.

In certain expert centers in the developed countries, organ preserving techniques are used for the management of rectal cancer post-CRT for those patients who exhibit good response. For those whose cancer regresses completely post CRT, watchful waiting is employed as the primary management with regular follow up and MR imaging used as a tool for surveillance of recurrence. This then leads to an improvement in their quality of life.

A profound radiological evaluation of rectal cancer, both pre- and post- CRT is needed for assessment of the loco-regional tumor status.

Morphological/anatomical MRI assessment of the tumor post CRT can have some limitations when it comes to the follow-up of disease post CRT. Due to the fibrotic changes that are a

sequelae of irradiation, it can be difficult to identify areas with residual tumor from the fibrosis that occurs following radiotherapy.

The addition of DWI/ADC (functional technique) can prove useful in further evaluation of the disease. These technique offers non-invasive assessment of the cellular and physiologic processes within the tumor.

MRI with DW/ADC imaging combines the anatomical and functional techniques leading to simultaneous assessment of the tumor's morphologic and biologic characteristics.

The use of gadolinium contrast enhanced studies have been shown to be beneficial in the assessment of rectal cancer in the pre-treatment stages with areas of early enhancement predictive of tumor. In the post-treatment evaluation, these studies can be used to assess for residual tumor and presence of extramural venous invasion. Dynamic contrast enhancement (DCE) MRI studies are favored in the post-treatment evaluation of residual tumor. DCE measures the inflow of injected IV gadolinium into vessels and its leakage into the extracellular space. A measure of tissue permeability can be calculated known as the transfer constant or k-trans which is dependent on the perfusion and permeability of the tumor vasculature. Gadolinium contrast agents are excreted through the renal system. Therefore, renal function screening of any patient who is to undergo gadolinium contrast enhanced studies is of importance. Oncologic patients have an increased risk of having impaired renal function therefore limiting the use of gadolinium contrast enhancement. This study will not include the use of gadolinium contrast enhancement. The reason for this is that the pre-treatment MRI protocol for rectal cancer patients in Kenya does not include the routine use of DCE studies. Another key reason is that for DCE studies to be done, an extra cost is incurred by the patient. Most of the patients in KNH are unable to afford this extra cost.

This dissertation hopes to investigate the MRI assessment of rectal cancer post-CRT using the following parameters:

a) Tumor size: use of RECIST criteria/tumor length
b) Fibrotic transformation: Use mrTRG
c) DWI/ADC map: Increase in ADC value

## 1.2 Assessment of Tumor Size

Traditionally, for solid tumors, a decrease in tumor size has been used as a measure of response to treatment. Using RECIST (Response Evaluation Criteria for Solid Tumors), a partial tumor response can be defined as a reduction of tumor size by more than 30%.

A reduction in tumor volume of 60-80% has been noted in literature to indicate good response to treatment.[6] RECIST is useful in solid tumors with regular margins that can allow for an accurate size measurement.

In cases where the tumor has an irregular or a spiculated margin, the 2016 ESGAR consensus [7] guidelines suggested the use of tumor length as a practical measurement of treatment response. Measurement of pre-treatment and post treatment tumor lengths can be used as an estimate of a change in tumor size as a measure of treatment response.

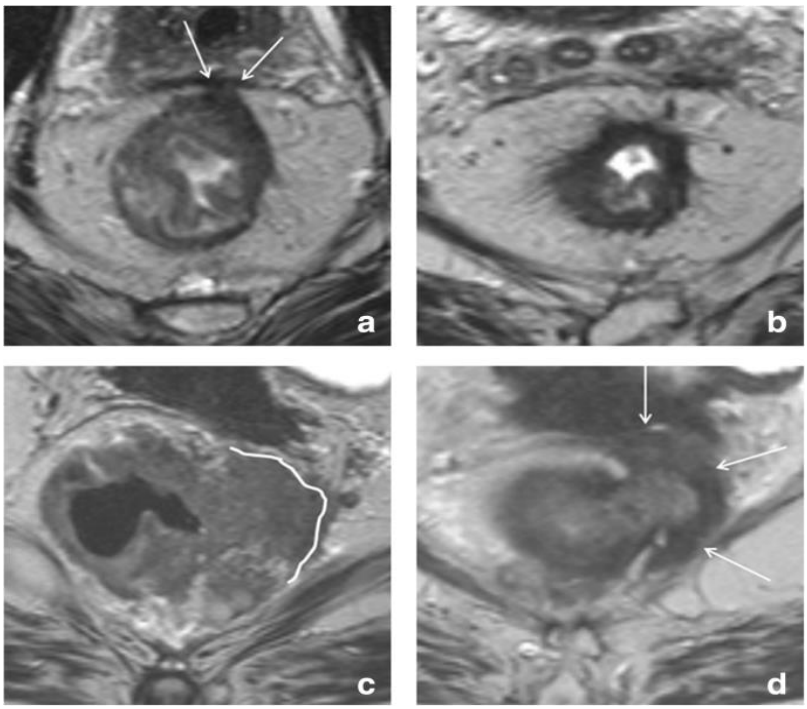


**Figure 2: Axial MR images of two different patients showing the change in tumor size post neoadjuvant chemoradiation**[8]

The images in the top row show a male patient who has a mid-rectal tumor that has invaded the MRF anteriorly (arrows in a). The tumor has withdrawn from the MRF after CRT (b), with only some fibrotic stranding towards the MRF persisting. After surgery, this patient's histology revealed a tumor-free MRF. The bottom row of images shows a female patient with a mid-rectal tumor with substantial MRF invasion on the left lateral side (white line in c). The tumor has shrunk in size after CRT (d). The MRF from 1 to 4 o'clock still has an isointense mass surrounded by hypointense fibrosis (arrows in d). This form of diffuse MRF infiltration accurately predicts ongoing MRF involvement, which this patient's histology verified following surgery.

## 1.3 Fibrotic Transformation

Untreated (non-mucinous) rectal tumors have an intermediate signal intensity on T2w MRI. The signal intensity is less than that of fatty tissue and is higher than that of the normal bowel musculature. When tumor is irradiated, it usually becomes fibrotic. When assessed on T2w MRI, there is considerable signal drop such that the tumor bed becomes markedly hypointense when compared to its untreated intermediate signal.

A minority of lesions demonstrate a mucinous response following CRT therefore leading to an increase in signal intensity on T2w MRI that was not present in the primary MRI scans. At histopathological assessment, these mucinous areas have been proven to contain no or minimal isolated tumor cells. Therefore, mucinous transformation can be considered a good prognostic sign.

The degree of fibrotic transformation can be classified using the MRI tumor regression grade (mrTRG). Although it is yet to be routinely used for rectal cancer restaging worldwide, it can be adopted as a measure of treatment response. The degree of fibrotic response on T2w MRI is graded using a 5-point scale:

**Table 1: TRG of rectal tumor on MR imaging**[9]

| TRG of rectal tumor on MR imaging | | |
|---|---|---|
| Grade | Response | |
| Grade 1 | Complete radiologic response | No evidence of tumor signal intensity or fibrosis only |
| Grade 2 | Good response | Dense hypointense fibrosis, minimal residual tumor |
| Grade 3 | Moderate response | Mixed fibrosis/mucin and intermediate signal representing residual tumor, but fibrosis still predominates |
| Grade 4 | Slight response | Minimal fibrosis/mucinous degeneration, tumor predominates |
| Grade 5 | No response | Tumor has the same appearance as baseline |

*Data from* Patel UB, Taylor F, Blomqvist L, et al. Magnetic resonance imaging-detected tumor response for locally advanced rectal cancer predicts survival outcomes: MERCURY experience. J Clin Oncol 2011;29(28):3753–60.

The mrTRG has been shown to be useful in distinguishing between good and poor responder (by literature reports from the UK). The pattern of fibrosis has been to shown to follow that of the initial tumor, such that spiculated/irregular tumors end up showing irregular fibrosis.

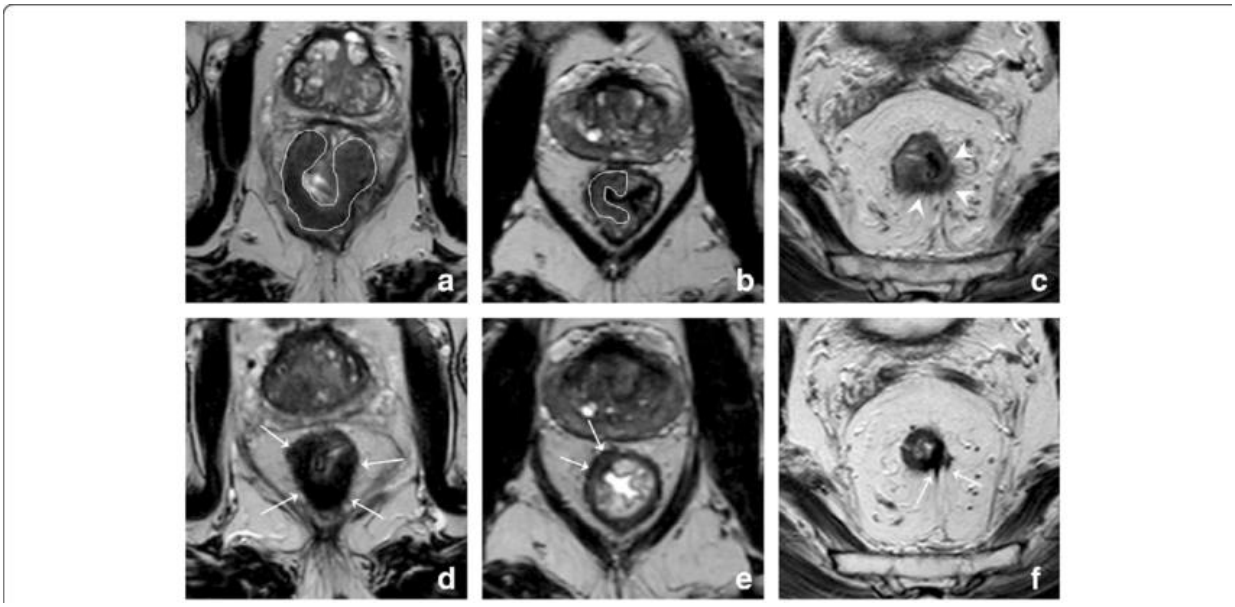


**Figure 3: MR images showing different fibrosis grading**[9]

Three male patients with low to mid-rectal tumors are shown in a series of pre-CRT (a-c) and post-CRT (d-f) T2-weighted images. A well-defined, almost round tumor mass is seen in the first patient (a). After CRT (d), the tumor has undergone fibrotic transformation, resulting in a semi-circular, full thickness fibrotic wall that follows the shape of the underlying tumor. The second patient has a semicircular tumor that is relatively tiny (b). Following CRT, a small focal region of fibrosis evident on the rectal wall is visible (e). The third patient has a spiculated, unevenly shaped tumor (c). The fibrosis takes on an irregular pattern after CRT, with persistent spiculations (f)

## 1.4 Diffusion Weighted Imaging (DWI)

This technique studies the movement of water molecules (diffusion) in certain tissues. Application of certain diffusion sensitization gradients to a T2 weighted sequence achieves this. The degree of diffusion weighting applied is known as the b value and usually has a range of b800-1000 s/mm2. Normal or low cellular tissues have free diffusion of water molecules, therefore a decay of the signal on high b value images occurs. Tissues with increased cellularity do not have free diffusion of water molecules. This means that the signal would be retained in high b value images.

Most malignancies, including rectal cancer, are high cellular tissues. This validates the use of DWI. DWI is typically accompanied by an Apparent Diffusion Coefficient (ADC) map. An ADC map represents the degree of water diffusion for each voxel in an MRI. A hyperintense signal represents free diffusion and hypointense signal represents restricted diffusion.

The basic principle for DWI/ADC in evaluation of tumor response is, hyperintensity on DWI and a hypo-intensity on ADC within the bowel wall or fibrosis of the tumor bed is indicative of diffusion restriction hence residual tumor.

A low signal on DWI and a high signal on ADC within the bowel wall or fibrosis of the tumor bed is suggestive of no residual tumor hence complete response.

Measurement of the change in ADC value has been used to quantitatively assess for response to treatment. By comparing the pre-treatment and post-treatment ADC values, an increase in the post-treatment ADC value can indicate response to treatment.

Some pitfalls can occur when using DWI/ADC for assessment of tumor response and they include:

**a)** T2 shine through effect: A bright signal on DWI that is not the result of diffusion restriction. In rectal DWI, this occurs when there is presence of fluid in the rectal lumen. Comparison with the ADC map can differentiate between luminal T2 shine through and residual tumor. Luminal fluids on ADC map will have a high signal.

**b)** ADC signal in fibrosis is low: This relates to the ADC map's low signal in fibrotic areas. The collagen content of dense fibrotic tissue is high, and the T2 relaxation period is short, resulting in a low signal. These spots can be misinterpreted as residual tumor when examining the ADC map alone. The use of a DWI comparison is crucial in avoiding this stumbling block. Only when low signal areas on the ADC coincide to high signal on the DWI should a residual tumor be detected.

**c)** Susceptibility artifacts: gas in the rectum is a common cause of these artifacts. They cause signal distortions that can make it difficult to interpret images correctly. Reduction of the amount of rectal gas in the lumen can be done by administering a pre-imaging micro enema to avoid these artifacts.

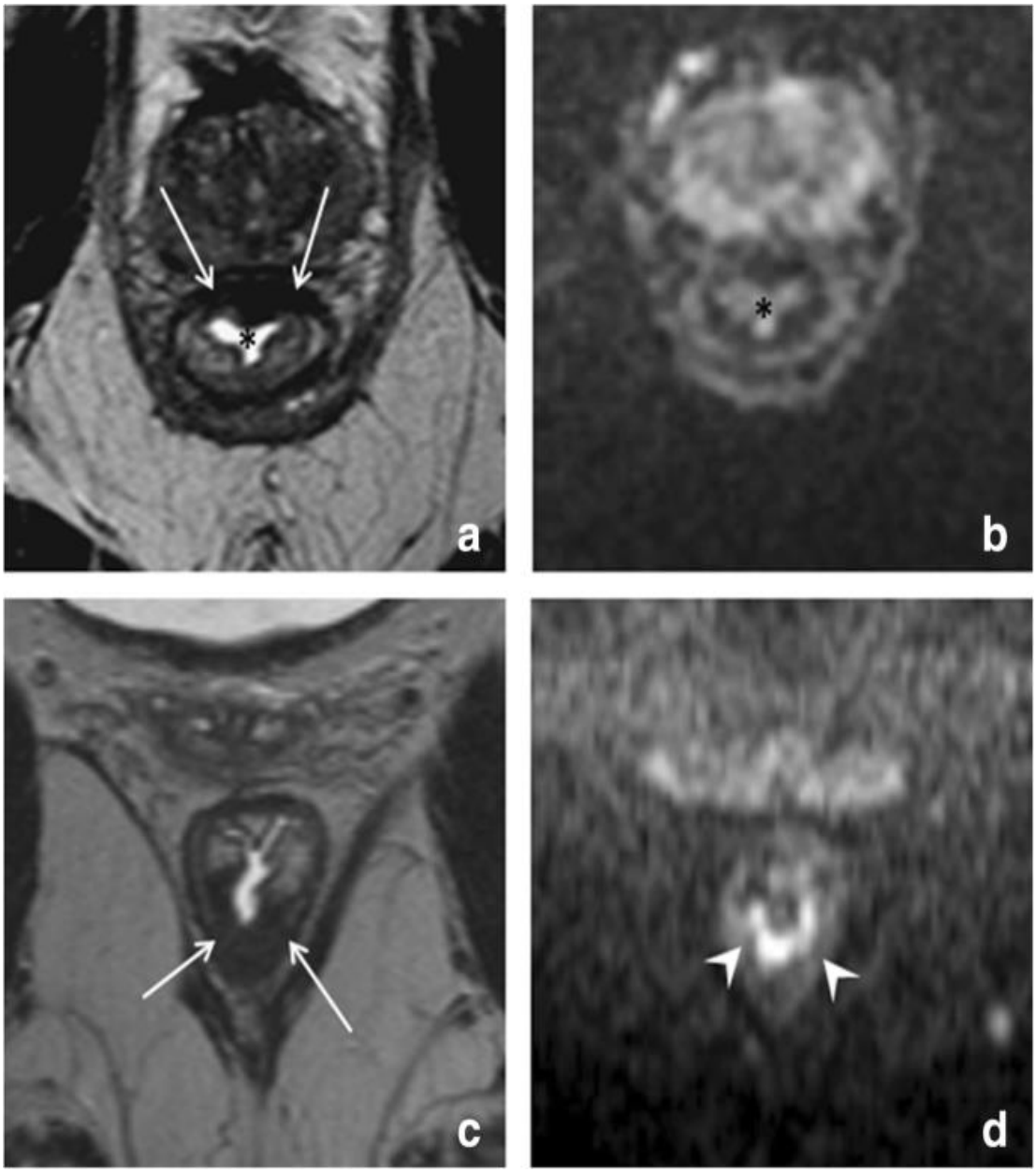


**Figure 4: MR images showing the importance of DWI imaging in assessment of rumor reponse.**[9]

Post-CRT T2-weighted (**a**, **c**) and diffusion-weighted (**b**, **d**) images of two male patients with rectal cancer who underwent neoadjuvant CRT. At histology, the patient in the top row had a full response, while the patient in the bottom row still had a ypT2 tumor remnant. Both patients had a very similar fibrotic wall thickening (arrows in a and c). A star-shaped signal (*) was detected in the rectal lumen of the top patient, which shows T2 shine-through of a little amount of fluid present in the rectal lumen. A bright signal with a more U-shaped structure was found in the inner margin of the fibrosis in the lower patient (arrowheads in d)

# 2.0 CHAPTER TWO: LITERATURE REVIEW

Use of conventional MRI is important in the pre-treatment staging of rectal cancer. Sensitivity and specificity of conventional MRI is known to be limited in the detection of response to neoadjuvant CRT. Addition of DWI/ADC has been shown to improve the diagnostic accuracy of response to neoadjuvant therapy. The choice of neoadjuvant treatment course remains debatable with no clear reason given to favor the use of one course over the other.

In a study done in 2016 to assess why long course treatment was favored over short course determined that no significant difference in outcome was observed with either of the treatment courses[10]. Another study done in 2013 to assess for long term quality of life after long course and short course treatment showed that no significant difference in quality of life was observed [11].

RECIST criteria is heavily relied on when it comes to assessment of tumor size. The guidelines were revised in 2009 to version 1.1 and a guideline was published using the revised RECIST criteria. For use in adult and pediatric cancer clinical trials, this guideline specifies a systematic approach to solid tumor measuring and definitions for objective assessment of tumor size change.[6]

Tumor volume/size reduction of more than 70% has been shown in literature to indicate good response to CRT. A study done in 2009 to assess MRI in prediction of response after pre-operative chemo-radiotherapy showed a mean tumor volume reduction after CRT of 77.4% in responders and 47.4% in non-responders. The percentage tumor volume reduction rate and morphologic MR imaging criteria were also found to be useful in the study, resulting in an overall accuracy of 86.8%.[12] Similarly, a study done in 2018 to assess if early tumor volume changes assessed on morphological MRI could predict response to treatment, showed that complete responders had almost no residual tumor seen in an MRI performed mid-CRT. Partial and non-responders showed no significant change in tumor volume in the Mid-CRT MRI. In the post CRT MRI, both partial and complete responders showed a change in tumor volume of 80%. [13] Therefore, a conclusion of a change in tumor size being an indicator of response to therapy can be drawn from these two studies.

Changes in the T2w signal intensity of the tumor has also been shown to indicate response to therapy. In a study done in 2013 to evaluate if the evolution of T2 weighted signal could predict pathological response to neoadjuvant treatment, showed that a significant drop in T2w signal of approximately 50% was seen in all patients who were complete responders. [14]Similarly,

a study done in 2017 to compare MRI and pathology in the assessment of tumor regression grading in rectal cancer, determined that the MRI sensitivity and specificity in identification of pathological response was 74.4% and 62.8%.[15] In contrast, a study done in 2009 to assess the accuracy of MRI in assessment of tumor downstaging post neoadjuvant chemoradiation concluded that the accuracy of MRI in evaluating for tumor response was low (47-52%) due to the inability to distinguish residual tumor from the fibrotic change that is a sequelae of chemo radiation.[16]

Addition of functional techniques in MRI assessment of rectal cancer post-CRT aids in the evaluation of the biology of the tumor therefore, increasing the ability to detect residual tumor. A study done in 2009 to assess the additional value of DWI in the evaluation of tumor response to neoadjuvant treatment determined that addition of DWI in assessment of tumor response had better accuracy than using conventional MRI only. An increase in diagnostic accuracy was shown by the area under the ROC curve. It improved from 0.676 to 0.876 for one reviewer and from 0.658 to 0.815 for the second reviewer[17]. Another study done in 2011 that compared conventional MRI volumetry and DWI in the assessment of complete response to preoperative neoadjuvant treatment, showed a higher performance for DWI volumetry than T2w volumetry. The AUC ranged from 0.91-0.93 for DWI versus 0.70-0.84 for T2w volumetry[18]. A study done in 2015 to validate the use of MRI and DWI volumetry in the identification of complete tumor responders post neoadjuvant chemoradiation, recorded similar results favoring DWI volumetry. The AUC in this study was 0.77-0.92 for DWI versus 0.73-0.82 for T2w volumetry[19]. In a systematic review done in 2014 to assess multiparametric MRI in the evaluation of tumor response used simple measurements of DWI and ADC in the assessment of response to therapy and showed that post-CRT DWI signal intensity provided a higher diagnostic accuracy than the ADC signal intensity of the tumor. The AUC for DWI was 0.86 versus that for ADC being 0.66[20]. A meta-analysis done in 2013 to assess the use of MRI in restaging of rectal cancer after neoadjuvant therapy examined the performance of DWI and T2 weighted imaging in assessing tumor response following CRT. With a sensitivity of 83.6% and a specificity of 84.8%, DWI demonstrated much better outcomes for tumor re-staging[21]. These studies therefore validate the use of DWI in assessment of tumor response post CRT. With regards to the change in ADC value as an indicator of response to treatment, a study done in 2011 to evaluate the benefit of a change in ADC values in predicting tumor response determined that an increase in the post-CRT ADC value was an indicator of treatment response. With a cut-off of a 42% increase in ADC value, an accuracy of 75% in predicting complete

response was recorded in this study. Therefore including a change in ADC values can add value to the use of DWI/ADC in prediction of treatment response post-CRT[22]

Dynamic contrast enhancement can be used for further assessment of rectal cancer in the pre-treatment and post-treatment stage of rectal cancer. However, its use is not widely used with debatable need for in in increasing the diagnostic capability. A study done in 2005 to assess the helpfulness of gadolinium contrast in the pre-treatment stage of rectal cancer showed that addition of contrast enhanced T1 did not significantly improve the diagnostic accuracy for assessment of tumor penetration and tumor extension[23]. Similarly, another study done in 2015 to compare the reader accuracy and agreement on rectal MRI with and without cancer for the detection of T4 disease showed that the use of gadolinium contrast did not significantly improve the radiologists' agreement of ability to detect T4 disease. This study used histopathology as the gold standard for reference[24]

## 2.1 Justification of the Study

There is a need for radiologists to know the changes seen on post-CRT MRI scans and accurately pick out good, partial or poor response to neoadjuvant CRT. Locally, there is no discrimination in the use of long or short course chemo radiation in locally advanced disease. This study will aid in assessing the MRI treatment features and give surrogate information on whether either of the two treatment forms are similar in their outcome or not.

## 2.2 Broad Objective

- To assess the pre-treatment and post-treatment MRI features of rectal tumors that underwent either long course or short course treatment, categorize and compare the treatment response categories between the two groups.

## 2.3 Specific Objectives

- To compare pretreatment MRI features of rectal tumor that underwent either long or short course neoadjuvant radiation.
- To compare MRI treatment response features for rectal tumors that underwent long or short course neoadjuvant treatment.
- To compare the MRI treatment response categories between the long and short course neoadjuvant treatment groups.

# 3.0 CHAPTER THREE: METHODOLOGY

## 3.1 Study Design

This study utilized a comparative cross-sectional design. The comparison groups that were included in the study were between patients with confirmed rectal carcinoma TNM staging T3 and T4 who had undergone short course neoadjuvant CRT and patients with confirmed rectal carcinoma TNM staging T3 and T4 who had undergone long course neoadjuvant CRT.

## 3.2 Study Setting

The study was conducted at Kenyatta National Hospital radiology department. Kenyatta National hospital is the largest referral hospital in the region with 1,800 bed capacity. Kenyatta National Hospital is the largest referral hospital in the country with 1,800 bed capacity. The institution also houses the University Of Nairobi College Of Health Sciences. The hospital is located about 3.5 km west of the Nairobi Central District. KNH has 50 inpatient wards and various outpatient and specialized units and clinics. The radiology unit forms a vital part in cancer treatment through staging and review of the extent of the disease using the MRI scan. The radiology department has one 3 Tesla MRI machine is available and four MRI consoles and 5 image viewers available in the reporting room. On average four patients per week have their restaging MRI conducted in the department post neoadjuvant chemo radiation. The MRI suite served as the catchment areas for the patients who were included in this study. The patients who met the inclusion criteria were selected as they came for the post-treatment MRI.

## 3.3 Study Population

The study included rectal carcinoma TNM staging T3 and T4 adult patients on either short or long course post treatment after neoadjuvant CRT.

## 3.4 Inclusion Criteria

These included:

- Patients with rectal carcinoma TNM staging T3 and T4 aged ≥18 years
- Patients with rectal carcinoma TNM staging T3 and T4 who have received either short or long course neoadjuvant CRT.
- Patients with images that have matched pre-treatment and post-treatment MRI protocols.
- Patients who consent to participate in the study.

### 3.5 Exclusion Criteria

These included:

- Patients with MRI images that are of poor quality which will be determined by presence of artifacts and/or poor contrast.
- Patients with MRI scans that have mis-matched pre-treatment and post-treatment protocols

### 3.6 Sample Size Determination

At Kenyatta national hospital, there are approximately 40 patients per annum on post treatment follow up with majority on long course neoadjuvant treatment group in a ratio of 3:1.5. (KNH health information, 2022). Thus, complete enumeration was done where all patients on post treatment follow up were included in the study 25 patients on long neoadjuvant treatment group and 15 patients on short course neoadjuvant treatment group.

### 3.7 Sampling Technique

Consecutive sampling technique was utilized in this study. Patients with rectal carcinoma TNM staging T3 and T4 who had undergone neoadjuvant CRT came for their repeat MRI scan in radiology department and who met the inclusion were recruited until the sample size was attained.

### 3.8 Study Variables

In addition to standard demographic data, other relevant variables were derived from the RSNA recommended MRI staging reporting template for the pre-treatment MR scans.

**Table 2: Rectal cancer primary staging MRI report template[25]**

**Rectal Cancer Primary Staging MRI Report Template**

**Clinical information:**

**Technique:**

**Comparison:**

**Tumor location and morphology:**
Location from the anal verge:
☐ Low (0–5 cm) - Distance of inferior border of the tumor to anal verge: [ ] cm
☐ Mid (5.1–10 cm)
☐ High (10.1–15 cm)
Distance of inferior border of the tumor to anorectal junction: [ ] cm
Relationship to anterior peritoneal reflection: ☐ Above ☐ Straddles ☐ Below
Craniocaudal length: [ ] cm
Circumferential location (o'clock position):
Morphology: ☐ Polypoid ☐ Ulcerating ☐ (Semi-)circumferential
Mucinous: ☐ No ☐ Yes

**T-category:** ☐ Tx ☐ T1-2 ☐ T3a ☐ T3b ☐ T3c ☐ T3d ☐ T4a ☐ T4b
If T4b, describe structures with possible invasion:
Genitourinary: ☐ Bladder ☐ [Left/Right] Ureter ☐ Cervix ☐ Uterus ☐ Vagina ☐ Prostate ☐ Seminal vesicle ☐ Urethra
Vessels: ☐ [Left/Right] Internal iliac vessels ☐ [Left/Right] External iliac vessels
Nerves: ☐ Lumbosacral nerve roots
Pelvic muscles: ☐ Obturator internus ☐ Piriformis ☐ Ischiococcygeus
Pelvic floor (levator ani): ☐ Pubococcygeus ☐ Iliococcygeus ☐ Puborectalis
Bones: ☐ Sacrum ☐ Coccyx ☐ Ilium ☐ Ischium ☐ Pubis
*** Low rectal tumors:**
Invasion of sphincter complex: ☐ No ☐ Yes
If yes:
☐ Internal sphincter only
☐ + Intersphincteric plane
☐ + External sphincter
Length of anal canal: [ ] cm

**EMVI:** ☐ No ☐ Yes

**CRM (for T3 only):**
Shortest distance of tumor to MRF (or anticipated CRM): [ ] cm - location (o'clock position)
☐ Not applicable (peritonealized portion of the rectum)
Separate tumor deposit, suspicious lymph node, or EMVI threatening (≤ 2 mm) or invading (≤ 1 mm) the MRF:
☐ No ☐ Yes [If yes, note location and distance]

**Suspicious mesorectal lymph nodes and/or tumor deposits:** ☐ No ☐ Yes
Number of suspicious lymph nodes: [ ]
Distance from tumor deposit to mesorectal fascia: [ ] cm

**Extramesorectal lymph nodes:** ☐ No ☐ Yes [If yes, note location.]

**Other findings/Additional comments:**
**Impression:**
- Stage: T [ ] N [ ]
- CRM: ☐ Clear ☐ Threatened ☐ Involved
- Suspicious node and/or EMVI near CRM: ☐ Yes ☐ No
- Sphincter involvement: ☐ Absent ☐ Present
- Suspicious extra mesorectal nodes: ☐ Yes ☐ No

For post-treatment images, the initial staging variables were included for re-assessment with changes thereof placed within the treatment response categories.

**Table 3: MRI tumor regression grade[9]**

| MRI tumor regression grade | |
|---|---|
| Grade 1: complete radiologic response | No evidence of tumor |
| Grade 2: good response | Dense (>75%) fibrosis with no obvious residual tumor |
| Grade 3: moderate response | >50% fibrosis or mucin with a minority of visible tumor |
| Grade 4: slight response | <50% fibrosis or mucin with a majority of visible tumor |
| Grade 5: no response | No posttreatment changes (same as before treatment) |

The full list of variables is shown in the table below.

**Table 4: Variables**

| INDEPENDENT | DEPENDENT |
|---|---|
| **Age** | |
| **Sex** | |
| Location of the tumor | |
| Morphology of the tumor | |
| Pre-treatment MRI features | |
| DWI/ADC characteristics of the tumor | Treatment protocol- Long/Short course |
| Circumferential resection margin status | |
| Extramural venous invasion | |
| T staging of the tumor | |
| Tumor regression grading | |

## 3.9 Tools and Equipment

The tools needed for this study were readily available at the KNH radiology department. They included:

- A reporting room
- An image viewer
- An MRI console

## 3.10 Study Duration

This study was conducted in a period of 1 year

## 3.11 Study Procedure

Patients who met the inclusion criteria were recruited from the radiology department and Cancer treatment center when they came for their post-treatment assessment by the principal investigator. A consent form was provided. The patients were informed in a language that they understood of the purpose of the study and that the study was voluntary with no influence on their ongoing management. Once the patients had all this information, the consent form was signed by them.

MRI safety screening was done whereby the renal function tests were reviewed and any other contraindication to MRI reviewed by the principal investigator. Buscopan, an antispasmodic agent, was administered prior to the scanning to reduce peristalsis. Patients were required to empty their bladder before imaging. If the patient was unduly agitated or in discomfort, sedation (0.3 to 0.35 mg/kg IV once, provided over 20 to 30 seconds) and analgesia (IM Diclofenac 50mg) was administered.

Administration of a bowel enema and distension of the rectal wall was not done. An endorectal coil was also not used. This has been shown to not be necessary.[26] An External pelvic phased array coil was used and covered the region from the level of the aortic bifurcation to the anal verge. Large field of view images of the entire pelvis were taken initially in axial plane without fat saturation. The scanning plane was perpendicular to the MRF. Small field of view (FOV) T2 weighted images were acquired in axial, sagittal and coronal planes. The axial images were taken perpendicular to the plane of the rectal part containing the tumor; the coronal images were taken parallel to the rectal part containing the tumor; the sagittal images were taken along the long axis of the tumor[27] A detailed MRI protocol as per KNH Rectal cancer scanning protocol is included in APPENDIX C. The pre-CRT and post-CRT MRI scans of these patients were assessed and compared by the principal investigator and confirmed by the supervisors. Reporting was done as per RSNA template of 2017 and all the features derived formed part of the variables for the study. Categories of tumor treatment response was assigned for each patient as per the mr-TRG criteria and status of post-treatment staging change, a figure of this is attached below.

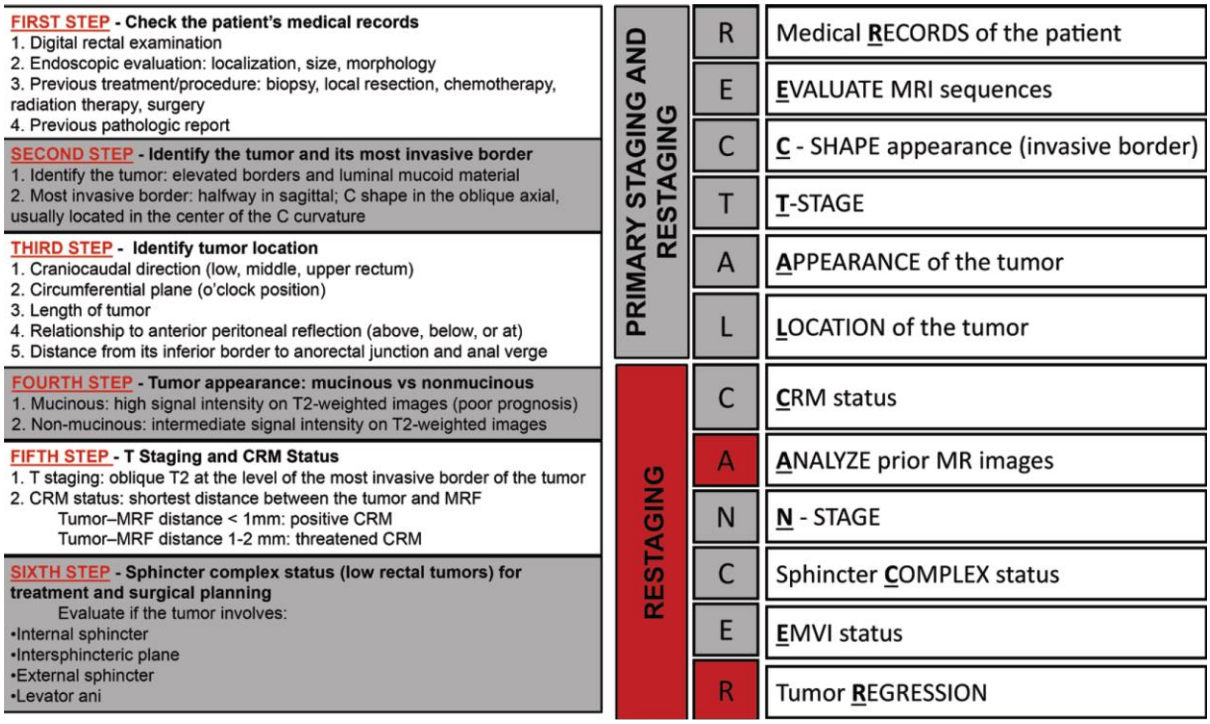


**Figure 5: mr-TRG criteria and status of post-treatment staging change [25]**

### 3.12 Study Flow Chart

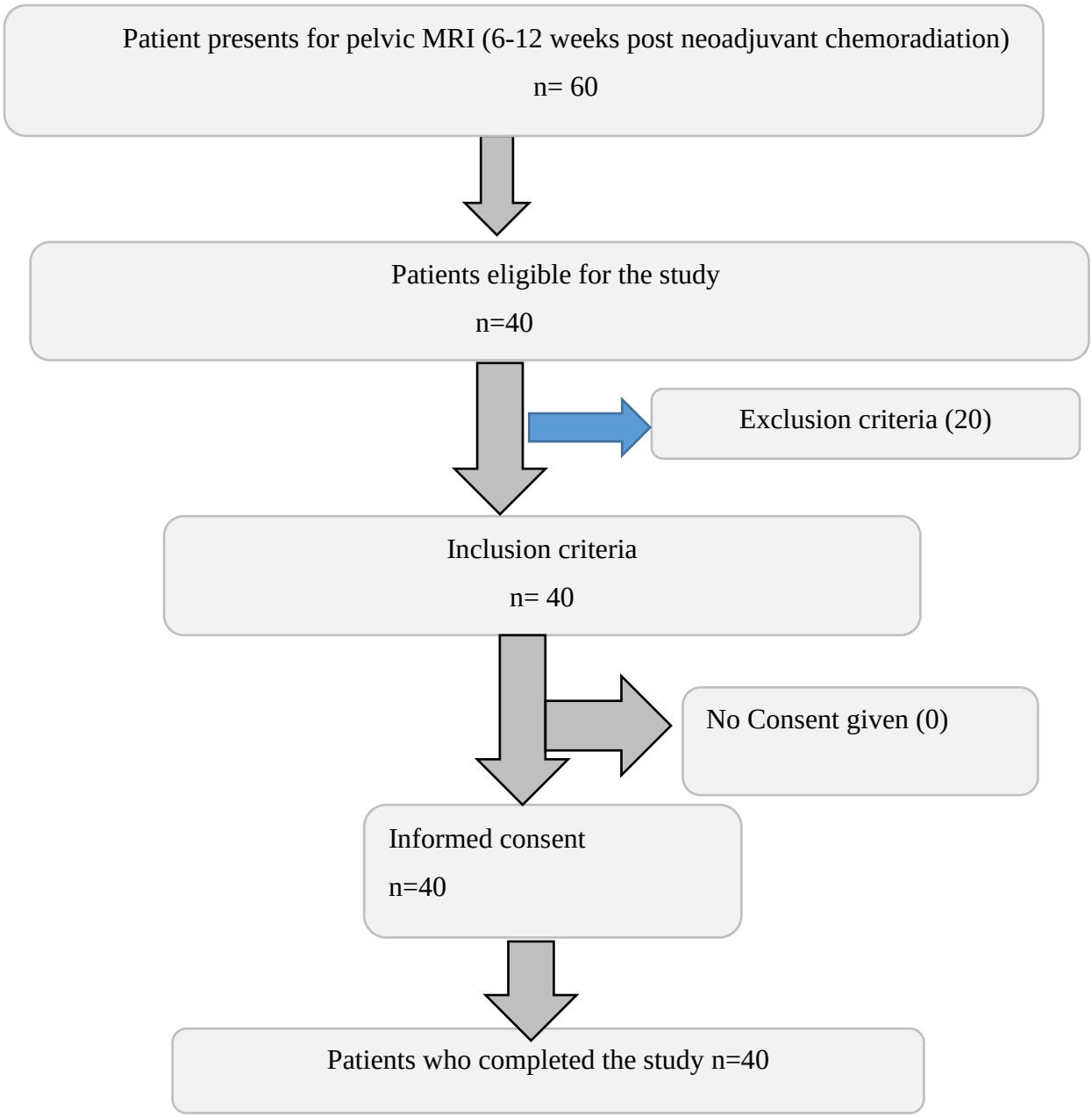


**Figure 6: Study Flowchart**

### 3.13 Data Collection Procedures

Demographic information was obtained from the patients as consent was being signed. The pre- treatment and post-CRT MRI scans were then assessed and compared by the primary investigator and verified by the supervisor consultant radiologist.

## 3.14 Data Management

Data was checked for completeness and error free prior to entry into a password protected Microsoft Excel spreadsheet 2017 that was only accessible to the principal investigator and the statistician. Thereafter the data was exported to the Statistical Package for Social Sciences version 28 for analysis. All statistical tests were considered significant where the p-value < 0.05.

## 3.15 Data analysis

The data was analysed objectively. Demographic characteristics were analysed descriptively. Continuous data was analysed using mean (SD) or Median (IQR) depending on the distribution of data. Categorical data was summarized using frequencies (n) and percentages (%) .

**To compare pretreatment MRI features of rectal tumor that underwent either long or short course neoadjuvant radiation.**

Chi-square test or Fischer's exact test for association was used to determine the association between long or short course neoadjuvant radiation based on the MRI features identified. Independent samples t-test was used to determine whether there was significant difference in continuous MRI features between long or short course neoadjuvant radiation. Odds ratio was calculated using binary logistic regression to investigate the extent of the association between long and short course based on MRI features investigated as shown in dummy Table 2 (APPENDIX E)

**To compare MRI treatment response features for rectal tumors that underwent long or short course neoadjuvant treatment.**

In comparing the MRI treatment response features, Chi-square test or Fischer's exact test for association was used to investigate whether there was an association between long and short course neoadjuvant treatment groups based on categorical MRI treatment response feature. Independent samples t-test was used to compare continuous MRI treatment response features between the two groups. Odds ratio was then calculated using binary logistic regression to investigate the extent of the association between long and short course based on MRI treatment response features as shown in dummy Table 3 (APPENDIX E)

**To compare the MRI treatment response categories between long and short course neoadjuvant treatment groups**

Chi-square test or Fischer's exact test for association were used to determine the association between long and short course neoadjuvant radiation based on the MRI treatment response categories. Odds ratio was calculated using binary logistic regression to investigate the extent of the association between long and short course based on MRI treatment response categories as shown in dummy Table 4 (APPENDIX E)

## 3.16 Quality Assurance Procedures

KNH has one MRI machine of 3 Tesla strength. Most of the MRI studies for this study were done on this machine. All the studies included in the study did not have artefacts secondary to motion, air or degraded by magnetic field inhomogeneity. As part of the standard protocol in KNH, antispasmodics were administered to reduce peristalsis. Patients who were overly anxious were sedated so as to prevent motion.

## 3.17 Ethical Considerations

This research was conducted once permission was sought from the KNH administration and approval from the KNH/UON Ethics and Research Committee was given. Ethical guidelines were employed in line with the World Medical Association Declaration of Helsinki. The name, religion and ethnicity of the patients were not documented. Patients were identified by the MRI number only to safeguard confidentiality. All the information obtained was used for the purpose of this study. Informed consent was taken from the patient before commencement of the study.

Following the Ministry of health directives on COVID 19 prevention, all patients were required to have a mask on during their recruitment and MRI study. The MRI machine was sanitized after every patient's examination. When a number of patients were being screened for recruitment into the study, a distance of 6 feet per patient was maintained. The principal investigator had a mask on at all times and ensured frequent hand sanitization.

No invasive procedures were needed for this study. No extra cost was incurred by the patient. The study findings will be disseminated to the Kenyatta National Hospital, presented in medical conferences and published in medical journals and public media where necessary for the benefit of the medical profession and the lay public. There should be no conflict of interest in this study.

# 4.0 CHAPTER FOUR: RESULTS

The study assessed the pre-treatment and post-treatment MRI features of rectal tumors that underwent either long course or short course treatment, categorize and compare the treatment response categories between the two groups. A total of 40 patients with rectal carcinoma TNM staging T3 and T4 adult patients were included in the study with 29 having undergone long course treatment and 11 having undergone short course treatment.

## 4.1 Demographic Characteristics of Rectal Carcinoma Patients on Post Treatment After Neoadjuvant CRT

The findings revealed that the average age was 54.7(SD±12.54) years with the youngest being 24 years and the oldest being 90 years. Out of the 40 patients, 26(65%) of patients were female and 14(35%) were male. The rectal location was also investigated and 14(35%) had low level tumours. Among those undergoing short course treatment, 4(36.4%) had tumour location in mid-level. For the patients who had undergone long course treatment, 11(37.9%) had low level tumour location. The average time post treatment to repeat MRI was 7.05(SD±1.0) weeks as shown in Table 5.

**Table 5: Demographic characteristics of rectal carcinoma patients on post treatment after neoadjuvant CRT**

| **Demographic factors** | | **Total** | **Neoadjuvant regimen** | |
|---|---|---|---|---|
| | | | **Short course** | **Long course** |
| **Age** | (Mean ±SD) | 54.7 ±12.54 | 55.55 ±16.6) | 54.38 ±10.9 |
| | <50 years | 12(30) | 3(27.3) | 9(31) |
| | 50 - 60 years | 15(37.5) | 5(45.5) | 10(34.5) |
| | >60 years | 13(32.5) | 3(27.3) | 10(34.5) |
| **Gender** | Male | 14(35) | 2(18.2) | 12(41.4) |
| | Female | 26(65) | 9(81.8) | 17(58.6) |
| **Rectal location** | Low | 14(35) | 3(27.3) | 11(37.9) |
| | Mid | 10(25) | 4(36.4) | 6(20.7) |
| | Mid-low | 7(17.5) | 2(18.2) | 5(17.2) |
| | Mid-upper | 4(10) | 1(9.1) | 3(10.3) |
| | Upper | 5(12.5) | 1(9.1) | 4(13.8) |
| **Duration post treatment to repeat MRI (weeks)** | (Mean ±SD)) | 7.05 ±1.0 | 6.55 ±0.8) | 7.24 ±0.95 |

## 4.2 To Compare Pretreatment MRI Features of Rectal Tumors That Underwent Either Long or Short Course Neoadjuvant CRT

Bivariable analysis using logistic regression was conducted to compare pretreatment features of rectal tumor among patients who underwent long and short course treatment as shown in Table 2. Patients who were on long course had a larger diameter of tumour with an average of 3.07(SD±1.05) cm compared to those who underwent short course 2.17(SD±0.97) cm, OR = 2.64, 96%CI: 1.11 – 6.27, p =0.028). Sphincteric involvement was also noted to be higher among the patients who underwent long course treatment at 11(37.9%) compared to 3(27.3%) in the short course group.Mesorectal fascia involvement was noted to be higher in patients who then underwent long course treatment at 13(44.8%) compared to those who then underwent short course treatment 1(9.1%)

The CRM was preserved to a larger extent among patients who underwent short course treatment with an average of 2.57(SD±1.36) mm compared to those who underwent long course, M =1.52 (SD±1.43) mm, OR = 0.59, 95%CI: 0.35 – 0.84, p =0.041) .The majority of patients who underwent long course treatment had a T staging of T3d at 15(51.7%) when compared to those who underwent short course treatment with the majority having T3c tumours at 5(45.4%). Nodal disease also investigated and noted to be higher among the patients who later underwent long course treatment with an average of 4.83(SD ±3.78) compared to 3.45(SD ±2.11 as shown in Table 6.

**Table 6:Comparison of pretreatment MRI features of rectal tumor that underwent either long or short course neoadjuvant CRT**

| MRI features | | Total n(%) | Short course n(%) | Long course n(%) | OR(95%CI) | P-value |
|---|---|---|---|---|---|---|
| | Staging | | | | | |
| **T stage** | T3b | 1(2.5) | 1(9.1) | 0 | | |
| | T3c | 10(25) | 5(45.4) | 5(17.2) | | 0.805 |
| | T3d | 18(45) | 3(27.3) | 15(51.7) | | |
| | T4a | 10(25) | 2(18.2) | 8(27.6) | | |
| | T4b | 1(2.5) | 0 | 1(3.4) | | |
| **N stage** | N0 | 11(27.5) | 4(36.4) | 7(24.1) | Ref | |
| | N1a | 1(2.5) | 0 | 1(3.4) | - | - |
| | N1b | 9(22.5) | 5(45.5) | 4(13.8) | 0.18(0.02 - 1.92) | 0.154 |
| | N2a | 8(20) | 1(9.1) | 7(24.1) | 0.40(0.02 - 8.07) | 0.550 |
| | N2b | 11(27.5) | 1(9.1) | 10(34.5) | 0.14(0.01 - 1.47) | 0.102 |
| **Distance from anal verge (cm)** | Mean ±SD) | 5.66 ±3.6 | 5.3 ±3.14 | 5.8 ±3.77 | 1.04(0.85 - 1.27) | 0.691 |
| **Distance from anorectal junction (cm)** | Mean ±SD) | 2.34(2.6 ) | 2.98(1.21) | 2.22(1.11) | 0.95(0.73 - 1.22) | 0.671 |
| **Length(cm)** | Mean ±SD) | 6.56(2.8 ) | 4.60(3.75) | 6.54(2.44) | 0.99(0.77 - 1.27) | 0.952 |
| Diameter | **Mean ±SD)** | **2.82(1.1 )** | **2.17(0.97)** | **3.07(1.05)** | **2.64(1.11 - 6.27)** | **0.028** |
| **SolidT2 signal** | Intermedi ate | 40(100) | 11(100) | 29(100) | | |
| **MucinonT2WPre** | Absent | 40(100) | 11(100) | 29(100) | | |
| **Fibrosis** | None | 40(100) | 11(100) | 29(100) | | |
| **EMVI** | Positive | 5(12.5) | 0 | 5(17.2) | | |
| | Negative | 35(87.5) | 11(100) | 24(82.8) | | |
| **Mesorectal fascia involved** | Yes | 14(35) | 1(9.1) | 13(44.8) | 0.12(0.01 - 1.09) | 0.061 |
| | No | 26(65) | 10(90.9) | 16(55.2) | Ref | |
| **Anterior peritoneal fold involvement** | Yes | 3(7.5) | 2(18.2) | 1(3.4) | 6.22(0.50 - 76.96) | 0.178 |
| | No | 37(92.5) | 9(81.8) | 28(96.6) | Ref | |
| CRM status(mm) | **Mean ±SD)** | **1.81(1.4 7)** | **2.57(1.36)** | **1.52(1.43)** | **0.59(0.35 - 0.84)** | **0.041** |
| **Nodal status** | Mean ±SD) | 4.45(3.6 ) | 3.45(2.11) | 4.83(3.78) | 1.12(0.91 - 1.38) | 0.281 |
| **Sphincteric complex involvement** | Present | 14(35) | 3(27.3) | 11(37.9) | 0.61(0.13 - 2.82) | 0.715 |
| | None | 26(65) | 8(72.7) | 18(62.1) | Ref | |
| **DWI signal** | Bright | 40(100) | 11(100) | 29(100) | | |
| **ADC value** | Mean ±SD) | 0.78(0.4 1) | 0.58(0.15) | 0.84(0.44) | 2.98(0.41 - 5.41) | 0.391 |

## 4.3 Comparison of Post-Treatment MRI Features of Rectal Tumor Among Patients Who Underwent Short and Long Course Neoadjuvant CRT

Bivariable analysis was conducted to investigate post treatment features of rectal tumors among patients who underwent short course and long course as shown in Table 3. The findings established that those who had long course treatment had a larger diameter of residual tumour (M =2.37, SD ±1.1) compared to those who had short course treatment (M =1.21, SD ±0.64), OR =5.41, 95%CI:1.49 – 19.64, p =0.010. The findings established that patients on short course treatment had a higher fibrosis score (M =4.55, SD ±0.32) compared to those who were on long course (M =3.83, SD ±0.85), OR =0.23, 95%CI:0.07 – 0.80, p =0.021).

The CRM was noted to have improved in patients on short course treatment (M =3.11, SD ±1.7) compared to those who had long course treatment (M = 1.68, SD±1.2), OR =0.65, 95%CI:0.43 – 0.98, p= =0. 039.An overall improvement in nodal disease was noted at 2.07(SD±1.8) compared to the pre-treatment value of 4.45(3.6%). Residual nodal disease was noted to be higher among the patients who underwent long course treatment at 2.55(SD±1.8) compared to those who underwent short course treatment at 0.82(SD±0.2).A rise in the ADC values was also investigated and the findings established that a higher value among the patients who underwent long course treatment at 1.19(SD±0.55) when compared to those who underwent short course treatment at 0.63(SD±1.2).

**Table 7:Comparison of post-treatment MRI features of rectal tumor among patients who underwent short and long course neoadjuvant CRT**

| | | Total n(%) or Mean (SD) | Short course n(%) | Long course n(%) | OR(95%CI) | P-value |
|---|---|---|---|---|---|---|
| | T3a | 5(12.5) | 1(9.1) | 4(13.8) | | |
| **T stage** | T3b | 6(15.0) | 3(27.3) | 3(10.3) | | |
| | T3c | 7(17.5) | 3(27.3) | 4(13.8) | | |
| | T3d | 21(52.5) | 4(36.4) | 17(58.6) | | |
| | T4a | 1(2.5) | 0 | 1(3.4) | | |
| **N stage** | N0 | 18(45.0) | 6(54.5) | 12(41.4) | | |
| | N1a | 3(7.5) | 2(18.2) | 1(3.4) | | |
| | N1b | 12(30.0) | 3(27.3) | 9(31.0) | | |
| | N2a | 4(10.0) | 0 | 4(13.8) | | |
| | N2b | 3(7.5) | 0 | 3(10.3) | | |
| **Distance from anal verge (cm)** | Mean ±SD) | 5.71±3.7 | 5.56±3.4 | 5.77±3.85 | 1.02(0.84 - 1.23) | 0.871 |
| **Distance from anorectal junction (cm)** | Mean ±SD | 2.35±1.3 | 2.79±1.31 | 2.18±1.8 | 0.91(0.70 - 1.19) | 0.496 |
| **Length(cm)** | Mean ±SD | 5.26±2.9 | 4.45±2.3 | 5.56±3.02 | 1.17(0.88 - 1.55) | 0.276 |
| Diameter | **Mean ±SD** | **2.05±1.08** | **1.21±0.64** | **2.37±1.1** | **5.41(1.49 - 19.64)** | **0.01** |
| **SolidT2signal** | Intermediate | 7(63.6) | 19(65.5) | 26(65.0) | Ref | |
| | Hypointense | 1(9.1) | 3(10.3) | 4(10.0) | 1.16(0.23 - 5.80) | 0.854 |
| | Heterogenous | 3(27.3) | 7(24.1) | 10(25.0) | 1.29(0.09 - 17.95) | 0.852 |
| **MucinonT2W** | Present | 2(18.2) | 9(31.0) | 11(27.5) | 0.49(0.09 - 2.76) | 0.694 |
| | Absent | 9(81.8) | 20(69.0) | 29(72.5) | Ref | |
| Fibrosis | **Mean ±SD** | **4.03±0.83** | **4.55±0.32** | **3.83±0.85** | **0.23(0.07 – 0.80)** | **0.021** |
| **EMVI** | Positive | 0 | 2(6.9) | 2(5.0) | | |
| | Negative | 11(100) | 27(93.1) | 38(95.0) | | |
| **Mesorectal fascia involved** | Yes | 1(9.1) | 13(44.8) | 14(35.0) | 0.12(0.01 - 1.09) | 0.061 |
| | No | 10(90.9) | 16(55.2) | 26(65.0) | Ref | |
| **Anterior peritoneal fold involvement** | No | 11(100) | 29(100) | 40(100) | | |
| **CRM status(mm)** | **Mean ±SD** | **2.08±1.9** | **3.11±1.7** | **1.68±1.2** | **0.65(0.43 - 0.98)** | **0.039** |
| **Nodal status** | Mean ±SD | 2.07(1.8) | 0.82(0.2) | 2.55(1.8) | 1.48(0.92 - 2.37) | 0.108 |
| **Sphincteric complex involvement** | Present | 3(27.3) | 11(37.9) | 14(35.0) | 0.61(0.13 - 2.82) | 0.715 |
| | None | 8(72.7) | 18(62.1) | 26(65.0) | Ref | |
| **DWI signal** | Bright | 10(90.9) | 26(89.7) | 36(90.0) | 1.15(0.11 - 12.44) | 0.701 |
| | Dark | 1(9.1) | 3(10.3 | 4(10.0) | Ref | |
| **ADC value** | Mean ±SD | 1.06±0.5) | 0.63±1.2) | 1.19±0.55 | 2.01(0.12 - 6.49) | 0.251 |

## 4.4 To Compare the MRI Treatment Response Categories Between the Long and Short Course Neoadjuvant CRT

Bivariable analysis using logistic regression was conducted to compare MRI treatment response categories between the long and short course treatment as showed in Table 8. This study determined that in the partial response category (18 patients), a greater percentage of patients were from the long course arm (52.6%) when compared to those from the short course group (47.3%). In the near complete group (5 patients), majority of the patients were from the long course group (80%). In the poor response category (17 patients), most of the patents were from the long course group (94%) with only one patient from the short course group exhibiting poor response to treatment.

**Table 8:Comparison of MRI treatment response categories between long and short course neoadjuvant CRT**

| Response to treatment | Total n(%) | Course | |
|---|---|---|---|
| | | Short course n(%) | Long course n(%) |
| **Poor** | 17(42.5) | 1(5.9) | 16(94.1) |
| **Partial** | 19(47.5) | 9(47.4) | 10(52.6) |
| **Near complete** | 5(12.5) | 1(20) | 4(80) |

# 5.0 CHAPTER FIVE: DISCUSSION, CONCLUSION AND RECOMMENDATIONS

## 5.1 Discussion

MRI evaluation of rectal cancer remains the gold standard for loco-regional staging in the primary and post-neoadjuvant treatment phases. This is due to its superiority in soft tissue delineation. Addition of functional imaging then boosts the accuracy of the tumour response assessment to neoadjuvant treatment. The present study compared the pre-treatment MRI features of tumours that had undergone either long or short course treatment. The study established that patients with bulky disease, i.e based on the size, MRF involvement, CRM status, EMVI and nodal disease underwent long course treatment. Majority of the patients had T3d or T4a with N1b disease staging.

Rectal tumour location and sphincter involvement were also assessed in the present study. The findings determined that majority of patients with low level disease and sphincter involvement were in the long course treatment group. These findings are comparable to a study done to determine why long course neoadjuvant treatment remains favoured over short course treatment in the US by Mowery et al that showed 95% of patients with bulky disease, sphincteric involvement and a positive or threatened CRM would be preferred to undergo long course treatment[10].

The present study sought to compare the MRI treatment response features for rectal tumours that underwent long or short course treatment. It determined that patients on long course treatment had a larger diameter/length of residual tumour, a higher degree of residual nodal disease, a lower fibrosis score and a higher degree of increase in ADC values. The patients on short course treatment had a smaller diameter/length of residual tumour and a higher degree of improvement in the CRM status. The study also sought to compare the MRI treatment response categories between the long and short course neoadjuvant treatment groups. The treatment response was categorized as complete/near complete, partial or poor response.

It determined that in the partial response category (18 patients), a greater percentage of patients were from the long course arm (52.6%) when compared to those from the short course group (47.3%). In the near complete group (5 patients), majority of the patients were from the long course group (80%). In the poor response category (17 patients), most of the patents were from the long course group (94%) with only one patient from the short course group exhibiting poor response to treatment.

These findings are comparable to a previous study done by Yeo et al that sought to assess the efficacy of short course treatment when compared with long course treatment in locally advanced rectal cancer which determined that short course treatment yielded poorer pathologic response when compared to long course treatment.[28]

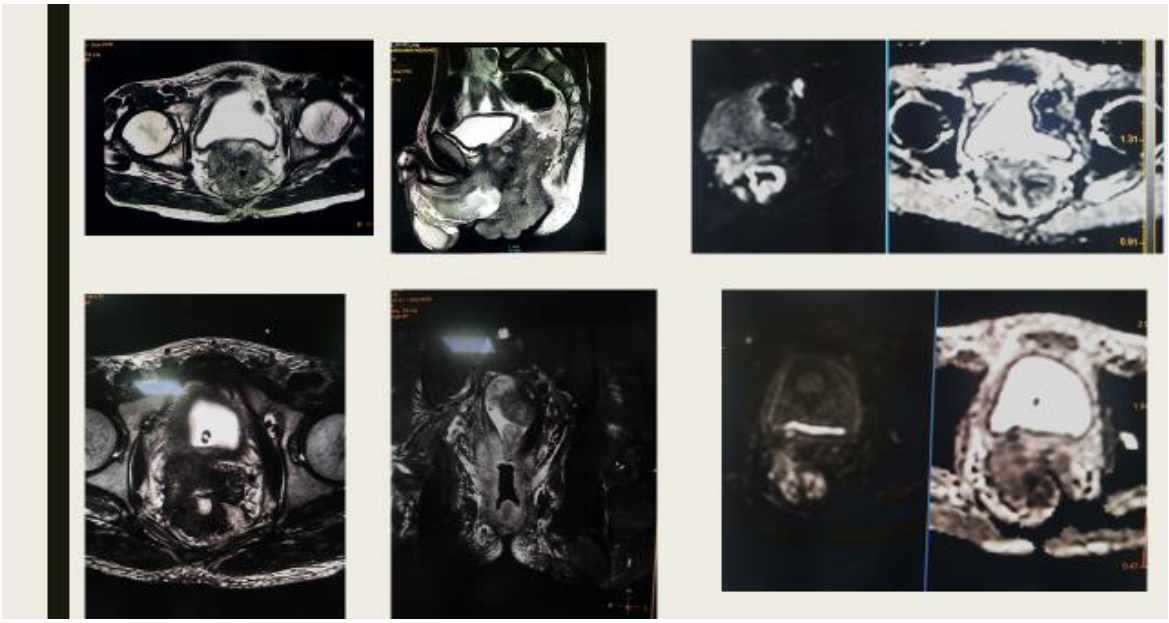

**Figure 7: 55-year-old male with mid-low level circumferential disease with extensive involvement of the anal sphincter and underwent long course of treatment. Interval progression of the disease was noted in the post-treatment MR images**

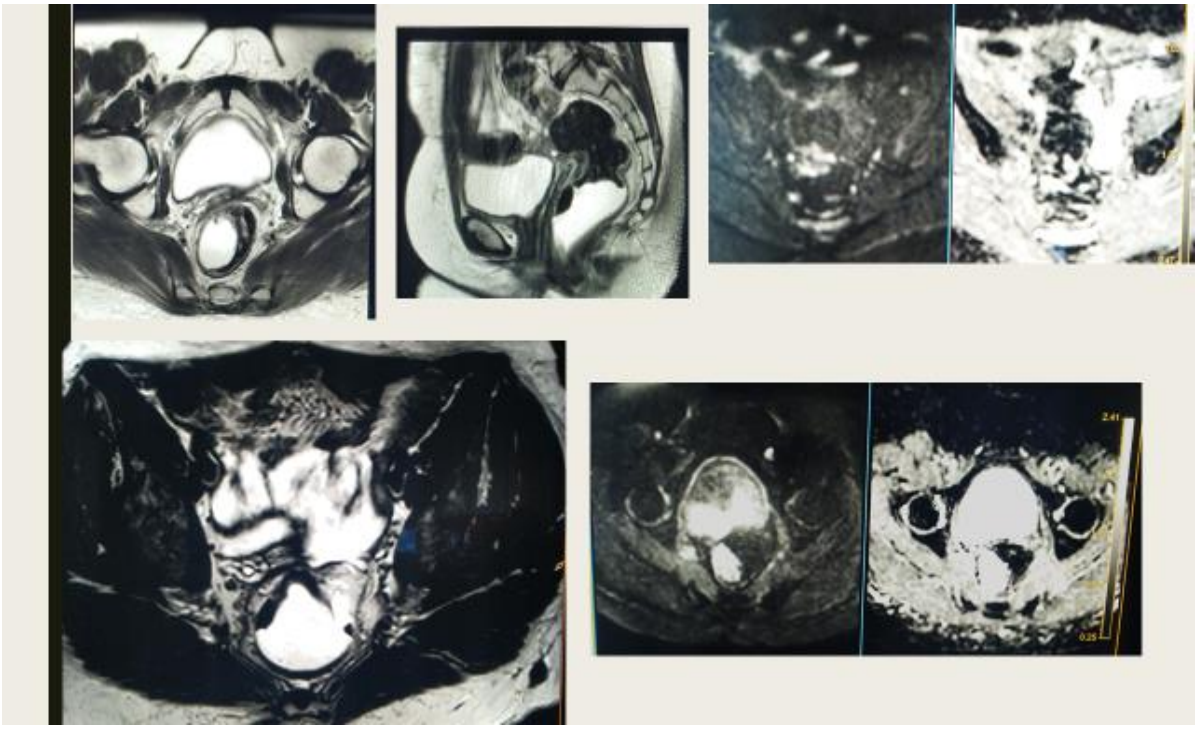

**Figure 8:42 year old female ptient who had mid-upper level disease at 11-2 o'clock position who then underwent long course treatment. The patient exhibited near-complete response in her post-treatment MR images**

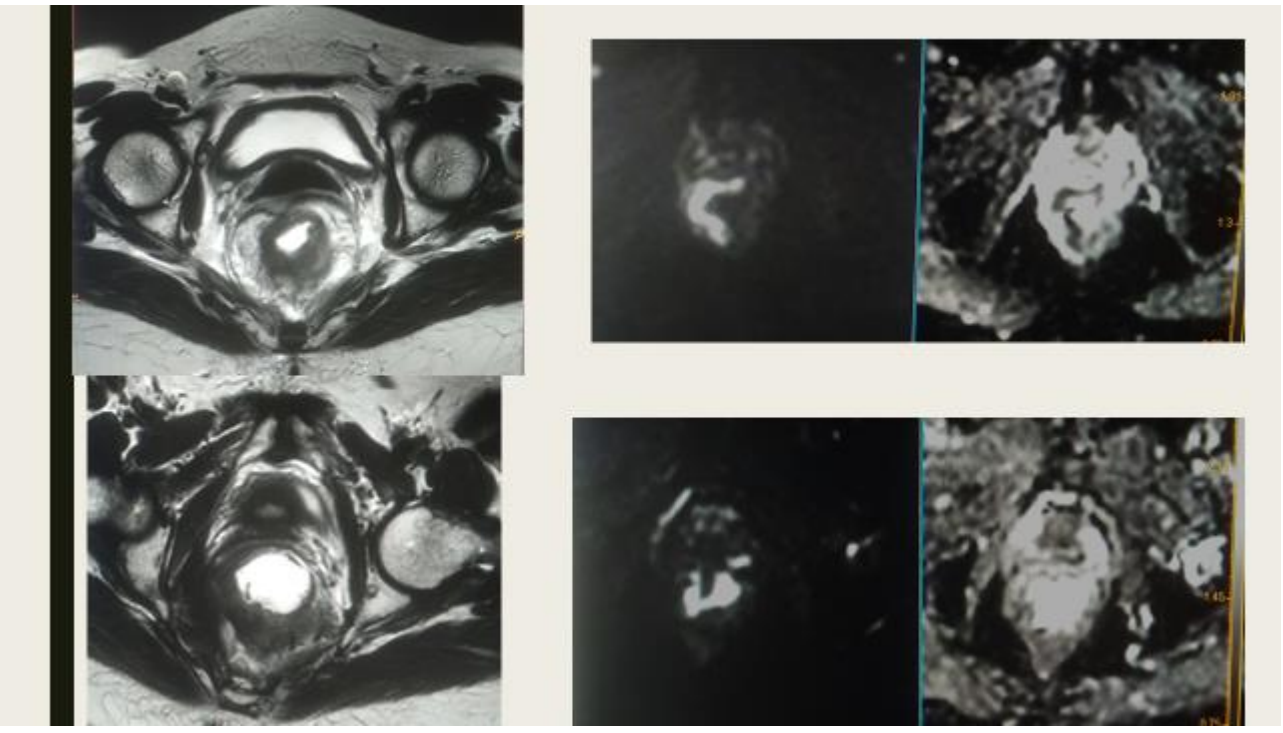

**Figure 9 :Comparison of MRI treatment response categories between long and short course neoadjuvant CRT56 year old male with mid-level circumferential disease who then underwent short course treatment. The patient had overall signs of poor response but a 50% increase in the ADC values was noted in the post treatment MR images.**

## 5.2 Conclusion

Locoregional evaluation of rectal cancer after neoadjuvant treatment determines key aspects in the overall patient management. Accurate assessment is therefore key in this regard. The choice of the course of neoadjuvant treatment has remained debatable with no clear guidelines given for the recommendation of either one. This study established that the overall radiological response to treatment was better in the long course group when compared to the short course group. This result may however have been secondary to the smaller number of short course patients sampled. Less bulky disease (T3a-T3c tumours) were more likely to have short course treatment recommended while low level, bulky disease with sphincter involvement were more likely to have long course treatment recommended. An increase in ADC values was established to have a role in the indication of tumour response to treatment.

## 5.3 Recommendations

- A larger study over a larger duration of tim e can be done to assess for differences in tumour response between patients who have undergone long and short course neoadjuvant treatment with pathological correlation.
- A study that compares the treatment response between the treatment courses can be done in patients who have a similar disease burden in terms of staging.
- Assessment and documentation of ADC values in the pre-treatment and post-treatment MR imaging of rectal cancer.
- Improvement in the PACS system at the KNH.
- Clear guidelines should be generated to guide the course of neoadjuvant treatment that a patient with locally advanced rectal cancer will undergo. Based on this study results, patients with rectal cancer staged at T3a-T3c can be considered for short course treatment. Those with bulkier disease, sphincteric involvement and nodal disease can be considered for long course treatment.

## 5.4 Study Limitations

- Lack of a good PACS system in the Department of Radiology that would have given access to all the patients images (pre- and post-treatment).
- Lack of ADC value documentation in most reports.
- A small number of patients sampled for the study.
- Lack of proper access to the patient’s health records

- Most patients preferring to have their imaging done at a different facility due to the longer waiting times at KNH.
- MR based tumor regression grade may not correctly correlate with the gold standard histopathology based one. As such, these findings can guide in making gross patient management decisions but do not substitute the need for histopathologic correlation.

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# APPENDICES

## Appendix A: Data Collection Form

Title: MRI assessment of Rectal cancer post CRT at the Kenyatta National Hospital

Investigator: Dr. Tabitha Muthoni Karuri, Resident in the Department of Diagnostic imaging and Radiation Medicine, University of Nairobi

1. Study ID No ……..
2. Neoadjuvant treatment regimen: short course/long course: …….
3. What is your age?.....
4. What is your gender?

   Male [ ] Female [ ]

Duration between completion of treatment and repeat MRI (weeks)…….

**Section B: Pretreatment and Post-treatment features**

| | | Pretreatment | Post-treatment | |
|---|---|---|---|---|
| 5. Location of tumor | Distance from anal verge (high-, mid-, low-rectal) | | | |
| | Clock face | | | |
| 6. Size | CC (cm) | | | |
| | Longest diameter (cm) | | | |
| 7. Morphologic features | Solid intermediate signal on T2W | | | |
| | Mucin on T2W | | | |
| | Fibrosis on T2W | | | |
| | Nodal status | | | |
| | Extramural venous invasion | | | |
| | Involvement of sphincter complex | | | |
| | Distance from sphincter complex | | | |
| | Peritoneal fold involvement/status | | | |
| | Circumferential Resection Margin status | | | |
| | | | | |
| 8. Functional features | DWI signal | | | |
| | ADC value | | | |
| 9. T N M stage | | | | |
| | | | | |

10. mr-TRG category:
11. RECIST category:

## Appendix B: Detailed MRI Protocol

| | **AXIAL T1 FSE** | **AXIAL T2 FSE** | **SAG T2 FSE** | **CORONAL T2 FSE** | **SAG T2 SPIR** | **CORONAL T1 GD SPIR** | **AXIAL DWI** |
|---|---|---|---|---|---|---|---|
| Repetition time (ms) | 529 | 3603 | 3603 | 3603 | 4170 | 574 | 3748 |
| Echo time (ms) | 8 | 100 | 100 | 100 | 80 | 8 | 86 |
| Number of slices | 30 | 30 | 30 | 30 | 25 | 30 | 38 |
| Field of view (mm) | 240 | 240 | 250 | 250 | 260 | 260 | 300 |
| Slice thickness | 3.5 | 3.5 | 3.5 | 3.5 | 4 | 3.5 | 3 |
| Slice gap (mm) | 2 | 1.5 | 1.5 | 1.5 | 0.4 | 2 | 1 |
| Matrix | 200 X 210 | 244 X 226 | 244 X 226 | 244 X 226 | 520 X 355 | 272 X 243 | 100 X 98 |
| Acquisition time (min) | 2.1 | 1.41 | 1.41 | 1.41 | 1.53 | 2.21 | 3 |

## Appendix C: Information and Consent Form (English)

**Information and Consent Form**

**Study Title: Comparison of pre-treatment and post-treatment MRI features of rectal carcinoma in patients undergoing long course versus short course neoadjuvant chemo radiation at the Kenyatta National Hospital.**

**Principal Investigator:** Dr. Tabitha Muthoni Karuri (Mmed student, University of Nairobi)

**Co-Investigators:** Dr. Timothy Mutala (University of Nairobi), Dr. Nelson Kimani (University of Nairobi), Dr. Eunice Omamo (Kenyatta National Hospital).

**Introduction:**

I would like to tell you about a study being conducted by the above-listed researchers. The purpose of this consent form is to give you the information you will need to help you decide whether or not to be a participant in the study. Feel free to ask any questions about the purpose of the research, what happens if you participate in the study, the possible risks and benefits, your rights as a volunteer, and anything else about the research or this form that is not clear. When we have answered all your questions to your satisfaction, you may decide to be in the study or not. This process is called 'informed consent.' Once you understand and agree to be in the study, I will request you to sign your name on this form. You should understand the general principles which apply to all participants in medical research:

i) Your decision to participate is entirely voluntary

ii) You may withdraw from the study at any time without necessarily giving a reason for your withdrawal

iii) Refusal to participate in the research will not affect the services you are entitled to in this health facility or other facilities.

We will give you a copy of this form for your records.

**May I continue? YES / NO**

**What is This Study About?**

The researchers listed above are conducting a research on the accuracy of magnetic resonance imaging in staging locally advanced rectal cancer post neoadjuvant chemo radiation. The aim of the research is to validate MRI as an accurate imaging modality in the assessment of rectal cancer post neoadjuvant chemo radiation. Approximately 30 patients will be selected for this study. We are asking for your consent to consider participating in this study.

**What Will Happen If You Decide to Be In This Research Study?**

If you agree to participate in this study, the following things will happen:

- You will undergo an MRI study to determine the rectal cancer stage post CRT
- The pre-treatment and post-treatment MRI scans will be compared for tumor response and restaging done.

**Are There Any Risks, Harms Discomforts Associated with This Study?**

Medical research has the potential to introduce psychological, social, emotional and physical risks. Effort should always be put in place to minimize the risks. One potential risk of being in the study is the loss of privacy. We will keep everything you tell us as confidential as possible. We will use a code number to identify you in a password-protected computer database and will keep all of our paper records in a locked file cabinet. However, no system of protecting your confidentiality can be absolutely secure, so it is still possible that someone could find out you were in this study and could find out information about you.

**Are There Any Benefits Being in This Study?**

You may not benefit directly as an individual, but the study will aid in development of standardized imaging protocols which are pivotal in imaging of rectal cancer. There will be no direct compensation for participating in this study.

**Will Being In This Study Cost You Anything?**

Participation is free and voluntary.

**Will You Get Refund For Any Money Spent As Part Of This Study?**

There is no expense involved in participating in this study. You will not be compensated.

**Contacts: What If You Have Questions In Future?**

If you have further questions or concerns about participating in this study, please call or send a text message to the Principal Investigator, Dr. Tabitha Karuri 07231268.

For more information about your rights as a research participant, you may contact the Secretary/Chairperson, Kenyatta National Hospital-University of Nairobi Ethics and Research Committee Telephone No. 2726300 Ext. 44102 email uonknh_erc@uonbi.ac.ke.

The study staff will pay you back for your charges to these numbers if the call is for study-related communication.

**What Are Your Other Choices?**

Your decision to participate in research is voluntary. You are free to decline participation in the study, and you can withdraw from the study at any time without suffering any negative consequences. You will continue to receive the care and treatment needed even if you do not wish to participate in this study.

**Consent Form (Statement of Consent)**

**Participant's statement**

I have read this consent form or had the information read to me. I have had the chance to discuss this research study with a study counselor. I have had my questions answered in a language that I understand. The risks and benefits have been explained to me. I understand that my participation in this study is voluntary and that I may choose to withdraw at any time. I freely agree to participate in this research study.

I understand that all efforts will be made to keep information regarding my identity confidential.

By signing this consent form, I have not given up any of the legal rights that I have as a participant in a research study.

I agree to participate in this research study: Yes No

**Participant printed name:** _____

**Participant signature / Thumb stamp** _____ **Date** _____

**Researcher's statement**

I, the undersigned, have fully explained the relevant details of this research study to the participant named above and believe that the participant has understood and has willingly and freely given his/her consent.

**Researcher's Name**: _____ **Date**: _____

**Signature** _____

**Role in the study**: _____

**Witness** (*If witness is necessary, a witness is a person mutually acceptable to both the researcher and participant*)

**Name** _____

**Contact information** _____

**Signature /Thumb stamp:** _____

Date: _____

## Appendix D: Information and Consent Form - (Kiswahili)

**MAELEZO KUHUSU UTAFITI/WARAKA WA IDHINI**

**STUDY TITLE: Comparison of pre-treatment and post-treatment MRI features of rectal carcinoma in patients undergoing long course versus short course neoadjuvant chemo radiation at the Kenyatta National Hospital.**

Mtafiti mkuu: Dkt. Tabitha Karuri (Chuo Kikuu cha Nairobi)

Watafiti weza: Dkt. Timothy Mutala (University of Nairobi), Dkt. Nelson Kimani (University of Nairobi), Dkt. Eunice Omamo (Kenyatta National Hospital).

**Utangulizi**

Ningependa kukueleza juu ya utafiti unaofanywa na watafiti waliotajwa hapo juu. Madhumuni ya fomu hii ya idhini ni kukupa maelezo unayohitaji ili kukusaidia uamuzi ikiwa Utahusishwa kwa utafiti huu au la. Jisikie huru kuuliza maswali yoyote kuhusu madhumuni ya utafiti, kinachotokea ikiwa unashiriki katika utafiti, hatari na faida iwezekanavyo, haki zako kama kujitolea, na kitu kingine chochote kuhusu utafiti au fomu hii ambayo haijulikani. Tunapojibu maswali yako yote kwa kuridhika kwako, unaweza kuamua kuwa katika utafiti au la. Utaratibu huu unaitwa 'kibali cha habari'. Mara unapoelewa na kukubali kuwa katika utafiti, nitakuomba kusaini jina lako kwenye fomu hii. Unapaswa kuelewa kanuni za jumla ambazo zinatumika kwa washiriki wote katika utafiti wa matibabu: i) Uamuzi wako wa kushiriki ni kikamilifu kwa hiari ii) Unaweza kujiondoa kwenye utafiti wakati wowote bila ya kutoa sababu ya uondoaji wako iii) Kukataa kushiriki katika utafiti hauathiri huduma unazostahili kwenye kituo hiki cha afya au vifaa vingine. Tutakupa nakala ya fomu hii kwa rekodi zako.

Naweza kuendelea? NDIO/LA

**Utafiti Huu Unahusu Nini?**

Mtafiti aliotajwa hapo juu atawaoji watu ambao wanafanyiwa uchunguzi wa MRI. Lengo la utafiti ni kutambua usahihi wa MRI kwa kuonyesha jinsi saratani ya puru inavyo fanana baada ya kupatiwa matibabu ya kidini na mionzi. Karibu wagonjwa 30 watashiriki katika utafiti huu. Tunaomba ridhaa yako kufikiria kushiriki katika utafiti huu.

**Ni Nini Kitakacho Fanyika Ukiamua Kuhusika Kwa Utafiti Huu?**

Ikiwa unakubali kushiriki katika utafiti huu, mambo yafuatayo yatatokea:

- Utapigwa picha ya MRI kuangalia uenezi wa saratani
- Picha za kwanza kabla ya matibabu na ambayo yamepigwa baada ya matibabu yatalinganishwa na uenezi wa saratani uangaliwe baada ya matibabu.

**Kuna Madhara Yoyote Yanayotokana Na Utafiti Huu?**

Utafiti wa matibabu una uwezo wa kuanzisha hatari za kisaikolojia, kijamii, kihisia na kimwili. Jitihada zinapaswa kuwekwa daima ili kupunguza hatari. Hatari moja ya kuwa katika utafiti ni kupoteza faragha. Tutaweka kila kitu unachotuambia kama siri iwezekanavyo. Tutatumia namba ya nambari ili kukutambua kwenye darasani ya kompyuta iliyohifadhiwa na nenosiri na tutahifadhi rekodi zote za karatasi kwenye baraza la mawaziri lililofungwa. Hata hivyo, hakuna mfumo wa kulinda siri yako inaweza kuwa salama kabisa, kwa hiyo bado inawezekana kwamba mtu anaweza kujua wewe ulikuwa katika utafiti huu na anaweza kupata habari kukuhusu.

**Kuna Manufaa Yoyote Kwa Kuhusika Kwa Utafiti Huu?**

Huwezi kufaidika moja kwa moja kama mtu binafsi, lakini utafiti huu utasaidia katika uteuzi utaratibu na mpangilio wa kufanya MRI kwa kupima saratani ya puru kabla ya upasuaji. Hutakuwa na fidia moja kwa moja ya kushiriki katika utafiti huu.

**Kuhusika Kwa Utafiti Huu Kutagharimia Chochote?**

Hakuna malipo ila tutachukua muda wa dakika kumi

**Utapata Malipo Yoyote Au Fidia**

Hakuna malipo au fidia ili kuhusika kwa utafitu huu

**Ukitaka Kuuliza Swali Baadaye Kuhusu Utafiti Huu?**

Wasiliana na Mtafiti mkuu, Daktari Tabitha Karuri kwa nambari ya simu: +254 723126844 Ama mwenyekiti au katibu msimamizi, utafiti, Hospitali ya Kitaifa ya Kenyatta na Chuo kikuu cha Nairob kupitia nambari 2726300/44102; au kwa anuani uonknh_erc@uonbi.ac.ke. Watafiti watakurejeshea pesa zilizotumika kwa mawasiliano kuhusu utafiti huu.

## Appendix E: KNH/UoN-ERC Letter of Approval

UNIVERSITY OF NAIROBI
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P O BOX 19676 Code 00202
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KENYATTA NATIONAL HOSPITAL
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Ref: KNH-ERC/A/153

14th April, 2022

Dr. Tabitha Muthoni Karuri
Reg.No. H58/34651/2019
Dept. of Diagnostic Imaging & Radiation Medicine
Faculty of Health Sciences
University of Nairobi

KENYATTA NATIONAL HOSPITAL APPROVED 14 APR 2022 KNH/UoN-ERC P.O. Box 20723 - 00202, NAIROBI

Dear Dr. Karuri,

**RESEARCH PROPOSAL: COMPARISON OF THE PRE-AND POST-TREATMENT MAGNETIC RESONANCE FEATURES OF RECTAL CANCER BETWEEN PATIENTS UNDERGOING LONG AND SHORT COURSE NEOADJUVANT TREATMENT AT THE KENYATTA NATIONAL HOSPITAL (P701/08/2021)**

This is to inform you that KNH-UoN ERC has reviewed and approved your above research proposal. Your application approval number is **P701/08/2021.** The approval period is 14th April 2022– 13th April 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 mus: 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 Chairperson, KNH- UoN ERC
The Assistant Director, Health Information, KNH
The Chair, Dept. of Diagnostic Imaging & Radiation Medicine, UoN
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Dr. Nelson Kimani, Dept. of Diagnostic Imaging & Radiation Medicine, UoN
Dr. Eunice Omamo, Consultant Radiologist, KNH

**Appendix F: Certificate of Plagiarism**

Comparison of Pre And Post Treatment Magnetic Resonance Features of Rectal Cancer Between Patients Undergoing Long And Short Course Neoadjuvant Treatment At The Kenyatta National Hospital

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